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FOOD AND DRUG ADMINISTRATION'S REVIEW PROCESS FOR PRODUCTS TO TREAT RARE DISEASES AND NEGLECTED TROPICAL DISEASES

HEARING

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

UNITED STATES SENATE

ONE HUNDRED ELEVENTH CONGRESS

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FOOD AND DRUG ADMINISTRATION'S REVIEW PROCESS FOR PRODUCTS TO TREAT RARE DISEASES AND NEGLECTED TROPICAL DISEASES

WEDNESDAY, JUNE 23, 2010

U.S. SENATE, SUBCOMMITTEE ON AGRICULTURE, RURAL DEVELOPMENT, FOOD AND DRUG ADMINISTRATION, AND RELATED AGENCIES, COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 2:05 p.m., in room SD–192, Dirksen Senate Office Building, Hon. Herb Kohl (chairman) presiding.

Present: Senators Kohl, Pryor, and Brownback.

OPENING STATEMENT OF SENATOR HERB KOHL

Senator KOHL. Good afternoon to all of you. And we appreciate your being here, particularly appreciate our witnesses who are with us today.

Senator Brownback asked me to convene this hearing.

And I will be brief.

It reflects Senator Brownback's longstanding concern about lack of therapies for rare diseases in the United States and neglected tropical diseases, such as malaria and tuberculosis throughout the world.

In the United States, rare diseases are defined as those which affect fewer than 200,000 people. According to the NIH, there are close to 7,000 rare diseases. In total, more than 25 million people in the United States have one.

Beyond our shores, the World Health Organization estimates that over 1 billion people, one-sixth of the world's population, suffer from one or more neglected tropical diseases. They often afflict the poorest populations, who live in remote rural areas, urban slums, or conflict zones. Three hundred to 700 million people get malaria each year, and an estimated 1.3 million people died from tuberculosis in the year 2008.

Last year, we included language in the appropriations bill, at Senator Brownback's, request to establish review groups that focus on these issues. Their mission was to look at the procedures by which both rare and neglected tropical diseases are approved, and to provide recommendations on how these procedures can be improved upon. These review groups have been created and are actively working, at this time.

Due to scheduling conflicts, I will not be able to stay on, and so I will now turn the hearings over to Senator Brownback.

Again, we thank all of our witnesses for their presence here today.

Senator Brownback.

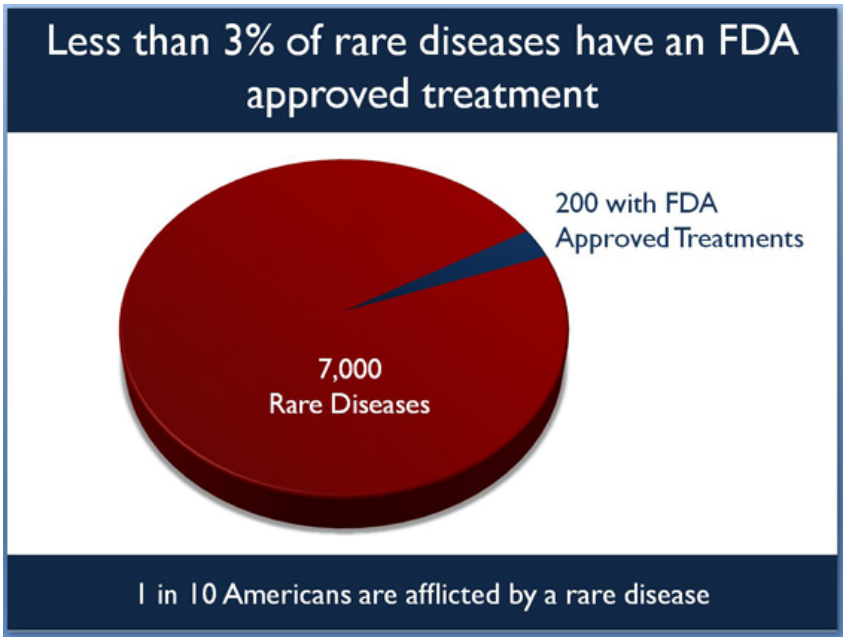
STATEMENT OF SENATOR SAM BROWNBACK

Senator BROWNBACK [presiding]. Thank you very much, Mr. Chairman.

And, to everybody here, I want to say, and to you directly Mr. Chairman, how much I appreciate your willingness to engage this topic and work on it. You've been absolutely outstanding and wonderful to do this. It's a key topic. It's an important topic.

But, you're in the majority, and I'm in the minority, and you don't need to do this. You are, because of your care and concern for this issue. And I deeply appreciate it. I know a lot of people around the world will, and do, as well.

The chairman noted the problem, and it is enormous, it's significant. I've got two charts that show some of the statistics. I just want to flip these up here for people to be able to see and notice what this problem is.



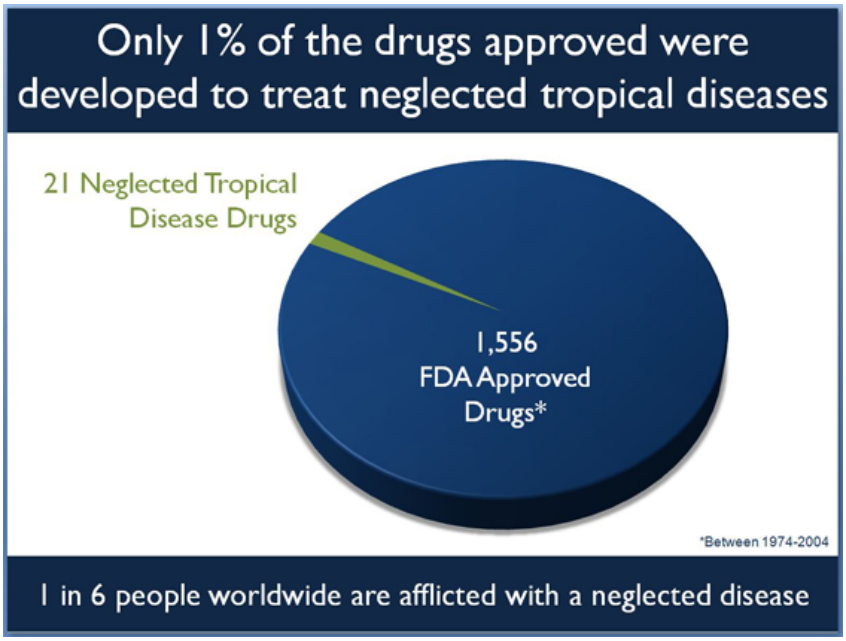
Less than 3 percent of the rare diseases have an FDA-approved treatment. So, if you get one of these diseases, God bless you. That's just about all we can say, because we don't have any treatment for you. And in my way of looking at the world, that's just not a sufficient answer, particularly not with the technology and the ability that we have today, that you just say, "We've got 200 approved FDA treatments for 7,000 rare diseases." It's just simply not. Rare diseases affect nearly 1 in 10 Americans, so we'd have

several people probably in this room with a rare or neglected disease that there's no treatment for—none.

The old model of a billion dollars to develop a drug doesn't work in this category, because there's just not a billion dollars of market with it. And we all recognize that. There's not a billion dollars, probably, of government subsidy to go into each one of these 7,000 different areas. So, we've got to do something different, and the model has to be different.

What I'm hearing, Mr. Chairman, from people I'm talking with, is that people are working very closely and carefully to try to come up with a different model. And we need to do that.

I've got a second chart here I just wanted to show you quickly, as well. This goes more for diseases around the world. We can look at it, and it's terrible what happens in the United States. We're talking millions in the United States, but you go around the world and we're talking billions of people that are affected. The chairman and I have both been in places around the world where somebody gets a tropical disease, and, again, you can just say, kind of, "God bless you," and that's about all we can do. It's just not good enough. I know we can do better than this.



About 1 percent of approved drugs are developed to treat neglected tropical diseases—21 out of 1,556. And you can say, "Well, that's not our responsibility. It's around the world." One in six people are affected. Yet, I also know that in the places around the world where the United States invests in helping people save lives, like we did with AIDS treatment, particularly in Africa, or like we've done recently with malaria, that people tend to really like the United States if we help save their life. It's a strange thing. I

mean, I just am amazed about that. But, people really tend to appreciate that.

I think continents like Africa are continents in play. We're certainly seeing the Chinese play aggressively in Africa. And if we're there, helping people to save lives, and investing to save lives, they're going to appreciate that. One of the best things we can possibly do.

Again, I think a big piece of it is that we've got to get our system adjusted so it doesn't cost a billion dollars to develop the drug, and that you can, hopefully, tempt companies, and us, as a government, into saying, "Okay, we can do this on a cheaper basis and develop, still, the quality product." So if you get one of these diseases you don't have to say, "I'm sorry, all I can say to you is, 'God bless you.'" I think this is really important.

I'm delighted at our first panel. I'm even more pleased about the second panel, which is the government panel, and the amount of effort that they're doing to work together to develop some different models and ways forward in this area, because in my way of thinking and looking around the world, there's this great parable about the good Samaritan. In the core of the parable, all these good people walk by somebody that's sick, and they walk on the other side of the road, because they don't want to really look at the sick person; they don't want to have their conscience pricked by the sick person. But, then somebody finally stops and helps them. And then, that's the one we hold up, "They're doing the right thing."

Well, let's not just walk by them. Yes, we have people that are sick, but let's not just walk by them. Let's see what we can do to invest just a little bit of money, and go and look at our system, and adjust our system, to see if we can save a whole bunch of lives.

And I am absolutely convinced, Mr. Chairman, we can do this. I'm absolutely convinced we can do it without jeopardizing our quality standards that we have. I know we can get this moving forward. And I know if we do, we're going to be a stronger country, and it's going to be a better world for it. And it will have been worth my time in the Senate, if we get something like this to move forward.

So, I'm deeply appreciative of the panel and of you, Mr. Chairman, for being willing to engage in this difficult but very important topic.

Mr. Chairman, I'll call and introduce the first panel, then.

I want to thank you very much for being here and willing to be a part of this hearing. This is also highly unusual for me, as a minority member, to be chairing the hearing, and the chairman has just been so kind to hold this hearing. I promise not to pass any bills out of committee—as if I could.

Our first panel is Dr. Emil Kakkis. He's president and founder of Kakkis EveryLife Foundation, and has worked in these areas for some period of time; Ms. Diane Edquist Dorman, vice president for public policy, the National Organization for Rare Disorders; and Mr. Thomas Bollyky, visiting fellow, Center for Global Development.

We're going a little bit backwards in this panel, in that we're having the private-sector panel ahead of the public-sector panel. But, I thought, really, that the private-sector panel had a lot of

thoughts to offer to the public-sector, and so, it was my hope, actually, you could put forward ideas that we'd have the public-sector panel react to afterwards. So, I hope you feel empowered to do that.

We have your written testimony. I appreciate that. And we'll now call on you to make your presentations.

Doctor, please, if you'd like to start.

STATEMENT OF DR. EMIL KAKKIS, PRESIDENT AND FOUNDER, KAKKIS EVERYLIFE FOUNDATION

Dr. KAKKIS. Thank you, Senator Brownback. I appreciate and thank you for your leadership in the rare disease community, in putting on this hearing, and everything else you have been doing.

I'm the founder and president of the Kakkis EveryLife Foundation, a foundation I established and funded to help improve the regulatory process for rare diseases. I have been working in the rare disease drug development area for 18 years, both in academia and in industry, developed three approved products, and put seven more into development. And, despite that success, I saw many challenges, both then and now, that make it more difficult to get drugs developed, and I think things could be improved.

There are still many patients out there; and every week, I get calls from patients and families that have been essentially struck by genetic lightning with some terrible, unusual, unpronounceable disease. And they call because the mother and the father are setting up a foundation so they can raise money and do drug development, an impossible task for many, and yet they still have to do it, for their children.

After some time in the development area, I decided to leave industry and develop this foundation and develop the Cure the Process Campaign. And this campaign is focused on what we felt were practical solutions to some of the problems that affect rare disease drug development, which I believe would greatly encourage drug development and successful treatment for patients.

We currently have 129 formal endorsements from rare disease patient organizations, other patient organizations, as well as the physician groups that specialize in genetic diseases.

What we have learned over the years, I think, can best be exemplified by what we know in the Aldurazyme example. Aldurazyme was a treatment that I developed—it was my original research—for a disease called MPS I, a very rare metabolic disease. There are only a couple hundred patients on therapy. Right? And it's a miracle that the treatment got developed at all, but I did it, through however I could, and managed to eventually get a biocompany to help us do it.

What we found out during the development is the number of the problems. One, that surrogate endpoints were very difficult to use—in fact, were rejected—because there was inadequate clinical information. In addition, clinical study design statistical issues caused some problems, as well, which caused further delays. Ultimately, the program went to advisory committee, which voted, 12–0, that the drug was effective and was approved, which maybe seems successful, however, it was a 3-year delay. And, I mean, at that time, a number of MPS I patients passed away. But, more importantly, the company canceled programs to treat MPS VII and

MPS IV A, two other MPS disorders, because without the surrogate approval pathway, the costs that were going to be involved made it impossible for us to do the product development.

Ten years later, MPS IV—Morquio disease—and MPS VII still do not have approved treatments.

So, when we look at some of the problems, one of the areas is the access to accelerated approval pathway. And I think, if you look at what's happened in genetic disease areas, there's really been only one approval using the accelerated approval pathway. Now, this pathway was designed to give access to life-threatening disorders, and it's been very helpful in cancer and HIV. And in HIV, it's been, I think, miraculous in taking a death-sentence disease to a chronic-managed disease. But, only one approved for genetic diseases, and even that one was approved only after an advisory committee voted that the endpoint was acceptable.

I think that there are clearly many biochemical disorders, which could be approved by this pathway, where the endpoints are even better than some of the ones that are currently accepted for drug approval.

Our foundation has done some work and shown that if you allowed the accelerated approval pathway to work it's possible that, for a $1 billion investment in clinical development costs, you could develop 40 drugs with the accelerated approval pathway, versus 10 to 12 by using a clinical development endpoint. So, I think that's a substantial boost in the kind of work we can achieve for a given investment.

Now, our hope in this campaign was also to develop a review group that would help develop these guidances and improve the review process. And we believe it's necessary to have specialists who know the disease area to develop these guidances, as well as to be involved in the review of drugs. This is what we're calling the Special Biochemical and Genetic Review Division. We think that having the right specialized people within the agency, with the right kind of academic connections to NIH to allow them to keep up to date with what's going on, is really a critical step in achieving adequate and great reviews.

We think the group could be creating guidances, and we think that the creation of guidance for studies and the surrogate endpoint accelerated approval pathway are also critical. If we make these changes, we believe that there would be immediate impact on new treatments.

It would be a strong signal, to the biotechnology industry, that the FDA and Congress is serious about improving the development path to rare diseases. And I think would stimulate substantially more investment.

Our estimate, based on analysis of other companies in rare-disease genetic areas, is that there is something like 300 to 600 new, high-paying quality jobs for each drug approval, direct jobs within that company, and probably five times as many in the surrounding groups.

For HIV, for example, the 29 drugs approved generated something like 78,500 jobs in the companies that made those. These are good jobs, ones that don't go away when the economy goes south.

We think that the improvement that we are proposing, which is a specialized review division, as well as improved access to the accelerated approval pathway and better clinical trial design paradigms, are the things that are very practical, sensible, not expensive, that could help improve the process and improve the investment and transformation of good science into great medicine.

PREPARED STATEMENT

So, I want to thank you for your leadership, again, and the opportunity to testify today.

Senator BROWNBACK. Thank you, Dr. Kakkis.

And also, thank you for your leadership on this. I know you've worked in the field, then got frustrated because you had the problems that you did in experiencing the system. But, instead of just taking your ball and going home, or taking your money and leaving the field, you've stayed in it. And that's really an important thing. And it's a great contribution to the overall effort. Appreciate that very much.

Dr. KAKKIS. Thank you.

[The statement follows:]

PREPARED STATEMENT OF DR. EMIL D. KAKKIS

Chairman Kohl and Ranking Member Brownback: Thank you for this opportunity to address the subcommittee today and for your leadership in working to improve the treatment of patients affected by rare diseases.

I am the founder and president of the Kakkis EveryLife Foundation, a 501(c)(3) public charity established to improve the development of treatments for patients with rare disorders. I have spent the last 18 years focused on developing treatments for rare diseases working both as an assistant professor at UCLA, and as chief medical officer at BioMarin. At BioMarin, I developed three approved products for rare genetic disorders, and despite this success, I saw many problems and challenges in development that prevent many rare diseases from ever being treated. To resolve these problems, I founded the Kakkis EveryLife Foundation to improve the regulatory process by proposing efficient and effective science-based changes that would improve the predictability and accessibility of many complicated rare diseases to treatment development. I provide the vast majority of the funds to support our Foundation's efforts and we do not accept financial support from industry for our initiatives.

Mr. Chairman, I am here today to support an additional funding appropriation to the Food and Drug Administration (FDA) to create a more specialized drug review division focused on the rare biochemical and genetic disorders. We respectfully request an incremental $10 million in the fiscal year 2011 Ag-Rural Development-FDA Appropriations bill for the FDA to establish a new review division for Biochemical and Genetic Diseases within the Center for Drug Evaluation Research, Office of New Drugs.

This is the first step toward the larger goal of improving the rare disease drug development process. My testimony today will provide the rational basis for this request and the greater context of how this first critical step will move rare disease treatments forward to patients.

The new rare disease review division or office is one core part of our three CureTheProcess campaign goals (Exhibit A). The campaign is now formally endorsed by 128 unique patient organizations and physician societies. Our three goals are:

—To establish a new specialized Division/Office of Drug Evaluation for Genetic and Biochemical Diseases.

—To improve the accessibility of the Accelerated Approval process by creating new criteria for surrogate and biomarker endpoints used to evaluate treatments for rare disorders.

—To establish efficient clinical study design and analysis paradigms for rare disease clinical studies.

By making these three changes, we can quickly and dramatically improve the current regulatory process for rare diseases without having to reinvent an entirely new process or a new approval pathway.

Why do we need change? There are more than 7,000 rare disorders that together affect over 25 million Americans and their families. The Orphan Drug Act (enacted in 1983) encourages pharmaceutical companies to develop drugs for diseases that have relatively small patient populations and has been very successful. Despite the success in the first 25 years with 1,892 orphan designations and 326 treatments approved [1], 95 percent of rare disorders remain without a specific treatment approved by the FDA. Treatments for many of these diseases may never be developed because the complexities of the regulatory environment make it difficult to attract investment for some very rare or difficult diseases, even though the science may be available.

In Exhibit B, orphan designations are increasing while approvals are flat over time. The approvals for ultra rare disorders (arbitrarily defined as those affecting less than 6,000 patients) show that only two or three are approved each year despite the fact that more than 80 percent of all rare diseases are in this ultra rare category [2].

To understand how current science is only generating 2 or 3 ultra-rare disease approvals each year, we evaluated the science to look for where the block to development might exist. Our analyses of the scientific literature found approximately 25 rare diseases for which good science exists for a treatment but for which little effort has occurred to translate this to patients. Some of these diseases are very rare, or they may have more difficult biology, but they could be treated. We must do more with the science we already have and turn the billions of dollars of promising research into life saving treatments.

While these data may define the statistics that describe the breadth and depth of the problem, the pain and tragedy of the problem is better captured by my personal experiences with rare disease. Nearly every week for the last few years, I have received calls and counseled families struck by genetic lightning, their small child affected by a devastating unpronounceable biochemical or genetic disease. These parents are seeking hope and inspiration that somehow their newly established foundation can manage to navigate the inner workings of drug development in order to save their kids, because no one else seems to be investing in those treatments. I do my best to help and support their efforts, but today I hope that we can do much more to change their tragedy into opportunity for all Americans affected by rare diseases.

To understand the challenges facing rare disease drug development, I would like to review the case of the enzyme replacement treatment Aldurazyme® (laronidase) used to treat the ultra-rare disorder mucopolysaccharidosis type-1 (MPS I). MPS I is caused by the body's inability to produce a specific enzyme required for the breakdown of specific sugar-like compounds. The deficiency causes the accumulation of these sugar-like materials in virtually every cell of the body. As a result, cells and tissues do not function properly and progressive damage accumulates throughout the body, including the heart, bones, joints, respiratory system and central nervous system. The disease is usually fatal by the first or second decade. Only about 200 patients in the United States have MPS I and treated with Aldurazyme today. From the development experiences of Aldurazyme, I will extract some of the key lessons that apply to many rare disease treatments and why these experiences form the basis for the CureTheProcess campaign.

The Aldurazyme project began in 1991 when I started my work in a World War II-era research bungalow at Harbor-UCLA with minimal funding to develop an enzyme replacement therapy. My work received critical financial support from the Ryan Foundation, formed by Mark and Jeanne Dant for their son Ryan, who has MPS I [3]. I completed development of the treatment at a startup biotech company, BioMarin. Our work was ultimately successful leading to the approval of the enzyme treatment called Aldurazyme and I am proud to report that Ryan is now a healthy 22-year-old young adult working for the Texas Rangers and going to college part-

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[1] Braun MM, Farag-El-Massah S, Xu K, Coté TR., 2010, Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. Nat Rev Drug Discov. 2010 Jun 7. [Epub ahead of print].

[2] BioMedical Insights report, "Ultra-Rare Disease Drug Development Trends", June 10, 2010, commissioned by the Kakkis EveryLife Foundation; Data based on information contained in the Orphanet database and other sources.

[3] Recounted by Margery Stein, "Saving Ryan", Reader's Digest, May 2001, p75.

time. He has been on Aldurazyme for 13 years. The challenges encountered during this program are instructive.

Despite the ultimate success of Aldurazyme, our work on this enzyme highlights the difficulties encountered in development that our CureTheProcess campaign aims to improve. There are only about 200 or so patients in the United States on Aldurazyme today, and this ultra-rare disease had never been considered for treatment prior to our efforts beginning in 1991. Exhibit C outlines the major challenges that affected this program, and almost every development program for a rare disease.

First, we were unable to use a reasonable biomarker based on the best science available to measure the improvement in our patients because there was no other independent clinical data to support its use. For rare diseases that have never been studied before, no prior clinical data exist. Somehow, we should still be able to use a biomarker and the Accelerated Approval pathway when the science is reasonable as it was in this case. The inability to use a reasonable marker that we believed (and still believe) "reasonably predicted clinical benefit", resulted in a substantial delay of the program. Today, there is no guidance on what can be qualified as a reasonable surrogate endpoint to meet Accelerated Approval requirements, meaning that no rare disease treatments can reasonably expect to be approved via this pathway.

Second, we ran into problems with our statistical analyses in which we were not allowed to use the more powerful methods that would help rare disease studies overcome the variable nature of the patients. The slight miss on one endpoint with the weaker statistical method, led to a requirement to collect additional clinical data, again delaying the program. For rare diseases, some understanding and agreement is needed to allow the very best and most powerful approaches to be used to help compensate for the small study sizes and variable patients. If these most efficient and powerful approaches are not allowed in order to best control of variation and extract the most information from the data, most rare disease studies will fail to achieve significance, even when the drugs are effective. Currently there is no guidance on the acceptable or optimal design and analyses for rare diseases.

Finally, it is very clear to me after 11 years at BioMarin, and with three drugs approved for three different rare genetic disorders, that the FDA is under increasing duress with limited resources for drug reviews, and is unable to provide the optimal level of time and staff required for complicated rare disorders. The Agency has been unable to support the sufficient degree of specialization of their review divisions that would allow them to hire specialists trained in the rare disease areas that are currently not well covered. Aldurazyme was reviewed by a neurologist, an oncologist and a pulmonologist, with no experience in MPS or biochemical genetic disorders. While they were intelligent and capable physicians, there is no adequate substitute for training and experience in the specific field of medicine. Reviewing drugs is an extraordinarily difficult challenge and the FDA needs to have the resources to be able to hire enough people with the right training and experience to accomplish this difficult task.

Aldurazyme was eventually approved and so this might not seem so important. However, the problems encountered during Aldurazyme development led to the canceling of programs for two other rare diseases, MPS IV A and MPS VII due to financial concerns and the inability to use the Accelerated Approval pathway. These diseases still do not have treatments approved. Currently, rare biochemical and genetic diseases cannot use the Accelerated Approval pathway because they are so rare that they lack the historical clinical data that is required to qualify surrogate endpoints, even though their scientific basis is strong. To see the breadth of this problem, we summarized the data in the table posted on FDA's Web site regarding Accelerated Approvals since implementation in 1992[4]. In Exhibit D, only one genetic disease has been approved via this pathway in 16 years. This particular approval did not have FDA agreement on the surrogate until after an Advisory Committee recommended its acceptance after all the studies were done.

Scientists, patients, Congress and regulatory authorities need to come to agreement quickly as to what science should be sufficient to allow access to the accelerated pathway and it must take into account the effect that rarity has on both the amount of clinical data that exists, as well as on the risk-benefit to society of the use of the surrogate endpoint. To achieve these changes in policy, we believe it is

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[4] Taken from the FDA Web site and collated by disease category. Genetic treatments include only those drugs specifically targeted to an individual genetic disease. For example, iron binding treatments were not considered genetic disease specific.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm121597.htm.

essential that a specialized review division be established to lead the way in guidance formation and policy based on the joint work of experienced FDA reviewers and disease experts.

A dedicated FDA review division will improve the development path. Providing funding for a new review division for biochemical and genetic diseases will help create a more specialized drug review by experts who understand complex genetic diseases (see Exhibit E). The new division/office should be structured to allow the reviewers to focus and gain experience on specific rare disease areas that need increased expertise. Reviewers may also provide assistance, as needed to other review offices with rare disease issues. By helping to facilitate collaboration with the Office of Orphan Product Development and links with the National Institutes of Health, the division/office will improve the overall academic environment and assure that the reviewers are keeping up with the latest scientific issues and advances. This division/office will also be essential to help implement the policy changes recommended by the Brownback/Brown Amendment[5] committee's findings and assure that the excellent work of Drs. Coté, McNeil and other FDA staff will not be lost.

We recommend that this new review division be responsible for rapidly creating new guidances for industry that could make the Accelerated Approval pathway available for more rare diseases and improve the clinical trial process. Among many possible recommendations from the FDA committee, we believe that two guidances should be included:

—New standards for the use of surrogate and biomarker endpoints for rare disorders, to allow treatments for these diseases to have full access to the Accelerated Approval pathway. Due to the rarity of the disorders, the use of direct, relevant surrogate or biomarker endpoints as primary endpoints in clinical studies is essentially impossible for some rare disorders because none of these surrogates have been validated or ever evaluated in clinical studies and are therefore unavailable for development use. However, biochemical markers relevant to biochemical genetic disorders may be far better predictors of disease and treatment effect than many of the approvable surrogate markers currently accepted for use in drug approvals for more common disorders[6].

—New clinical study design and analysis paradigms for rare diseases that properly account for clinical heterogeneity and disease complexity to accurately and efficiently establish treatment effects. While traditional randomized, controlled studies have been used in rare diseases, this design is relatively insensitive to changes in heterogeneous patients and fails to allow the assessment of all types of patients with all types of disease outcomes. A creative effort is needed to develop new paradigms in study design and optimal statistical analyses that capture individual benefit in a broad array of patients, utilizing all the clinical data to establish efficacy. The medical science needs to drive the statistical analysis.

An improved development path for rare diseases is good for patients and the economy.

—*New Treatments*.—A streamlined development path will shorten timelines and reduce the financial risk associated with development of rare disease therapeutics. The result should be a surge in development activity for even the rarest disorders. Certain treatments for rare biochemical or genetic disorders that are now unaddressed because of the difficulty in assessing the clinical outcome, will now be targets of drug development as appropriate surrogate markers are identified. More patients with rare biochemical and genetic disorders will get earlier access to specific, effective treatments.

—*Improved FDA*.—A new division or office with experts trained and knowledgeable in the disease area will allow for an improved and more specialized FDA review. Allowing the reviewers to stay focused and gain experience, will allow them to become more expert in the details and nuances of science and medicine of their specialized areas that is required for excellent regulation.

—*New Jobs*.—Improved FDA regulation will drive more U.S. biotechnology job creation. The creation of the new division will also provide a strong signal to the biotechnology industry and investors that the FDA is working to improve the regulatory path for thousands of rare disorders. This new review division, combined with new policy, will drive more investment in early stage biotechnology companies focused on rare diseases while at the same time pro-

[5] Brownback Brown Amendment for Rare and Neglected Diseases in the Fiscal Year 2010 FDA Appropriations Budget, H.R. 2997, Section 740.

[6] Patricia Dickson, Maryn Peinovich, Michael McEntee, Thomas Lester, Steven Le, Aimee Krieger, Hayden Manuel, Catherine Jabagat, Merry Passage, and Emil D. Kakkis Immune tolerance improves the efficacy of enzyme replacement therapy in canine mucopolysaccharidosis I (2008), J. Clin. Invest. 118: 2868.

ducing a positive impact in local communities by creating new, high-paid, U.S.-based biotechnology jobs. Our estimate is that each new rare disease product will likely create 300–600 direct new jobs[7] in biotechnology and about five times that many in the greater economy.

Small regulatory changes can make a huge impact. In the early 1990s the FDA was uncertain about blood markers predictive value for HIV/AIDS treatments. The need for clinical endpoints would require substantially more time and cost for clinical studies, which would have impaired investment and innovation, and lead to many deaths. Activists spurred the FDA to create "Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Diseases" in 1992. This allowed FDA to accept a surrogate endpoint for a measurement of the treatment effect if the surrogate was "reasonably likely to predict clinical benefit". At the time T-Cell counts were qualified as surrogate endpoints based on sound scientific data that the T-Cell count directly correlated to how sick the patient was.

Over time, better science improved the marker choice to viral load, but the explosion in innovation was remarkable. As you can see in Exhibit F, over the following 16 years, 29 new drugs were approved that used six different mechanism of action, devised by multiple startup companies generating approximately 78,500 new jobs[7]. Four of those drugs were complex combinations that would never be developed without an efficient marker endpoint like viral load. More importantly, HIV went from a certain death sentence to a managed disease for many patients.

The changes we are proposing can do the same thing for rare diseases as Accelerated Approval did for HIV. By our Foundation's analyses of relevant clinical development costs, access to the Accelerated Approval process could potentially treat three to fourfold more diseases for the same investment. We estimate that a billion dollars spent on clinical development costs using the current pathway would cover only 10–12 products; with access to Accelerated Approval you could develop nearly 40 products for the same investment.

Mr. Chairman, thank you for your time. I commend your efforts to convene this hearing and your leadership to improve the FDA's review process for products to treat rare diseases. Given the considerable impact an improved regulatory process would have on the economy and the millions of patients without treatment, we hope that you will join the 128 patient and physician organizations and support our request to appropriate $10 million to establish a new Division/Office of Drug Evaluation for Genetic and Biochemical Diseases and start us down the path to an improved development process for rare disease treatments.

[7] BioMedical Insights report "Ultra-rare Therapeutic Employment Analysis" commissioned by Kakkis EveryLife Foundation, June 15, 2010.

EXHIBIT A

Improving the Regulatory Pathway:
The CURETHEPROCESS Campaign

1. ESTABLISH A NEW DIVISION/OFFICE OF DRUG EVALUATION FOR GENETIC & BIOCHEMICAL DISEASES
   - REQUESTING $10 MILLION APPROPRIATION
2. IMPROVE THE ACCESSIBILITY OF THE ACCELERATED APPROVAL PATHWAY (SUBPART H)
3. DEVISE NEW CLINICAL STUDY DESIGN & ANALYSIS PARADIGMS FOR RARE DISEASES

EXHIBIT B

Approvals rate **flat** relative to designations

Both for drugs treating all Orphan and ultra-rare diseases

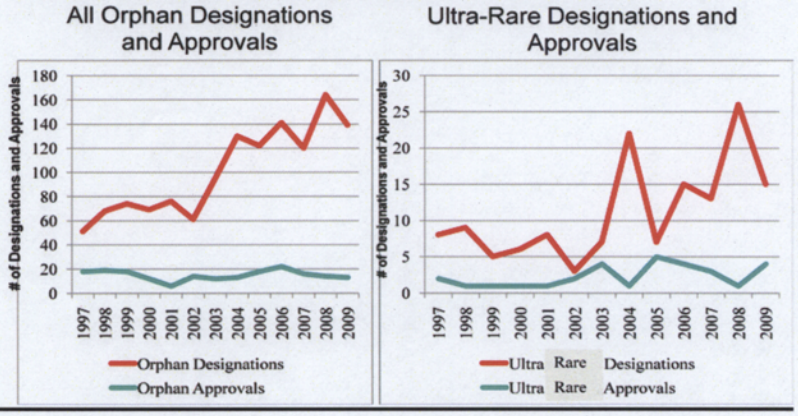


EXHIBIT C

Aldurazyme eventually approved after a 3 year delay

- Urine GAG surrogate endpoint rejected
- Delayed again after Phase 3 related to statistics
- Advisory Committee voted drug effective 12-0 on 1/15/2003
- Approved in April 2003

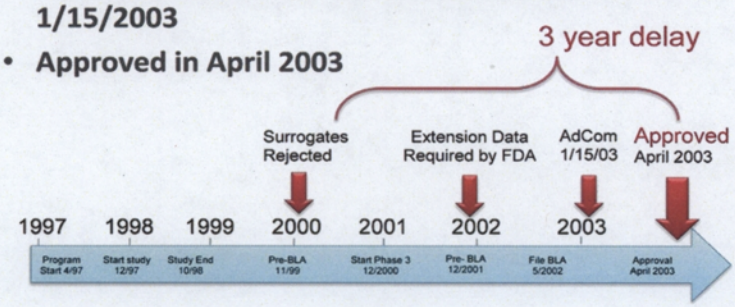


EXHIBIT D

Few diseases categories benefit from Accelerated Approval Regulations

Usage of the Subpart H or E approvals: 64 NDA's and 9 BLA's since 1992*

Only 1 genetic disease treatment approved in 16 years

Therapeutic Area	Number of Accelerated Approvals	Surrogate endpoint	Other
Cancer	26	Tumor load/PFS	Most pivotal studies without a control group
HIV	29	CD4 or viral load	Combination therapies also approved
Other	17	Variety	PAH, MS, hormones, iron, Crohn's, antibiotics
Genetic	1	Renal pathology	Fabrazyme

*Taken from the FDA.gov website table on accelerated approvals

EXHIBIT E

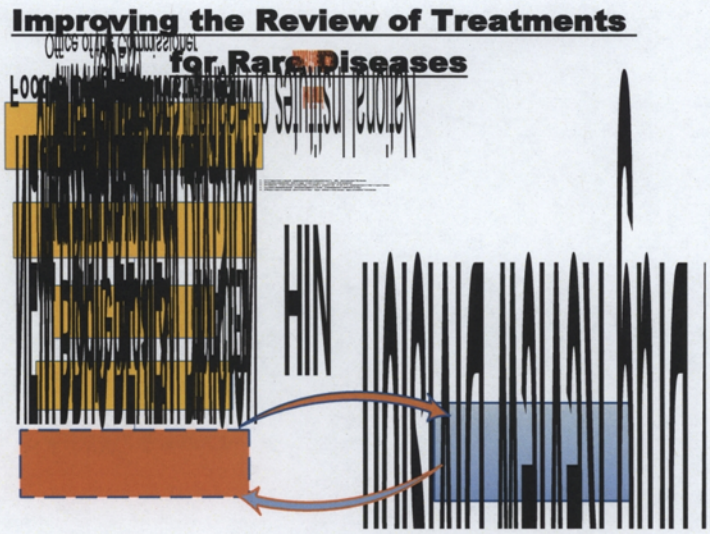
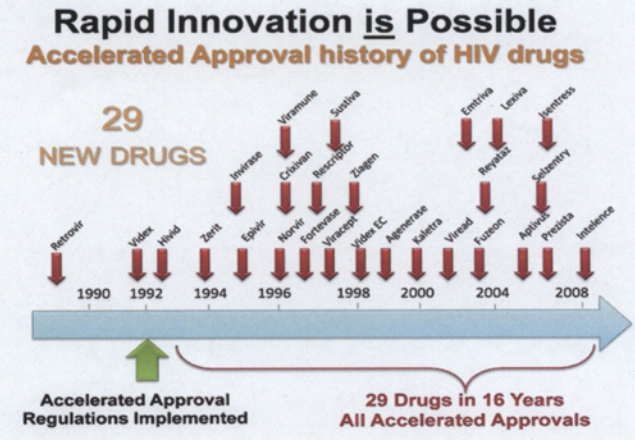


EXHIBIT F



Senator BROWNBACK. Ms. Dorman.

STATEMENT OF DIANE EDQUIST DORMAN, VICE PRESIDENT FOR PUBLIC POLICY, NATIONAL ORGANIZATION FOR RARE DISORDERS

Ms. DORMAN. Senator Brownback, thank you so very much for having me here today.

The National Organization for Rare Disorders was founded in 1983 to advocate for the enactment of the Orphan Drug Act, and remain today the leading advocate for the 30 million American patients with the estimated 7,000 known rare diseases.

In addition to our advocacy efforts, we also run patient assistance and patient support programs, have compiled the largest database of information about rare diseases in the world.

There are many Federal agencies and State agencies whose programs and policies affect people with rare diseases, including the NIH and CDC and SSA, but none is more important than the Food and Drug Administration. The FDA is the gatekeeper for the drugs, devices, and medical foods that are needed by patients with rare diseases. The FDA sets the standards for studying new medical products, and therefore plays a central role in research, as well as product approvals.

NORD advocates for full funding for the FDA. We were instrumental in founding an organization, now known as the Alliance for a Stronger FDA, which now includes more than 180 members representing all of FDA's stakeholders, and which has the singular purpose of advocating for increased funding for the entire agency.

We have witnessed what happens when FDA is underfunded. The agency cannot meet its review times for new drugs and medical devices, cannot provide the guidance that researchers so desperately need and seek, and cannot maintain the public's confidence in the regulatory system.

Delays in review times and lack of guidance affects our patient constituency especially hard, because, despite the great advantages in medicine, there are approved drugs for only, as you have said, about 200 of the estimated 7,000 known rare diseases.

Many of our patients are treated with approved products being used off-label. And many are not being treated at all, because there are no treatments at all.

NORD's top priority, in addition to the support services we provide to the patients with rare diseases, is to advance medical research and the development and approval of new therapies for our patients. This with this perspective that we support, in principle, any steps that would advance medical research or provide FDA with the resources it needs to carry out its critical public health functions.

We were encouraged by the creation, earlier this year, of a new position within the FDA's Center for Drug Evaluation and Research, a position dedicated exclusively to rare diseases. We advocate for more training and support for FDA personnel who interface with the researchers who develop orphan products. And we support more transparency in the regulatory system so that investigators and drug and device manufacturers can make the right decisions as they develop new products.

The current leadership of the FDA has demonstrated its sensitivity to the vulnerability and special challenges of people with rare diseases. We understand the constraints on the budgets of Federal agencies, but, at the same time, the FDA needs more resources if it is to fill the commitment it has made to the rare-disease community.

PREPARED STATEMENT

Mr. Chairman, I would be pleased to answer any questions you may have. And, again, thank you very much for allowing me this opportunity.

Senator BROWNBACK. Thank you, Ms. Dorman. Appreciate it.

[The statement follows:]

PREPARED STATEMENT OF DIANE DORMAN

Mr. Chairman, thank you for the opportunity to testify before you today. I am Diane Dorman and I am the vice president for public policy of the National Organization for Rare Disorders, or NORD. We were founded in 1983 to advocate for the enactment of the Orphan Drug Act, and we remain today the leading advocate for the 30 million American patients with the estimated 7,000 known rare diseases. In addition to our advocacy efforts, we also run patient assistance and patient support programs and have compiled the largest database of information about rare diseases in the world.

There are many Federal and State agencies whose programs and policies affect people with rare diseases, but none is more important than the Food and Drug Administration. The FDA is the gatekeeper for the drugs, devices and medical foods that are needed by patients with rare diseases. The FDA sets the standards for studying new medical products and therefore plays a central role in research as well as product approvals.

NORD advocates for full funding of the FDA. We were instrumental in founding an organization now known as the Alliance for a Stronger FDA, which now includes more than 180 members representing all of FDA's stakeholders and which has the singular purpose of advocating for increased funding for the FDA. We have witnessed what happens when FDA is underfunded: the agency cannot meet its review times for new drugs and medical devices; cannot provide the guidance that researchers so desperately seek; and cannot maintain the public's confidence in the regulatory system.

Delays in review times and lack of guidance affects our patient constituency especially hard, because despite the great advances in medicine, there are approved drugs for only about 200 of the estimated 7,000 rare diseases. Many of our patients are treated with approved products being used off-label, and many are not being treated at all because there are no treatments.

NORD's top priority, in addition to the support services we provide to patients with rare diseases, is to advance medical research and the development and approval of new therapies for our patients.

It is with this perspective that we support in principle any steps that would advance medical research or provide FDA with the resources it needs to carry out its critical public health functions. We were encouraged by the creation earlier this year of a new position within the FDA's Center for Drug Evaluation and Research, a position dedicated exclusively to rare diseases.

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The current leadership of the FDA has demonstrated its sensitivity to the vulnerability and special challenges of people with rare diseases. We understand the constraints on the budgets of Federal agencies, but at the same time the FDA needs more resources if it is to fulfill the commitment it has made to the rare disease community.

Mr. Chairman, I would be pleased to answer any questions you have. Again, thank you for the opportunity to appear before you on behalf of the 30 million men, women and children with rare diseases.

Senator BROWNBACK. Mr. Bollyky, good to have you here.

STATEMENT OF THOMAS J. BOLLYKY, VISITING FELLOW, CENTER FOR GLOBAL DEVELOPMENT

Mr. BOLLYKY. Ranking Member Brownback, Senator Pryor, thank you for recognizing the importance of neglected diseases to global health and U.S. interests.

I'm grateful for this opportunity to testify today about ways in which FDA may expand its leadership role in supporting the development of drugs, vaccines, and diagnostics for these diseases that afflict the world's poorest and threaten Americans at home and abroad.

My testimony today reflects the work I have the honor of leading at the Center for Global Development, as well as the substantial input of the Global Health Technologies Coalition.

Over 1 billion people, including 400 million children, suffer from one or more neglected diseases. As defined under law, these diseases include malaria and tuberculosis, which, as you mentioned, kill 2.5 million people annually, but also other diseases, such as Dengue fever and Rotavirus, which may be less familiar, but have a large and often lethal toll.

Neglected diseases do not just kill, they adversely affect pregnancy outcomes, undermine the development of school children and worker productivity, and perpetuate the cycle of poverty, insecurity, and infirmity in the communities in which they are endemic. In short, neglected diseases rob the world's poorest community of their hopes for a better future.

Neglected diseases, however, are not just a concern for the developing world. Americans, when they travel abroad, are exposed to these diseases, as they are when they serve in the U.S. military. Neglected diseases cross borders with trade and travel, and the health and economic consequences of their outbreaks are significant.

Given that one out of six people worldwide suffer from neglected diseases, it may seem surprising that there are few, if any, effective treatments for many of these diseases. The extreme poverty of those afflicted, however, greatly undermines the potential market return on the substantial investment that you mentioned it takes to develop a drug or a vaccine. Accordingly, of the nearly 1,400 products, new chemical entities that were approved between 1975 and 1999, fewer than 40 were for neglected diseases.

The good news is that there is a potential for this to change. Over the last decade, there have been efforts led by public-private partnerships and the support of the U.S. Government and the Bill and Melinda Gates Foundation, there are now dozens of products in the pipeline for neglected diseases. These drugs, vaccines, and diagnostics will be, for many neglected diseases, the first product in a generation available to address those diseases. For other neglected diseases, they will simply be the first tool ever available.

The challenge is that there are regulatory gaps and inefficiencies that undermine the development of these products in the pipeline. Those challenges are twofold:

First, the regulatory environments in many developing countries are inadequate to support the clinical trials necessary to complete the clinical development of the products in the pipeline.

Second, the pathway for approval for these neglected disease products is poorly coordinated and a multistep process that involves the FDA, the World Health Organization, and regulators in the developing countries in which these products will ultimately be used.

Gaps and inefficiencies abound throughout this pathway. FDA reviewers may not have the experience and expertise with the particular target neglected disease, as it is not endemic to the United States. The WHO's prequalification program, which assesses products for procurement by U.N. agencies, lacks sufficient dedicated resources, and is often slow. Regulators in developing countries often do not have the mandates, the experience, or the expertise to assess and approve products.

Through the efforts of this subcommittee, FDA has recently established a review group for neglected diseases, which offers a good opportunity to address these gaps and inefficiencies.

As part of that effort, we would recommend that they pursue three measures:

First, a collaborative review process for neglected disease products in which FDA review and WHO prequalification are effectively simultaneous and mutually supporting.

Second, capacity-building arrangements with the World Health Organization and developing countries, priority developing countries, which would involve dedicating more FDA reviewers to conduct prequalification assessments on behalf of WHO, working with NIH and USAID to support regional platforms for a clinical trial regulation in developing countries, and an exchange program with WHO and developing-country regulators.

Last, FDA should issue detailed guidance and initiate a mentoring program for public-private partnerships and other nontraditional product developers which may not have the experience with late-stage clinical development and product registration.

PREPARED STATEMENT

I provide further details on all these proposals in my testimony.

I look forward to your questions, and thank you for your time and your leadership on this issue.

Senator BROWNBACK. Thank you, Mr. Bollyky.

[The statement follows:]

PREPARED STATEMENT OF THOMAS J. BOLLYKY

Chairman Kohl, Ranking Member Brownback, and other distinguished members of the Subcommittee: Thank you for recognizing the importance of neglected diseases to global health and U.S. interests. I am grateful for this opportunity to testify about ways in which the U.S. Food and Drug Administration (FDA) may expand its leadership role in supporting the development of products (drugs, vaccines, and diagnostics) for diseases that afflict the world's poorest.

The essence of the problem is this: while philanthropists and private companies have increasingly seen the value in devising products for heretofore neglected diseases, the regulatory infrastructure necessary to develop and introduce these therapies to the developing world is sadly inadequate. Regulatory inefficiencies and gaps add costs to product development, deter private investment, and delay patients' access to potentially life-saving treatments. Building the needed regulatory infrastructure is a substantial challenge and unprecedented opportunity to improve the lives of millions around the globe and promote the well-being of Americans at home and abroad. The United States Government and FDA in particular should take a leadership role in improving the clinical development and regulatory pathways for neglected disease products.

My testimony will proceed in four parts. First, I will summarize the burden that neglected diseases impose on affected people and their communities. Second, I will discuss the tremendous promise of the current pipeline of candidate products to address neglected diseases. Third, I will give an overview of how novel therapies are developed and approved for use in the developing world and the persistent regu-

latory gaps that undermine this process. Last, I will offer recommendations on how FDA can help bridge those gaps.

My testimony today reflects the work I have the honor of leading at the Center for Global Development with the support of the Bill & Melinda Gates Foundation and the substantial input of the public private development partnerships (PDPs) and nongovernmental organizations that comprise the Global Health Technologies Coalition.

THE BURDEN OF NEGLECTED DISEASES

Neglected diseases are a heterogeneous collection of predominantly infectious conditions for which few, if any, effective therapies exist. An estimated one billion people, including 400 million children, suffer from one or more of these diseases. As defined under U.S. law, "neglected diseases of the developing world" include malaria, tuberculosis (TB), and a dozen other parasitic, soil transmitted, bacterial, and tropical infections endemic to Africa, Asia, tropical regions of Latin America, and parts of the Middle East.[1]

Neglected diseases have a staggering impact on the individuals and communities which they afflict. Many of these diseases exact a large and lethal toll, with tuberculosis and malaria alone killing an estimated 2.6 million people annually.[2] Other neglected diseases are less deadly, but disable, deform, and increase their sufferers' vulnerability to other infectious diseases like HIV/AIDS. Children and pregnant women suffer disproportionately. In 2008, an estimated 8.8 million children worldwide under the age of five died from largely preventable causes, many of which are related to neglected diseases.[3] Neglected diseases cause adverse pregnancy outcomes and impair children's cognitive development, school attendance, and earning potential for the decades that follow.[4] In sum, neglected diseases rob the world's poorest communities of their hope for a better future. They sap current and future worker productivity, undermine economic development, and perpetuate the cycle of poverty, insecurity, and infirmity in the communities in which these diseases are endemic.

Neglected diseases also threaten the well-being of Americans at home and abroad. These diseases cross borders with trade and travel; the health and economic consequences of outbreaks are significant.[5] Americans travel to neglected disease-endemic countries and the women and men of the U.S. military serve there. Neglected diseases undermine the security of our allies and the economic development of our potential trading partners.

Given that approximately one out of six people worldwide suffer from one or more neglected diseases, it may seem surprising that there are few, if any, effective therapies for them. The extreme poverty of those afflicted, however, greatly limits the potential market return on the substantial investment needed to develop therapies for neglected diseases.

Accordingly, of the nearly 1,400 new chemical entities approved worldwide between 1975 and 1999, fewer than 40 were for neglected diseases.[6]

THE PROMISE OF THE CURRENT PIPELINE OF CANDIDATE THERAPIES

A confluence of private philanthropy and enlightened government intervention has dramatically changed the landscape for neglected diseases over the last decade. Led by the efforts of PDPs and fueled by the support of the Gates Foundation and U.S. Government actors (including members of this subcommittee, National Institutes of Health, USAID, FDA, and Department of Defense), dozens of such products are now in development.

The therapies, diagnostics, and preventative tools in the product pipeline will be, for many neglected diseases, the first new tools in a generation and, for others, they will be simply the first. Promising examples include:

—A malaria vaccine candidate in late-stage clinical testing which, if approved, will be the first vaccine against malaria (a disease that kills 900,000 annually) and the first vaccine against a parasite approved for use in humans.

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[1] Section 524(a)(3) of the U.S. Food, Drug, and Cosmetic Act (21 U.S.C. 360n(a)(3)).

[2] WHO, Global tuberculosis control: A short update to the 2009 report (2009) and WHO, World malaria report 2009 (2009).

[3] UNICEF, Table of Basic Indicators, accessed at http://www.unicef.org/rightsite/sowc/pdfs/statistics/SOWC_Spec_Ed_CRC_TABLE%201.%20BASIC%20INDICATORS_EN_111309.pdf (last visited June 16, 2010).

[4] Hotez PJ, Ferris MT. The antipoverty vaccines. Vaccine 2006; 24: 5787–99.

[5] Ruth Levine, Healthy Foreign Policy: Bring Coherence to the Global Health Agenda in White House and the World, Center for Global Development 43–45 (Birdsall ed. 2008).

[6] Tufts Center for the Study of Drug Development, Drug Approvals for neglected diseases increase along with more R&D Funding, 11 Impact Report (2009).

—Nine new TB vaccine candidates in clinical trials worldwide, including the first late-stage infant study of a TB vaccine in over 80 years. There are also eight new TB drug candidates in testing, which, if approved, would become the first new TB drugs in over 40 years. These therapies could help reduce the 8 million new TB infections and 1.7 million TB-related deaths that happen each year.
—New vaccines for rotavirus (the most common cause of childhood diarrhea) and pneumoccus pneumonia, which together kill millions of children under five each year.

THE PERSISTENT GAPS IN THE DEVELOPMENT PATHWAY FOR NEGLECTED DISEASE THERAPIES

Discovery of a novel therapeutic which may be effective against a target disease is only the first step in bringing that therapy to patients. Developers must demonstrate the safety and efficacy of the candidate therapy in a series of clinical trials and register that therapy for use in disease endemic settings. In the case of neglected diseases, substantial gaps and inefficiencies in the development and regulatory pathway for these products threaten to delay or derail their introduction to patients.

Late-stage clinical trials must be conducted in settings where individuals suffer from the target disease and under the circumstances in which the product will be ultimately used. For neglected diseases, those settings are generally developing countries, with, in many cases, limited clinical research capacity and under-developed regulatory systems. It is difficult to conduct ethical, sufficiently regulated trials in such environments. Lack of regulatory capacity and clear rules hinders trial planning, initiation, and patient recruitment, and may lead to regulatory non-compliance. That risk of non-compliance and harm to subjects deters private investment. The shortcomings of these regulatory environments are further exacerbated by the complexity of the diseases and products involved and highly vulnerable, often pediatric subjects.

Upon completion of the necessary trials, sponsors must usually advance through multiple regulatory processes in order to register their product for use in the target neglected disease-endemic countries.

FDA Approval

In practice, most sponsors first submit their novel therapy for marketing approval by a developed country regulator, like FDA, in order to minimize the risk of liability and to take advantage of that regulator's experience in assessment, resources, and clear protocols and rules. The challenge is that FDA may be unfamiliar with the neglected disease (since it is not endemic in the United States) and the conditions and patient populations in which the product will be used. This may delay FDA's assessment of the safety and efficacy of the product and reduce the value of that assessment for the national regulatory authority (NRA) in the disease endemic country where the product will be used.

WHO Prequalification

Upon receiving marketing approval, the sponsor will next submit its product to the WHO prequalification program, which ensures that drugs, vaccines, and diagnostics meet prescribed standards of quality, safety, and efficacy and are appropriate for procurement by U.N. agencies. WHO is not a regulatory authority. A novel therapy must first be approved by an NRA which the WHO deems to be "fully functional" (such as FDA) in order to be eligible for prequalification. Many developing country regulators, however, rely heavily on WHO prequalification and will not approve a novel therapy without it.

Unfortunately, WHO prequalification can be a slow process. The average time to prequalify is 18 and 24 months for drugs and vaccines, respectively.[7] These delays often result from the inexperience of nontraditional product developers in preparing dossiers and the time required for WHO to assemble each assessment team ad hoc.

Approval by the Local Regulatory Authority

Once WHO prequalifies a novel drug or vaccine, the sponsor can finally submit it to the NRA in the target neglected disease-endemic country for its approval. Even with WHO prequalification, substantial delays may occur at this step. Many NRAs, particularly in Africa and Southeast Asia, have limited experience, resources, and mandates for assessing, approving, and registering innovative products. Assessment of novel products can be complicated even for well-resourced and experienced developed country regulators; the historical mission of many developing country NRAs

[7] The George Institute, Registering New Drugs: The African Context 13, 18 (2010).

has been to provide their population with affordable generic medicines, rather than assuring timely access to innovative products.

The average time required for a novel drug or vaccine to advance through this multistep regulatory pathway is approximately 3 years.[8] These delays and the uncoordinated and sequential nature of these processes defer patients' access to potentially life-saving treatments, deter private investment, and add significant expense. Realizing the promise of the current product pipeline for neglected diseases will require not only increased funding for clinical trials and developing country NRA capacity building, but also greater attention to how clinical development and regulatory pathways for these products may be improved to reduce unnecessary costs and delays.

HOW FDA CAN IMPROVE THE DEVELOPMENT PATHWAY FOR NEGLECTED DISEASE THERAPIES

FDA already plays a central role in the development of safe, effective, and high quality therapies for neglected diseases. FDA administers the Orphan Drug Act and priority review voucher program to provide useful incentives for developing novel therapies for neglected diseases. FDA pathways for priority review and accelerated and fast track approval offer important opportunities for consultation on clinical development plans and submissions, and expedited product assessment. In 2008, the FDA Center for Biologics Evaluation and Research (CBER) issued guidance confirming the scope and availability of the FDA approval process for developers of vaccines against infectious diseases or conditions not endemic in the United States.[9]

While FDA has performed admirably in its role, there remain significant organizational and logistical challenges particular to reviewing therapies intended for foreign use. The challenges are twofold.

First, resource limitations and FDA reviewers' unfamiliarity with neglected diseases and the conditions and patient populations in which the product will be used often delay and reduce the utility of FDA's product assessment. Put simply, FDA is performing a job it is not fully empowered, resourced, or designed to do.

Second, FDA regulatory pathways and programs are not well coordinated with or sufficiently supportive of the other entities involved in developing and approving these products. FDA approval is important, but it is a component of a larger, multistep process that also involves WHO and developing country NRAs. Accordingly, while it is important that the resources and pathway for FDA approval of products for neglected diseases be improved, it will not be sufficient if those improvements do not address the gaps and inefficiencies in the larger process for approving therapies for use by the patients who need them.

Pursuant to the efforts of this subcommittee and the requirement in the fiscal year 2010 Department of Agriculture appropriations bill, FDA recently established a new review group to prepare recommendations for the FDA Commissioner and Congress on "appropriate preclinical, trial design, and regulatory paradigms and optimal solutions for the prevention, diagnosis, and treatment of neglected diseases of the developing world."[10] This review group provides an excellent opportunity for FDA to develop new mechanisms and strategies for bridging the persistent gaps in the development pathway for neglected disease therapies.

As part of that effort, I respectfully recommend that FDA consider adopting the following measures:

An Integrated, Sufficiently Supported Neglected Disease Product Approval Process

Simultaneous, coordinated reviews by all the regulatory entities—FDA, WHO, and the developing country NRA—involved in the approval of a potential therapy would minimize duplication of scarce regulatory resources and reduce delays in product approval and introduction. It would combine FDA's resources and expertise in assessing novel and complex therapies with WHO and developing country NRAs' understanding of neglected disease presentation and local conditions, patient populations, and health care delivery platforms.

FDA should consult with WHO to develop a formal collaborative process, akin to that which exists between the European Medicines Agency (EMA) and WHO, in which FDA would commit to address the requirements for prequalification as part of its approval process and WHO would commit to an expedited decision on prequalification post-FDA approval. This collaborative process should be formal and

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[8] Id. at 18.

[9] Food and Drug Administration, U.S. Department of Health and Human Services, General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases (2008).

[10] Fiscal Year 2010 Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, § 740 (2009).

the details of its operation made public in order to improve its predictability for prospective product developers. The process should also include:

—*WHO and Developing Country Expert Observers.*—FDA reviews of neglected disease products should include, with the consent of the sponsor, WHO and developing country experts as formal observers.

—*Confidential Information Sharing Arrangements.*—There should be arrangements in place between all FDA Centers, WHO, and priority developing country NRAs to share confidential data and inspections reports on neglect disease product submissions.

—*Developing Country Experts on Advisory Committees.*—The budgets of advisory committees should be sufficient to enable the active participation of developing country experts.

—*More FDA Reviewers With Relevant Expertise.*—FDA should hire more full-time reviewers with tropical disease expertise and experience.

There is precedent for such an approach. In conjunction with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), FDA has a program to review the safety, efficacy, and quality of HIV/AIDS medications manufactured in countries where they are off-patent, prior to the expiry of those patents in the U.S. FDA works with eligible sponsors to help prepare applications for this program and for inspections. It prioritizes review of submissions and, as part of its assessment process, engages with the WHO prequalification program and developing country NRAs to facilitate the products' assessment and adoption.

Strengthen FDA's Ability To Support Its WHO and Developing Country NRA Partners

The efficiency and productivity of the development pathway for neglected disease therapies depends on the capacity of the WHO prequalification program and priority developing country NRAs. FDA should support that capacity with:

—*More Resources for WHO Prequalification.*—FDA should commit additional experienced and qualified FDA reviewers to conduct prequalification assessments on behalf of WHO in priority neglected disease areas (similar to FDA's role in prequalifying PEPFAR products) or a fixed number of neglected disease product dossiers per year.

—*Regional Platforms for Clinical Trial Regulation and Product Registration.*—Regional approaches can pool scarce regulatory resources and provide a more efficient vehicle for FDA technical assistance. WHO has used ad hoc regional, joint reviews to support African countries' regulation of vaccine clinical trials; working with partner U.S. Government agencies such as NIH and USAID, FDA could help foster the improvement, expansion, and formalization of those programs.[11]

—*Employee Exchanges With WHO and Developing Country NRAs.*—Initiating a pilot project for 1- to 2-year rotations of mid-career FDA reviewers into developing country NRAs and WHO prequalification programs would help build the capacity of regulatory counterparts and improve mutual understanding. If successful, this program could be expanded to other areas such as food and drug safety and serve as the foundation of a FDA version of the successful Epidemic Intelligence Service (EIS) at the Centers for Disease Control.

Enhance FDA Support and Guidance for Nontraditional Developers (I.e., PDPs).

Intermediary nonprofit organizations and PDPs manage a significant portion of global neglected disease product development, but may not have experience with late stage clinical development, dossier preparation, or product registration. FDA should support these PDPs and intermediaries and attract more interest in neglected disease product development with:

—*Guidance for Prospective Developers of Neglected Disease Therapies.*—FDA should issue clear and detailed public guidance on the full menu of support services that FDA offers for neglected disease drug, vaccine, and diagnostic candidate development and registration, including incentives, fee waivers, and accelerated reviews.

—*More Support for Neglected Disease Product Submissions.*—FDA should institute a program to work with PDPs and other nontraditional product developers on their submissions to ensure clinical development plans are both scientifically sound and cost-effective, and that those developers take full advantage of the tools, incentives, and expedited pathways available to them under the FDA's In-

[11] See Thomas J. Bollyky, Bridging the Gap: Improving the Clinical Development and Regulatory Pathway for Health Products for Neglected Diseases, Center for Global Development, forthcoming June 2010.

vestigational New Drug (IND) and Therapeutic Biologic Applications (BLA) application processes.

By adopting these measures and assuming a leadership role in improving the development and regulatory pathways for neglected disease therapies, FDA can do much to further the interests of all Americans in controlling these diseases and improve the lives of millions around the globe.

Senator BROWNBACK. I've been joined by Senator Pryor from Arkansas.

Delighted to have you here, Senator Pryor. I gave an opening statement. I'd sure invite you to give one.

Senator PRYOR. Thank you.

Senator BROWNBACK. Okay.

I'm going to have a few questions, and then I'll turn it to you, Senator Pryor, on this, as well.

But, I want to thank the panel for putting these ideas forward and for your work on this issue.

You're right, about Americans traveling and then getting exposed to these diseases. My oldest son did a study abroad program, and his roommate had Dengue fever. And we weren't exactly sure what it was, but it sounded really bad. It's one of those things that as people travel more, you're going to have more exposure, and so, there's good reason for us to work in it.

I am very appreciative of people and groups, particularly the Gates Foundation that you mentioned, that are working on these issues. I think they've just brought an energy, a focus, an intensity, and an efficiency into this field, that I think has been very helpful, from what I've observed over the years. So, I really applaud them or anybody that may be associated with them that are here.

Let me start with you, Mr. Bollyky, if I could. To your last point about a detailed guidance, I take it what you're saying is, it's not a change of the process. Perhaps just saying to alternate pathway groups rather than large pharmaceutical companies, "If you will go this route, you'll be successful." Is that what you're saying with that proposal?

Mr. BOLLYKY. Thank you, Senator.

To your question, it's less of a guarantee of success, of course, but a lot of these public/private partnerships are new initiatives to develop products specifically for these neglected diseases. And they may not have the experience to know all the benefits available to them, both under the IND, investigational new drug, process or the BLA process, for vaccines. FDA has recently issued guidance, its Center for Biological Evaluation Research (CBER) has issued guidance specific for vaccines. We'd like to see more extensive guidance on that front, but also guidance issued around drugs and diagnostics, as they're an important part of this program.

Senator BROWNBACK. And you think that would encourage more people to get into those fields, then, if they did that?

Mr. BOLLYKY. I think that's exactly right. It would do both. It would encourage more investment in development of neglected-disease products, as well as allowing them to capitalize on the investments that have already occurred in the products in the pipeline, by helping them through this last stage of the process.

Senator BROWNBACK. Dr. Kakkis, we've talked, previously, about this special review group that you were talking about, the new Division of Biochemical and Genetic Diseases. You've been kind

enough to come by my office and talk about that. There are some people in the system that don't care for that idea. They don't want to see a separate division. Why do you believe that this is an important innovation that needs to take place within FDA?

Dr. KAKKIS. Well, the FDA currently does have separate divisions that are assigned different scope of diseases. What we're saying here is that they need to have a division that has particularly trained people in these diseases that are both biochemical or neuromuscular or some of the other genetic rare disorders that require specialized expertise. And that group needs to be a group that is trained in the pediatric subspecialties, not in other specialties.

In the Aldurazyme case, I had a neurologist, a pulmonologist, an oncologist review a disease that they never see in training, and are not knowledgeable about. And in order to get the best regulation, you should have physicians that are actually very knowledgeable and have been trained in the field of medicine. And, throughout FDA, there are certainly specialists in every area, but, in certain areas, there's not good coverage. And I think that, in this rare genetic disease area, there is not as good a coverage as there could be.

So, we're hoping you take some of the experienced people within FDA that are scattered in different places, consolidate them, bring in additional staff, and build a division, where people can get expertise and leverage their experience, and stay together as a group, rather than having the expertise diffuse and not leveraged over time.

Senator BROWNBACK. You don't think they could just do that on almost a task-force basis, as drugs come through—you're saying the expertise is there throughout FDA, that you could pull it together for particular reviews?

Dr. KAKKIS. Well, when you apply to go in a clinical trial, you get a particular division applied. I think it's very hard to have other people impacting a review that are not really the ones who have to be responsible as reviewer and division head. We think that it makes sense to have that division group be specialized so they can gain experience over time. When you have them disseminated, that causes them to have to review things, for example, that are large market drugs, or different, or expect people to be able to shift from different types of large market diseases to small rare diseases. And we think it requires more training and experience and focus to be able to make that happen. This is why we believe a specialized group is necessary.

It's not something that's unusual; the FDA has a lot of groups that are designed. We just think that there are certain areas that are not well covered. We're not expecting this review group to be for all rare diseases. We're expecting for certain areas of the rare disease groups that are not currently well represented at FDA. There are definitely people that are talented and experienced at FDA that have reviewed these, but very often they are called on to do other tasks. And we think it would be better to have them focused and develop experience and get that group to be efficient and understand the process well. And I think that's where you can get better decisionmaking.

Senator BROWNBACK. Ms. Dorman, you heard Dr. Kakkis say that there was only one product for genetic disorders that went through the accelerated pathway. And there's been a number that have been cancer drugs approved in that accelerated pathway, I believe this was his testimony. You've worked and tracked this field for some period of time.

Why do you think the accelerated pathway has not been more accessible or used in this rare and neglected disease category?

Ms. DORMAN. Well, that's something that we're attempting to address right now. We're working with the FDA and the NIH right now, in a task force, to address some of those issues. And I think the FDA is trying to do the same thing, as well, with Dr. Pariser's Office of Rare Diseases at FDA. There have been two courses on the development science of small clinical trials. And, in October, we're going to be working with FDA and NIH and Duke University to address some of these really important issues with people in academia, because we see a great lack of knowledge in the world of academia. They don't understand how to develop a product. They don't understand the regulatory process.

So, we recognize that there are certain roadblocks and issues, but I think both the FDA and NIH have been really proactive in that space, to try to address them. So, we're really excited about that.

And also, you know, next week, FDA is going to be having a public hearing on orphan products, a public hearing for 2 days, at which NORD will speak, as well, looking at those problems, and trying to fix them in some way.

Senator BROWNBACK. I hope we can.

Senator Pryor.

Senator PRYOR. Thank you. And thank you for conducting this hearing today.

I have a question—let me start with you, Ms. Dorman—and that is really a followup to Senator Brownback's question, of a moment ago, that it's not universally accepted that people should follow Dr. Kakkis's recommendations there. Do you have any views on whether—does NORD have any views concerning his proposal?

Ms. DORMAN. We are somewhat concerned because we feel a separate division would in some way create additional silos.

And I'll use the example of the Office of Rare Diseases at NIH. They're a small office, under the Office of the Director, and their Director is able to leverage opportunities across all centers and all Institutes, all 27 of them, because he doesn't have any barriers to opportunities. And we think that's very, very important, the possibility of setting up an ad hoc group of sort at the FDA to address some of these problems. But, creating an additional silo, in our opinion, may cause additional problems to access. And I would hope that the FDA would also be willing to work with the NIH to, you know, tap into the experts there.

Senator PRYOR. Dr. Kakkis, do you have any response to that?

Dr. KAKKIS. Well, I think the challenge is that if you don't have the expertise among those actually doing the reviews, I think it's very difficult to expect other people from elsewhere to have input. So, the Office of Orphan Product Development does advocate across the agency. But, they cannot affect the review process for drugs in a way that's fundamental. If the reviewers don't want to approve

your drug, there's nothing the Orphan Product Office can do. Truth is that, within the group or division, they're personally responsible, as reviewers, to make those decisions. And it is important to have them have the right training.

Just like you wouldn't want to go get heart surgery from a pediatrician, I think you'd want your drugs that are being reviewed to be reviewed by people trained in the area, and that specialize in it and really understand it. It's fairly simple.

They do have this in various areas at FDA. It's just certain areas that are not well covered. We certainly don't expect all rare diseases to be included in this one group. We're talking about only certain ones that are not well covered. Other rare diseases can be elsewhere. And we're highly supportive of the Office of Rare Disease that has been created, with Acting Director, Ann Pariser, who's here today, to help coordinate across the agency, within the review division. But, I still think there are certain groups that are not well covered, and that we do need some additional support.

Senator PRYOR. Thank you.

Mr. Bollyky, let me ask you a quick question, and that is, From your standpoint, are there things the FDA has done, or could do, related to the approval process for medicines to treat rare diseases, that you believe could be beneficial to the treatment of neglected diseases?

Mr. BOLLYKY. Thank you for asking that question, because it also provides me the opportunity to say something that I didn't emphasize enough in my testimony, which is, the men and women on the FDA, I find, on this issue, to be excellent, and really, in the last couple years, particularly committed to the issues around neglected diseases. And I think on the part of CBER, they've done quite a bit, in terms of, as I mentioned to Ranking Member Brownback, issuing guidance about infectious diseases that are not endemic. We'd certainly love to see them do more along those lines on the drug and diagnostic side. We'd certainly, as I mentioned in testimony, like to see more cooperation with the WHO to reduce the time gap that occurs currently between FDA's approval process and the WHO's approval process. The thing to recognize is, FDA is really just a step in the pathway for these products to get to the patients in the countries in which they will be used.

So, we'd love to see that. I know that they're starting to take steps in that direction as part of this review group. We encourage that. We'd love to see it go forward.

Senator PRYOR. Okay.

Ms. Dorman, let me ask you a couple of last questions. And that is—you know, one doesn't have to be too observant—just basically turn on the television, and see that there apparently are a lot of economic incentives out there for drugs to treat baldness, toenail fungus, sexual performance, and a lot of other things that you see all these ads for. Are there steps you believe that Congress should take to encourage private enterprise to address more pressing public health issues, instead of develop just more lifestyle medicines? That maybe seems to be where the money is, but I don't know.

Ms. DORMAN. Well, that's the $64,000 question, Senator. I've been asking myself that question for about 10 years right now.

I really have to say, when we're talking about neglected diseases, NORD has always encouraged research and product development into neglected diseases, because they can realize the 7 years of marketing exclusivity under the Orphan Drug Act. Unfortunately, they have never taken the bite, so to speak. But, that always has been a holy grail for orphan product development. And companies willing to develop these products for neglected diseases can take advantage of that, 50-percent tax credit for clinical trials, as well as being free of the user fees for an NDA or a BLA. So, there are a lot of opportunities.

Were you addressing, specifically, neglected diseases?

Senator PRYOR. Uh-huh.

Ms. DORMAN. Okay.

Senator PRYOR. Let me ask another question.

And, Mr. Chairman, this will be my last one. You've been patient with me.

But, I've noticed that there are a lot of—seems like, in recent years—more private foundations and patient groups who are pushing very hard to get certain things through the approval process. And is that a trend, that you're seeing more of that? And are the pharmaceutical companies themselves, at least in some areas, not pushing very hard and leaving it up to foundations and patient groups?

Ms. DORMAN. Right. I mean, you know, it's interesting; in the rare disease world, it's somewhat unique, because so many of the diseases are so small in numbers. And, I mean, they work really hard to have their bake sales and their lemonade stands to amass just a little bit of money to encourage the development and do research of possible product development. So, they're intimately aware, probably more than their physicians are, about the mechanism of their disease.

So, they play a very, very key role in the process and work very closely with academia, with medical hospitals, and also with industry, to encourage them to develop those products. And that's very, very important.

So, it's a very different, unique kind of place for people with rare diseases. So, they play a very key role. For example, the Cystic Fibrosis Foundation and MS Society are seeing where things are not moving fast enough, and they're kind of taking control of that.

Senator PRYOR. So, let me go back——

Ms. DORMAN. But, in a smaller space——

Senator PRYOR. Let me go back——

Ms. DORMAN [continuing]. Is a little bit different.

Senator PRYOR [continuing]. To the economics, as well, though——

Ms. DORMAN. Yes.

Senator PRYOR [continuing]. Because the drug companies may want to do the ones that they can really mass-produce have a big market for, and some of these are very small markets.

Ms. DORMAN. Very small. I mean, I understand that the development of orphan products can be very, very challenging. They're small populations. Sometimes, they're dispersed worldwide. There are not a lot of people willing to take on that risk, especially companies willing to take on that risk. So, I sometimes find as if I'm

walking around with a Damocles sword around my neck. On the one hand, I really do want to encourage them to develop the products. I intellectually understand why so many of them are expensive. But, on the other hand, I want to ensure that the patients get access to them as quickly as possible.

Senator PRYOR. Thank you.

And thank you.

Senator BROWNBACK. Thank you, Senator Pryor.

I've had the same question many times.

Thank you, panel. Appreciate that very much, your input and your thoughts, your life commitments. And I'm glad that you were able to give that in front of the public-sector witnesses, as well, who I know you're engaged with.

I'd call for our second panel on this: Ms. Gloria Steele, Senior Deputy Assistant Administrator for Global Health, U.S. Agency for International Development; Dr. Christopher P. Austin, Director of Chemical Genomics Center, and Senior Advisor to the Director for Translational Research at the National Institutes of Health; and Dr. Jesse Goodman, Chief Scientist and Deputy Commissioner for Science and Public Health at the Food and Drug Administration.

Delighted to have this panel here.

We do have some wonderful Kansas connections that I would be remiss if I didn't acknowledge. Let's see, Ms. Steele, I believe, got a advanced degree from Kansas State University, the always fighting, and sometimes successful, Mighty Wildcats. She was there at that institution to get a master's degree in agriculture economics which is what I got my undergrad in at K State.

And then, I'm also appreciative of Dr. Austin and the National Chemical Genomic Center, National Institutes of Health, for your partnership with one of the Nation's leading pharmaceutical research universities, University of Kansas School of Pharmacy. In fact, the University of Kansas has its own drug discovery pipeline, which includes potential drug targets associated with today's hearings, and that's on rare and neglected diseases. They've got a rapid throughput process that they can test these chemicals on. And I've certainly been encouraging them, saying this is a fabulous area.

And I also think it's a market trendsetter that, while we may be looking at lifestyle drugs now, as the rest of the world develops, if we develop the drugs that they need in a lot of these areas, we're going to be first there, with the right piece of the market. And so, I'm appreciative of your working with KU Pharmacy School on that, as well.

We've heard from the experts outside. I know a number of you have worked with them, as well. So, we appreciate the chance of this panel coming together and telling us how you're working together, and what, if any, legislative support or help you may need.

Ms. Steele, we'll start with you.

STATEMENT OF GLORIA STEELE, SENIOR DEPUTY ASSISTANT ADMINISTRATOR FOR GLOBAL HEALTH, U.S. AGENCY FOR INTERNATIONAL DEVELOPMENT

Ms. STEELE. Senator Brownback, thank you very much for inviting me to testify today on interventions to combat rare and neglected diseases.

As you know, the Agency for International Development is the principal agency providing development in humanitarian assistance worldwide. We are particularly concerned about the neglected diseases that you presented earlier on.

I especially want to thank you and Senator Brown for your efforts over the years to promote access to medicines for neglected diseases, such as TB, malaria, and other infectious diseases, that, as you said, primarily afflict the poor people in poor countries around the world.

We are delighted that the Brownback-Brown provisions have led to initiatives, such as the Priority Review Voucher Program and the establishment of the Technical Review Group in FDA, that will help us have access to the medicines and the diagnostic tools that we need to be able to do our job as we help developing countries fight the neglected diseases. We are very hopeful and are very interested in working with FDA in this process, because it does benefit us to have the drugs and the vaccines and diagnostic tools out, available.

The question that you raised with Administrator Shah during the budget hearing is very timely. As you're aware, we have launched the Global Health Initiative, which promotes exactly the kinds of measures that are needed to help accelerate the availability of drugs, vaccines, and diagnostic tools. One of them is the importance of working in a whole-of-government approach, so that we don't work in silos, you know, working by ourselves, without looking at what FDA is doing, or NIH, or CDC. So, we are working very hard to collaborate and work in an integrated manner.

We are also focused on developing local capacity. We have talked about the need to develop drugs and vaccines and diagnostic tools. And that is a very important issue. But, an issue, too, is the ability—is developing the ability of the countries in which we work to be able to access this—to have the local systems, and to have the technical expertise to be able to distribute and administer the drugs that they need in order to address the issues that they are faced with. And so, we are really very mindful of the help that you have given in this area, and the work that NIH and FDA have done in order to make our work more viable for us.

We have developed considerable experience, both upstream and downstream, around FDA's regulatory process. By "upstream," I mean by supporting late-stage pharmaceutical product development, as well as providing technical assistance for pharmaceutical companies to be able to help meet product quality standards. And "downstream," by actually purchasing the drugs and making this available and enabling the countries in which we work to be able to access and use them.

I would like to describe in more detail the support that USAID is currently providing around the approval process by FDA and other regulatory authorities. We are, in particular, employing a research-to-use strategy to guide our investment in innovations of low-cost and effective health products. Through our product development plans, we work to ensure that, as new products become available and proven to be effective, that they can be quickly introduced and scaled up in the countries in which we work.

In the area of malaria, for example, we are providing support to product development through the Medicines for Malaria Venture, which is a nonprofit public/private partnership that was created in 1999 with the World Health Organization, the World Bank, and other bilateral donors. The focus of the Medicines for Malaria Venture is on discovery and development of drugs that will be affordable to populations living in areas where malaria is endemic, and to drugs that can be used safely by young children and pregnant women, which are the primary target population of our presidential malaria initiative. In 2010, we are going to make available $2,500,000 to MMV.

Just last year, USAID was pleased to see the approval of the first drug that made use of FDA's Priority Review Voucher Program, which is a fixed-dose combination tablet of an antimalaria drug that belongs to the most effective class of antimalarials, which is the artemesinins. And, additionally, with USAID support through MMV, and Novartis, a dispersible formulation of the same drug was launched. This is significant. It's very important in our efforts in malaria.

We are also funding the Malaria Vaccine Development Program to accelerate the development of a vaccine that can be used as part of our malaria control efforts. The program emphasizes support for promising vaccine candidates through production and testing of investigational vaccines. The MVDP works closely with academia, the commercial sector, and other government agencies.

In the area of TB, another neglected disease, the USAID supports late-stage product development of needed TB drugs to the Global Alliance for TB Drug Development and through the Tropical Disease Research Partnership. We are supporting the continuation of late-stage clinical trials of four medicines, or compounds, with the aim of shortening the duration of TB treatment. Our research strategy for TB also funds new diagnostic technologies that will increase the sensitivity and specificity of TB testing and enable or promote more rapid detection of drug resistance.

Finally, in the area of neglected tropical diseases, USAID focuses, currently, on seven diseases which are "tool ready"—in other words, diseases for which medicines are available for mass drug administration. We hope, moving forward, working with NIH, FDA, and CDC, that more tool-ready medicines will become available for other neglected tropical diseases that you highlighted in your chart.

On the downstream side, USAID supports the introduction in countries of many high-impact medical products that have achieved proof of principle. For example, we have helped introduce zinc as a treatment for childhood diarrhea through supporting product manufacturers, promoting policy adoption by national governments, and training of service providers.

PREPARED STATEMENT

In conclusion, we stand ready to support initiatives to shorten pathways for medicines against neglected diseases. Neglected diseases can be beaten, as you have said, if there is full engagement of all government agencies, in collaboration with the private sector and the foundations, to be able to develop the drugs, the vaccines, and the diagnostics. USAID is one link in the chain, and we all

need to work together in order to be able to combat the neglected diseases that we are all very concerned about.

Thank you.

Senator BROWNBACK. Thank you. Thank you for the work in that area.

And I have noticed that a lot of key scientists around the world, some of the most cost-effective things we could do to improve lives of the most people is micronutrients. And it's pretty cost-effective, and it can impact a lot of lives. So, it's one of those really good areas that I think we need to watch a lot more.

[The statement follows:]

PREPARED STATEMENT OF GLORIA STEELE

INTRODUCTION

Chairwoman Kohl, Ranking Member Brownback, distinguished members, thank you for inviting me to testify on interventions to combat rare and neglected diseases.

The U.S. Agency for International Development (USAID) is the principal U.S. agency providing development and humanitarian assistance in more than 100 countries. On behalf of my staff at USAID and the people we serve, I want to thank members of Congress for your longstanding support of health programs.

I especially want to thank Senators Brownback and Brown for their efforts over the years to promote access to medicines for neglected diseases such as tuberculosis, malaria, and other infectious diseases that primarily afflict developing countries. These diseases disproportionately impact poor and rural populations who lack access to basic health services and essential medicines.

We are delighted that the Brownback-Brown provisions have led to such initiatives as the "priority review voucher" program and the establishment of a technical review group on neglected diseases within the Food and Drug Administration to consider and make recommendations to the FDA Commissioner on the appropriate preclinical, trial design and regulatory paradigms and on optimal solutions for the prevention, diagnosis and treatment of neglected diseases in the developing world. USAID is pleased that the FDA review group for neglected diseases held its first meeting in March. We look forward to the recommendations it will issue by March 2011.

USAID is hopeful that the FDA priority review voucher program will encourage private sector companies to invest more of their research dollars and talent in the fight against these terrible diseases.

USAID welcomes Senator Brownback's recommendation to Administrator Shah to support the review process to shorten pathways for neglected diseases. The suggestion is timely, given that the recently launched Global Health Initiative applies a "whole-of-government" approach to global health, mandating that USAID build upon and complement the innovative work of other U.S. Government agencies. The ambitious targets of the Initiative also give us a mandate to increase our focus on supporting innovation and applying new technologies.

USAID is eager to support the review process and ensure that the U.S. Government makes maximum use of the fruits of FDA's regulatory efforts to encourage development of new health products for neglected diseases.

USAID has developed considerable experience both upstream and downstream of the FDA regulatory process: (1) upstream by supporting late-stage pharmaceutical product development as well as providing technical assistance for pharmaceutical companies to help meet product quality standards, and (2) downstream by actually purchasing these drugs and working with developing country Ministries of Health to make sure they are aware of innovative new products, and that these products are quickly introduced and scaled up within national programs. USAID stands ready to share its experience and knowledge of product development and introduction in developing countries. This knowledge and experience may be useful to the FDA review group on neglected diseases as it works to identify ways that could help shorten the pathways for bringing medicines for neglected diseases to the market and to the patient. USAID also stands ready to contribute to implementation of any recommendation by the FDA review committee within the confines of its mandate as a development agency.

I would like to describe in more detail the support USAID currently is providing around the approval process by the FDA or other regulatory authorities. This is the area of most immediate interest to the FDA review committee. I will focus in par-

ticular on product development efforts in malaria, tuberculosis, and neglected tropical diseases.

USAID and the Global Health Initiative place a high priority in the rapid introduction of new technologies in the field. USAID employs a "research to use" strategy to guide its investment in innovations of low-cost and effective health products. Through its product development plans, USAID works to ensure that as new products become available and are proven to be effective, they can be quickly introduced in developing countries.

USAID PROMOTION OF PHARMACEUTICAL INNOVATION

In the area of malaria, USAID provides support to product development through the Medicines for Malaria Venture (MMV), a non-profit, public-private partnership created in 1999 by the World Health Organization, the World Bank, and bilateral donor governments. MMV's goal is to register at least one new antimalarial drug every 5 years; its focus is on discovery and development of drugs that will be affordable to populations living in malaria endemic areas; that are effective against drug-resistant strains of P. falciparum; and that can be used safely in young children and pregnant women. MMV's current portfolio contains more than thirty projects actively pursuing novel compounds and promising analogues. USAID will contribute $2.5 million to MMV in fiscal year 2010.

USAID also funds the Malaria Vaccine Development Program (MVDP) to accelerate the development of a vaccine that can be used as part of malaria control efforts. The Program emphasizes support for promising vaccine candidates through the production and testing of investigational vaccines. The MVDP works closely with academia, the commercial sector, and other government agencies. Experimental vaccines manufactured by several companies have been tested under the program.

In the area of TB, USAID supports late-stage product development of needed TB medicines through the Global Alliance for TB Drug Development and Tropical Disease Research partnership. USAID is supporting the continuation of late-stage clinical trials of four medicines or compounds with the aim of shortening the duration of TB treatment. Our TB Research Strategy also funds new diagnostic technologies that increase the sensitivity and specificity of TB testing and evaluates new diagnostic technologies that more easily detect TB, enable rapid detection of drug resistance, and detect latent TB infection.

Finally, in the area of neglected tropical diseases, USAID focuses currently on approaches that are "tool ready," in other words, for which medicines are already available and have proven to be safe and effective and amenable to mass drug administration. Going forward, USAID hopes to support late-stage trials of new drugs that may accelerate progress toward the elimination of some NTDs and may enable the inclusion of other NTDs as "tool ready." As safe and effective new drugs and tools become available for other neglected diseases, USAID looks forward to adding these diseases to its program.

NEGLECTED DISEASES AND THE GLOBAL HEALTH INITIATIVE (GHI)

All of USAID's work is coordinated with other donors, the private sector and host country groups through operational partnerships in each of the priority countries, as well as with other Federal agencies such as the Centers for Disease Control and Prevention.

This approach guides not only all USAID-led programs, but also whole-of-government Presidential Initiatives in global health, global climate change, and food security.

So let me take a few minutes to describe the core components of the Global Health Initiative, and how they relate to neglected diseases. The goal of the Global Health Initiative is to achieve dramatic improvements in sustainable health outcomes, with a particular focus on improving the health of women, newborns and children. USAID's efforts to reach the goals of the GHI will depend on significant progress against neglected diseases.

The United States will invest $63 billion to help the approximately 80 partner countries where the U.S. Government provides health assistance to improve health outcomes, including the continuation of commitments for HIV/AIDS, tuberculosis and malaria, with a particular focus on improving the health of women, newborns and children. The GHI is a global commitment to invest in healthy and productive lives, building off of, and expanding, the U.S. Government's successes in addressing specific diseases and issues. Addressing wide-ranging health needs in partnership with governments, communities and other partners represents an ambitious agenda that can be met only if we work together, aligned toward common goals, with a commitment to fundamentally improve the way we do business.

Achieving major improvements in health outcomes is the paramount objective of the Initiative. To that end, the GHI supports the following goals and targets with regard to rare and neglected diseases:

—*Malaria.*—USAID, in partnership with the Centers for Disease Control and prevention, will seek to reduce the burden of malaria by 50 percent for 450 million people, representing 70 percent of the at-risk population in Africa. USAID was very pleased that malaria was included in the definition of neglected diseases within the context of the Brownback-Brown amendment.

—*Tuberculosis (TB).*—The U.S. Government's tuberculosis program will save approximately 1.3 million lives by reducing TB prevalence by 50 percent. This will involve treating 2.6 million new TB cases and 57,200 multi-drug resistant (MDR) cases of TB. The Brownback-Brown amendment's inclusion of TB drugs within the review committee's purview will be essential in helping us address the long-term challenge of tuberculosis control, particularly with the emergence of multi-drug resistant strains of the disease.

—*Maternal and Child Health.*—Save approximately 360,000 women's lives by reducing maternal mortality by 30 percent across assisted countries. The GHI strategy seeks to improve health systems in ways that particularly target maternal health, including through the expansion of support for antenatal care, and for significant increases in the number of trained health care providers. These health systems can also provide a foundation for the diagnosis, treatment and prevention of neglected diseases, ensuring that newly developed drugs are procured and prescribed as needed.

—*Child Health.*—Save approximately 3 million children's lives, including 1.5 million newborns, by reducing under-5 mortality rates by 35 percent across assisted countries. Some of the highest mortality and morbidity associated with rare and neglected diseases occurs in children. The GHI cannot meet its goal of reducing mortality of children under 5 years of age without addressing rare and neglected diseases.

—*The Neglected Tropical Diseases (NTDs) Program.*—USAID's NTD Program seeks to reduce the prevalence of 7 NTDs by 50 percent among 70 percent of the affected population, contributing to: (1) the elimination of onchocerciasis in Latin America by 2016; (2) the elimination of lymphatic filariasis globally by 2017; and (3) the elimination of leprosy. This program began in five countries in 2006 and has since expanded to integrated NTD control in 14 countries—Bangladesh, Burkina Faso, Cameroon, Democratic Republic of Congo, Ghana, Haiti, Mali, Nepal, Niger, Sierra Leone, Southern Sudan, Tanzania, Togo, and Uganda. As anticipated, following 4–6 years of repeated mass drug administration, transmission of some NTDs is being interrupted. Ghana, supported by USG efforts since 2006, has eliminated trachoma as a blinding disease and may be able to stop annual drug administration for lymphatic filariasis after the coming year.

INNOVATION AND THE GHI

And finally, one of the hallmarks of the GHI is its emphasis on innovation. The GHI strategy puts at its an understanding of the importance of United States leadership in research and robust use of rigorous peer-reviewed research that is already available. The U.S. Government recognizes that advancements in health often occur through the discovery and development of new biomedical technologies, including not only new drugs but also diagnostics and vaccines; medical devices, such as the female condom; and information and communication technologies, such as mobile telephones and other data transmitting devices that have the potential to improve people's health.

Although the GHI is not expected to make direct investments in clinical trials for new products, we will take advantage of opportunities to link the results of these trials with the means for improving service delivery. The GHI also will look to accelerate the appropriate use of existing technologies as well as create favorable conditions for more rapid introduction and successful scale-up of technological advances that have been demonstrated to improve health outcomes.

The GHI will work with in-country partners to overcome bottlenecks and accelerate delivery pathways to ensure that innovative technologies can be widely adopted, including improving demand forecasting for new products, supporting evidence-based decision making within partner countries, and conducting operational and implementation research. These systems will pay particular attention to the FDA review processes, to ensure that they translate discoveries in the lab into success in clinical care in developing countries. Operational and implementation research will help identify critical problems and improvements, including: sustainable and cost-

effective service delivery approaches; obstacles to rapid scale-up and approaches to reduce such obstacles; and strategies to help improve health service delivery models.

Given the whole-of-government approach of the GHI, the Initiative will work through existing governmental mechanisms and partner with private sector donors and foundations to support research. Synergies will be sought between GHI programmatic activities and existing research partnerships of the National Institutes of Health, the Centers for Disease Control and Prevention, and other agencies that have active biomedical and public health research programs, and the FDA priority review voucher program and the neglected diseases review group will be important parts of those efforts.

CONCLUSION

In conclusion, USAID stands ready to support initiatives to shorten pathways for medicines against neglected diseases. Neglected diseases can be beaten if there is full engagement of all concerned government agencies throughout the product development continuum: from basic research to efficacy trials, to regulatory review and promotion and distribution of new products into the hands of health care workers. USAID is one link in this chain. We will work with our colleagues across the U.S. Government to ensure that innovative new products are developed and put to use in developing countries to combat malaria, TB, and other neglected diseases.

Thank you.

Senator BROWNBACK. Dr. Austin, thank you for being here. Appreciate your attendance. And the floor is yours.

STATEMENT OF CHRISTOPHER P. AUSTIN, DIRECTOR, CHEMICAL GENOMICS CENTER; AND SENIOR ADVISOR TO THE DIRECTOR FOR TRANSLATIONAL RESEARCH, OFFICE OF THE DIRECTOR, NATIONAL HUMAN GENOME RESEARCH INSTITUTE, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. AUSTIN. Good afternoon, Mr. Chairman. Thank you for the opportunity to speak to you this afternoon about NIH's activities to promote the development of therapeutics for rare and neglected diseases.

I'm pleased to tell you about some of the exciting new scientific programs and partnerships we've initiated, and particularly with those with the FDA, to bring about more efficient development of treatments for patients afflicted with these devastating diseases.

Scientifically and medically, we live in exciting though paradoxical times. Thanks to the Human Genome Project and other spectacular scientific successes, we know more about ourselves than we ever have in health and disease. At the same time, however, the number of new drugs approved every year has stayed constant, or even declined, over the last decade. This paradox is no more acute than in rare and neglected diseases.

As a neurologist—my original training is in neurology and as a doctor in rural Africa—I routinely took care of patients with these illnesses, and felt the hopelessness of those for whom medicine had little or nothing to offer.

But, now the genetic sequences, the genetic basis of over 2,000 rare diseases, is known, and we have the full genome sequences of almost every organism that causes a tropical neglected disease. Thanks to research performed at NIH and funded by NIH over the last 50 years, we're finally at the point of being able to translate these discoveries, sometimes rather directly, into therapeutics. But, achieving this promise for rare and neglected diseases will require new kinds of science, new collaborations, and new ways of oper-

ating. Under Dr. Collins' leadership, and with the support of the Congress, NIH is moving aggressively to realize this promise.

A fundamental problem, that you noted, is that rare and neglected disease drug development requires expertise that has traditionally been present, virtually exclusively, in biotechnology and pharmaceutical companies. But, these diseases do not offer a return on investment sufficient for companies to work on them.

Incentives such as the Orphan Drug Act and, more recently, the Voucher Program for Tropical Disease Therapeutics, have done a great deal to encourage companies to work on these diseases. However, the scale of the need, as you described—over 6,000 rare diseases with no treatment—tell us that fundamental changes in the way therapeutic development has always been done are needed.

The NIH Therapeutics for Rare and Neglected Diseases, or TRND, program is directly addressing the structural and scientific issues that limit drug development for these diseases. It was congressionally mandated beginning in fiscal year 2009. TRND is a collaborative program to develop new drugs for rare and neglected diseases, as well as technologies and paradigms to improve the success rate of drug development more generally. TRND combines new internal NIH drug discovery and development resources with specific disease expertise that exists in university researchers, in patient advocacy groups, foundations, and biotechnology and pharmaceutical companies. Importantly, every project TRND does is a collaboration across what have traditionally been separate domains.

TRND has already had early successes in its pilot programs that will move three projects into the clinic for rare diseases in the next 12 months. Among these is a potential new drug for Niemann-Pick-C disease, which is a devastating neurodegenerative disease of children. It's a joint project between ourselves, TRND–NIH investigators, university researchers at Washington University in Saint Louis and Albert Einstein College of Medicine in New York, and a patient advocacy foundation who is deeply involved in the project.

Other TRND pilot projects include the one that you mentioned, the collaboration with the University of Kansas and a nonprofit disease foundation on a drug for chronic lymphocytic leukemia, a project with a Boston-area biotechnology company on sickle cell anemia, and a project with the NIH Clinical Center on a rare muscle wasting disease. TRND's pilot neglected disease project is a collaboration with Rush University in Chicago and Yale University, on schistosomiasis and hookworm, two diseases that affect—together, infect over 500 million people worldwide.

Importantly, while TRND is, and will, develop drugs for individual rare and neglected diseases, it is also intensely focused on the scientific and systems problems that hold back efficient drug development for these diseases more generally. A key partner for TRND, and NIH more broadly in these efforts, is the FDA. A TRND–FDA working group meets every month to discuss issues in TRND projects and to develop new ideas to address the roadblocks in drug development for these diseases. TRND is working closely with the FDA Office of Orphan Product Development to coordinate activities, including leveraging the excellent FDA Rare Disease Repurposing Database that was released by FDA last week.

In addition to these staff contacts, the FDA and the NIH recently formed a flagship partnership announced by Drs. Collins and Hamburg, which will support research programs in regulatory science.

PREPARED STATEMENT

In summary, the NIH, through TRND and other research initiatives across the agency, is poised to make fundamental advances in the development of therapeutics for rare and neglected diseases. The availability at NIH, for the first time, of resources and expertise previously restricted to the biopharmaceutical community, and the generation of vitally needed alternatives to traditional drug development pathways, in partnership with the FDA, provides new hope for millions of patients and families afflicted with these devastating diseases.

Thank you very much for the opportunity to testify today, and I'd be glad to take any questions.

Senator BROWNBACK. Thank you, Dr. Austin. I appreciate that, and it's encouraging. I want to dig into it some more during the questions.

[The statement follows:]

PREPARED STATEMENT OF DR. CHRISTOPHER P. AUSTIN

Good afternoon, Mr. Chairman and distinguished members of the subcommittee: Thank you for the invitation to speak to you this afternoon about the National Institutes of Health (NIH) activities to promote the development of novel therapeutics for the treatment of rare and neglected diseases. In particular, I am pleased to talk to you about some of the exciting scientific opportunities that we are pursuing and the strong partnerships that we and others at the NIH have built with the Food and Drug Administration (FDA) over many years to facilitate the efficient development of treatments for patients afflicted with these devastating diseases.

Over the last 60 years, the research and drug development infrastructure of the United States, contributed to by the public and private sectors, has produced medicines that have reduced suffering and death from many diseases, including heart disease, diabetes, osteoporosis, many types of cancer, and infections such as AIDS and pneumonia. However, due to the high cost of developing a new drug, most drug development resources are focused on diseases that are highly prevalent in the developed world. While this focus has contributed greatly to the public health of the Nation, it has left many in the United States who suffer from rare diseases (those defined by the Orphan Drug Act as affecting fewer than 200,000 Americans), and many more in developing nations who suffer from neglected diseases, without treatments. In fact, of the 7,000 human diseases, over 90 percent are classified as "rare" or "neglected"[1] [2]. Collectively, these affect more than 25 million people in the United States.

Biopharmaceutical companies are reticent to take on rare and neglected disease studies due to the historically high rate of failure and the relatively low return on investment. The recent contraction of the biopharmaceutical sector has further exacerbated this problem.

The success of the research performed and funded by NIH over the last 50 years, and especially over the last decade, has brought us to the point where basic scientific discoveries can be more rapidly and efficiently translated into medical treatments. Thanks to the Human Genome Project and related initiatives, the genetic basis of over 2,000 rare diseases is now known, and the infectious organisms that cause neglected tropical diseases are understood in unprecedented detail (see, for example[3]). Over the years, NIH has supported basic research and the elucidation of biological pathways as a means to understand human health and disease. Since much basic mechanistic research remains to be done in these areas, it is critical that NIH continue to support these avenues of scientific inquiry. NIH also recognizes the

[1] http://rarediseases.info.nih.gov/.
[2] Hopkins AL, Witty MJ, Nwaka S. (2007). Mission possible. Nature 449:166–169.
[3] Berriman M, Haas BJ, LoVerde PT, et al. (2009). The genome of the blood fluke Schistosoma mansoni. Nature 460:352–358.

opportunity and the imperative to pursue translational initiatives to apply basic scientific knowledge to health needs. Our conviction is that these more applied projects will accelerate diagnostic and treatment development, particularly for rare and neglected diseases.

The Molecular Libraries Initiative, funded by the NIH Common Fund, for example, has made tools and resources accessible to academic researchers that were previously only available in large pharmaceutical companies. Specifically, scientists at universities and medical centers have been provided access to industry-style assay development, high-throughput screening, and medicinal chemistry infrastructure not previously available in academic settings. In doing so, this program has produced more than a hundred chemical "probe" compounds that are used to study rare and neglected diseases in cellular or animal models. These compounds are traditionally referred to as "small molecules"—they are organic chemicals made up of carbon, hydrogen, nitrogen, oxygen, and a few other atoms in a wide variety of combinations, and can be thought of as chemical "shapes" that can interact with a host of cellular targets. Such compounds are the first steps toward drug development, but the development of small molecules suitable for testing in humans requires an additional 3–4 years of development.

The academic sector currently lacks the infrastructure and expertise required for the pre-clinical pharmaceutical development needed to transform a chemical research probe into a candidate compound suitable for testing in patients. Individual NIH Institute and Center programs have been established to move candidate compounds further down the development path—the Neuroscience Blueprint Neurotherapeutics program, the NINDS Spinal Muscular Atrophy Project, NCI's Experimental Therapeutics (NExT) program, and the NIAID BioDefense Product Development Program are but a few examples. These programs, as critical as they are, together address fewer than 100 individual diseases.

Announced in May 2009, the Therapeutics for Rare and Neglected Diseases initiative, abbreviated TRND, is a collaborative research program that builds on efforts across NIH to develop candidate compounds for clinical testing en route to developing therapeutics for rare and neglected diseases. TRND is a trans-NIH program overseen by the Office of Rare Diseases Research in the Office of the Director, NIH, and administered by the National Human Genome Research Institute. Building on the Molecular Libraries Initiative, TRND will empower academic investigators to pursue pre-clinical work through high-throughput resources not previously available outside the biopharmaceutical sector. In most cases, the starting point for TRND will be a chemical "probe," or compound, known to have some biological effect in laboratory models of a given rare or neglected disease. The end-point deliverable will most often be a candidate compound with sufficient data for an Investigational New Drug (IND) application to the FDA.

The pursuit of novel partnerships with biopharmaceutical companies and patient advocacy groups will be another hallmark of this program that brings together the necessary expertise and patient communities to realize therapeutic development success in the rare and neglected disease realm. It is expected that in most cases, TRND's candidate compounds will ultimately be licensed to biopharmaceutical companies for clinical development, permitting TRND to focus on the most scientifically challenging stages of pre-clinical drug development. In this way, TRND intends to "de-risk" projects sufficiently to make them enticing to groups outside of NIH to pursue final development, even for less common diseases with limited markets. TRND's scientific activities will include everything from iterative medicinal chemical modification of promising compounds to testing optimized compounds in laboratory disease models; in cases that lack sufficient private-sector interest and present compelling health needs, NIH may even conduct the early clinical trials necessary for safety and efficacy analyses, using the substantial resources of the NIH Clinical Center and the network of 46 Clinical and Translational Science Awards (CTSAs) across the country.

Significantly, beyond delivering candidate compounds for clinical testing in individual rare and neglected diseases, TRND will focus on improving the overall efficiency of drug development for these types of diseases. Currently, drug development is an unavoidably long and failure-prone process, requiring 4–8 years and carrying a failure rate well over 90 percent. This high-failure rate and extended timeline is due in large part to the unpredictable nature of the biological effects of new candidate compounds. NIH aims to advance the underlying drug development processes through open and broad dissemination of the information learned in the course of candidate compound development. To achieve this goal, TRND will focus on mechanisms able to cut across traditional disease or organ system boundaries, allowing each drug developed potentially to target the underlying pathology for more than one disease. Successes and failures will be investigated and published, and specific

technology development programs addressing the two most common causes of new drug failure—toxicity and efficacy in humans—will be launched.

To expand some of the unrealized potential of earlier drug development projects, an alternative approach—known as drug "repurposing"—will seek to identify drugs for rare or neglected diseases from among those already approved for use in people by FDA or another regulatory agency outside the United States. The opportunity of this approach is that it potentially allows for rapid therapeutic advances, with a treatment available 1–2 years after the initial tests. The challenge is the relatively small number of compounds (i.e., drugs) that have been approved for human use, and therefore that are available for repurposing (approximately 3,000, compared to 100–1,000 times the number of new candidate compounds available). As part of its program to take every approach to speeding the development of new drugs for rare and neglected diseases, TRND will be testing clinically approved drugs for new activities in assays related to 100 rare diseases. This effort will complement TRND's traditional compound development pathway, and will provide information on the critical question of what percentage of rare and neglected diseases can be treated to some extent by the current pharmacopoeia.

Since one of the organizing principles of TRND is a systems approach to drug development, all rare and neglected disease areas will be suitable for TRND. Because TRND is explicitly designed to address any rare or neglected disease, and identify and capitalize on biological/pathway commonalities among these diseases regardless of the organ systems they affect, the program's success will rely and actively draw upon the knowledge and expertise resident in all the NIH Institutes and Centers. TRND will draw many of its projects from extramurally supported investigators as well, and look to them for insights into the molecular pathogenesis of diseases, and for collaborations on pharmacological and animal models for lead optimization and pre-clinical testing. This coordinated and universal approach to rare and neglected diseases should with time lead to therapeutic strategies for additional diseases not directly studied by TRND.

To launch the scientific program and begin to develop the operational processes necessary for the management of these types of atypical research partnerships, five initial projects—at a variety of stages of development, with different types of collaborators, and with different disease types—have been initiated in fiscal year 2010.

—The first pilot is focused on schistosomiasis and hookworm, which are highly prevalent and neglected tropical parasitic diseases that affect over 500 million people worldwide. This project is an early pre-clinical ("probe optimization") stage project, and involves a collaboration with two extramurally-funded NIH investigators.

—The second project is a mid-stage drug "repurposing" project for a rare disease, Niemann-Pick Type C (NPC), which is allowing the piloting of the later stages of pre-clinical development including formulation, pharmacokinetics, pharmacodynamics, blood-brain barrier penetration issues, and challenging clinical trial design. NPC is a rare pediatric neurodegenerative disease, and the project is a collaboration with both extramural and intramural scientists. Importantly, this project also involves several patient advocacy groups who support and coordinate NPC research.

—A third project is a collaboration with a research-driven disease foundation and extramural collaborators, focusing on repurposing an approved drug for treatment of Chronic Lymphocytic Leukemia. This project is currently at the later "pre-IND" stage of the drug development pathway.

—A fourth TRND project involves a rare muscle-wasting disorder that occurs in mid-life, known as Hereditary Inclusion Body Myopathy. In this instance, the project involves a new candidate compound, but is also at a late stage, requiring only discrete toxicology studies before moving into clinical testing. This project involves a collaboration with an investigator at the NIH Clinical Center and a biotechnology company, and is allowing TRND to pilot processes to incorporate the unique resources of the NIH Clinical Center and also to work through business issues related to partnering with the private sector.

—The final pilot project focuses on sickle cell disease, and brings together nonprofit, intramural and extramural investigators to focus on a new candidate compound at the mid-stage of pathway development.

If TRND is to succeed in achieving its objective to increase the number of therapeutics available to combat rare and neglected diseases, an integral part of the commitment must be regular dialog and coordination with the FDA. To accelerate and enhance TRND activities, a working group of TRND and FDA staff meet monthly to discuss conceptual issues in existing TRND projects, and to develop new ideas to address the principal roadblocks in drug development for these diseases. FDA participants include representatives from the Office of New Drugs and the Office of

Translational Science, with expertise in rare disease drug development, toxicology, and policy. The NIH staff includes TRND leadership and individual scientists working on the particular projects being discussed. Separately, TRND is working closely with the FDA Office of Orphan Product Development (OOPD) to coordinate activities and leverage OOPD programs to advance mutual goals.

In addition to these critical staff contacts for TRND, the NIH recently formed a flagship partnership with the FDA. Through a recently announced Joint Leadership Council, co-chaired by NIH Director Francis Collins and FDA Commissioner Margaret Hamburg, the two agencies will work closely together to ensure that sound regulatory considerations are an integral part of research planning. The initiative involves two interrelated scientific disciplines: translational science (the shaping of basic scientific discoveries into treatments); and regulatory science (the development and use of efficient and effective tools, standards, and approaches to develop products and evaluate product safety, efficacy, and quality). Both disciplines are needed to turn biomedical discoveries into products that benefit people. Through research programs in regulatory science, innovative mechanisms and processes will be explored to devise optimal methods for drug development and review.

This multi-pronged approach for collaboration between FDA and NIH in support of the development of novel products to treat and diagnose rare and neglected diseases will promote the development of new pathways through which safety, quality, and efficacy can be assessed, improving the overall efficiency of clinical research as a whole.

In summary, the NIH, through TRND and other research initiatives across the agency, is poised to make extraordinary advances in the development of potential therapeutics and treatment strategies for rare and neglected diseases. The opportunity to pursue new scientific directions through the availability of resources traditionally restricted to the biopharmaceutical community, and to generate vitally needed alternatives to traditional drug development pathways in partnership with the FDA, presents new hope for the ultimate success of bringing better clinical options to patients afflicted with rare and neglected diseases.

Thank you very much for the opportunity to testify before the committee this afternoon. I would be happy to take any questions that the panel may have.

Senator BROWNBACK. Dr. Goodman, most of the bulk of the effort falls on your shoulders. Everybody's here to help, but it's the FDA approval process, I think, that most of the focus tends to be on. And so, I hope you can illuminate us on what's taking place, and what we can do to try to help out and get more products through the system in this rare and neglected disease category.

STATEMENT OF DR. JESSE GOODMAN, CHIEF SCIENTIST AND DEPUTY COMMISSIONER FOR SCIENCE AND PUBLIC HEALTH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. GOODMAN. Thank you very much, Senator Brownback. And I'm really happy to be here today to represent FDA and talk some about our efforts in this area.

My biggest message for you is that we're very engaged, and it's exciting for me to be here and hear some reflections of that engagement, you know, from numerous people we're partnering with, whether its patient groups, our colleagues at NIH, the nongovernmental organization community, or across the government in the Global Health Initiative. So, thank you.

TWO CHALLENGES

I hope, because the scope of our activities and my inability to ever compress things into the tiniest little oral statement, that you'll be a little patient with me. So, I'm going to try to cover the waterfront a little, and also make an effort to be responsive to some of the issues that have been raised.

First of all, I want to say, I'm a practicing infectious disease physician. I still take care of patients, including at Walter Reed, in the Navy, so I still see tropical diseases. And I'm also trained in oncology. So, I certainly have seen, and still see, the devastating impacts of these diseases, and appreciate the concern and compassion you're bringing to this.

TB, MALARIA AND HIV

Another point I frequently make in my job is that infectious diseases like TB, malaria, HIV—most recently, pandemic influenza—these diseases have no boundaries, and if they're a threat to anyone in the world, they're a threat to us, as well. So, not only there are these compelling humanitarian reasons we should do—take care of this problem, there are also really pressing U.S. and global security and public health reasons for our country.

You know, I want to say—and, again, I appreciate the recognition that, in my former position as director of the Biologic Center at CBER, we made this a very high priority, including our engagement in WHO. And this is a very high priority for me in my new position and, I know, for Dr. Hamburg, as well.

Now, for both rare diseases and those that are perceived, at least, to affect primarily impoverished communities and people, I think there are really two major challenges. You know, and we've heard about them.

First, is that clear-cut and sufficient market incentives to drive product development to the degree that we see in other areas are often lacking.

The second one is that there are actually some real scientific challenges here. And, as Chris said, even though we know lots and lots, and know things on the molecular level, that doesn't always translate into ability to treat a disease or come up with a product. And, in fact, I like to say to people that these same diseases that are so clever in infecting people all over the world, like HIV and TB and malaria, they do that, for example, on the vaccine front, because we don't make a very good immune response to them, or a very effective one. And then, when we turn around and our colleagues at NIH try to make vaccines against them, you find it's very hard to get a vaccine that makes an effective immune response. So, there are some real scientific challenges there, but it's exciting to see them—the investment in solving those challenges.

I want to also emphasize that the standards and expectations that we have in this country, that products be safe and effective, are important. People with rare and neglected diseases are classic examples of people in a vulnerable situation, or a vulnerable population. They're vulnerable because they have that disease, and we need to get them the treatment, and we share that motivation. They're also vulnerable to potential misuse or ineffective products, due to their poverty or where they live, et cetera, or to—how important it is for them to get treatment.

SCIENCE-BASED DECISIONS

And people everywhere, all over the world, look to FDA to make solid risk-based, science-based decisions. And people everywhere want medicines that they take, or vaccines their children take, to

be safe and effective. So, we take that very particular responsibility we have at FDA very, very seriously.

I also want to be sure that there isn't any misunderstanding that, you know, if a product is promising, we are going to work closely with the sponsors. And if that product works, we're going to approve it. Okay?

There's—a big problem here is, there are not enough effective products to fill in that circle which we would all like to do. And there are a lot of reasons. But, we want to do all we can to facilitate that process, from development to evaluation.

ORPHAN DRUG ACT

Now, I'd just like to go through some of the things we're doing to try to help, and acknowledge your help; Congress has really helped. As you've heard from Ms. Dorman, the Orphan Drug Act provided incentives and assistance to developers of drugs. Prior to it, there was almost nothing out there. And, while we need much more, there were 357 products shown to be safe and effective, and approved as a result, since that time. And that's good. And, thanks to you and Senator Brown, we got the Priority Review Voucher Program, which is going to provide additional incentives for neglected diseases.

ORPHAN PRODUCT OFFICE

Our Orphan Product Office, which Dr. Tim Cote, who is right here with us, is the Director, and who's here with me, is a focal point for the agency, of these activities. And there are many, many things they do, but just some major examples is providing assistance to the kind of people we've heard about who might lack product development experience; to work with patient advocacy groups and patients themselves, who we think have an important voice in this; to identify drugs that could be promising for rare diseases, and try to encourage partners to study those drugs, and help them to do it; to conduct outreach and training that will help in this.

And you've heard about some of the recent activities. We've had a course to teach small science behind small clinical studies. Fifteen hundred people participated in that last course, including many FDA reviewers.

And you heard about our cosponsorship with NORD and NIH of the first rare disease investigator course that's going on this year. This is a substantial effort, here.

TRND PROGRAMS

And then, as Chris said, we're collaborating closely, as they bring about this program. We're very excited, in the TRND program, to help bridge the gap from very basic science to get promising concepts and drugs ready to go into studies in humans.

And you heard that, just this February, FDA created this new position of Associate Director for Rare Diseases in the Center for Drug Evaluation and Research. And again, Anne Pariser, who is here—I'm delighted—is in that position now. And what she's really doing is very consistent with the goals that we share with Dr. Kakkis, you know, for a coordinated high-quality, consistent

science-driven review process. So, she's working to have the best guidances, the best policies, the best practices across the very large and diverse Center for Drugs. And part of that is bringing the best people to bear on specific applications, and really making this process go smoothly.

Now, I want to also point out that we're very committed to flexibly applying standards that are risk-based to the review of these products, and to point out that, for many rare diseases, they've been, in fact, approved on studies with extremely limited numbers of patients, often less than 20. So, when there are very few patients there, we work with sponsors to go out and get them. And if the data are strong, we can approve it, if they're effective.

When good information is available, we also have supported assessing the benefit of a drug by comparing it to historically untreated controls in our databases. And we've helped sponsors do that.

And I'll come back to it, but where surrogates or biomarkers are available to predict benefit, we can take an accelerated approval, or even a full approval, pathway, if those surrogates are well validated, and get effective products to patients faster. But, this is only possible when the science is there that tells us that that will predict benefit to patients. Because we don't want patients to find out, 10 years later, that something didn't work.

Now, while there have been many successes, the unmet needs are huge. And you've profiled them very graphically here. And we want to work with you to meet those needs.

Thanks to your leadership, we've established the Rare Disease and Neglected Disease Workgroups that you've heard about. And they're going to look at all of the ideas we've heard here, the ideas we're soliciting in public meetings. And also, they're working with our review staff to get their ideas, because many of them have seen how things work, and what doesn't work. So, we're looking forward to providing a report to Congress and issuing guidance, as instructed by this legislation.

NEGLECTED DISEASES

I want to talk briefly about neglected diseases. We fully support the Global Health Initiative, which you heard about today from Ms. Steele. We've—I've been tremendously excited, personally, about how the NGOs, the NIH, and industry have gotten interested in neglected and global diseases. I think that's great. We need to do more. But, as part of this, we've dramatically increased our engagement.

Examples are: issuing the guidance you heard about for vaccine development against global disease. We also are, in fact, meeting early and working very closely with NGOs and these public/private partnerships, to try to help them when they don't have experience in product development. We provide, hundreds of times a year, technical support, expertise to WHO, both at working technical level and at a high leadership level. That's a very constructive engagement. The Biologic Center serves as a reference national regulatory authority, and does prequalification of vaccines for global use for WHO. And Dr. Bollyky's comments about coordination of that process are very good. And we, in fact, are working with WHO on

an evaluation of their process to try to strengthen it. And we're very active partners with them.

Also consistent with Mr. Bollyky's suggestions, the countries that these products are used in need the capacity, themselves, to feel that they can evaluate them, that clinical trials can take place safely in their countries, that they can monitor the safety of the products. And we have a very large effort, particularly in the vaccine area, to—working with WHO—to help train and have scientific interactions with regulatory colleagues around the world, including in Africa and through something called the Developing Country Vaccine Regulators Network. And this has been very fertile. Both the Biologic Center and the Drug Center and the Device Center have put on training courses in regulation, and have frequent scientific exchanges with other regulators throughout the world.

And then, finally, I want to talk a little bit about science, because in this area we have a unique research program that is designed to help define new measures of safety and efficacy, and improved approaches to product quality, particularly for vaccines against diseases like TB, malaria, HIV, meningitis, Leishmania—the list goes on.

I want to mention our efforts in regulatory science, as, in almost every aspect, all the problems that we're looking at today have science at the root. And science is also—often what determines whether a project is successful, or fails. As we heard from Chris, we've defined the genetic basis of thousands of diseases, and identified even potential drug targets for many of these diseases. But, that hasn't really translated into products yet. So, the promise is incredible, and it's another reason why we need to act now. And we think that regulatory science can help bridge this gap.

The tools we develop in regulatory science are particularly critical for rare and neglected diseases. For example, we heard from Dr. Kakkis about the desire to take advantage of accelerated approval mechanisms, which really means, instead of approving it on something like "you survived longer," that we have a marker in the patient's response—it could be a blood test, a urine test, a tissue biopsy, or whatever—that predicts for us that that will happen, or that that will likely happen. I—we need much more of that, and that takes science, to be able to safely predict that, rather than have a situation where, 10 years later, we find out it didn't work, and somebody else didn't develop a product that did work, because they thought this product was there, and there was no market.

This is very important.

I want to correct something—or, not really correct it, but supplement it, and point out that we have approved many drugs for metabolic disorders based on surrogate markers. Many of these are full approvals. There—for example, in phenylketonuria, where we know that the levels of the substance correlate with the clinical response, we've been able to approve those products, based on surrogates, and for many rare cancers, too, where those surrogates exist. But, we need much more science, to move that forward more broadly. And I agree that we can take advantage of that much more.

So, for example, recently we sponsored a TB workshop that is really aimed at trying to develop surrogate markers of response to TB drugs, and the diagnostic tests to measure those responses.

A couple of other examples of how collaborative regulatory science can really help things. FDA's biochemists developed an improved method for complex biochemistry around meningitis vaccines. And this has helped a vaccine that was stalled become a candidate for development to prevent meningitis all over the world, in a partnership supported by PATH, a major nonprofit.

Now, the good news is that, you know, thanks in part to Congress and the administration, our 2011 budget contains the first dedicated funding for FDA to begin to rebuild its scientific infrastructure and develop these kinds of tools. We really appreciate that.

You heard about how Drs. Collins and Hamburg, with all of our support, have announced a new partnership and joint grants in regulatory science, and we're very excited about that. And I think we see that as an avenue where, in the rare disease field, we can make an impact.

This enhanced science needs to inform, also, our review processes and interactions. We've heard a lot about, how can we make that as strong as possible? And we think the scientific backbone there is critical. Strong science is in critical—is critical in supporting an intense interactive review process that we know can help improve product development and the odds for success. And I want to second what others said, that not only are the beneficiaries of success in this product development the patients—and that's what we really care about—but, our economy and the innovation power of this country also—often benefit—also benefits. And that's important.

We want FDA scientists to be able to meet with sponsors early in development. They can identify and resolve critical issues. They can comment on proposed development plans. And these interactions, even though they're labor- and resource-intensive, are really important for rare and neglected diseases.

And one very specific recommendation I want to close with here is that sponsors, developers, our work with TRND at NIH, some of the work with NORD and others, that you come to us early in development. We want to be available. We want to work with you. We want to be sure there's good understanding of the pathways. If there are scientific gaps that need to be filled, we're much better off to identify those and work together with our colleagues at NIH and academia to solve those early, rather than to discover them several years down the line. So, this is very important.

PREPARED STATEMENT

So, in conclusion, we are really committed to doing what we can in this area. We share with you the compelling need and vision and desire to make a difference here.

So, I really appreciate your having this hearing. And we welcome all these suggestions and are going to consider them very carefully.

[The statement follows:]

PREPARED STATEMENT OF DR. JESSE GOODMAN

INTRODUCTION

Good afternoon Chairman Kohl and members of the subcommittee. I am Dr. Jesse L. Goodman, Chief Scientist and Deputy Commissioner for Science and Public Health at the Food and Drug Administration (FDA). I appreciate the opportunity

to be here today to describe the role of FDA in encouraging and speeding the development of drugs, vaccines, and diagnostic tests for rare and neglected diseases.

There are more than 6,000 rare diseases, defined by the Orphan Drug Act as a disease affecting fewer than 200,000 people in the United States, and numerous neglected tropical diseases that predominantly affect impoverished or disenfranchised populations of the developing world. Around the world, more than 1 billion people are affected by at least one neglected tropical disease, such as tuberculosis (TB), malaria, hook worm infection, and leprosy. As a practicing physician and a researcher specializing in infectious diseases and also trained in oncology, I have personally witnessed the devastating human face and social impacts of many of these diseases.

As a physician and a public health official, I want to take this opportunity to remind our Nation that infectious diseases know no boundaries. Threats to health anywhere are threats to everyone. Witness the risks to the United States from multi-drug resistant TB and the disruption that a single infected traveler caused in 2007. In May 2010, the Centers for Disease Control and Prevention (CDC) reported that, for the first time, cases of dengue—the most common mosquito-borne viral disease, causing 50 to 100 million infections and 25,000 deaths each year around the world—were identified in Florida residents who had not traveled overseas. Thus, there are compelling global humanitarian as well as U.S. health and national security reasons to bring the best possible science to bear in protecting against what are often considered "tropical diseases."

Yet, for both rare diseases and diseases that are perceived to affect primarily poor regions and people, market incentives are often lacking to drive the commercial interest and investment critical for developing medical products. In addition, some of the major diseases, such as malaria, TB and HIV, present scientifically formidable challenges in drug and vaccine development. Finally, clinical studies of rare diseases, or of diseases occurring in resource poor environments, are often hard to accomplish. For all of these reasons, the needs and opportunities are enormous and FDA can help make a real difference.

I welcome your shared interest and commitment to this issue and am pleased to be here today to provide you with an overview of our major efforts to enhance the development and availability of products that can improve the lives of those affected by rare and neglected diseases.

THE ORPHAN DRUG ACT AND FDA

The 1983 Orphan Drug Act (ODA) created financial incentives, including grants, for the developers of new drugs for people with rare diseases. Under this system, developers of promising drugs or biologics can, prior to submitting applications for approval of those products, apply to receive "orphan drug status" designation for their products. If products so designated are subsequently shown to be safe and effective and receive marketing approval, the developers receive market exclusivity for 7 years.

FDA Office of Orphan Products Development (OOPD) serves as the contact for all parties interested in making new therapies for people with rare diseases, often providing significant assistance to scientists who may lack product development and regulatory experience. OOPD also fosters new approaches throughout FDA to advance development of therapies for rare diseases. For example, last week OOPD announced the availability of a new tool, the Rare Disease Repurposing Database, which identifies drugs that are deemed promising for rare illnesses and are already approved by FDA for another disease. A novel feature and major advantage of this database is that it focuses on drugs that have already gone through the FDA approval process. Thus, repurposing of these drugs for a new rare disease indication might be attainable quickly, relatively inexpensively, and at great benefit to the patients involved.

ODA has been extremely successful in changing the landscape and success rate of orphan drugs and improving the lives of many patients. Prior to the existence of ODA there were few new products for people with rare diseases, but, since 1983, more than 2,150 medical therapies have been officially designated as "orphans" and 357 of these therapies have gone on to receive full marketing approval. This program also benefits those affected by rare and neglected tropical diseases, as drugs for the treatment of the neglected diseases of the developing world generally also qualify as orphan drugs because most neglected diseases affect fewer than 200,000 persons in the United States.

OOPD's engagement in the area of neglected tropical diseases is exemplified by an ongoing project to stimulate manufacturers to identify and evaluate certain products approved for the treatment of intestinal parasites in veterinary medicine for potential human use.

The FDA Amendments Act of 2007 (FDAAA) granted FDA the authority to award priority review vouchers beginning in 2009 to a company that submits and, after review, receives marketing approval for a product for 1 of 16 neglected "tropical" diseases listed in the legislation. Under the law, developers of treatments for neglected diseases are rewarded with priority review vouchers to be applied to other drugs, such as profitable cardiovascular therapies, that would not otherwise qualify for such an expedited review. For a blockbuster drug, these 4 months of earlier market access could translate into hundreds of millions of dollars. Already, one such voucher has been issued to Novartis, for its anti-malarial drug Coartem. OOPD has informed major human pharmaceutical companies that also own veterinary medicines that appear promising for neglected human diseases that they could qualify for a priority review voucher if evaluation for human disease indications supported marketing approval for 1 of 16 neglected tropical diseases listed in the legislation. It also should be noted that many orphan designated products, other than those for products to treat the 16 identified neglected tropical diseased, qualify for FDA priority review.

ODA has established FDA's largest grants program, $16 million per year, managed by OOPD. Forty-seven products have been found to be safe and effective as a result of data generated in part by those grant monies. The humanitarian use device (HUD) program is another legislative program established in 1990, which creates an alternative pathway for getting market approval for medical devices that help people with rare diseases. For example, the adjustable titanium rib, which for children with thoracic insufficiency syndrome prevents the child's body from collapsing on itself, was a HUD-designated device invented by a pediatric orthopedic surgeon who received an OOPD grant; this surgeon recognized the need for such a device that could be adjusted as a child grows. Also, in 2007 Congress established a system of pediatric device consortia, also administered by OOPD, for creating new medical devices for children.

Along with a rapid expansion in new drugs for people with rare diseases, the 27 years since enactment of ODA have seen remarkable growth in the biotech industry. The incentives offered by ODA motivated investments by biotech firms in products aimed at rare diseases, and the financial success of key biotech companies has further stimulated this sector. Consequently, ODA's fundamental principles have been adopted by many other countries, most notably by the European Medicine's Agency (EMA) in 1999. While FDA remains the world leader in orphan drug regulation, this international expansion of ODA, combined with Internet linkages among patient groups and a pharmaceutical industry without borders, has made global harmonization an important component of the work at OOPD. Accordingly, EMA and FDA now have a joint application form for orphan designation.

FDA EFFORTS TO ENHANCE DEVELOPMENT AND REVIEW OF PRODUCTS TO TREAT RARE DISEASES

Expanding on its commitment to facilitate the development and approval of safe and effective drugs for Americans with rare diseases, in February 2010, FDA created the position of Associate Director for Rare Diseases in the Center for Drug Evaluation and Research (CDER). The activities led by the Associate Director for Rare Diseases complement the work of FDA's OOPD.

The Associate Director for Rare Diseases serves as CDER's focal point within the Center and to the rare disease drug development community and assists stakeholders and developers of drug and biologic products in navigating the complex regulatory requirements for bringing safe and effective treatments to patients in need. In conjunction with OOPD, the Associate Director for Rare Diseases supports collaboration among scientists and clinicians throughout FDA, promoting scientific and regulatory innovations to help facilitate timely development and approval of new treatments for patients with rare diseases.

Since 2008, FDA has sponsored an annual course designed to teach FDA reviewers and other interested clinicians the science of conducting and analyzing small clinical trials, which are especially useful for testing medical products for rare diseases. In October 2010, FDA will co-sponsor the 1st Annual Rare Disease Investigator Training Course, in collaboration with the National Institutes of Health (NIH) and the National Organization for Rare Disorders (NORD). FDA is planning a series of scientific workshops to address important and difficult rare disease research issues and is developing a "rare disease database" to establish the natural history of rare diseases to assist with planning trials to test rare disease therapies. Lastly, FDA is enhancing collaborations to increase transparency, share advice, and establish new programs with several pertinent organizations, including NORD, NIH Office of Rare Diseases Research (ORDR), Therapeutics for Rare and Neglected Dis-

eases Program (TRND), the National Institute of Neurological Disorders and Stroke (NINDS), patient advocacy groups, academia, and the Institute of Medicine (IOM).

FDA is fully committed to applying the requisite flexibility in the development and review of products for rare diseases, while fulfilling its important responsibility to assure that the products are safe and effective for these highly vulnerable populations. There are numerous examples of drugs approved for treating rare diseases where FDA's flexibility and sensitivity to the obstacles of drug development for rare diseases has brought forth a successful treatment. Many of the 357 approved orphan drugs have been successfully tested on extremely limited numbers of patients, serving as a testament to FDA's commitment to these patients. This is possible when the best science is flexibly applied and when therapies are truly effective. Successful examples include:

—*Carbaglu (carglumic acid) for the treatment of NAGS deficiency, the rarest of the Urea Cycle Disorders (UCDs).*—This disease affects fewer than 10 patients in the United States at any given time and fewer than 50 patients worldwide. This drug was approved in March 2010 based on a case series derived from fewer than 20 patients and comparison to a historical control group.

—*VPRIV (velaglucerase) for the treatment of Gaucher disease, a rare genetic disorder.*—This disease affects approximately 2,000 people in the United States and approximately 5,000 worldwide. This drug was approved in February 2010 based on a development program that included about 100 patients and a pivotal study of 25 patients.

—*Myozyme (alglucosidase alfa) for the treatment of the infantile variant, and rapidly fatal, form of Gaucher disease.*—The variant of this disease affects about 1,000 patients in the United States and about 3,000 patients worldwide. This drug was approved in April 2006 based on a clinical development program of fewer than 80 patients and a pivotal study that included 18 patients.

—*Ceprotin (human plasma derived protein C concentrate) for the treatment of severe congenital Protein C deficiency.*—There are fewer than 20 known patients with this disorder in the United States. This biologic drug product was approved in March 2007 based on a study of 18 patients using comparison to historical control data.

FDA RARE AND NEGLECTED DISEASES REVIEW GROUPS

While there have been many successes in the development of products for rare and neglected diseases, because of the remaining needs and great interest on the part of multiple stakeholders, it is timely to examine what more may be possible. With the support of Senator Brownback, Section 740 of the fiscal year 2010 Appropriation Act (Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriation Act, 2010, Public Law 111–80) directs FDA to establish internal review groups to address rare and neglected diseases, to report to Congress 1 year after establishing the review groups and to issue guidance relating to rare and neglected diseases.

To implement section 740, in March 2010, FDA established two new expert working groups, the Rare Disease Review Group and the Neglected Disease Review Group. The Rare Disease Review Group includes 24 expert FDA staff scientists from a broad array of pre-clinical and clinical disciplines. They have been asked to consider how FDA currently evaluates drugs, biologics and medical devices for treating rare diseases and how that process can be optimized. The Neglected Disease Review Group is composed of experts in infectious diseases from all FDA medical product Centers and the Office of the Commissioner. This group is reviewing present FDA guidance and the different local and international programs that encourage development of medical products for these diseases and, similarly, will identify opportunities to enhance FDA's efforts.

These review groups are already active and on track in evaluating current activities and plan to present recommendations to the FDA Commissioner regarding potential options to further support and facilitate the development and evaluation of medical products to prevent, diagnose, and treat rare diseases and neglected diseases of the developing world.

FDA believes public input to be very important in this evaluation and will also be holding meetings for that purpose. A meeting on rare diseases is scheduled for June 29 and 30, 2010, and 26 speakers are already signed up to provide comments. Another Part 15 hearing, to allow FDA to seek public input on the challenges and possible solutions encouraging development of products for neglected tropical diseases, is planned for September 2010. Finally, FDA and NIH are co-sponsoring an IOM study, begun in the fall of 2009, to review national policy for rare disease research and related medical product regulation. The results and recommendations of

that study are due at the end of September 2010, and FDA review groups will consider the IOM study findings in their ongoing work.

Based on the Working Groups' deliberations, and the input we receive from stakeholders, I look forward to issuing a report to Congress, as well as development and issuance of guidance, and taking whatever further steps are feasible to enhance these programs.

THE ROLE OF REGULATORY SCIENCE

Researchers have now defined the genetic basis of more than 2,000 rare diseases and identified potential drug targets for many rare and neglected diseases. However, a large gap exists between advances in basic scientific research and applied product development and evaluation research, a gap that is reflected in the lack of real products getting to patients for many such diseases, despite advances in basic sciences. FDA is launching a new regulatory science initiative to help bridge this gap and to facilitate development and availability of safe and effective products to meet public health needs.

Regulatory science is the development of new tools, methods, assays, standards, and models that help speed and improve the development, review, and approval of innovative products. These tools, and better improved evaluation methods, are particularly critical for facilitating development of products for which commercial incentives may be weak or uncertain, or where scientific complexities in evaluating product effectiveness are major challenges. Examples relevant to our hearing today include the need for better, faster ways, including biomarkers and novel clinical trial designs, to predict and monitor effectiveness of treatments both for rare diseases and for many neglected tropical diseases, such as TB.

With this regulatory science initiative, FDA seeks to rebuild its critical scientific infrastructure and capacity to leverage the opportunities provided by 21st century science and to enhance its scientific collaborations. Through collaboration, FDA will foster new opportunities for patients and consumers. One recent example of a collaborative success involved the work of FDA biochemists to help improve a complex vaccine manufacturing process and making the information available to collaborators engaged with PATH, a major international non-profit organization, in developing new meningitis vaccines for the developing world.

Investments in regulatory science will allow FDA to develop standards for products employing new and emerging technologies, modernize the standards for evaluating existing products, and accelerate the development of essential medical therapies, while at the same time assuring the new products are safe and effective. FDA's initiative to advance regulatory science seeks to improve efficiency of clinical trials, speed product development, and reduce attrition rates of products under development. In February 2010, FDA and NIH announced a new collaboration on regulatory and translational science to help speed the translation of research into medical products and therapies, and we see real opportunities in working together to help move promising therapies for rare and neglected diseases from concepts to realities.

Enhanced regulatory science at FDA also is intended to inform and strengthen our review processes and interactions. Strong science, whether lab based, clinical or involving population and statistical sciences, is critical in supporting the kind of intensely interactive review processes that we know can improve the odds of success in product development. This is particularly for diseases where experience is limited or to support product developers with more limited experience. FDA scientists can meet with sponsors early in product development, even before human studies are planned, to help identify and resolve critical issues and provide input on proposed development plans. Such meetings, and continued high quality scientific interactions, while labor intensive, are particularly critical in identifying and resolving scientific issues with respect to products for rare and neglected diseases.

Tuberculosis—A Case Study

The World Health Organization (WHO) estimates that one in three people in the world is infected with latent, or dormant, tuberculosis bacteria that can become active as a result of a weakened or senescent immune system. Today, there are no simple, rapid and accurate tests to diagnose tuberculosis. This gap impedes timely detection and treatment of this contagious, and too often deadly, infectious disease.

The conference report for the fiscal year 2010 Appropriations Act directs that not less than $6,000,000 be used for FDA Critical Path Partnerships. $2,000,000 of this appropriation is to support research partnerships encouraging the development of treatments or rapid diagnostic tests for tropical diseases, with an emphasis on tuberculosis.

On June 7 and 8, 2009, FDA hosted a TB diagnostics workshop, in collaboration with the CDC and NIH. The workshop identified scientific gaps in the TB diagnostic armamentarium, opportunities to harness new technologies, and the feasibility of prospectively collecting specimens from patients participating in TB trials to support the development of new diagnostic tests. The workshop was attended by approximately 150 registrants from government, academia, industry, and non-profit organizations, both from the United States and overseas. The workshop laid the groundwork for interagency collaboration on programs for developing TB diagnostic tests and for establishing a repository of specimens from participants in TB clinical trials. This repository may serve to identify biomarkers that can expedite future clinical trials.

FDA established a TB cross-center working group to recommend priority areas for TB medical product development. As a result of this effort, FDA will soon publish a Request for Applications (RFA) soliciting proposals from outside scientists for collaborative initiatives to address areas of need in the treatment, diagnosis, and prevention of TB and other tropical diseases.

FDA is also collaborating with the Clinical Data Interchange Standards Consortium (CDISC). This consortium is working to develop uniform data collection standards to be used in clinical trials for tuberculosis. This type of collaborative effort is critical to facilitate the collection of standardized clinical data and expedite TB drug development.

FDA COLLABORATION WITH THE WORLD HEALTH ORGANIZATION (WHO) ON VACCINES FOR RARE AND NEGLECTED DISEASES

FDA recognizes the tremendous unmet need to engage globally in an effort to assist other regions and nations in assessing vaccines for approval by their governments and in helping to ensure their quality and safety. Further, FDA recognizes the need to develop new innovative regulatory pathways for candidate vaccines for global diseases to reach developing countries.

FDA has traditionally worked with manufacturers to approve vaccines for the U.S. population. However, new paradigms of vaccine development supported by the Gates Foundation and other initiatives, along with an increase in regulatory submissions to FDA for global vaccines—to prevent or treat diseases often endemic outside the United States—have provided an impetus for the development of new regulatory strategies at FDA. In 2008, FDA issued guidance on the development of vaccines to protect against global infectious diseases. The guidance was extremely well received by the global health community.

A core component of FDA's efforts in this regard is its commitment to support and complement the efforts of the WHO. FDA's contribution to the WHO vaccine quality and safety goals is long-standing and was formalized in 1998 with its designation as a Pan American Health Organization (PAHO)/WHO Collaborating Center for Biological Standardization. In recent years, FDA's support has grown beyond the routine collaboration of providing expert input to WHO consultations and laboratory collaborations for international reference standards. FDA now is an active partner with the WHO in its vaccine prequalification program and its efforts to build regulatory capacity in developing countries.

The WHO Vaccine Prequalification Program

The vaccine prequalification program is a service provided by WHO to United Nations (U.N.) agencies that purchase vaccines, providing independent guidance and advice to the United Nations on the quality, safety, and efficacy of vaccines being considered for purchase. This assistance helps to ensure that each vaccine under consideration is suitable for target populations and complies with established standards of quality. In 2007, WHO designated FDA as a "reference" national regulatory authority (NRA) for WHO prequalified vaccines. In 2008, FDA and WHO signed confidentiality agreements specific to communications that would be undertaken in the context of the WHO vaccine prequalification process. Currently, CBER is the referenced NRA for a total of seven U.S. licensed vaccines.[1]

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[1] Rotavirus Vaccine, Live, Oral, Pentavalent (Tradename: RotaTeq®); Prequalified October 7, 2008;
Influenza Virus Vaccine (Tradename: Fluvirin®); Prequalified December 4, 2009;
Influenza A (H1N1) 2009 Monovalent (No tradename; Manufacturer: Novartis Vaccines and Diagnostics Limited), Prequalified by WHO December 9, 2009;
Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Tradename: Prevnar®), Prequalified by WHO December 28, 2009;
Influenza Virus Vaccine (Tradename: Fluzone®), Prequalified January 21, 2010;

Continued

Building the Requisite Regulatory Capacity in the Developing World

CBER provides support to several WHO regional vaccine networks to enhance scientific and regulatory capacity needed to assure the development of high quality vaccines. Specifically, CBER actively engages with the WHO Developing Country Vaccine Regulator Network (DCVRN), a WHO-funded network of NRAs from Brazil, China, Cuba, South Korea, India, Indonesia, the Russian Federation, South Africa, and Thailand. The DCVRN builds regulatory capacity among vaccine-producing developing countries through information sharing, training, and mentoring activities. Representatives from member DCVRN countries meet on a biannual basis to gain timely information from independent experts and developers on specific issues relating to vaccine trials occurring in developing countries and to develop institutional plans and other activities that aim to strengthen regulatory capacity.

CBER also provides expert input to the WHO African Vaccine Regulatory Forum (AVAREF). WHO coordinates this forum in conjunction with the WHO African Regional Office to assist in defining the role of NRAs of African nations in regulating clinical trials of vaccines, in interactions with national and local IRBs and ethical committees and in strengthening the capacity of the NRAs to regulate new products. In this capacity, FDA participates as expert advisors, in particular sharing the regulatory mechanisms used to evaluate the safety and efficacy of investigative products.

CONCLUSION

FDA is fully committed to doing all we can to help facilitate the availability of safe and effective therapies to patients in need. FDA has an ongoing broad range of vibrant programs to facilitate the development and improve access to medical products to treat and prevent rare and neglected diseases, and these activities have helped benefit people in our country and globally. Advances in regulatory science offer tremendous promise to improve product evaluation and translation of advances in basic science to products that can benefit people in the United States and globally. Thank you again for this opportunity to discuss rare and neglected diseases. I welcome your comments and questions.

ADDRESSING TRND DELAY

Senator BROWNBACK. Thank you, Dr. Goodman.

I want to thank the panel. And please express my appreciation, to all the heads of your organizations, for your interest and your focus on this issue. I've been working in this space for 5, 6 years now, and I've not seen any collaborative effort near this degree. So, I'm deeply appreciative of that.

Having said that, I'm frustrated, because I've been working in this space for 5 or 6 years, and I'm kind of, "All right. Where's the product, here?" I appreciated, Dr. Austin, your statement about a couple of products that you're seeing coming through the TRND process. I had hoped there would be a lot more.

If I could just have a blunt conversation with you and I appreciate, really, what everybody is doing, and I think it's very important, and there's a lot that's going on, but it seems like we just haven't either been able to get the market signals right, or the regulatory approval process right, or maybe it's just too complicated, or the science isn't there. But, we did the priority approval process bill, Senator Brown and I did, and Washington Post did an article and said that the program's been rarely used. It's out there. It's tempted some people to look at these diseases. But, it hasn't been used that much. We've had accelerated approval process in some fields, but it hasn't been used much, or it hasn't tempted many people.

Influenza A (H1N1) 2009 Monovalent (No tradename; Manufacturer: Sanofi Pasteur, Inc.), Prequalified January 27, 2010; and

Influenza A (H1N1) 2009 monovalent (No tradename; Manufacturer: MedImmune LLC), Prequalified February 25, 2010.

And I get frustrated, in that I remember our early days in the AIDS crisis, and people just said, "Look, we have got to get on top of this." And we threw everything at it and moved forward. And people are alive today because we did that. It doesn't seem like we're getting there yet with rare and neglected diseases. Now, maybe this more recent collaborative effort will work.

But, I wonder if you, Dr. Goodman, did a scientific internal review, and you said, "We're going to put a matrix together of the number of people impacted by a particular disease, and the likelihood of us getting a success based on what we know today, technology-wise, about a particular set of drugs and we're going to take the top 100 of the 7,000 that are here, and we're going to quarterback a process to get a drug approved in this area, not just as a regulator, but we're going to quarterback the process. And we're picking the top 100 with potential success." We've got to be able to have a reasonable prospect of getting a product through. And it affects a whole bunch of people. And then, you say "We're going to go out and shop for the team to develop this product. We're going to go to the University of Kansas Pharmacy School, and say, 'We want your vast throughput process.' We're going to go to Gates Foundation and say, 'We want you to put some money into this one.' We're going to go to the scientists at the University of Washington that know his field, and have been working on it and we're going to tell them, 'Look, we're going to put you in the priority approval process. We're going to court our friends at AID to put a little money behind you. Not going to put a lot of money behind you, because we don't have a lot of money. But, we're going to put a little money behind you, and we are going to do everything we can to move this product through.'"

"Now, I'm a regulator. I don't work this way, normally. What's in my in basket is what I take."

I'm not saying you do that but I used to run a regulatory agency, and it's generally what comes in your in basket is what you deal with.

"But, I'm out here on these hundred products, because I think we can really move this forward."

What about doing that sort of quarterbacking process, by FDA or NIH? But, it does seem like, to me, FDA is the place that that would prove to do that.

Dr. GOODMAN. Well, I think it's a very good vision, in many ways. You know, I want to comment on it, specifically, and provide some perspectives, and, again, back up to the big picture.

I think that, for things to work—you know, I give talks, and I say that, you know, really the product development and achieving health—you know, not just for rare diseases; for anything—were—it takes many, many people, and it's a very complex system. So, it really is about bringing people together, and bringing the best people together in multiple different domains. So, I think you've really hit on something there, with the team approach. And this is the kind of thing where, you know, I think in our partnership with NIH, we can help broker that.

I do want to say that there is a huge issue around what people see as the markets are, because, you know, even if you have very targeted and effective product development, it does cost real

money, and people will expect a return on investment. So, that economic issue you've identified—and try to tackle in some of the ways you've mentioned—is a real issue, and there may need to be other inputs in that domain to help drive it.

But, given all that, I think having teams work together—and both within the FDA, and with others—on things that are high-priority and offer real promise for health benefit, is a very good approach. And that's what we are working toward with NIH. And you heard about some of the collaborations with NORD and others.

And that's also—now, what I did want to say is, you know, recently—and I mentioned, right before the hearing, I've been involved as FDA's point person, both for our pandemic response and preparedness, and then in our review of the medical countermeasure enterprise of the United States for the Secretary and for the President. And what we've seen there is, on the positive, what people talking—working together across the agencies, partnering with industry in many cases, could achieve, in terms of, even though we have a long way to go, advancing our pandemic preparedness and response, such as was done. That took investment, but it also took the kind of partnerships and teamwork you described. And I believe those models can be applied.

One of the things, in discussing the countermeasure enterprise that also has been attractive, is this kind of working together and bringing all the resources together from diverse places around our highest public health goals.

So, I think the principle is a very good one. It does take investment. It does take commitment by leadership. And it does take diverse organizations, with different cultures, as you point out, that are used to doing *x*, *y*, or *z*, to say, "What we're really focusing on here is the outcome."

The good news, and the reason I think you're seeing what you're seeing in this room in the last couple years, that you commented on, is because there is leadership and culture within many of our organizations, and people who really do care, around—about the outcome.

So, I think we're well positioned to work together to change how we do this. And that's needed. But, I would not underestimate some of the challenges.

ROLE OF FDA

Senator BROWNBACK. With FDA quarterbacking the process? I don't want to give somebody leadership, if you guys have worked it out internally, but it sure seems like——

Dr. GOODMAN. I think that this may differ, for a lot of different situations. And I would—one thing I would comment about the role of FDA, for both the American public and everyone—it's also very important that people know that we are also there to do this very important, unique job, which is, at the end of the day, to look very carefully at this and be sure it's safe for people, it's well made, and that——

Senator BROWNBACK. But, you——

Dr. GOODMAN. You know, we say, sometimes, there's a thin line between hype and hope.

CHALLENGES

Senator BROWNBACK. I agree. But, your ability to identify areas to work on——

Dr. GOODMAN. Yeah.

Senator BROWNBACK [continuing]. And to tempt companies and other entities to put money into something, if the FDA says, "We'd really like a product in this field. And it looks to us, after surveying the scientific field and NIH and AID and everybody else, that there's a real prospect here," I wouldn't discount the possibilities of that really tempting money from private groups, private companies, and other governmental entities, saying, "You know, if FDA is sending that kind of signal, and they're saying, 'We're not going to approve something that's not good and doesn't meet our scientific rigors.'" You say that at the outset, "But, having said that, we think there's a real prospect here." I wouldn't discount the ability of a regulator to tempt the marketplace to respond.

Dr. GOODMAN. Well, and I think one thing—I—you know, and I think that's even more powerful when it's together with our entire——

Senator BROWNBACK. Sure.

Dr. GOODMAN [continuing]. Public health and health enterprise.

Senator BROWNBACK. Yeah.

Dr. GOODMAN. You know, I was going to say, one area where we can really help is say that, in these high-priority areas—and I'm saying it today about rare diseases, and you—we're meaning it, within the ability of our resources, by—you know, seeing Dr. Cote and Dr. Pariser here—we are saying this is a priority. And one area where FDA can help is to try to do what we can to have the best evaluation process to identify challenges, and work with people to resolve them in a very interactive way. So, I think—and that does start—it has to start earlier on, as I said. And, in that sense, bringing teams like this together earlier on is a good thing.

I think it's a great model. I also think, honestly—you know, think about people with common diseases, you know——

Senator BROWNBACK. Yeah.

Dr. GOODMAN [continuing]. Diabetes and——

Senator BROWNBACK. Yeah.

RESOURCE CONSTRAINTS

Dr. GOODMAN. You know, there's a lot we can bring to bear there, too. And one of the things—again, this is a key part of our Regulatory Science Initiative—one of the things we do uniquely see—the gap between the basic science and what it takes to have a product that people can make and consistently give people and help people. So, we can really work with NIH and academic investigators and small companies, you know, to help them cross that space and identify issues.

And, frankly, we also see the development of our scientists and review staff, such as Dr. Kakkis mentioned, as an important thing in that space, because, by our people interacting with people innovating in the newest technology, it benefits our capacity, too.

So, we're very supportive of this. We just have to be very careful about the—protecting the integrity of the FDA role. And we're also

very—we also are limited—you know, even though we have tremendous resources—and, frankly, we really appreciate it, and we recognize all the constraints, you know, on the Federal budget, et cetera—we are constrained by our resources, in terms of how much we can do.

NIH COLLABORATION

Senator BROWNBACK. Dr. Austin, you've heard the conversation here. Do you have any technical response or thoughts to it?

Dr. AUSTIN. Yeah, I appreciate the opportunity to comment on that. And I loved your term, "quarterbacking the process," because, as a matter of fact, when I talk about this, I frequently refer to it as a football game, actually. And so, let me explain what I mean by that. There are two things.

One is that drug development, particularly for these diseases, is a team sport. And one of the things that holds back development is the fact that science is culturally, for the most part, a game of golf. It's viewed—scientists are viewed as sort of rugged individualists who work alone and they need to—and that's the model of basic research. And it's appropriate for basic research. But, you can't do drug development that way. So, one of the things that we're doing within NIH, which is a cultural battle which we're waging and I think we're having some success on, is getting people used to the idea that, yes, you need a quarterback, but you also need a wide receiver and you need some blockers. You need people who are excellent in their own fields, but can bring expertise, if you're going to score a touchdown.

The second way it's relevant is that—if we think about the journey from a gene to a drug as a football field, which is actually how I think about it and how I talk about it, the traditional handoff from the public sector to the private sector was on about the 5-yard line. Right? So, the public sector would discover a gene, put it out there, and the private sector would do everything else. Now, you must not have used that analogy, if you didn't know football well enough to know that if you take possession on the 5-yard line, the likelihood of your scoring is very low. So, what NIH started doing, about 6, 7 years ago, was a process of going from a target to about the 30-yard line. So, now we take it further down the field through something called the Molecular Libraries Program and some other programs that NIH has.

TRND is going from about the 30-yard line to about the 40-yard line on the other side of the field. And so, when we hand off from the public sector to the private sector, the private sector says, "Huh. I can see my way though here. The defense is still pretty strong, but my special return team has made my likelihood of scoring good enough that now I'm going to pick this up. I'm going to take a risk on this that I'm going to be able to score." And so, that's really the direction that NIH has been going in.

Fundamentally, trying to attract private-sector organizations to this area is strictly a business question.

Senator BROWNBACK. Right.

Dr. AUSTIN [continuing]. And it makes great sense, from their standpoint, that, if you have something which is very expensive, and it has a 99 percent failure rate, it's hard to argue to your board

that that's what you ought to use their shareholders' dollars to do. And so, if you want to attract partners, and particularly for a disorder where you have low return on investment, you have to have a lower investment requirement. And so, what that means is, someone else has to do more of the work to carry the football down further down the field to de-risk that program—and that's probably a term that you've heard to "de-risk" the program enough that it can be picked up, with reasonable certainty of having a return on investment, even if the population is small. And so, that's the sort of role that NIH is seeking.

TRND QUARTERBACKING METHODOLOGY

I think the last thing to say is that TRND is a quarterbacking initiative. That is exactly the model of TRND. We will bring in projects, and TRND people will drive the project. And we're doing that already. And our collaborators, whether they would be in a biotech or an academic organization or a foundation, they rely on us for the quarterbacking, which we call "project management." But, it's exactly the point that you're saying, because you can't score a touchdown without a quarterback and a coach. And so, that's exactly the model.

REVIEW GROUPS

Senator BROWNBACK. It's my hope we can move this process on forward, and in doing that, target this. I think just, maybe because of the randomness that we've placed on this issue previously, that it would be helpful and probably tempt more money out of the private sector if we were more targeted, where we were out there saying, "We really would like something in this area."

You're going to start, the next few days the public meetings that we had set up, in this subcommittee a year ago, on rare and neglected diseases. Do you want to update me on that, Dr. Goodman, where that's set to go—

Dr. GOODMAN. The review groups——

Senator BROWNBACK. Yes.

Dr. GOODMAN [continuing]. And their activities?

Senator BROWNBACK. Yes. You and Dr. Austin are both——

Dr. GOODMAN. They've all met. The review groups have met multiple times. They are collecting information and ideas internally. They have these plans for, as you've heard, external information-gathering. Folks are also meeting groups and appropriate, you know, partners, as well. And so, this process is ongoing. We're looking forward to looking—getting all these ideas and putting together some options and—as well as taking information from our colleagues here, and providing ideas to Dr. Hamburg for consideration. So, this is—people are very engaged and excited about it.

Senator BROWNBACK. I hope you'll be willing to come to the Congress if there's statutory authority that's needed by you, NIH, AID, others, and tell us how we move this process forward.

Dr. GOODMAN. Absolutely.

Yeah. And we're always happy to work with you and your staff to provide assistance on ideas that you have and put forward.

Senator BROWNBACK. Ms. Steele, I haven't engaged you as much in this, as I wanted to get honed in right at FDA on it. Anything that you'd——

Ms. STEELE. Well——

Senator BROWNBACK [continuing]. Like to add?

Ms. STEELE [continuing]. I can't speak football-speak. And I did go to school where football—we tried very hard to do well in football. But, I did want to speak as an——

Senator BROWNBACK. Now, you're not speaking of Kansas State University, here, are you?

Ms. STEELE. I was talking about University of Wisconsin.

Senator BROWNBACK. Oh, okay. All right. There you go. That's better.

Ms. STEELE. I do want to go back to the—a key issue here, which is the economics. And I think that if we look more—look at it more broadly and provide incentives beyond—where the costs are lower—for instance, offshore companies that could produce—if our interest is in addressing the issue and making drugs available at a more affordable cost, then maybe we should look beyond our shores and see where pharmaceutical companies can develop the drugs at a less expensive cost, and therefore make it more accessible, still realizing, of course, that a very strict regulatory system is necessary.

The other thing I think is, we need to take a look at more innovative ways of financing this. I just want to—in the health sector, and particularly in the area of immunization and vaccines for childhood diseases, we have—under GAVI, for instance, other donors have come together to look at ways where they could support the marketing and the shaping of the markets for drugs and vaccines so that they become more affordable to the countries where we need to get them delivered; assuring markets for some of the drug companies, for instance, for a certain period of time, to give them an incentive to produce; and also—and making them committed with us to address some of the issues.

I think we should really look at a key issue, which is the economics of—you know, FDA and NIH can do all the work they can, but if the drug companies do not step in and deliver for us, it'll continue to be a major challenge.

Senator BROWNBACK. Ms. Steele, may I ask you, you know, in your position with AID, and your working with so many developing countries around the world, it would seem to me to be a valuable thing if you surveyed some of the countries you work with the most, and asked them what drug development would be the highest priority—or, what 10 would be the highest priority for them—because you're out there—I've been with many AID——

Ms. STEELE. Yes.

Senator BROWNBACK [continuing]. People in the field. They're always out there trying to work within the space that they're in to help out as much as possible. But, I wonder if you've surveyed some of the countries and places you're working, and ask them for the top 10 priorities that they had, if that would be an interesting piece of data to feed back into the system.

Ms. STEELE. That's absolutely one of the most important things. And, again, under the GHI, making it a country-led approach——

Senator BROWNBACK. Right.

Ms. STEELE [continuing]. So that they will own the processes that drives the vaccines that we come up with, and help us deliver them, looking at what their priorities are—What are the most important things? And then, you know, a company—we are also working with local organizations, NGOs, to make them understand what each of the diseases mean and what it—how it impacts their social and economic progress. And so, its effect—you know, looking at their priorities, but also, informing them, as they develop what their priorities are, and making sure they understand what the implications are, as they make decisions about where they put their resources.

Senator BROWNBACK. So, on how they might be willing to invest their dollars——

Ms. STEELE. That's right.

Senator BROWNBACK [continuing]. To help out. So, it's not just us putting funding in——

Ms. STEELE. That's——

Senator BROWNBACK [continuing]. But it's them investing some themselves.

Ms. STEELE. That's exactly right. In—for instance, in the Global Alliance for Vaccine and Immunization, one of the things that we have done is get proposals from the countries, but also ask them to cofinance.

Senator BROWNBACK. Yeah.

Ms. STEELE. You know——

Senator BROWNBACK. Absolutely.

Ms. STEELE [continuing]. Because it's really important for them to own this process. And we're not going to be there forever, but for them to understand, this is important for them, as well as for the global community, as a whole.

Senator BROWNBACK. Thank you.

Dr. Goodman?

Dr. GOODMAN. Yeah, I was very stimulated by some of the points, to make a couple of additions here.

You know, one is that I think, both in this domain, but more generally, it will benefit health if we can actually reduce the cost of development of these products. And I think there's a whole science around that, again, that, you know, we think FDA can really be helpful with, because we see what works and what doesn't. We see where a lot of costs are built in. And I think we can work with people, including with industry, to do that. And I think industry is realizing there need to be some new models—the small clinical trials, personalized medicine; those are domains where we ought to be able to both improve outcomes and reduce costs. You know, maybe sometimes we can actually do that.

The other comment I was going to make is, people—even though we focus on medical products at FDA, and it's tremendous that everybody's engaged in trying to develop these products, certainly once you get out of this country into developing nations, and—you know, often, our—the priorities of people, and people who care about *x* disease and *y* disease, may be very different from the priorities in those countries. So, it's very important to recognize that, you know, if—people may have much more pressing priorities at

that time, or they may not have a delivery system or a public health system. So, I think the Global Health Initiative, efforts of USAID to not just treat medical interventions in isolation, are very important. And certainly, even in this country, we have issues with people getting access, you know, to the care they need.

And the other thing I was, finally, going to say is, in terms of the team we're talking about that can work—you know, and there could be many different people driving it, or quarterbacks—in some cases, industry does see economic markets. I mean, they have developed some products for rare diseases, some of which are quite profitable, in fact. But, in all of these cases, to bring benefits to people—and certainly in these partnerships involving government, nonprofit, et cetera—you know, I think it is very important that FDA and FDA scientists be there at an early time point, because we often will know—you know, an investigator could be the—I mean, because, I was in academia before, and you could be the world's expert in infection A or B or—and, as you heard, not really have a clear concept of what it takes to show that something could work in people, to investigate whether it's going to be safe, to be able to then manufacture it. The kind of pilot programs we've heard at NIH can help with that, but it's—we really want to offer, to the ability we can, our engagement throughout that process, because we can often identify much better-defined early, if there's a problem, in terms of the cost of development, or where we've seen a good solution, to bring that to bear and help share it, like some of the examples I mentioned.

So, we really do want to be able to do that.

Senator BROWNBACK. Well, I want to thank the panel.

It's my hope that, in the future, when the good Samaritan story is told, it's the United States that's the one that stops and helps. And I think we can. I think the people that are here that have a good heart are willing to do that. So I hope we can move forward with this process, and really develop some of these products that can make a life-and-death difference for a whole bunch of different people.

I thank you very much.

The hearing record will remain open the requisite amount of time, if there are additional statements that you want to put into the record for use.

All my best, and Godspeed to this process, because we really need some solutions.

CONCLUSION OF HEARING

The hearing is recessed.

[Whereupon, at 3:39 p.m., Wednesday, June 23, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

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