

**TREATING RARE AND NEGLECTED PEDIATRIC  
DISEASES: PROMOTING THE DEVELOPMENT  
OF NEW TREATMENTS AND CURES**

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**HEARING**  
OF THE  
**COMMITTEE ON HEALTH, EDUCATION,  
LABOR, AND PENSIONS**  
**UNITED STATES SENATE**  
**ONE HUNDRED ELEVENTH CONGRESS**

SECOND SESSION

ON

EXAMINING TREATING RARE AND NEGLECTED PEDIATRIC DISEASES,  
FOCUSING ON PROMOTING THE DEVELOPMENT OF NEW TREAT-  
MENTS AND CURES

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JULY 21, 2010  
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Printed for the use of the Committee on Health, Education, Labor, and Pensions



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U.S. GOVERNMENT PRINTING OFFICE

76-592 PDF

WASHINGTON : 2012

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**WEDNESDAY, JULY 21, 2010**

U.S. SENATE,  
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,  
*Washington, DC.*

The committee met, pursuant to notice, at 10:03 a.m. in room SD-430, Dirksen Senate Office Building, Hon. Tom Harkin, chairman of the committee, presiding.

Present: Senators Harkin, Dodd, Sanders, Brown, Casey, Franken, and Enzi.

OPENING STATEMENT OF SENATOR HARKIN

The CHAIRMAN. The Committee on Health, Education, Labor, and Pensions will come to order.

Good morning, everyone. We meet today to discuss a profoundly important issue: the lack of effective treatments for rare and neglected diseases. Over the years, Congress has devoted extraordinary sums for research into major diseases that afflict millions of Americans. Mostly this goes through the National Institutes of Health. Some, not an insignificant amount, goes through the Department of Defense. But, we've been less generous, and less successful, in mobilizing the research community to come up with therapies and cures for rare and neglected diseases.

In the United States, rare diseases are defined as those that affect fewer than 200,000 people. According to the National Institutes of Health, there are nearly 7,000 rare diseases, affecting more than 25 million Americans. Yet, there are FDA-approved treatments for only as few as 200 of these diseases. And many of them afflict the most vulnerable members of our population, including children, and their effects can be profound.

I know that there are several people, who are in the audience today, living with different diseases. I thank you for being here today to bear witness to what we need to do here, in terms of getting better, and more, research into this area.

In addition to the rare diseases, the World Health Organization estimates that, beyond our borders, over a billion people suffer from one or more neglected tropical diseases. These are a group of parasitic and bacterial infections. They ravage the poorest populations in the world, and they disproportionately affect children.

The conventional wisdom is that these diseases are ignored by drug and device companies because there are inadequate market

incentives for engaging in the costly process of developing products for FDA approval. Our discussion this morning will explore the accuracy of that belief and what can be done to improve the current situation.

Of course, in 1983, we passed the Orphan Drug Act, which provides certain tax benefits and market exclusivity for developing medicines to treat rare diseases. And in 2007, Congress added a tropical disease provision to the Federal Food, Drug, and Cosmetic Act.

Most recently, Congress directed the FDA to convene a working group to recommend appropriate trial design and regulatory paradigms to optimize prevention and treatment of rare and tropical diseases. That working group convened in March, and we're supposed to have a report from them by March 2011.

And I'm also heartened that the Department of Health and Human Services is taking steps on its own to try to address this challenge. The Center for Disease Control and Prevention is working with the World Health Organization on combating certain neglected tropical diseases. In addition, the FDA recently created an Office of Rare Diseases, in its Center for Drugs, to assist sponsors in navigating the Agency's clinical trial and approval requirements.

All of these steps seem to be moving in the right direction. But, today we'll hear from witnesses, inside and outside government, who are confronting this crisis on the front lines.

We'll have two panels. The first, from the Department of Health and Human Services, the second will be from our nongovernment witnesses. Each has a different perspective to share.

Regrettably—I think I can speak for Senator Dodd—both of us will have to leave about 10:30 to go down to the White House for a signing ceremony. Senator Brown, who has been one of the great champions in the Senate, and certainly on this committee, of focusing on rare and neglected diseases, will take over the chairmanship at that time. He has been an outspoken voice, an advocate, for these rare diseases.

And with that, I want to thank our former chair and Ranking Member, Senator Enzi, for his interest over a long time in this area, and will recognize him for an opening statement.

#### STATEMENT OF SENATOR ENZI

Senator ENZI. Thank you, Mr. Chairman. I want to thank you for calling the hearing on this important issue of rare and neglected diseases, focusing on rare pediatric diseases.

The Food and Drug Administration defines a "rare disease" as one that affects fewer than 200,000 Americans. Nearly half of rare diseases affect fewer than 25,000 people. According to the National Institutes of Health, there are about 6,800 rare diseases affecting 25 to 30 million people, total. Most of these conditions have no treatment or cure, and companies are unlikely to undertake the expensive, lengthy, and difficult research to develop a drug if they can't recoup their investment in such a small market.

In 1983, Congress enacted the Orphan Drug Act to overcome these obstacles and encourage the discovery and development of treatments for rare diseases. The Orphan Drug Act includes: tax

credits for up to 50 percent of the costs of research to develop the product; grants to assist with the costs of clinical testing expenses; a 7-year period of market exclusivity for the orphan indication, after approval of the orphan product; and waivers of FDA application fees and annual product fees. Since its enactment, there have been over 300 orphan products approved by the FDA.

The Orphan Drug Act is not the only mechanism to address rare diseases and conditions. Many diseases that occur in children are less common than in adults. Pediatric diseases face the same market disincentives that apply to other rare diseases. Treating children also creates unique issues because of their size, their metabolic rate, and their growth.

Over the past decade, Congress has provided a number of incentives to overcome these obstacles and develop better treatments for children. Because of these incentives, we know how kids respond to drugs like ADHD, asthma, arthritis, depression, diabetes, epilepsy, hepatitis, HIV/AIDS, hypertension, influenza, kidney transplants, leukemia and other cancers, malaria, obesity, OCD, pain, seizures, and many other conditions.

Three years ago, Congress passed the Food and Drug Administration Amendments Act, which included a number of important measures to encourage the development of treatments for rare, neglected, and pediatric diseases. We're beginning to see the effects of that work, and I hope we can continue to build on those achievements so that we can have a similarly successful reauthorization in 2012. This hearing will help us understand where there may still be barriers to success, and how we might lower those barriers.

The 2007 FDA overhaul also established an innovative incentive system for the development of treatments for certain diseases that affect global populations that otherwise might not have sufficient market incentives. These products can be rewarded with a voucher for priority review of a drug. The voucher can be used for another product, or even sold to another company. This sort of creative thinking is very helpful to the debate. We must continue our commitments to the continued development of these products.

We've also made investments in research in the area of rare and neglected diseases through the National Institutes of Health. The Office of Rare Disease Research, established in 1993, has the mission of coordinating NIH activities to ensure our Nation's biomedical research investments do not overlook the importance of investments in rare and neglected diseases.

In 2009, Congress mandated the office establish the Therapeutics for Rare and Neglected Diseases, or TRNDs, to encourage and spend the development of new drugs—speed the development of new drugs for rare and neglected diseases. Congress appropriated \$24 million for the initiative. The goal of the program is to reduce the risk associated with developing drugs for rare and neglected diseases to meet FDA requirements for an investigational new drug application. Once the drug is ready to be licensed, the NIH will work with industry to find a partner to continue clinical development.

I hope to hear from Dr. Guttmacher today about the Agency's activities through the TRND program, and about other innovative ap-

proaches to increasing investments in rare and neglected diseases, like the Bench-to-Bedside Program.

I would also note that this topic brings up an important point about how we allocate funding for the NIH. We worked tirelessly to pass the NIH Reform Act to end a funding structure that targeted specific diseases in response to political, rather than scientific, reasons. The funding should be directed toward research grants that are based on scientific merit, not popularity. If it was based on popularity, probably the Senate would put all the money into prostate cancer.

[Laughter.]

A strategy for determining how NIH funding should be allocated is certainly necessary, but tying funds to specific diseases will only tie the hands of the Agency and prevent the scientists from innovating and conducting research in areas that could benefit a multitude of diseases and conditions. This is directly related to the topic of our hearing today. If a “rare disease” is defined as impacting less than 200,000 individuals, then we’re talking about groups that have significantly smaller lobbying force to request increases in funding, which is not a fair or scientific process for determining funding allocations. We should continue in our practice of providing funding to the Institutes and allowing the scientists to determine which grants have scientific merit to receive funding, and not impose strict funding requirements that are based on successful lobbying by advocates for a specific disease.

I’d like to thank Senators Alexander, Dodd, and Brown for their tireless work on pediatric and rare and neglected disease issues.

I have some statements here from outside groups, and I ask unanimous consent that they be entered in the record. One of them is from venture capitalists, which was kind of a surprise.

But, I look forward to the testimony today.

[The information referred to may be found in Additional Material.]

The CHAIRMAN. Thank you very much, Senator Enzi.  
Senator Dodd.

#### STATEMENT OF SENATOR DODD

Senator DODD. Thank you very much, Mr. Chairman. And, like Senator Harkin, we’ll have to be leaving a little early today. I’m sorry to do this. The timing is unfortunate, because this is an area that my colleagues on the committee know that I dedicate an awful lot of my time, during the Senate years, on these subject matters. And I’d be remiss if I didn’t point out that Jeannie Ireland, sitting in the front row up here with my staff person—we did a lot of this work—and is now with the FDA.

Jeannie, good to see you. Thank you for your tireless work over the years on this subject matter, as well.

I just have a brief couple of comments, if I can, Mr. Chairman, about this.

This is the opening round. We’ve got some reauthorization to do, and won’t get it done in this Congress. But, I can’t commend you enough for beginning the conversation. There were very contentious debates, going back some years ago, as we talked about the subject matter, generally speaking, and went through a number of



rounds dealing with pharmaceuticals, then medical devices, as well, going back to the orphan drug issue that both you and Senator Enzi have discussed and talked about. Obviously, it's an ongoing discussion, debate, how we do a better job of this, all the way along. So, I think it's really worthwhile we begin the conversation this early on, and you couldn't have better witnesses to do that.

Dr. Goodman has done a terrific, terrific job. Dr. Frattarelli, who'll be coming up later—I won't be here to hear his testimony, and Dr. Rich Gorman, who testified at our hearing on pediatric drugs and devices in 2007, and a wonderful individual, as well.

So, let me just share some thoughts. Today's hearing is an important topic not just for children's health, but family health. And I spend a good part of my time in this committee working on—I'm pleased to see so many friendly faces in the audience—the reality is, we can't talk about rare diseases without talking about children, because most of the approximately 7,000 rare diseases are pediatric diseases.

When Congress first began looking at the issue of safety and efficacy of pharmaceuticals for children, it was at a time when children were rarely included in studies of medical treatments, and therefore, we knew little about how children responded to these products. The majority of companies invested little or no resources into pediatric research. For some companies, the prospect of clinical trials in children posed problems of finding enough children to comprise a trial, while grappling with the ethical questions about conducting research involving children. The good news is that most children are healthy. And so, the idea is—as an audience, as a constituency—relatively small numbers of children find these problems. So, the incentives really weren't there. For the most part, the economic incentives, in fact, to pursue research in the smaller market of pediatrics was lacking, and all of those were realities we were dealing with. As a result, doctors and nurses had to guess at which treatments were best, at what dosage, for their pediatric patients. That's not because they were bad people or they were practicing bad medicine at all. They did the best they could for their patients with the limited information that they had.

The situation today is vastly different as the result of an awful lot of work, primarily in this committee, I might add, by Democrats and Republicans, alike, working on this issue together. With the passage of the Better Pharmaceuticals for Children Act, in 1997, where my partner in that bill was Mike DeWine of Ohio, we began that process of really looking at pharmaceuticals for children and how we could engage in better information.

The subsequent reauthorization, in 2002 and 2007, has led to more than 385 drug labels that have been revised with new safety, effectiveness, and dosage information. The studies completed under this program revealed that, in some cases, our children were being overdosed and, in some cases, under-dosed. In others, we discovered that the drug was simply not effective in children.

The Pediatric Research Equity Act, which was part of that reauthorization that Senator Clinton, our former colleague, and I were deeply involved in—she had originally issued a rule, when she was in the White House—the Executive order, back when President

Clinton was in the office—and that was overturned, at one point. And so, we began to then incorporate, legislatively, her language.

One of the things we did, unfortunately, with that bill is to sunset the requirement of trials to be done with children, which I regret. We don't do that with adults at all. But, that sunset provision was written into the legislation, back with the reauthorization of the bill.

With the Better Pharmaceuticals for Children's Act—it's a voluntary program. The incentive structure produces benefits for children, because the FDA can and does set the requirements for what companies must study. And the FDA has the final say over whether the 6 months of exclusivity can be granted. But, with the experience, we learned new things about the program, and we learned how to make it better.

During the most recent reauthorization of the Better Pharmaceuticals for Children Act, in 2007, we made improvements that have resulted in companies conducting studies earlier in the patent life of their products, meaning more and faster labeling changes, improved adverse-event reporting, and we created, as I mentioned, the Pediatric Review Committee, which has better integrated pediatrics across the review divisions in a consistent and productive way.

In 2005, the Institutes of Medicine published a report, entitled, "Safe Medical Devices for Children." In it, the ILM experts called for systemic attention to children's needs in medical device design, use, and evaluation, as well as a better functioning system of postmarket surveillance for medical devices to safeguard children. As a result, along, again, with Senator Mike DeWine, my partner in that legislation, we authored the Pediatric Medical Device Safety and Improvement Act, which became law in 2007.

The development of pediatric devices shares obstacles similar to those faced in drugs, but the incentive structures are different. The law has produced the first pediatric humanitarian-use device approved as a result of the incentives under this program. And the FDA is running a robust new grant program encouraging the development of new pediatric devices, thanks to the funding from our good friend from Wisconsin, Senator Herb Kohl, who chairs the Agricultural Appropriations Subcommittee.

As I head into my final months in all of this service in the Senate, Mr. Chairman, there's still much to be done in the area of rare and neglected diseases in children. As we've made an awful lot of progress with the passage of the Orphan Drug Act, but only 200 of the nearly 7,000 rare diseases currently have FDA-approved treatments. We've made headway with identifying newborns for rare, but debilitating, genetic conditions, through the expansion of newborn screening. And I authored that bill along with—Lamar Alexander, of Tennessee, who was my partner on that, as well—as we did in the premature birth legislation, as well. I point out, this is the kind of cooperation we've had on this committee in dealing with these issues, historically. And hopefully that will be the case again, as we move forward.

Here we've improved the availability of safe and effective treatment options for children, but many of these children will remain and have lifelong problems. There, their parents struggle with in-

insurance coverage, because, oftentimes, treatments for children are considered investigational or are, in fact, off-label. And when I see people like Sherrod Brown and Al Franken here, as relatively new members of this committee—even though I'll be leaving in January, I'm very encouraged that the same kind of effort that's been made in the past 20 or 30 years, working on these issues, will continue.

And obviously Al Franken, coming from Minnesota, the home of the medical device industry, for the large part, has a great familiarity with the subject matter. We would like a little more cooperation from the device industry in this legislation, I'd point out to my friend from Minnesota. He might want to look into that, and talk to us about it, as well, since we passed the legislation.

But, nonetheless, these are some great starts in this area. And again, wonderful witnesses today to set the tone, in my view, as we look forward now to the reauthorizations that will have to occur.

And I thank you, Mr. Chairman, for the time.

The CHAIRMAN. Well, thank you, Senator Dodd. And again, thank you for all your years of focus and attention on this and all the various pieces of legislation that you worked with others on to get through. We're going to miss you on this committee, but, as you pointed out, we have other champions here.

Senator Brown has devoted a large part of his service, in both the House and the Senate, in focusing on this issue. He's been one of the true champions of rare and neglected diseases. And so, we'll have a good person to carry on here.

Senator DODD. Thank you, Mr. Chairman.

The CHAIRMAN. Senator Brown, I'll recognize you for an opening statement.

#### STATEMENT OF SENATOR BROWN

Senator BROWN. Thank you, Mr. Chairman.

I appreciate so much your work on this committee on these issues, Senator Dodd and Senator Enzi, and Senator Dodd's work on children's issues for his whole career, and what it's meant to so many young people in our country, and so many families.

There's been a lot of partisanship in the halls of Congress recently. But, I don't expect partisanship in this room today, and that's to the credit of this committee's leadership. The unfortunate reality is that, whether we're talking about education or poverty or violence or health, the well-being of our Nation's children is not made a high enough priority. Great strides are being made, with respect to children's health, thanks to Medicaid, CHIP program, and the recently passed health reform legislation, but there are still areas where our efforts fall substantially and woefully short.

One such area, as we know, is research and development for pediatric diseases and conditions. Despite the fact that children and adolescents account for one-fifth of our Nation's population, pediatric research by NIH accounts for a mere 5 to 10 percent of the total NIH budget. Despite the fact that children account for some 20 percent of our Nation's population, most drugs on the market have never been tested in children.

If we're falling short in our efforts to cure and treat pediatric diseases and conditions, we're falling woefully and inadequately short

in our efforts to cure and treat rare and neglected pediatric diseases and conditions.

Seven thousand known rare or orphan diseases afflict nearly 30 million Americans—approximately 50 percent of whom are children. Even with millions affected by these rare diseases, research opportunities remain all too scarce; and approved therapies, even scarcer.

One of these rare diseases is epidermolysis bullosa, otherwise known as EB. EB is a debilitating, disfiguring, potentially deadly skin disease directly affecting approximately 12,000 people in the United States, most of them children. Because these children are born without the typical anchors that hold the epidermal and dermal skin layers together, any form of pressure creates unbearable friction, and can make the simplest of activities, like hugging and playing, even sleeping, calamitous. The most common characteristics of EB are chronic blistering and ulcers and scarring. Though the genes causing all types of EB have been identified, a cure continues to elude the medical community, primarily because funding is insufficient to support full clinical trials, and, as my predecessors on this committee, said, because market incentives simply don't exist for this rare pediatric disease. With no cure and limited treatment options, children and families struggling with EB continue to suffer as they wait and hope for cures and treatments that have yet to be developed.

Waiting and hoping for a cure that may or may not materialize is, all too often, the reality for families affected by rare and neglected diseases. Because these rare diseases affect fewer than 200,000 people in the U.S., and because neglected diseases often affect impoverished or disenfranchised populations in developing countries, there exist significant barriers and very limited market incentives for research and for development. Because the unique set of circumstances discourage innovation in this field, thinking outside the box becomes a necessity.

I would like to commend Senator Brownback, from Kansas, who's been a leader in developing innovative ways to encourage research in diseases that lack a large market incentive. Senator Brownback and I were successful, 3-plus years ago, during the FDA authorization, in authorizing a Priority Review Voucher Program that awards a voucher for expedited FDA review to any company that obtains approval for a treatment for a neglected tropical disease. And we already have begun to see the impact of that in tuberculosis and other mostly developing-world diseases. We're working now to expand that program to include rare childhood diseases like EB.

Another innovative strategy, this one spearheaded by Senator Specter, is the Cures Action Network. This grant program, authorized under health reform and housed within the Office of the Director at NIH, was established for the express purpose of helping ensure that treatments and cures for rare diseases make it over the finish line when funding for later-stage research is holding them back. The next step is to fund this tremendously promising program so we can realize its critical goals.

Examining solutions like these, as well as barriers to research and development, is why we're here today, why I appreciate so much Chairman Harkin holding this hearing.

Witnesses in our first panel will be able to talk about current research and development initiatives taking place with respect to rare and neglected pediatric diseases. Dr. Goodman and Dr. Guttmacher will discuss ongoing efforts at FDA and NIH to enhance research and development for rare and neglected pediatric diseases.

And witnesses in our second panel will discuss barriers that hamper our efforts to cure and treat these diseases, and provide suggestions about how we move forward.

For instance, I know the National Organization for Rare Disorders, NORD, has long advocated for more transparency in the regulatory system so that investigators and drug and device manufacturers have a better handle on expectations for the approval of new products. I know the American Academy of Pediatrics has long fought, and continues to fight, to ensure that drugs and devices are studied and labeled for pediatric purposes. I know the biotech industry is developing some of the most effective and innovative treatments for rare pediatric diseases, but that attracting sufficient capital for these efforts is always a challenge.

And finally, I'm pleased that Alex and Jamie Silver are here today with us. The father of the son with EB, Mr. Silvers, fought tirelessly, along with his wife Jamie, to raise awareness about this rare pediatric disease. He will be offering a number of suggestions to improve private and public efforts. I thank him personally for work he's done with my staff. I know there's no better advocate than a parent, and I appreciate him and the parents here who are working not just on behalf of their own children, but for children whom they don't even know, and thank them for that.

Thank you, Mr. Chairman.

[The prepared statement of Senator Brown follows:]

#### PREPARED STATEMENT OF SENATOR BROWN

Thank you, Chairman Harkin. I would like to begin by thanking both you and Senator Enzi for working with me to put together this important bipartisan hearing.

There has been a lot of partisanship in the halls of Congress recently, but I do not expect partisanship in this room today—and that is to the credit of this committee's leadership.

The unfortunate reality is that—whether we're talking education, poverty, violence, or health—the well-being of our Nation's children is not made a high enough priority.

While great strides are being made with respect to children's health—thanks to Medicaid, the Children's Health Insurance Program, and the recently passed health reform legislation—there are still areas where our efforts fall short.

One such area is research and development for pediatric diseases and conditions.

Despite the fact that children and adolescents account for more than 20 percent of our Nation's population, pediatric research by the National Institutes of Health (NIH) accounts for a mere 5–10 percent of the total NIH budget.

Despite the fact that children account for more than 20 percent of our Nation's population, most drugs on the market today have **never** been tested in children.

If we are falling short in our efforts to cure and treat pediatric diseases and conditions—we are falling woefully and inadequately short in our efforts to cure and treat *rare* and *neglected* pediatric diseases and conditions.

Seven thousand known rare or orphan diseases afflict nearly 30 million Americans—approximately 50 percent of whom are children.

Even with millions affected by rare diseases, research opportunities remain scarce, approved therapies even scarcer.

One of these rare diseases is Epidermolysis (ep-uh-derma-lo-sis) Bullosa (otherwise known as “EB”).

EB is a debilitating, disfiguring, and potentially deadly skin disease directly affecting approximately 12,000 people in the United States, most of them children.

Because these children are born without the typical anchors that hold the epidermal and dermal skin layers together, any form of pressure creates unbearable friction and can make the simplest of activities—like hugging, playing, or even sleeping—calamitous.

The most common characteristics of EB are chronic blistering, ulcers, and scarring.

Though the genes causing all types of EB have been identified, a cure continues to elude the medical community—primarily because funding is insufficient to support full clinical trials and because market incentives simply do not exist for this rare pediatric disease.

With no cure and limited treatment options, children and families struggling with EB continue to suffer as they wait—and hope—for cures or treatments that have yet to be developed.

Waiting and hoping for a cure that may or may not materialize is, unfortunately, all too often the reality for families affected by rare or neglected diseases.

Because rare diseases each affect fewer than 200,000 people in the United States—and because neglected diseases often affect impoverished or disenfranchised populations in developing countries—there exist significant barriers and limited market incentives for research and development.

Because of the unique set of circumstances that discourage innovation in this field, thinking outside the box becomes a necessity.

I would like to commend Senator Brownback—who has been a leader in developing innovative ways to encourage research on diseases that lack a large market incentive.

Senator Brownback and I were successful in authorizing a “priority review voucher program” that awards a voucher for expedited FDA review to any company that obtains approval for a treatment for a neglected tropical disease.

We are working now to expand that program to include rare childhood diseases—like EB—in that program.

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Dr. Jesse Goodman and Dr. Alan Guttmacher will discuss ongoing efforts at FDA and NIH to enhance research and development for rare and neglected pediatric diseases.

And witnesses on our second panel will discuss barriers that hamper our efforts to cure and treat these rare diseases and will provide suggestions about how we can move forward.

For instance, I know the National Organization for Rare Disorders (NORD) has long advocated for more transparency in the regulatory system so that investigators and drug and device manufacturers have a better handle on expectations for the approval of new products.

I know that the American Academy of Pediatrics (AAP) has long fought—and continues to fight—to ensure that drugs and devices are studied, and labeled, for pediatric populations.

I know that the biotech industry is developing some of the most effective and innovative treatments for rare pediatric diseases, but that attracting sufficient capital for these efforts is an ongoing struggle.

And, finally, I am so pleased that Mr. Alex Silver is here today.

As the father of a son with EB, Mr. Silver has fought tirelessly to raise awareness about this rare pediatric disease and he will be offering a number of suggestions to improve private and public efforts.

I'd like to thank Chairman Harkin and Senator Enzi again for their commitment to rare and neglected pediatric diseases and I'd like to thank all of our witnesses for taking the time today to discuss these issues, which are so close to all of our hearts.

The CHAIRMAN. Senator Brown, thank you very much.

Senator Franken.

#### STATEMENT OF SENATOR FRANKEN

Senator FRANKEN. Mr. Chairman, thank you for holding this hearing on rare and neglected pediatric diseases.

This is an issue that touches the lives of thousands of Minnesotans. I'm looking forward to hearing from our witnesses, one of whom has worked at the University of Minnesota.

Every day, I receive letters from Minnesotans of all ages who suffer from rare or under-studied conditions, and that have little or no prospect for care. The most heartbreaking stories are about kids, children with little-known diseases that have been frozen in time. Decades have gone by, and there's still been no progress on new treatments. And I also hear the stories of kids with conditions that we do have treatments for, but the therapies or devices they need aren't covered yet by insurance.

We need to do more for all of these cases. I'm heartened by the progress brought by laws like the Orphan Drug Act and the Pediatric Medical Device Safety Act. And I want to thank my senior colleagues on the committee who have championed these bills.

Today I'm interested in learning what the next steps are, so we can develop treatments more quickly and make sure that they reach kids who need them the most. For example, many of the humanitarian-use devices now available have come from companies with Minnesota ties, a fact that all Minnesotans are proud of. But, I'm concerned that we still don't have equivalent incentives for devices as we have for drugs. I think we can do more, and I look forward to exploring this issue with the panel.

The fact is that, here in Congress, we have lots of disease-specific bills that try to bring resources to these rare and neglected diseases. These bills are worthwhile, but it's a real challenge, because there are thousands of these diseases. I believe there has to be a better way to make sure our scientific infrastructure and financial incentives produce treatments for both prevalent and rare diseases. And I look forward to hearing from the panel.

Thank you, Mr. Chairman.

The CHAIRMAN. Thanks, Senator Franken.

As I said, we have two panels. The first would be the Food and Drug Administration and the National Institute of Child Health and Human Development, at NIH. And then, another second panel.

As I mentioned earlier, both Senator Dodd and I have to leave, like right now, because of the presidential signing of the bill, downtown. And so, I apologize for that. But, I want to reassure everyone that your testimonies have been read—I do those the night before—and that all of your testimonies will be made a part of the record in their entirety.

I leave you in the good hands of both Senator Enzi and Senator Brown and Senator Franken—as you can tell, all great champions of this issue, and have a great deal of interest in it.

So, I'm going to have to excuse myself. And I will yield the gavel to Senator Brown for the remainder of the hearing.

[Pause.]

Senator Brown [presiding]. For the first panel, I would like to introduce Jesse Goodman and Alan Guttmacher. I have a couple of words in introduction, and then I'd like you to proceed for 5 minutes or so, and then, of course, we'll ask you questions.

I'd like to welcome Jesse Goodman from the Food and Drug Administration. He's a chief scientist, deputy commissioner for science and public health at the FDA, formerly served as the director for the Center for Biologics at the Food and Drug Administration; and continues to be an active clinician and teacher who's board-certified in internal medicine, oncology, and infectious diseases. Dr. Goodman's a staff physician and infectious diseases consultant at the National Naval and Walter Reed Army Medical Centers.

Alan Guttmacher is our second panelist, acting director of the National Institute of Child Health and Human Development. He's a pediatrician and medical geneticist. He's also served in a number of roles at the National Human Genome Research Institutes at the National Institutes of Health, where he oversaw the Institute's effort to advance genome research and integration of that research



into healthcare, an extraordinary effort. Dr. Guttmacher is a member of the Institute of Medicine and a fellow of the American Academy of Pediatrics.

Dr. Goodman, if you would proceed.

**STATEMENT OF JESSE GOODMAN, M.D., M.P.H., CHIEF SCIENTIST, U.S. FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD**

Dr. GOODMAN. Thank you very much, Senator Brown, and good morning. And thank you, Senator Enzi and Senator Franken. I'm very pleased to be here with you.

I'm also with members of my team that I'll introduce a little later. And I'm happy to be here to talk about FDA's efforts to encourage development of medical products for children with rare and neglected diseases.

I do want to send a very—I hope I'll convey a very strong message that we're engaged on every front. And I'd like to sort of start out with the key message being, I think there are two critical ways we can help. One is in a very highly interactive science-based review process with sponsors and investigators. And the other is through our regulatory science efforts, which really are to bring science to bear that can move things across this gap, from promising ideas in basic science to products that really help people.

Just to start, as a practicing physician I see, frequently, the impacts of these diseases. We've heard some about the suffering they cause in children and their families. I like to always take the opportunity to remind folks that it's not just that these neglected diseases that affect others around the world cause tremendous impacts and there are humanitarian reasons to face them, but our country, too, is at risk for these diseases, as we see with the spread of influenza, tuberculosis, etc. So, I would argue that there's both pressing humanitarian reasons to act, but also national public health and security reasons that we should be on top of infectious diseases.

Now, for both these rare diseases and neglected diseases, as has been identified, there's really two big barriers to getting products. First is the market incentives that are not always clear, as we've heard about. But, second, and not always recognized, is, there are some serious scientific challenges in translating basic science and getting enough basic science to translate ideas and concepts into products.

For the neglected diseases—and excellent examples are TB, malaria, and HIV. Actually, in those areas, despite a lot of basic science investment, we still don't have clear answers. And part of what makes these diseases so good at infecting people is also what makes them so hard to develop vaccines and drugs against, which is how they evade the normal host defenses and immune response. So, there are scientific needs.

Now, I want to emphasize FDA's particular role here in assuring that products are safe and effective. And I also want to say that people with rare and neglected diseases are particularly vulnerable, due to either their illness, their poverty, etc. So, it's very important that we do our job, and be sure these products are safe and

effective. People around the world, in fact, look to FDA to make the best risk-based decisions about medical products.

Also, I want to really clearly emphasize that if a product is promising, FDA wants to work with product developers to help that product succeed in the development process. And then if a product works, we're going to approve it.

The essential problem here is that there are simply not enough effective products being developed. And so, we want to join with you, our colleagues at NIH and elsewhere, and industry, to do everything we can to facilitate the development of these products. This is a huge task, but we're very committed to it.

Now, as you've heard—and rightfully credited Senator Dodd, particularly, with—Congress has helped, in a bipartisan way, in this fight against rare and neglected disease. And we thank you. And we're pleased to be part of that effort.

As you've heard, the Orphan Drug Act accomplished a lot. Before it, there were very few products for rare diseases. Since it, there are 358 approved products. And many of these actually do address some of the rarest diseases. But, obviously, looking at that, we have a long way to go.

And I wanted to recognize and introduce to you Dr. Tim Cote, who is here and directs our Orphan Product Program. And I want to point out that they have a number of activities: a large grants program to help people develop products; personalized assistance to people in the development process; working with patient groups who we think are extremely important and can help inform us. They've helped identify drugs that could be promising in rare diseases, and put those out there for industry and academic interest. We do a huge amount of outreach and training, including courses in how to develop products for rare diseases in small clinical trials, etc, one recently attended, online and in person, by 1,500 people, including both FDA reviewers and outside investigators. And Dr. Guttmacher will talk more about it. But, we're working very closely with NIH, including working with them up front in this very exciting TRND program that you'll hear about.

Now, as Senator Enzi noted, children are not just small adults, and we need a lot of data about their diseases. And again, thanks to your leadership, we have the Best Pharmaceuticals for Children Act and the Pediatric Research and Equity Act that work together to help achieve this goal. Before these acts were present, 80 percent of products approved had no information about pediatric uses, forcing clinicians, essentially, to do their best and guess.

Today, we still have a lot more work to do, but pediatric information, as a result, is routinely included in the product labeling. And again, part of our team, Dianne Murphy—Where are you, Dianne?—is here, and she leads our Pediatric Therapeutic Office that coordinates this effort.

You've mentioned the Humanitarian Device Exemption Program. We think this is a creative program. It, again, has allowed people—device-makers to target devices to small populations and allow their approval based on a probable-benefit standard, which provides flexibility to help get these products to people.

And Dr. Barbara Buch, from CDRH, our Device Center, Is she here somewhere? Barbara? Hi, Barbara.—is also here, and an important part of that team.

Also, just in February, FDA created a new position, associate director for rare diseases in the Drug Center, where much of the review activity is located. Anne Pariser is running this activity. She's here. I see Anne. This program is to really promote best practices and innovation throughout the FDA and in collaboration with outside stakeholders.

Now, I want to also point out that we are fully committed to applying flexibility in the development and review of these products. That doesn't mean we will necessarily always agree with every proposal that every sponsor makes, but we really want to be open to those proposals, and be flexible.

It's really important to point out—and I have details in my written testimony—that we've approved quite a number of products based on very small clinical trials—10, 20 people—and often on one trial, where all the information can be reasonably applied, and where the product has worked.

The issue of surrogates, biomarkers, things that can allow us to predict effectiveness more quickly, and not have to wait for years, in a long-term clinical trial, that's an area where—we also are very open to, and I agree with several of the other people testifying today, that we can develop the science there. I'll come back to that a little.

Again, as a result of your and Senator Brownback's leadership, we have a review going on—new review groups for both rare and neglected diseases. And we do look forward to gathering all that input and providing Commissioner Hamburg with our best ideas and coming back to you with a report.

Now, on neglected diseases, I want to say, we have seen tremendous increase in interest, both from Congress, from the American people, from the Administration, from nongovernment organizations, from—even from industry on this—in developing products that can meet this incredible humanitarian and public health need. And we are very excited about that, very engaged in it. This was a very high priority for me, when I directed the Biologic Center at FDA with all our relationships with WHO, and it remains one for me and Dr. Hamburg.

I'd like to mention a few things we've done in the neglected disease area. We've issued a guidance on development of vaccines for global infectious diseases. We provide a huge amount of technical support and expertise to WHO in their efforts to set high standards for the world. We serve as a reference national regulatory agency, for WHO, that can approve products for their programs, that distribute them throughout the world. We're involved with them in trying to build capacity, throughout the world, for other regulatory agencies so that places like Africa—where there are other developing countries—can exercise appropriately their autonomy in looking at products, but also can be partners that help those products get effectively developed and evaluated. And then we do a lot of training for foreign regulators.

I want to finish up by mentioning our regulatory science work. In the area of neglected diseases, we have a very large program to

develop better measures of safety and effectiveness and quality, for example, of vaccines for diseases like HIV, TB, malaria, meningitis, Leishmania.

Now, I want to talk a little bit about our highly applied and targeted regulatory science efforts, because most of the problems that we find we're dealing with—and the difference between success and failure in product development is often based on, What is the science we have, and how can we apply it?

As you know, researchers have defined the genetic basis of thousands of diseases. We have all the information from the human genome. But, there still is this very persistent and troubling gap between all that basic science knowledge and product development and products that can benefit people. And this is part of the reason we have that gap in getting to those products. We believe that, through our regulatory science efforts and the kind of interactive review I talked about, we can help bridge that.

This is particularly important for rare and neglected diseases. For example, we do want to see more accelerated approvals and markers for effectiveness and safety that can help us approve products and develop them more quickly. But, to do this, you need the science. You have to have endpoints that are sound, or we end up with products that are approved and then later found not to work, as we've seen occasionally in the drug world.

We're very actively engaged with other partners, through consortia, through our own research efforts, in trying to develop better surrogate markers for effectiveness. And we recently had a TB workshop, just focused on this, that involved our colleagues at NIH and CDC, as well as industry.

Some examples of the success of some of our fairly limited but, I think, robust and focused regulatory science program includes the work of FDA biochemists that solved a manufacturing problem for a meningitis vaccine that is then allowing a major NGO to produce meningitis vaccine for much of the world, where it's a huge problem. Another thing is work that FDA chemists are doing now to better understand how dosing forms, like tablets, of drugs are handled by children, and how we can improve that. And those are just a couple of examples.

We thank Congress, and our 2011 budget of the Administration includes the first dedicated funding, in fact, for FDA to rebuild its scientific infrastructure, and develop these kinds of tools that can help turn ideas into products. We're also very excited about our new collaboration, led by Dr. Hamburg and Collins, our Leadership Council between FDA and NIH, and our grant program on applied regulatory science that we're doing together.

And then, to close, I'd like to say that strong science is critical in an intensely interactive review process that we know improves the chances of the outcome of success. That success is good for patients, but also for our economy, where our leadership in product development is critical.

FDA science can and should meet with scientists from companies and sponsors early in development, and help identify issues and problems, and help to solve them, to increase the odds of success. And these interactions are very labor-intensive for FDA, but we've seen, for example, in our medical countermeasure review, a very

different subject, but with some similarities, that the more we can work with sponsors early on, and identify and solve problems, the higher the likelihood of success.

And perhaps my most important suggestion—I make it every day to people who call me—is that sponsors seek and engage in this kind of approach, meeting with us early, including with my colleagues that I identified here.

Finally, I want to reemphasize that we are really committed to this, our leadership and so much of our staff. And we really welcome your engagement and ideas.

Thank you very much.

[The prepared statement of Dr. Goodman follows:]

PREPARED STATEMENT OF JESSE L. GOODMAN, M.D., M.P.H.

#### INTRODUCTION

Good afternoon, Chairman Harkin and members of the committee. I am Dr. Jesse L. Goodman, Chief Scientist and Deputy Commissioner for Science and Public Health at the Food and Drug Administration (FDA), an agency of the Department of Health and Human Services. I appreciate the opportunity to be here today to describe the role of FDA in encouraging and speeding the development of drugs, vaccines, devices, and diagnostic tests to improve the lives of children affected by rare diseases.

There are more than 7,000 rare diseases, defined by the Orphan Drug Act (ODA) as diseases affecting fewer than 200,000 people in the United States, and many of these affect children. Some diseases, such as severe genetic diseases, predominantly or exclusively affect children. As a practicing physician and a researcher specializing in infectious diseases and trained in oncology, I have personally witnessed the devastating human face of diseases like these.

While we have made great progress in addressing this challenge, there are still an estimated 20 million Americans suffering from rare diseases for which there are no approved therapies available. Factors responsible for this are only magnified for children. In many cases, and even when the basic scientific problem is understood, the applied scientific knowledge is still not there to identify or develop good candidates. In addition, market incentives may be insufficient to drive the sustained commercial interest and investment necessary to develop new medical products for pediatric rare diseases. Furthermore, conducting clinical trials to treat this population presents real challenges. As with all rare diseases, the number of patients available for clinical trials is small, and our knowledge about the history and best management of these diseases is often limited. Small populations are made even smaller when we consider that diseases and therapies may affect children differently at different ages—and not all children are the same. A product that is effective in an infant may not work for an older child or a teen. In addition, with limited information about rare diseases, we may have difficulty determining whether a child's response to therapy in a clinical study is related to intervention with a medical product or is a result of the natural course of the disease over his or her lifetime. Other factors that impact all clinical trials in children, such as limitations on the amount of blood that can be drawn from a child, also come into play. All of these issues complicate progress in this area.

In the face of these challenges, FDA believes it can contribute collaboratively to achieve progress, and we are taking a multifaceted approach to supporting the development of medical products for pediatric rare diseases. I welcome your shared interest and commitment to this issue, and I 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 pediatric rare diseases.

Congress has empowered FDA with many innovative tools to help address pediatric rare diseases. I will begin by providing a summary of the statutory authorities under which we are currently conducting these efforts, followed by a discussion of other related activities at FDA.

## FDA STATUTORY AUTHORITIES TO ADDRESS PEDIATRIC RARE DISEASES

*The Orphan Drug Act*

The 1983 Orphan Drug Act (ODA) created financial incentives, including grants, to support the development 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. If products so designated are subsequently shown to be safe and effective and receive marketing approval, their developers receive market exclusivity for 7 years.

FDA’s Office of Orphan Products Development (OOPD) serves as a focal point for FDA’s efforts to address rare diseases, and can provide 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 month 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 358 of these therapies have gone on to full marketing approval. Of these products, approximately 67 (19 percent) are for diseases that occur exclusively among children and 201 (57 percent) of these are for diseases that occur among both children and adults. ODA also established FDA’s largest grants program, \$15.2 million for fiscal year 2010, 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. Of these products, approximately 11 (24 percent) are for diseases that occur exclusively among children and 28 (62 percent) of these are for diseases that occur among both children and adults.

The approved products now on the market that qualified for orphan product designation are a testament to the important accomplishments and successes of the program. Success stories include:

- Carbaglu (carglumic acid) for the treatment of NAGS deficiency, the rarest of the Urea Cycle Disorders, which are diseases that lead to elevated ammonia levels in the blood and cause seizures, poor muscle tone, respiratory distress, coma, and even death. NAGS deficiency affects fewer than 10 patients in the United States at any given time. This drug was approved in March 2010, based on a case series in 23 patients.
- Myozyme (alglucosidase alfa) for the treatment of Pompe Disease, which is a rare genetic disease resulting in progressive skeletal and respiratory muscle weakness caused by an accumulation of glycogen (a carbohydrate). About 1,000–2,000 patients in the United States suffer from Pompe Disease, of which only a few hundred are infants. In infants, the disease can be rapidly fatal due to respiratory failure. This drug was approved in April 2006, based on the results of a single, pivotal study in 18 patients.
- Ceprotin (Protein C Concentrate) for treatment of severe congenital Protein C deficiency, the prevention and treatment of venous thrombosis (blood clots in the vein), and purpura fulminans (life-threatening bleeding and tissue death). The life-threatening form of the disease affects about 1 in 500,000 to 1 in 750,000 newborns. This drug was approved in March 2007, based on a clinical study involving 18 patients.
- Kogenate FS (Antihemophilic Factor (Recombinant)) to prevent bleeding episodes and the risk of joint damage in children with hemophilia A. The disease affects about 15,000 individuals in the United States, nearly all of whom are male. This drug was approved for this indication in October 2008, based on a clinical development program of 65 boys under 30 months of age.

*Best Pharmaceuticals for Children Act and Pediatric Research Equity Act*

Under the leadership of Senator Dodd and the members of this committee, over the past decade, Congress created and reauthorized two critical programs that have dramatically improved the practice of medicine for children: the Best Pharmaceuticals for Children Act (BPCA), first enacted in 1997 as part of the Food and Drug Administration Modernization Act, and the Pediatric Research Equity Act (PREA), first enacted in 2003. Together, BPCA and PREA create a “carrot and

stick” approach to the development of important new safety, effectiveness, and dosing information for medical products used in children. BPCA is an incentive program that grants market exclusivity to sponsors that elect to study their product in children according to protocols set by FDA. PREA gives FDA the authority to require pediatric studies under certain conditions. Before these laws were enacted, an estimated 80 percent of medication labels did not include information about use in children. Without pediatric studies, doctors treating children most often have to use medical products without important information about correct dosage or safety and effectiveness. Today, using the tools that Congress provided with BPCA and PREA, we have worked with industry to add new pediatric information to the labels of 385 products.

The Food and Drug Administration Amendments Act of 2007 (FDAAA) established the Office of Pediatric Therapeutics (OPT) within FDA’s Office of the Commissioner. Its primary mission is to ensure access for children to innovative, safe, and effective medical products. OPT includes four distinct yet interrelated programs to support FDA efforts to improve pediatric access to medical products:

- The OPT Ethics Program supports FDA efforts to ensure that children are only enrolled in clinical studies which are both scientifically necessary and ethically appropriate.
- The OPT Safety Program coordinates the mandated review by the Pediatric Advisory Committee of the safety of drug and biologic products 1 year after labeling changes, in response to voluntary and required pediatric studies.
- The OPT Scientific Activities Program works with FDA scientists and reviewers to ensure that pediatric studies are rigorously designed and conducted in accord with current scientific understanding of such issues as exposure-response and extrapolation.
- The OPT International Program facilitates communication and collaboration between FDA and partner regulatory agencies around the world as well as other regions, such as Europe.

#### *The Priority Review Voucher Program*

FDA has long had in place a review system to ensure that the most critical medical products are reviewed on a priority basis. Priority review applications for products that treat life-threatening and serious diseases are reviewed in a 6-month period, compared to the 10-month period for other products. Most products to treat pediatric rare diseases are entitled to get this quicker review cycle, which does assist in getting needed products to market more quickly.

Thanks to the leadership of Senator Brown and others, the FDAAA granted FDA the authority, beginning in 2009, to award priority review vouchers 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. While these diseases are not rare in the global context, they often affect fewer than 200,000 individuals in the United States and are therefore eligible for orphan drug status designation. If transferred to apply to a blockbuster drug, the 4 months of earlier market access available when a priority review voucher is redeemed could translate into an incentive worth hundreds of millions of dollars. Already, one such voucher has been issued to Novartis, for its anti-malarial drug Coartem (artemether, lumefantrine). FDA 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 diseases listed in the legislation.

#### *The Humanitarian Device Exemption Program*

Also included in FDAAA is the Pediatric Medical Device Safety and Improvement Act, which expanded the Humanitarian Device Exemption (HDE) program. The HDE program provides an exemption from the otherwise applicable effectiveness requirements for devices that are designed to treat or diagnose diseases or conditions that affect fewer than 4,000 individuals in the United States per year. To qualify for this exemption, certain criteria must be met, including a determination by FDA that the probable benefit outweighs the risk of injury or illness from use of the device. FDAAA provided an additional incentive for development of devices intended for treatment or diagnosis of rare pediatric diseases by lifting certain restrictions on charging for the device. An example of a device granted an HDE is the adjustable titanium rib for children with thoracic insufficiency syndrome, a condition where the child’s chest cannot support normal growth of the lungs or spine. This device prevents the child’s body from collapsing on itself, allowing for growth and maturation of lungs and spine in patients who otherwise might not survive. The inventor, an

orthopedic surgeon, recognized the need for a device that could be adjusted as a child grows.

FDAAA also established a grants program to fund pediatric device consortia that facilitate the development, production, and distribution of medical devices for children. These consortia serve to connect pediatric medical device innovators with potential manufacturers and provide advice and assistance. So far, four consortia have been established. Since their inception in October 2009, the consortia have assisted in the evaluation and development of more than 50 pediatric medical devices, including development of a critical pediatric ventricular assist device, which (at least on a temporary basis) partially or completely replaces heart function for children with heart disease while they await a transplant.

#### ADDITIONAL FDA EFFORTS TO ADDRESS PEDIATRIC RARE DISEASES

##### *Establishment of Rare Diseases Director Position Within FDA Center*

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 a position of Associate Director for Rare Diseases in the Center for Drug Evaluation and Research (CDER). In conjunction with OOPD, the Associate Director for Rare Diseases supports collaboration among scientists and clinicians throughout FDA, including with the Office of Pediatric Therapeutics, promoting scientific and regulatory innovations to help facilitate timely development and approval of new treatments for patients with rare diseases.

##### *Training and Collaboration to Support Rare Disease Product Development*

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 pediatric rare diseases. In October 2010, FDA will co-sponsor a larger and more comprehensive 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's Office of Rare Diseases Research, Therapeutics for Rare and Neglected Diseases Program, and other NIH Institutes and Centers; patient advocacy groups; academia; and the Institute of Medicine (IOM).

##### *FDA Rare and Neglected Disease Review Groups*

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) directed 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.

Last month, a meeting was held on rare diseases, at which 26 speakers provided comments. Those comments will be made available when FDA finalizes its report to Congress on March 11, 2011. A similar meeting to discuss neglected diseases is planned for September. Finally, FDA and NIH are co-sponsoring an IOM study, which began 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.

##### *Office of Special Health Issues*

FDA's Office of Special Health Issues (OSHI) serves as a liaison between FDA and patients, patient advocates, health professionals, and their representative organizations. OSHI staff encourages and supports active participation of these stakeholders in forming FDA regulatory policy to ensure the Agency's decisions are based upon a full range of perspectives. OSHI also is responsible for communicating important safety and regulatory information to health professionals and patients. This office is a resource to patients with rare diseases who have questions about FDA-regulated products or seek access to investigational new products. It is also a resource for parents whose children are suffering from rare diseases.



*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 needed applied product development and evaluation research, a gap that contributes to the lack of real products getting to patients for many such diseases, despite advances in basic sciences. This gap can be filled in part through enhanced regulatory science, which is the development of tools, methods, assays, standards, and models that help speed and improve the development, review, and approval of innovative products.

The President's fiscal year 2011 budget for FDA includes dedicated funding for the Agency to strengthen its critical scientific capacity to leverage the opportunities provided by 21st-century science and to enhance its scientific collaborations. 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.

Through collaboration, FDA will foster new opportunities for patients and consumers. Regulatory science at FDA holds great promise for bridging the gap in our scientific knowledge about how medical treatments impact children specifically and for unlocking their potential for children. For example, during the 2009 influenza pandemic, FDA's regulatory science work on dosing of the antiviral drug Tamiflu (oseltamivir phosphate) in children under the age of 1 year was adopted by countries around the world. As another example, FDA scientists from the Agency's Center for Biologics Evaluation and Research originated a collaborative effort with the National Toxicology Program to improve the safety of gene therapies, in order to design vectors that can deliver needed curative genes to children with genetic diseases, but without the serious risk of malignancy seen in some studies.

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 true 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 pediatric rare diseases.

## CONCLUSION

FDA's multifaceted and collaborative approach to addressing the obstacles of product development for pediatric rare diseases has resulted in many successes and real progress, but much more work remains to be done to meet the tremendous needs of this population. Through the statutes already in place, Congress has granted FDA important authorities that we have found very useful to help address this challenge. In addition, both new initiatives and enhanced efforts engaging many FDA components, including in interactive review and regulatory support for sponsors, collaboration and training, and in regulatory science, are underway to facilitate development and evaluation of needed products. We look forward to continuing to work with you and our colleagues in the public health arena to address the challenges that we face. Thank you again for this opportunity to discuss pediatric rare diseases. I welcome your comments and questions.

Senator BROWN. Thank you Dr. Goodman.  
Dr. Guttmacher.

**STATEMENT OF ALAN E. GUTTMACHER, M.D., ACTING DIRECTOR, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT, BETHESDA, MD**

Dr. GUTTMACHER. Thank you, Senator Brown and Senators Enzi and Senator Franken, for your interest in this truly important topic, and for the opportunity to testify.

We appreciate your interest in a topic which is so important to the many, many individual children who are affected by rare diseases, and to their families.

I'd like to begin by illustrating this with one of the literally millions of stories that really bring home to me, why this is an important topic. It's a story of one of my former patients, Kevin Hartmann, whom I've known since the day he was born, when I became his physician. Kevin is now a young adult with Marfan syndrome, an inherited rare disorder that affects the body's connective tissue. Perhaps its most serious manifestation is that the aorta can become distended and stretched so thin that it tears, requiring emergency surgery, or even resulting in sudden death, as was the case with U.S. Olympic volleyball star Flo Hyman, several decades ago.

Individuals with Marfan syndrome are usually counseled to avoid physical stress to their hearts, as is caused by many athletic activities, and must be monitored closely their entire lives. Having Marfan syndrome affects both the activity and the personality and lives of individuals who have it, even when they are children.

The availability of a medication that could slow aortic growth and prevent its tearing would make an enormous difference to Kevin and to the many other children with Marfan syndrome. When Kevin was a young child, the only such drugs we knew of, so-called beta blockers, were not as effective as we wished for. However, a few years ago, groundbreaking research supported by the NIH showed that another drug, already on the market and approved by the FDA for other indications, Losartan, dramatically prevented aortic enlargement in a mouse model. Therefore, we are quite excited about the potential of an ongoing clinical trial, funded by the National Heart Lung and Blood Institute at the NIH, comparing Losartan with the beta blocker Atenolol to see whether Losartan is also better in humans at slowing the speed of aortic enlargement, which would make a real difference in the lives of Kevin and other children and young adults with Marfan syndrome. Kevin hopes that this kind of approach will enable him to avoid the serious surgical complications that, for instance, his father had from this same condition.

Many such examples exist across the NIH. Although the NICHD supports the bulk of research on child health and development, most of the NIH's 27 institutes and centers include pediatric research in their portfolios.

In fiscal year 2009, the last for which we have complete data, the NIH funded nearly \$3 billion in pediatric research from its annual appropriation, and another \$500 million through the American Recovery and Reinvestment Act. This 2009 funding included over \$86 million in pediatric grants in the orphan drug category.

Developing and testing drugs in children has long posed a particular challenge because of children's particular vulnerabilities. The Best Pharmaceuticals for Children Act, or BPCA, seeks to address the lack of information on medication safety, effectiveness, and dosing in children. The NIH is authorized to identify therapeutic gaps in pediatrics and support the research necessary to fill them. Led by the NICHD, all of the NIH institutes and centers that have significant pediatric portfolios contribute funds and expertise to implement the BPCA.

Current projects include a number on understanding and treating rare diseases. For example the National Cancer Institute's Children Oncology Group is performing five BPCA pediatric cancer

drug studies. And the NICHD is funding a pharmacokinetic and safety study of baclofen to treat spasticity in children with cerebral palsy. Our BPCA implementation efforts also include training to address the dearth of pediatric pharmacologic researchers. In partnership with the National Institute of General Medical Sciences, the NICHD is now co-funding six postdoctoral trainees in pediatric clinical pharmacology.

Some rare conditions affect individuals systemically, thus requiring the expertise of the NIH institutes. One way to deal effectively with such situations is a trans-NIH working group. For instance, NICHD leads one such effort, the NIH Fragile X Research Coordinating Group. Nine participating NIH institutes and centers meet regularly to discuss implementation of the research plan on Fragile X. Through support from several NIH institutes and the private foundations Autism Speaks and FRAXA, scientists are testing a compound in healthy adults as a potential treatment for Fragile X syndrome. Should the results from these adult trials prove promising, the compound will then be assessed for pediatric safety and in clinical trials in children. Such public/private partnerships can help leverage investment and other resources for rare disorders.

Individually, the NIH institutes and centers are engaging in a wide variety of research projects on pediatric rare diseases, and a sampling of those projects is included in my written statement.

Established in 1993, the NIH Office of Rare Disease Research, or ORDR, helps to coordinate and support these activities across the NIH. The ORDR, in collaboration with six other NIH institutes, oversees the Rare Disease Clinical Research Network, which comprises 10 consortia with more than 70 sites across the United States. The goals of these sites are to make investigational studies and treatments more accessible to patients with rare diseases, and to facilitate the recruitment of patients for clinical trials. Researchers affiliated with the network study more than 40 rare diseases, many of them pediatric. The network also targets early-stage investigators, to encourage them to focus their careers on rare diseases.

Another new NIH program specifically developed therapeutics for rare diseases, including pediatric condition. Launched in May 2009, the Therapeutics for Rare and Neglected Diseases, or TRND, initiative is a trans-NIH collaborative program, which has already been mentioned today. In most cases, a TRND investigator will begin with a chemical compound that is known to have some biological effect in the laboratory for a given rare disease and progress to a candidate compound suitable for a new drug application to the Food and Drug Administration. And, as Dr. Goodman has referenced, this is one of a number of new endeavors where NIH and FDA are increasingly working closely together to try to overcome the many obstacles in drug development for rare diseases.

In terms of TRND, often the candidate compound will be licensed to pharmaceutical companies for clinical testing, permitting the TRND program to remain focused on the more scientifically challenging stages of preclinical development. Our goal is to derisk development of new drugs for less common diseases, to make them more attractive to private companies.

Among the projects initiated in 2010 is a re-purposing project. That is, testing a drug previously developed for another purpose,

this time for the rare pediatric neurodegenerative disease Niemann-Pick Type C.

Newborn screening is a mainstay for improving the lives of many children with rare diseases. It permits referral to medical specialists and treatment for numerous pediatric rare diseases to occur as soon after birth as possible. The NICHD leads NIH efforts to increase the number of rare and common conditions for which newborn tests are available through the Hunter Kelly Newborn Screening Program, aimed at identifying new screening technologies and furthering research on managing and treating conditions that newborn screening can detect.

For families whose children have a rare disorder, obtaining a diagnosis can be a devastating process requiring years of frustrating effort. For many conditions, even if there is no cure, a diagnosis is essential to receive appropriate treatment. Together, the ORDR, the National Human Genome Research Institute, and the NIH Clinical Center recently organized the NIH Undiagnosed Diseases Program. The goals of this new program, which sees both pediatric and adult patients, are to provide answers to patients with mysterious conditions that have long eluded diagnosis, and to advance our basic understanding of rare diseases.

With this breadth of NIH-funded research, and armed with new resources such as the Human Genome sequence, we are entering an historic era of greater understanding of the biology of many rare diseases, and thus, for the development of more effective therapies.

Thank you, again, for the opportunity to testify today, and I would be pleased to answer any questions you might have.

[The prepared statement of Dr. Guttmacher follows:]

PREPARED STATEMENT OF ALAN E. GUTTMACHER, M.D.

Good morning, Mr. Chairman and members of the committee, my name is Alan E. Guttmacher, and I am representing the National Institutes of Health (NIH), an agency of the Department of Health and Human Services (HHS), at today's hearing on pediatric rare diseases. By background, I am a pediatrician and medical geneticist and currently serve as Acting Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the NIH. We appreciate the committee's interest in this topic, which is so important to the individual children who are affected by rare diseases and to their families. A rare (or orphan) disease is generally considered to have a prevalence of fewer than 200,000 affected individuals in the United States.

Let me begin by offering a specific example: one of my former patients, Kevin Hartmann, has Marfan syndrome. This is a genetically inherited disorder which affects the body's connective tissue. Individuals with this condition tend to grow extremely tall and thin, have unusually lax joints and share certain other physical features. One of the most serious issues associated with this condition is that the aorta can become stretched so thin that it tears, requiring emergency replacement of the aortic root or sometimes resulting in sudden death, as was the case with the U.S. Olympic volleyball star, Flo Hyman. Individuals with Marfan syndrome are usually counseled to avoid physical stress to their hearts or other tissues caused by many sports, and must be monitored closely all their lives. Kevin has made a terrific video about his life with Marfan syndrome, <http://vimeo.com/12005105>.

Clearly, the availability of a medication that could slow aortic growth and prevent tearing would make an enormous, literally potentially lifesaving difference to Kevin, his family, and others with Marfan. In 2007, a clinical trial began, funded by the National Heart, Lung, and Blood Institute (NHLBI) at the NIH and conducted through its Pediatric Research Network, comparing two drugs—Atenolol and Losartan, which are already on the market—to see if one is better than the other at slowing the speed of aortic enlargement. Both of these drugs are commonly used to lower high blood pressure, but groundbreaking research using a mouse model and published in 2006, supported by several NIH Institutes and Centers (ICs), showed

that Losartan prevented aortic enlargement and other features seen in individuals with Marfan syndrome.

Many such examples exist across the NIH. Although the NICHD supports the bulk of research on normal and abnormal child health and development, most of the NIH's 27 ICs include pediatric research in their portfolios. In fiscal year 2009, the last year for which we have complete data, the NIH funded nearly \$3 billion in pediatric research, with another \$505 million for pediatric research from funding under the American Recovery and Reinvestment Act. Although the NIH does not report specific funding information on rare diseases, it does collect and report on the category of orphan drugs; in fiscal year 2009, the portion of grants funded by the NIH in the Orphan Drug category that was also reported in the Pediatric category was just over \$86 million.

Developing and testing drugs in children has long posed a particular challenge, even for drugs used to treat more common conditions, because of the vulnerable nature of this population and because children change substantially as they grow. The Best Pharmaceuticals for Children Act (BPCA), most recently reauthorized in 2007, sought to redress the lack of information on medication safety, effectiveness, and dosing in children through several means. Under the act, the NIH is authorized to identify therapeutic gaps in pediatrics and support the research necessary to fill those gaps. Led by the NICHD, all of the NIH ICs that have a significant pediatric portfolio contribute funds and expertise to implement the BPCA. Current co-funded projects include many studies on understanding and treating rare diseases: the National Cancer Institute's (NCI) Children's Oncology Group is performing five BPCA pediatric cancer drug studies, the NHLBI is supporting the "Baby HUG" trial, aimed at demonstrating whether the drug hydroxyurea is effective at decreasing painful crises and preventing chronic organ damage in young children with sickle cell disease, and the Foundation for the NIH has contributed to NICHD's pharmacokinetic and safety study of Baclofen to treat spasticity in children with cerebral palsy.

Some rare conditions affect individuals systemically, thus requiring the expertise of several of the NIH ICs. One mechanism used at the NIH to deal effectively with such conditions, is the establishment of a trans-NIH working group. The NICHD leads one such group, the NIH Fragile X Research Coordinating Group. Fragile X syndrome (FXS) is the most common inherited cause of intellectual and developmental disabilities. Nine participating NIH ICs meet regularly to discuss implementation of the Research Plan on Fragile X and Associated Disorders, which the group developed with the input of outside experts and published in fiscal year 2008. Each goal area of the plan is being addressed by grants funded across the member institutes. One excellent example is a Phase I trial of a novel drug that may effectively compensate for the missing protein in individuals with Fragile X; through support from several NIH ICs [the NICHD, the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS)] and the private foundations Autism Speaks and FRAXA, scientists at Seaside Therapeutics are testing a leading compound in healthy adults as a potential treatment for FXS. Results suggest that the medication is safe and tolerable; a Phase II clinical trial study of dosage and efficacy in adults with FXS is planned. Should the results from these adult trials prove promising, the compound will be assessed for pediatric safety and clinical trials in children. Such public-private partnerships can help leverage investment and other resources for rare disorders for which no treatment is currently on the market.

Individually, the NIH ICs are engaging in a wide variety of research projects on pediatric rare diseases. Established in 1993, the NIH Office of Rare Diseases Research (ORDR) helps to coordinate and support these activities across the NIH and to provide information to the research and patient communities about these conditions, potential treatments, and ongoing research opportunities. Among other activities, the ORDR, in collaboration with six other NIH ICs, oversees the Rare Diseases Clinical Research Network, which comprises 10 consortia with more than 70 sites across the United States. The goals of these sites are to make investigational studies and treatments more accessible to patients with rare diseases, and to facilitate the recruitment of patients for clinical trials. Researchers affiliated with the Network study more than 40 rare diseases, many of them pediatric, such as intellectual and developmental disorders, rare bone marrow failure conditions, and rare pediatric liver disease. Many Network members are testing the safety and efficacy of new therapeutic agents, including pediatric therapeutics. For example, the NINDS supports several of the research consortia within the Network, including the Inherited Neuropathies Consortium and the Lysosomal Disease Network, both of which include research on disorders affecting children. The Network also is targeting early stage investigators to encourage them to center their careers in rare diseases; in

September 2010, the Network and the NIH Clinical and Translational Science Awards (CTSAs) are cosponsoring a conference to teach new researchers and junior faculty about rare disease research methodology.

Another new NIH program is aimed specifically at the issue of development of therapeutics for rare and neglected diseases, including pediatric conditions. Announced in May 2009, the Therapeutics for Rare and Neglected Diseases (TRND) initiative is a trans-NIH, collaborative program overseen by ORDR and administered by the National Human Genome Research Institute (NHGRI). TRND investigators will begin with a chemical compound that is known to have some biological effect in the laboratory on a given disease, and progress to a candidate compound for a new drug application to the Food and Drug Administration. Often, the candidate compounds will be licensed to pharmaceutical companies for clinical testing, permitting the TRND program to remain focused on the most scientifically challenging stages of preclinical development. The goal is to “de-risk” development of new drugs for less common diseases to make them more attractive to private companies. At the same time, this innovative program will advance the entire research enterprise by allowing open dissemination of the information learned during the initial testing phases, expanding the overall research base and potentially shortening the time period for the development of new drugs. Among the new projects initiated in 2010 is a mid-stage “re-purposing” (testing a drug developed for another purpose) project for the rare pediatric condition, Nieman-Pick Type C (NPC), a neurodegenerative disease. As will be true of many of TRND’s efforts, this project is a collaboration of government, academic scientists, and patient advocacy groups.

In addition to the research activities already mentioned, a sampling of the types of research across the NIH illustrates the range of basic to clinical research activities underway and also provides a sense of why therapeutics for some pediatric rare conditions remains so elusive.

- The NCI’s Childhood Cancer TARGET Initiative is a public-private partnership developed to harness the power of cutting-edge genomics technologies to identify valid therapies for childhood cancers rapidly. The program’s initial focus was on neuroblastoma and acute lymphoblastic leukemia (ALL) but was expanded with ARRA funds to include several other conditions. As a result of TARGET, there will be a virtually complete catalogue of gene mutations and other gene alterations that occur in these childhood cancers.

- The Children’s Oncology Group (COG) develops and coordinates cancer clinical trials at over 200 member institutions throughout the United States and around the world. Through the COG network, children with cancer can access state-of-the-art therapies regardless of where they live. One of the many consortia of investigators within COG, the Pediatric Brain Tumor Consortium, aims to rapidly conduct phase I and II clinical evaluations of new therapeutic drugs, biological therapies, and radiation treatment strategies for children.

- The National Eye Institute has sponsored research that provides health care professionals with improved prognostic indicators and treatments options for retinopathy of prematurity, a blinding disease that affects premature infants. The Early Treatment for Retinopathy of Prematurity study demonstrated that therapy administered in the early stages produced far better outcomes than traditional timing of treatment. The study also resulted in an improved risk assessment model to identify those infants at highest risk for developing severe vision loss.

- In addition to its research on rare pediatric genetic diseases, such as cystic fibrosis, sickle cell disease, thalassemia and hemophilia, which has resulted in many individuals with these conditions living into adulthood, the NHLBI also supports research on rare acquired pediatric diseases. For instance, the NHLBI funded the development of recombinant surfactant to improve the lung function of the children with bronchopulmonary dysplasia, a serious lung condition that primarily affects children who received oxygen therapy when they were premature neonates.

- Medulloblastoma, the most common form of pediatric brain tumor, is relatively responsive to traditional cancer treatments (surgery, chemotherapy, and radiation), but long-term survivors often suffer from life-long developmental, behavioral and cognitive disturbances. Investigators supported by the National Institute on Aging are working to understand the basic mechanisms underlying medulloblastoma, so novel treatments can be developed to target tumor cells specifically, without damaging the developing brain.

- The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports a broad portfolio of basic, translational, and clinical research on primary immune deficiency (PID) diseases. PID diseases, such as DiGeorge syndrome, Hyper-Immunoglobulin E syndrome, and Severe Combined Immunodeficiency (SCID), are rare genetic diseases that lead to recurring, often life-threatening infections in affected individuals. Among other research-related activities, the NIAID-

supported Primary Immune Deficiency Treatment Consortium is a multi-center collaborative network focused on studying children with PID diseases and the treatment, with hematopoietic stem cell transplantation, of these diseases.

- Epidermolysis bullosa (EB) is a group of rare, inherited blistering conditions. Recessive dystrophic EB (RDEB) is a particularly severe form of the disease, with debilitating, chronic wounds of the skin, mouth, and esophagus. Researchers supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) have succeeded in healing wounds in a mouse model of this disease by injecting the mice with RDEB patient cells in which the gene defect has been corrected. This approach may be useful in developing therapies for RDEB. On another front, the NIAMS helped to establish the Childhood Arthritis and Rheumatology Research Alliance, a nationwide network of pediatric rheumatologists. The group is completing a clinical study of the effects of statins (drugs used to lower “bad” cholesterol) against fat buildup in the blood vessels of children with lupus, which could lead to preventive treatments for these pediatric patients.

- Recurrent respiratory papillomatosis (RRP) is a disease in which non-cancerous tumors grow in the air passages leading from the mouth and throat into the lungs. The tumors may grow quickly, requiring surgical removal to prevent blockage of the respiratory tract and suffocation. Caused by a virus possibly contracted during childbirth, the tumors often recur, requiring additional surgeries. Researchers funded by the National Institute on Deafness and Other Communication Disorders are exploring whether the use of a common anti-inflammatory drug may delay or prevent the recurrence of these tumors, as well as examining the genetic makeup of individuals of those who are exposed to the virus but do or do not develop RRP.

- In the early 1960s, the life expectancy of a child born with cystic fibrosis (CF) was just 10 years; current life expectancy for individuals with CF has almost quadrupled to 37 years. The 1989 discovery of the CF gene by now-NIH Director Francis Collins opened important windows into understanding the CF disease process, and suggested potential therapeutic approaches. While there is, as yet, no cure for CF, ongoing research provides hope for continued improvement of medical care for CF. Scientists supported by the National Institute for Diabetes and Digestive and Kidney Diseases recently developed a pig model of the disease, which provides an important tool for testing therapeutic strategies. New medications are currently in development, including one which may provide a protein for patients with some versions of the gene, and others to improve the salt-water balance in people with CF to enable them to clear mucus from their lungs.

- Understanding environmental exposures that can lead to clinical disease is critical to the prevention of those diseases or development of therapies to treat them. For example, investigators funded by the National Institute of Environmental Health Sciences are studying cognitive and motor development related to prenatal exposure to organophosphate pesticides in 3- to 9-year-olds. The study is evaluating the effects of these exposures on brain structure, metabolism, and connectivity among regions of the brain, and assessing attention deficit hyperactivity disorder, pervasive developmental problems and sleep disorders in these children.

- To build on new opportunities made possible through gene discoveries and other basic science advances, the NINDS supports translational research programs to develop therapies for spinal muscular atrophy, muscular dystrophies, and other rare pediatric neurological diseases. Some of these therapies are now entering early clinical trials, and a new clinical trials network that will help expedite such research for these disorders is underway. In May 2010, the NINDS and the NIAMS launched a 5-year natural history study of Duchenne muscular dystrophy, which aims to validate non-invasive approaches to monitor the progression and treatment of this disease, with the potential to facilitate the development of promising new therapies.

For many parents whose children have just been diagnosed with a rare condition, it is difficult to find reliable information about that condition. The Genetic and Rare Diseases Information Center (GARD) was created in 2002 by the NHGRI and the ORDR to help people find useful information about these diseases by providing timely access to experienced information specialists who can offer information on what research is being conducted, what genetic testing services are available, and which patient advocacy groups to contact for a specific rare or genetic disease (see <http://rarediseases.info.nih.gov/GARD>). Genetics Home Reference is a free online health resource from the National Library of Medicine (NLM). It is designed to give patients, families, and caregivers basic information about genetic conditions and the genes or chromosomes related to these conditions. This Web site includes summaries of more than 500 rare genetic disorders, many of which directly affect the health of infants and children. The site also provides background materials to help the public understand the significance of genetic disorders and newborn screening. Genetics Home Reference is available at <http://ghr.nlm.nih.gov>.

For many families whose children have a rare disorder, even obtaining a diagnosis can be a devastating process taking years of frustrated effort. For many conditions, a diagnosis can be essential in allowing the patient to receive appropriate treatment, even if there is no cure. Early treatment or other intervention can often ameliorate the full impact of the disease. The NIH is taking steps to expand scientific knowledge around rare diseases and diagnoses.

Together, the ORDR, the NHGRI, and the NIH Clinical Center recently organized the NIH Undiagnosed Diseases Program. Using a combination of the extensive scientific and medical expertise available at the NIH, the twin goals of this new program are to provide answers to patients with mysterious conditions that have long eluded diagnosis, and to advance medical knowledge about rare diseases. Any patient, whether a child or adult, with an undiagnosed medical condition can be referred by his or her physician for possible evaluation in the program.

Genetic screening shortly after birth permits referral to medical specialists and treatment for pediatric rare diseases to occur as soon as possible. Starting in the 1960s, with a screening test for a rare disorder (phenylketonuria, or PKU), a majority of States now screen for 29 conditions. The NICHD is leading research efforts to increase the number of genetic tests for a wide range of rare and common conditions through the Hunter Kelly Newborn Screening Program, formally established in 2009 to honor the son of National Football League Hall of Fame quarterback Jim Kelly, who died in 2005 of Krabbe disease, a rare, fatal genetic disorder affecting the nervous system. The NICHD program is aimed at identifying new screening technologies and research on managing and treating conditions that newborn screening can detect.

Because most conditions targeted by newborn screening are rare, large sample sizes are needed for research, and standard coding and terminology are required so data can be compared and pooled across State jurisdictions. In collaboration with other HHS agencies, the NLM created a Newborn Screening Coding and Terminology Guide, a free online resource that provides guidance to promote efficient electronic exchange of standardized newborn screening data. The goal is to encourage widespread use of these national data guidelines for transmitting newborn screening results to support the creation of regional and national data registries that will be used for detection, prevention, and treatment of rare conditions that affect the pediatric population, and facilitate more timely diagnosis and follow-up in the medical home.

Research on pediatric rare diseases, and future breakthroughs, are dependent on the interest and expertise of well-qualified scientists. In addition to the NIH's ongoing research training and career development programs, the NIH's Office of Science Education, in collaboration with ORDR, has developed a science education module for middle schools focused on medical genetics and rare diseases such as Marfan syndrome, childhood leukemia, and flesh-eating bacteria. After taking the lessons, students will have investigated what constitutes scientific evidence, will understand the fundamentals of inheritance and learn that this explains why some rare diseases are more prevalent in some groups than others, and will understand that many people with rare diseases can lead meaningful lives and should not be stigmatized. This curriculum will be available in September and free to teachers, in the hopes that it will engage young people on these topics and catalyze their thinking about choosing scientific careers.

With this breadth of NIB-funded research, and armed with such new resources as the human genome sequence and approaches such as the TRND program, we are poised for an era of greater understanding of the biology of many rare diseases and thus, more effective therapies. Thank you for the opportunity to present today, and I would be pleased to answer any questions you may have.

Senator BROWN. Thank you, Dr. Guttmacher.

The testimony from both of you really underscores the importance of coordination in research. Senator Bond and I introduced legislation to create a nationally coordinated research network to pursue new treatments and cures for childhood diseases, the Pediatric Research Consortia Establishment Act, based in part and modeled after the highly successful NCI sort of efforts to coordinate.

And in light of that, I'd like to ask—starting with Dr. Guttmacher—a concern I've heard a number of times is, "The current research environment does not include adequate incentives to encourage better sharing of information among researchers." And I



think that's especially a problem on rare pediatric diseases, where the population base is so small, and collaborative efforts are that much more important for learning more about diseases, making that lack of cooperation and coordination and sharing especially troublesome.

Talk to me about what steps NIH is taking to make sure that important research into rare pediatric diseases is made more widely available among researchers in the scientific community.

Dr. GUTTMACHER. You raise several very important issues. One of them is this question about cooperation, collaboration in scientific research. And I think, in some ways, the most fundamental advance that we've made in scientific research in the last decade is changing the culture of scientific research. The Human Genome Project, which has been mentioned previously, and for which the Congress should be justifiably proud for funding it and really sparking it, in many ways, many people make the obvious sort of observation that the reason for doing this was to sequence the human genome. That was the reason for doing it, but I would argue that its most fundamental contribution to science has been helping to change the culture of science.

A fundamental aspect of that program was that, every 24 hours, all of the research data developed was made publicly available for anyone who had a computer and paid their electricity bill, and therefore, could download the data. That has been instrumental, along with a number of other advances, in changing the culture to say that data that's derived in biomedical research, particularly biomedical research that's funded by the Federal Government, does not belong to the principal investigator, it belongs to society, and that we need to come up with ways to encourage collaboration, to make research data available not just to the person who developed it, but to the entire research world.

This is particularly important, this cultural change, when we talk about rare diseases. Because there will be a relatively small group of researchers involved in these diseases, it's particularly important that they work collaboratively to tackle this.

I think it also has caused the NIH to think of new and creative ways to work across the silos that are the NIH institutes too often. NIH institutes were founded for various reasons, but today's science tends to go to looking at the basic sort of biological causation of disease, and that does not observe the silos that we happen to have at NIH. So, NIH has come up with many ways to make sure that we fund creative research that goes across the traditional boundaries that we've had, which, again, is particularly important, I think, when we talk about both pediatric research and rare disease research, let alone the combination of the two.

Senator BROWN. Thank you.

Dr. Goodman, you mentioned, in your opening statement that conducting clinical trials for rare pediatric diseases, presents particular challenges. Our second panel's witnesses will talk about the need to ensure that requirements for clinical trials are stringent enough to provide reasonable assurances of safety and efficacy, but also take into account that patients with rare diseases might be—and, I think, are, in many cases—willing to accept higher levels of

risks than other patients might be willing to do. So, speak to that issue for a couple or 3 minutes, if you would.

Dr. GOODMAN. Yes, I think—this is a very important point—I think, not just in pediatrics, but, I will say, quite generally, the clinical trial enterprise and developing the clinical information we need to develop products in this country is very threatened. And it's a whole other subject that I think we could spend a lot of time on.

With respect to clinical trials in general, we do look at, and we must look at this, in a risk-benefit manner. Obviously, the equation of what could go on, and at what point in a product's development, really depends on, What are the available treatment options for that individual? What do we know about the product? So, we approach looking at proposed clinical trials in very much of a risk-based manner. We've recently made it possible to test compounds, certain compounds, where appropriate, earlier in individuals. We had a number of initiatives to increase access to investigational therapies, where appropriate. So, we're really behind this.

I would also say there's a whole science behind clinical trials. And I think we need—we are moving, as part of both personalized medicine and as we incorporate genomic information into clinical studies, from very—the necessity for very large trials that might observe a benefit only in a proportion of the population, to much more targeted trials that can be much more efficient and effective. And we're developing science around how to analyze data from much smaller numbers of patients to reach conclusions.

So, I think there's a lot of promise in this area, but there's a lot of need. Bottom line: we do look at what patients need and the specific product and trial in mind when they come to FDA.

Senator BROWN. Thank you, Dr. Goodman.

Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman.

And I do have a number of questions, for both of you, which I won't have time to be able to do this morning. So, I will submit a number of the more technical ones in writing, and would hope that you would respond on them. It will be helpful as we proceed on this.

But, I'll begin with Dr. Goodman. I like the idea of these NIH and FDA initiatives linking up to cover the span of product research, development, and then commercialization. It seems that the baton is passed well from initiative to initiative, but are there any gaps?

Dr. GOODMAN. Yes. I think there are huge gaps. And essentially, there's been a—the academic and basic science enterprise has been a very distinct one with a distinct culture and in distinct locations, and it's very different from the product evaluation and development and manufacturing enterprise, where industry and FDA are major players. And I think one of the things we really want to look at in our new NIH/FDA partnership—and frankly, we've been doing, in targeted areas—is how we can identify the biggest opportunities to fill that gap and increase the success of the enterprise.

So, I would say, in general, there are many gaps there. And, as I mentioned, there are also scientific gaps. How do we move an idea for a product, or something in an academic laboratory, into a

product we can safely give people, study and understand its safety and effectiveness.

What we want to do is not try to do everything—we'd love to do everything, but obviously there are resource constraints—but, identify, where we can, where we can bridge this gap to really meet the needs of our medical system, public health, and also of these terrible needs of patients with rare diseases. So, we're very interested in doing that. A lot of it is about how we do things and how we work together.

Senator ENZI. Thank you.

Dr. Guttmacher, how has the NIH Common Fund improved the Agency's ability to fund research on rare and neglected diseases? And what about pediatric research?

Dr. GUTTMACHER. Sure. I think, Senator Enzi, that's a wonderful example of this very problem that I was mentioning before of following the way that's—scientific discovery goes these days, which is across the traditional divisions that we've had between and among NIH institutes. The Common Fund allows us to approach biological issues in a more creative kind of way, to have funding that can look at the various manifestations.

What happens with many rare diseases is that they are multi-system diseases, so that, while one NIH institute, historically, may have taken the lead in working with that disease, it's very important that the community of researchers involved in that disease come from very different perspectives, very different disciplines. And the Common Fund allows a form of funding that really is better, often, at bringing these somewhat large and very broad teams together to look at diseases.

One of the rare diseases I've had a particular research interest in, myself, is one called hereditary hemorrhagic telangiectasia. It's even rarer to find someone who can spell it. But, it's a rare disease, and that's one that affects the lungs, the brain, the skin, the GI tract, etc. So, I know full well, from my own experience, that it's been important to come up with ways to fund research that goes across many areas. And the Common Fund has been a very good mechanism for doing that.

Senator ENZI. Good. How many therapies or research projects will the Agency be able to conduct and complete with the \$24 billion? On average, how much is necessary to—and I realize averages don't work very well—but how much, on average is necessary to successfully develop a candidate compound that's ready to be tested in patients and licensed to the private sector?

Dr. GUTTMACHER. To some degree, we don't yet know the answer to that question. And that's because both—that the costs do vary significantly, depending upon exactly what compound you're looking at and what disease you're looking at. But also, part of what the TRND program is trying to do is to come up with some new processes for going through these steps in developing new medications. And so, it's both an experiment, in terms of finding some new therapies, but also an experiment in seeing if we can't do the process somewhat more efficiently than has been done historically.

We're hoping that—to get to that stage in drug development, it will cost somewhere, we would suspect, between \$5 million and \$8

million per compound. But, we don't really know until we have enough of them out of the pipeline.

Senator ENZI. OK. Thank you.

And my time is expired.

Senator BROWN. Thank you, Senator Enzi.

Senator Franken.

Senator FRANKEN. Thank you, Mr. Chairman.

Thank both of you gentlemen, for your testimony.

And this is to both of you. There seems to be significant differences between the incentives for developing orphan drugs, on the one hand, and humanitarian-use medical devices, on the other. Could either, or both, of you please comment on these differences?

Dr. GOODMAN. Yes. Well, I think, you know, we do operate under the laws that we have. And, you know, I would say it's good that it has been recognized that devices intended for small populations and rare diseases face some of the same economic and development challenges that drugs do. This is recognized in the humanitarian device legislation. I think it's good that that's recognized. And it is having an effect. We're seeing—I think there's been about 50 devices approved under the humanitarian device exemptions. So, that's good.

Drugs and devices are different, so it's understandable that you have some differences in this legislation. But, I would say, many of the challenges are the same.

Senator FRANKEN. What are some differences that you see? For example, I know that a drug developed under this system has a long life, and so the patent on it is valuable.

Dr. GOODMAN. Right.

Senator FRANKEN. But, the devices tend to have a shorter life. So, that's a difference, isn't it?

Dr. GOODMAN. That's right. One of the very exciting and interesting things about the device development process is they tend to be frequently improved. There's a lot of innovation around engineering and technology.

Senator FRANKEN. So, you don't have quite the same incentive there.

Dr. GOODMAN. So, the——

Senator FRANKEN. I'm trying to find——

Dr. GOODMAN. Right. And the original approval paradigms are different, so that, for example, the major incentive in the orphan program, of the additional exclusivity, is not applied to devices. So, I think that's definitely one difference there.

Senator FRANKEN. I'm proud that many humanitarian-use devices have been generated by companies with Minnesota ties. But, I think they could do more, under the right conditions. I'd like to ask GAO to look into this issue further and do a thorough analysis of how the incentives in the drug industry compare to those in the device industry. We need to make sure that we're doing all we can to get devices to the kids who need them. I'll be following up with the GAO shortly to pursue this question. And I look forward to revisiting the issue with the committee.

Dr. Guttmacher, I'm sorry, I want to ask you a specific question. I was pleased to work with Senator Brown to request appropriations for research on epidermolysis bullosa, which is a terrible ge-

netic—skin disease that affects about 30,000 Americans, mostly children. But, in reality, we can't do a separate request for each disease.

In Congress, we hear from many groups advocating or progress on rare disease—parents, family members, and patients themselves. And there are a lot of disease-specific bills to advance research on these rare conditions, which is difficult, because there are really so many of them—really thousands.

Would you agree that we need more of an overarching plan for rare and neglected diseases, to enable the basic science and clinical research for these diseases? And, if so, what do you think that would look like, or should look like?

Dr. GUTTMACHER. I think we already have some elements of such a plan, and I think it is the way to approach this. Because, what one really wants to be able to do is to follow the scientific opportunities, the ones that are most likely to be able to make advances. And sometimes, particularly when one's talking about basic science, you're not even exactly sure where it's going to lead—what disease it's going to have an impact on, for instance.

So, I think having both funding and programs in place, it allows one to look broadly across rare diseases. Many rare diseases do have relationships to others so that sometime one can make an advance in one area that also goes to benefit another. I think that one needs to follow the scientific opportunities.

I think, also, though, that there, increasingly, have been partnerships between, for instance, the NIH and various specific disease advocacy organizations and groups, looking at creative ways together, and moving forward research in that area. That can be very important, not simply in terms of providing resources, though that is helpful, but also often bringing together communities of researchers who may not be paying attention to a specific disease. The public advocacy groups, the patients themselves, in working in concert with the NIH and the FDA, can often make real progress that neither could make by themselves. Sometimes these programs, and often, simply relationships, and having discussions, and making sure that one is getting the perspectives of multiple groups involved in doing it.

Senator FRANKEN. Yes.

Dr. GOODMAN. I'd like to add an example to that, if possible. One of the things we can do, and we've done with our colleagues at NIH—it's involved patient groups, product developers—is where we see an area where the science isn't all there yet, but there's a lot of interest, there's a lot of innovation. People have new products.

We will frequently hold workshops that essentially bring all the developers together, all the scientists—basic and applied, the clinicians—and say, you know, "What is the best approach to moving this field forward?" For example, we've done this in a number of areas of stem cells. So, if we want to investigate stem cells for cancer, for heart disease, for replacing insulin in diabetes, to get islet cells, for example. What are the things—build in, up front—What are the things we're going to need to know at FDA? What are the tools the scientific community needs and the issues they need to resolve to say, "Does this work? Can we make this product in a way that can be a real product that helps people?"

So, we have quite a number of these workshops that advance this applied science that really bridges to get the products to patients. And, you know, I think we need to be much more strategic, and have that be our normal practice, rather than the exception.

Senator FRANKEN. Thank you.

Senator BROWN. Thank you, Senator Franken.

#### STATEMENT OF SENATOR CASEY

Senator CASEY. Thank you very much.

I want to thank Dr. Goodman, Dr. Guttmacher, for your testimony and for the work you do on so many of these issues.

I also want to thank both Senator Brown, Senator Enzi, and especially Senator Brown, for calling this hearing and highlighting all of the challenges that we face when it comes to these diseases and the strategies that we employ to deal with so many difficult issues here.

For me and for, I think, a lot of Members of Congress, we can't go through a week, or sometimes even a day, without being both informed and inspired by constituents who come to us with a problem, or sometimes more than one problem, and they give us ideas about how to solve it or how to deal with a particular problem. Senator Specter and I had a visit, going back a number of years ago, from the mother of Nino Todaro. And Nino's mom, Lori, was what every child should have, a passionate advocate for her son. And in this case, he had the blessing of a wonderful mother, who was a fierce advocate on his behalf, and also the blessing of medical technology and all of the wonders that come with that.

But, the problem he had was that even though the NIH was treating him for his illness, a rare disease known as, periodic fever syndrome—and he was getting that treatment—the problem was that after his treatment at NIH ended, the treatment was then denied by his insurance company because it was, “experimental.”

And so, Senator Specter and I introduced Senate bill 406, which would deal with that kind of gap that a lot of families and children have to deal with everyday.

So, I'd ask you about that basic problem, where you have treatment and progress made for an individual or a group of individuals—in this case, children—and then you have that gap because their treatment is considered experimental.

Then I want to ask a second question, in the limited time that I have, about antibiotics. We have had spectacular success with infant mortality in the United States going from 20 percent in the 19th century to under 1 percent in the most recent number I have here, which is 1998. But, you have antibiotic strategies that are then adversely impacted when you have resistance built up.

So, can you speak to both of those issues? What's the strategy for making sure that when resistance is built up, you have a strategy to deal with that kind of resistance, No. 1? And No. 2, is the type of investment that has to take place to deal with that basic problem. I know that's a lot, and you've got a minute and 40 seconds to do it. But, we'll try to revisit it if your time gets short. We can do it on the second round.

Dr. GUTTMACHER. I think, to address the issue of antibiotic resistance, there are two major steps. One is to make sure the anti-

biotics are being used appropriately. One of the real reasons for antibiotic resistance is through inappropriate overuse of antibiotics, whether they be in humans or in other animals. So, one real way to prevent it is to use antibiotics when indicated, and not at other times, because the more widely they're used, the more resistant strains you're going to develop.

The other one, of course, is to try to move more quickly than the bugs do; that is, to advance, in terms of new drugs, more quickly than the various bacteria are able to evolve to be resistant to the old ones. And that's going to be—no matter what else we do—it's one of the major reasons why we need to develop new antibiotics, because old ones do tend—not all—but, they do tend to develop—or, strains develop resistance to them. So, I think it's both a question of use and in terms of development of new antibiotics.

Senator CASEY. But new investments are needed here?

Dr. GUTTMACHER. New—I think, clearly, as in the rest of developing pharmaceuticals, whether it's antibiotics or other pharmaceuticals, it takes investment, in terms of both basic research and then also more translational applied research, to be able to do it.

Senator CASEY. Dr. Goodman, any thoughts?

Dr. GOODMAN. Well, I have a lot of personal interest here, and passion about it. When I was at the University of Minnesota, we had a very strong program in how we used antibiotics in trying to reduce development of resistance. So, I agree with Alan that how we use antibiotics, in human use and agriculture, is very important. And that's one target.

I would say that it's interesting you brought this up here, and very appropriate, because it is another area very similar to what we've heard about rare diseases or device development for small populations, where the economic incentives for development do not always drive the public health outcome we seek. So, I think it's very reasonable for you to consider that issue, you know, How do we incentivize development of new drugs?

The other thing about appropriate use is, as we think about healthcare reform and having a very good learning and effective health system, really, How do we develop science about something very practical? It's not typically done in university laboratories, which is—What is the best way we use our therapies, to keep them useful and avoid problems? So, I think this is a very important and fertile area, and not unrelated, because of the incentive issue, to the issue of rare and neglected diseases. In fact, resistant bacteria start out rare. And for a developer who wants to make a product for that specific bacteria, the audience or market at that time may be very small, and the incentives may be unclear, and then, particularly if we in the medical system want to say, "Use that very appropriately, and just for those resistant organisms."

Senator CASEY. Thank you.

[The prepared statement of Senator Casey follows:]

#### PREPARED STATEMENT OF SENATOR CASEY

I would like to start off by thanking my colleague and friend Senator Brown for calling this hearing today to draw attention to rare and neglected diseases in children. I would also like to recognize the leadership of this committee for the past work that has been

done on this important issue—and the progress that has followed as a result of bipartisan efforts.

Today, we gather to discuss the challenges facing individuals with rare diseases, their families, friends and caregivers. While each of the 6,000 or 7,000 rare diseases that we know of affects only a small number of people, collectively these diseases affect 25 to 30 million Americans—almost 10 percent of our population. Many of those affected are children.

The diagnosis of a rare disease can be frightening even to an adult; for a child, it is particularly devastating. I am glad that progress has been made over the last two decades to improve children's access to treatments for rare diseases. But much remains to be done. Among children with the most common rare diseases, one in four will not live to see their first birthday. This startling and disturbing fact should evoke not just concern, but action.

When I consider the challenges of confronting rare diseases and legislative actions that will protect our children, I am reminded of my father's work as a public official over many years in Pennsylvania. As a State senator in the 1960s, he learned that a simple test for PKU, a birth defect that prevents an individual from metabolizing certain foods, was not required in Pennsylvania. Children with undiagnosed PKU often end up with severe intellectual disabilities. So he introduced a bill requiring that all children born in Pennsylvania be tested at birth for PKU; the bill passed, and many children's lives were immeasurably improved by one simple law. Thirty years later, after serving as Governor, he remembered the bill as one of the best things he ever did as a public official.

I, too, believe that helping every American child reach their full potential is one of the most important things that we, as public officials, can hope to do. This committee has shown great leadership on this issue in the past, and I am committed to seeing it continue to ensure progress continues for children with rare and neglected diseases. Too often, there is no effective therapy for a rare or neglected disease, let alone a cure. The treatments that are available are often experimental, "off-label," meaning that in addition to battling the disease afflicting their child, parents must battle with insurance companies to pay for treatment.

I have heard from many of my constituents about the challenges they face with rare diseases, including some of the diseases that I believe our witnesses will discuss today. In 2007, I met with a group of mothers who shared their struggles and frustrations in getting ongoing and consistent treatment for their children, each of whom suffers from a rare disease. Many of these parents had been able to enroll their children in clinical trials at the National Institutes of Health (NIH) and had found experimental treatments for their children that had proven extremely successful. The doctors at NIH do miraculous work in finding treatments for children with rare genetic diseases. However, when the trial ends, these children and parents are often left on their own, with no access to the previously free and effective treatment that their children were receiving.

If the treatment is a drug that has not been approved by the Food and Drug Administration or has not been specifically approved for a child's particular disease, then insurance companies



typically will not cover it because the treatment is considered “off-label” or “experimental.” If a family has enough insurance and there is off-label FDA approval, sometimes families can get coverage of the drugs. If not, the resulting cost to families is astronomical—ranging anywhere from \$10,000 to \$30,000 per month.

This is what happened to Nino Todaro, a young boy from Carlisle, PA, and that is why Senator Specter and I introduced *Nino’s Act*, S. 406, which will allow children to transition out of successful treatment in NIH studies without a gap in treatment. There are thousands of children like Nino across this country who desperately need the continuity of ongoing successful treatment for their rare disorders. These are children who have been very ill, sometimes incapacitated, and have been able to resume normal childhoods through successful drug treatment.

With all our medical technology and advancements, no child in this country should ever be denied medical treatment that is available and proven effective. Nino’s Act will give these children and their parents the peace of mind in knowing that when a study ends, their children’s successful ongoing treatment will not end. To address this, Nino’s Act will require Medicaid to cover the cost of treatment in the event that a child’s health insurance does not.

I hope that today’s hearing will help us chart a path forward. I would like to thank our witnesses for their testimony today, and for sharing with us their insights as researchers, parents and advocates for children with rare diseases.

Dr. GOODMAN. Sure.

Senator BROWN. Thank you, Dr. Goodman.

Senator Casey, if you have further questions, you can submit them for the record, of course, for them.

Thank you very much, Dr. Guttmacher and Dr. Goodman. You’re dismissed and I’d like to call the second panel.

[Pause.]

Thank you all for joining us.

I will begin the introductions, from left to right. And I know that Senator Sanders wants to introduce Ms. Moon, which he will certainly be given an opportunity to.

Alex Silver will start off our second panel. I’d like to begin by welcoming him and his family, including his wife, Jamie, his mother, Margaret, his father, David, and his father-in-law, Edward, and the good family and grandparents they are. So, thank you for joining us. He’s a partner at P2 Capital, a private investment firm in New York, holds an MBA from Harvard Business School, a BA in Political Science from Brown University. Mr. Silver is a trustee of the Dystrophic EB Research Association of America, an organization dedicated to finding a cure for EB. He recently founded the Jackson Gabriel Silver Foundation, a nonprofit dedicated to both increasing research and finding a cure. The foundation is named after the Silvers’ 2½-year-old son, Jackson.

Our next witness, Diane Dorman, is vice president for public policy for the National Organization for Rare Disorders. She is the primary Washington representative for more than 20 million Americans who have one of the 7,000 known rare diseases. Since joining NORD in October 2000, Ms. Dorman’s advocacy has been instrumental in the passage of two new public laws. She’s been influen-

tial in the adoption of numerous programs and regulations that touch the lives of patients with rare disorders.

John Crowley is president and CEO of Amicus Therapeutics. Mr. Crowley has worked with several top pharmaceutical companies, and was instrumental in finding a treatment for Pompe disease, which is a fatal neuromuscular disorder. His involvement with this disease is personal, rooted in the 1998 diagnosis of two of his children, Megan and Patrick. His dedication toward finding a treatment was highlighted in several television shows, was featured in a book entitled "The Cure: How a Father Raised \$100 Million and Bucked the Medical Establishment in a Quest to Save His Children." His efforts to develop a treatment for his children were also chronicled in the movie "Extraordinary Measures."

Thank you, Mr. Crowley, for joining us, too.  
Senator Sanders.

#### STATEMENT OF SENATOR SANDERS

Senator SANDERS. Thank you very much, Mr. Chairman. I am pleased to welcome our next witness. Ms. Suerie Moon is a member of the board of directors of Doctors Without Borders U.S.A., known internationally—forgive my French here—Medecins Sans Frontières, or MSF. In 1999, MSF received the Nobel Peace Prize, "in recognition of the organization's pioneering humanitarian work on several continents." MSF is an international independent medical and humanitarian organization. And I want to applaud MSF for all the wonderful work they do.

In this country, MSF is most widely known for emergency response during armed conflict or following cataclysmic natural disasters. What is not so widely known is that it has been engaged for decades in providing care and treatment to impoverished people suffering from diseases so neglected that most people in developed countries have not even heard of them.

Ms. Moon's own experience spans three continents over more than a decade, including field work in the Democratic Republic of Congo and China, and research and analysis on access to medicines and innovation policy issues.

It is my pleasure to introduce her today.

Senator BROWN. Thank you, Senator Sanders.

Our last witness will be Dr. Daniel Frattarelli, who's the chair of Committee on Drugs at the American Academy of Pediatrics. He's a practicing pediatrician and an expert in clinical pediatric pharmacology. Dr. Frattarelli is chair pediatrics at Oakwood Hospital Medical Center in Dearborn, MI, not far from my State.

Welcome, to all of you.

Mr. Silver try to keep your testimony close to 5 minutes. And if that means—we have all your testimony in the record, if you want to summarize, however you want to do it.

Proceed, Mr. Silver.

#### STATEMENT OF ALEXANDER J. SILVER, FOUNDER, JACKSON GABRIEL SILVER FOUNDATION, NEW YORK, NY

Mr. SILVER. Thank you. I would like to thank Ranking Member Enzi, Senator Brown, a real champion in this area, Senators Casey and Sanders, and the rest of the committee for inviting me to

speak today on behalf of the children who have epidermolysis bullosa, also known as EB.

I would like to thank the committee members who supported Senate Resolution 180, establishing national EB awareness week. With your continued support, EB can be cured. I would like to recognize Megan Barron, Joella Murray, Kati Ward, Michelle Hall, and Wyeth Carpovich, all who are here today, and all who suffer from EB. Thank you for being with us. Your burden, one that no one should face, inspires us to do what we must: cure this disease.

EB is a devastating disorder that affects a child from the moment of birth. A child suffering from EB lacks the critical protein which acts as a Velcro between the layers of skin. Without this, skin slides apart, blisters, and sheers off, causing severe pain, disfigurement, including fused toes and fingers, shredded corneas, closed throats, and, in too many cases, premature death.

To give you a sense of what EB life is like, I'd like to tell you about my 2½-year-old son, Jackson, who was born with a severe form of EB. We learned of his EB when nurses removed a Bandaid from his newborn heel and it ripped off all his skin. Every morning, my wife Jamie and I wake up and hope that Jackson hasn't torn the skin off his neck and face. We hope his mouth and throat have not blistered, preventing him from eating. We check his body for blisters, and we lance any, with large needles. Jackson takes stinging baths with bleach, every day, to kill the bacteria in his open wounds. He sits patiently through bandage changes. A fall on the playground can tear the skin off his palms. Every day, we witness his body being ravaged by this disease, and it does not have to be this way.

The Government considers EB to be a catastrophic disease. Catastrophic only begins to describe what life with EB is like. Respectfully, Senators, please take a moment and imagine your son or daughter as one of these innocent and helpless children, painfully having their bodies transformed into one devastated by infected wounds, blisters, and scarring. Imagine the simple act of hugging your child could tear the skin off. This describes a fraction of what these children experience. Everything we do in life impacts our skin.

Perhaps the most hopeful aspect of EB today is the quality of research being performed. EB research is at a stage where treatments and cures have the potential, with your help, to become a reality. We are not at the beginning of this journey. With more funding, a finish line can be in sight.

The solution must be a combined effort between public and private sectors. To give EB children a chance, they need more research funding and incentives for private research, a streamlined approval process, and affordable treatments.

Fewer than 3 percent of rare diseases have treatments available. Only 0.3 percent of the NIH's 2009 budget was spent directly on rare diseases. I estimate that only \$16 per affected person per year is spent on searching for cures—\$16.

The 2010 Federal budget calls for \$3.4 billion for carbon capture technology. Investing in the future of American energy is important. Shouldn't investing in the future of the leaders of America be

at least as important? The authorized, but unfunded, Cures Acceleration Process is a good start, but we need to do more.

When curing a disease is the mathematics of how many children are afflicted verse the profit potential of a treatment, we have gone far astray of our fundamental American values. Private funding will not cure a disease affecting too few people. We need you, our government, to provide incentives to spark private development of therapies. The proposed Priority Voucher Program is a fantastic example. It encourages companies to focus on rare drug disease development, providing commercial benefits without costing the taxpayers anything.

Achieving the balance of safety of treatments and the devastation of rare diseases is a tremendous challenge. Because of the horrific symptoms of EB, individuals and their parents are more willing to accept risks that may be inherent in emerging therapies. I am not advocating that safety be cast aside. I am saying that a person with EB defines safety differently than a healthy person, because simply living is unsafe. As CureTheProcess suggests, the FDA should consider issuing new guidelines to give rare diseases an accelerated and streamlined approval process.

Treatments of rare diseases often lead to discoveries with wider applications. By devoting the resources to protein, stem cell, and gene therapies to combat EB, we could be aiding many other Americans. This potentially includes brave veterans who suffer burns on the battlefield, and those suffering from chronic wounds and ulcers that will not heal.

In closing, while there is promising research focused on helping children with EB, the current system fails them. The solutions are clear: more public and private funding, an accelerated review process, and affordable treatment. With this committee's help Jackson, Joella, Megan, Michelle, Kati, and Wyeth, and other kids with EB, can grow up to live healthy and pain-free lives, but only if we give them that chance. Inaction is not a choice. We can cure this disease. Let's turn that hope into a reality, and let's do it now.

Thank you for the opportunity to testify today.

[The prepared statement of Mr. Silver follows:]

#### PREPARED STATEMENT OF ALEXANDER J. SILVER

##### SUMMARY

My testimony presents a parent's perspective of the painful day-to-day experience of living with Epidermolysis Bullosa (EB) and conveys the devastation that this disease has ravaged on my son and other children who suffer from it. I aim to raise awareness about EB as well as to provide solutions that are within our grasp to treat and cure EB and other rare diseases. My testimony describes the current state of EB research and recommends the following measures be taken as soon as possible: (i) increase funding for EB and rare disease research; (ii) create and refine private market incentives to spur development of treatments and cures; (iii) redesign and streamline the approval process for rare diseases; and (iv) ensure treatments are attainable to those who need them.

##### WHAT IS EPIDERMOLYSIS BULLOSA?

- EB is a disorder that impairs a child's layers of skin from staying together. This child is missing a protein that acts as the "velcro" between the layers of skin causing his or her skin to blister and shear off with movement. There are three major EB subtypes—Simplex, Junctional and Dystrophic. Only 2 to 4 out of every 100,000 children are born with EB. My son Jackson was born with Recessive Dystrophic EB (RDEB), one of the most severe subtypes, in October 2007.

## THE DEVASTATION OF EB

- EB profoundly impacts every aspect of life. Skin is the body's largest organ. Children with EB may be unable to walk, eat, play, sit, write, hug or even sleep without significant risk of skin shearing off their little bodies. Fingers and toes can become fused together forming mittens and unusable feet. The esophagus can close due to injury from eating. Malnutrition, infection, ocular and dental issues, constant pain and cancer at an early age characterize the lives of these children.

## CURRENT EB RESEARCH AND THE REASONS EB PATIENTS CONTINUE TO SUFFER NEEDLESSLY

- There is high quality research being performed today that can render this disease livable and curable. Researchers know exactly what causes this disease and have encouraging knowledge of how to fix it. We are failing to marshal the resources needed to get there. EB is at a stage where treatments and cures have the potential, with more funding, to become a reality.
- Major areas of research being conducted include protein replacement as well as stem cell and gene correction therapies. Many of these researchers are hoping to commence Phase I trials as soon as possible.
- Children with EB needlessly continue to suffer because the target market of EB children is not large enough to attract commercial interest on its own. When curing a disease devolves into the mathematics of how many children are afflicted versus the profit potential of developing attainable treatments, we have gone astray from our fundamental American values.

## WHAT IS NEEDED TO BEAT EB, OTHER RARE DISEASES AND SAVE AMERICA'S CHILDREN

- *More Funding*—Of the 7,000 rare diseases affecting 30 million Americans (10 percent of the population), less than 0.3 percent of the 2009 NIH budget was spent on finding cures for these diseases and likely less than \$16 annually of Federal funds is spent per person suffering from a rare disease to find a cure. This is not a question of additional spending but one of our priorities.
- *Public/Private Partnerships and Commercial Incentives*—For a disease that affects too few people to spark commercial interest, the government must provide incentives for private development of drugs and therapies. The proposed priority voucher program encouraging drug development for rare pediatric diseases enables a company to focus on orphan drug development because it can enjoy commercial benefit and also serve a social good. This would bring additional solutions to the market quickly, which would help children with EB and other rare diseases without costing the taxpayers anything.
- *Streamlined Approval Process*—Achieving a balance between the safety of treatments and the devastation of rare diseases remains a tremendous challenge for regulators. Because of the horrific symptoms of EB, individuals with EB and their parents are more willing to accept risks that may be inherent in emerging therapies. The CureTheProcess campaign suggests that the FDA create a new review division for rare biochemical diseases; and for the FDA to issue new guidelines to give the rarest diseases access to an accelerated approval process. By working together, CureTheProcess, the NIH TRND Program, Cures Acceleration Network and others can ensure patients with rare disorders get earlier access to effective treatments.
- *Affordability of Treatments*—Potential treatments for EB and other rare diseases must be made affordable to those who need them most. A cure for EB is useless to the child shut out because he or his family cannot afford to pay for it.
- *Wider Application of Treatments Developed for EB*—Treatments for rare diseases often lead to discoveries with much wider applications. A few examples are Remicade, Rituxan and Epogen. By devoting resources to protein, stem cell and gene therapies to combat EB, we may also aide many other Americans. This potentially includes brave veterans who suffered burns that resulted in blistering and scarring while serving our country, as well as victims of other burn injuries and those who suffer from wounds and ulcers that will not heal. These individuals share many characteristics with severe RDEB children. EB is worthy of curing in its own right, but many Americans could benefit as well.

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I would like to thank Chairman Harkin, Ranking Member Enzi, Senator Brown and the entire committee for allowing me to speak today on behalf of the children, and their families, who suffer from Epidermolysis Bullosa, also known as EB. I would also like to thank the members of the committee who supported Senate Resolution 180 in 2006, which established National EB Awareness Week. Specifically, I

would like to thank Senator Hatch, who was a co-sponsor of this resolution. S. Res. 180 passed the Senate by unanimous consent and without amendment. With your continued support, we can transform EB into a treatable and curable disease. I would also like to recognize Megan Barron, Joella Murray and Leandro Santos who are in attendance today. These individuals all suffer from EB. They endure more pain than one can imagine. Their burden, one that no child or person should face, inspires us to do what we must—cure this disease.

#### WHAT IS EPIDERMOLYSIS BULLOSA (EB)?

EB is a debilitating and devastating genetic disorder that affects a child from the moment he or she is born. EB is not specific to any ethnicity or gender. A child who suffers from EB lacks the critical protein that binds his or her layers of skin together. This protein acts as the “velcro” that attaches one layer of his or her skin to the other. Without this “velcro” when this child moves, his or her skin slides apart, blisters and shears off leading to severe pain, disfigurement, and in too many cases, a premature death from an aggressive form of skin cancer called Squamous Cell Carcinoma. Within certain subsets of EB, the cumulative chance of developing this cancer is almost 100 percent. A child with a severe form of EB can have a 60 percent cumulative risk of dying by age 15. There are three major EB subtypes—Simplex, Junctional and Dystrophic and within each type there are multiple subsets. The difference among them is the level at which a blister forms within the skin and which particular protein is missing or impaired.

My experience with EB began on October 11, 2007. On that day, my wife Jamie and I were blessed with the birth of our beautiful son Jackson, who is the light of our lives and a joy to everyone around him. Yet, our lives were nearly shattered with the diagnosis that Jackson was born with a form of EB called Recessive Dystrophic EB (or RDEB for short). Despite being born at a major metropolitan hospital, the physicians caring for Jackson had never seen a case of RDEB before, which made his condition difficult to diagnose, an experience most EB children share. RDEB is considered to be one of the worst forms of EB. Jackson, like all those with RDEB, is missing the protein Collagen VII. This became evident on the day after Jackson’s birth, when nurses removed a bandaid from his newborn left heel and the adhesive tore off his precious skin. Most of my comments will focus on RDEB, although there are equally horrific forms of EB which share many characteristics with RDEB.

Like most people, I had never heard of EB and had no awareness that our son would suffer from this condition until he came into this world. We did not know about EB because it is an orphan disease, which is defined as a disease affecting fewer than 200,000 people. Figures from the National Institutes of Health estimate that between 2 and 4 out of every 100,000 children are born with EB. Based upon these figures, EB would be an “ultra-orphan” disease defined as a disease that affects fewer than 20,000 people in the United States. The Government considers EB a “catastrophic illness.” “Catastrophic” only begins to describe life with EB.

#### THE DEVASTATION OF EB

To say that EB impacts every aspect of a child’s life is a gross understatement. Skin is the body’s largest organ. Among its most important functions, skin is the first line of defense to protect the body from trauma and infection. Everything we do in life impacts our skin—walking, eating, playing, sitting, writing, hugging, sleeping—the list goes on. For children with EB—like our son Jackson—every aspect of their lives at every moment is overshadowed by this terrible disorder. These children are often born missing large areas of skin leaving gaping wounds that never heal; walking and standing are impaired over time because their toes become fused as the result of continuous injury; the simple joy of holding a crayon to draw becomes impossible because their fingers fuse and contract turning their young hands into mittens; eating is painful and sometimes impossible because the esophagus closes due to injury and scarring, which is only temporarily relieved by a surgical procedure in which the esophagus is stretched open. When this solution stops working, a gastric feeding tube is placed in their small bellies in order to enable proper nutrition and hopefully stave off growth retardation and anemia. Even the fundamental act of sleeping is extraordinarily difficult because of the level of pain and discomfort that these children experience 24 hours a day.

Like all kids, children with EB rub their eyes when they are sleepy. Only in their case, rubbing their eyes can tear their eyelids and corneas, prohibiting these children from opening their eyes in the morning without suffering extreme pain. Naturally, children with EB also want to play alongside their peers. However, falling down on the playground can remove all the skin from their little palms or produce

blisters on their knees the size of oranges. Respectfully Senators, please take a moment and imagine yourself, your son or your daughter, or a relative being one of these innocent and helpless children—slowly and painfully having your little body transformed into one devastated by infected open wounds, blisters and scarring. Imagine that the simple act of hugging your child could tear the skin off his or her body. This describes just a fraction of what these children experience, as it does not account for the social scrutiny and the stares they receive by simply walking or being wheeled down the street. In its entirety, EB impacts vision, speech, nutrition, mobility and indeed every single aspect of a child's life. Unfortunately, a recent study determined that approximately 50 percent of children with RDEB are *always* in pain.

During a typical day, a child with RDEB undergoes a special bath and a bandage change. Given the large areas of skin missing from such a child's body, bathing is an extraordinarily painful experience. Bandage changes can last anywhere from 30 minutes to several hours and bandages can cost a family as much as an astounding \$14,000 per month. An EB child's meals consist mostly of soft foods and liquids, assuming he or she has not been forced to resort to receiving nutrition through a feeding tube. When skin blisters or tears, it must be treated as soon as possible, causing parents to carry a costly arsenal of needles and bandages anytime that they leave the house. For a child with EB, the joyful act of participating in sports—such as little league or youth soccer—is often out of the question due to the skin tears, blisters and scarring that would result. For this reason, even playing with other children can be impossible. Simply put, this disease prevents a child from just being a child.

Speaking for a moment as Jackson's dad, every morning Jamie and I wake up and hope that Jackson hasn't torn the skin off his neck and face from rubbing during his sleep. We hope he does not have a blister in his mouth or his throat that prevents him from eating that day. Throughout the day, we check his body for blisters that have developed and lance any with large needles when we see them. Sometimes this can be extremely painful to Jackson but we are forced to physically restrain our son and do it anyway. We dress him in special shoes and only soft clothing. We keep bacterial culture kits at home and use them all too often to check him for infection. Like many EB patients, our son must avoid crowded places that kids love such as zoos, museums and birthday parties. And we must stay indoors during the bulk of the summer because the heat and humidity exacerbates his blistering. Every day, Jackson takes a bath with vinegar or bleach to help kill the bacteria on his little body. This bath often causes stinging pain to Jackson's many open wounds. He sits patiently through his uncomfortable bandage changes; sadly, our little boy does not know any differently. He endures physical, occupational and feeding therapies as well as specialized nursing visits six times per week to keep his body as mobile and healthy as possible. And yet, through all these painful challenges that would cause most of us simply to give up, our brave Jackson's smile lights up a room even though his body is slowly being ravaged by this disease. Some additional examples: as noted above, our son lost all of the skin on his heel from the removal of a bandaid the day after his birth which has never grown back normally; his hands are severely scarred and the quality of his skin is poor due to the continuous damage they endure; that damage continues to progress up his arms everyday. It's critical to note that—despite the pain and discomfort I have just described—Jackson has a moderate case of RDEB. Children with more severe cases suffer exponentially more.

With this background, the key questions are: (i) where are we now; (ii) where can we can go; and (iii) what is needed to succeed at giving these children the fundamental American right of a chance at living good lives.

CURRENT EB RESEARCH AND THE REASONS EB PATIENTS CONTINUE TO  
SUFFER NEEDLESSLY

Perhaps the most hopeful aspect of EB today for Jackson, and all children living with EB, is the quality of research being performed in the United States and internationally that can render this disease livable and ultimately a disease of the past. Due to research dating as far back as 1974, which has been funded by NIH grants as well as private donations; EB is at a stage where treatments and cures have the potential, with your help, to become a reality. Indeed, researchers know exactly what causes this disease and have encouraging knowledge of how to fix it. But where we are failing is in marshalling the resources needed to get there. To reiterate, we are not at the beginning of this journey. Technology has caught up to the research and, with more funding, a finish line can be in sight for the thousands of children, like our son Jackson, who were born with this disease.

Some of the major areas of research currently being conducted in the United States include protein therapy by Doctors David Woodley and Mei Chen of the University of Southern California and Doctor Peter Marinkovich of Stanford University. The concept of this research is straightforward. EB researchers estimate that a person needs only 35 percent of the typical level of Collagen VII for the skin to behave normally. Drs. Woodley and Chens' concept is to replace the protein that is missing in RDEB kids—Collagen VII—with localized injections. Drs. Woodley and Chen have proven in a mouse model that this method works. They are now looking to commence a Phase I trial as soon as possible. Experts indicate that with the *sufficient resources*, a commercialized therapy could be available in 5 to 8 years. Imagine what that would mean to a child whose skin tears off in her shoes to have a localized injection that renders the skin on her feet potentially normal. For years, doctors have administered localized injections of Collagen I for cosmetic purposes. Collagen VII and Collagen I are related. In this proposed treatment, the doctors would simply administer Collagen VII in a similar fashion as Collagen I is administered in a cosmetic setting. In other words, doctors have the knowledge to apply this treatment as soon as it is available. While not a cure, this would be a truly viable “game changing” treatment, allowing a child like my son to live a better life.

Other potential cures are being pioneered both at the University of Minnesota and at Columbia University by Drs. Wagner, Tolar, Christiano and Cairo. These are stem cell therapies and the basic concept is to replace the bone marrow of an individual with EB with a donor who has the proper Collagen VII production capability. As the body's wounds heal and the skin regenerates, the theory is that Collagen VII would be produced, which in turn would keep an EB patient's layers of skin together. There are currently trials ongoing at both locations, which have shown promise as a systemic cure.

At Stanford University, Drs. Lane and Khavari have labored over a form of gene therapy to treat EB. In this approach, a small section of skin is removed from a person with EB and the gene “error” is corrected to produce Collagen VII. The corrected skin is grown into larger amounts and then grafted back onto the body. We hope that they can commence a trial very soon.

In addition to these efforts, internationally, there has been work by Dr. John McGrath in the United Kingdom in which individuals with EB received injections of donor cells that produce Collagen VII. Results, though early, have been promising.

So why hasn't Collagen VII been developed commercially? Given that its unquestionably important life saving purpose? The answer is that the target market of EB children is not large enough to attract commercial interest on its own. Development costs—which can run into the hundreds of millions of dollars—trump the profit that can be made. Simply said, the economics do not work in most cases—and children like our son Jackson are the victims of this unfortunate and unfair fiscal reality. When curing a disease devolves purely into the mathematics of how many children are afflicted with EB versus the profit potential of developing this attainable treatment for these children, we have gone astray from our fundamental American values. As I described earlier, there are real therapies and treatments in the works that—with appropriate funding—can offer these children suffering from EB a chance at a “normal” life. What keeps these children in bandages is the lack of funds, the difficulty in attaining any funds that may exist and the cumbersome approval process of potential treatments.

#### WHAT IS NEEDED TO BEAT EB AND SAVE AMERICA'S CHILDREN

I believe the solution must be one of a combined effort between the public and private sectors. For EB children to have a chance at a life free of pain—one where they can “truly” be kids—they need more available funding for researchers, more incentives to fund this research via a public/private partnership, an approval process that considers both safety as well as the devastating effects of EB, and finally a mechanism to ensure the treatments are affordable to those who need them.

The National Organization for Rare Disorders (NORD) estimates that there are 7,000 rare diseases affecting 30 million Americans. Of these disorders, only approximately 200 have FDA-approved treatments. Less than 3 percent of these diseases have treatments available. According to figures provided by the NIH, it provided only \$118 million in research funds for orphan drugs out of its \$30 billion budget in 2009. Unfortunately, this amounts to 0.3 percent of the NIH budget. The Office of Orphan Drug Development provides approximately \$15 million annually in grants. Assuming there is additional funding via other Federal sources, it may be safe to assume that approximately \$500 million in Federal funding per annum is available for orphan diseases. To put this in context, Genzyme, a biotechnology com-



pany, estimates that it cost over \$500 million to develop a treatment for a rare disorder called Pompe disease. It also means that of the 10 percent of the U.S. population affected by rare diseases, roughly \$16 per person is spent per year in searching for cures. *ONLY \$16*. The U.S. Federal budget is \$3.5 trillion. Of that amount, the 2010 budget calls for \$3.4 billion to support carbon capture and storage technology. Investing in the future of American energy is very important. But it begs the question; shouldn't investing in the future leaders of America—including our son and the many other bright young stars afflicted with this horrible disease—be at least as important? Given the current economic environment, I understand as well as anyone that there is little room for additional spending and we have many pressing issues at hand. It is a question of what our priorities should be as Americans who value human life and the right to have a “normal” and carefree childhood.

The Government cannot provide the solution itself, nor should it be expected to. However, for a disease that—although devastating and debilitating—affects too few people to spark commercial interest, the Government must lead and provide incentives for private development of drugs and therapies. The proposed priority voucher program encouraging drug development for rare pediatric diseases, which is a refinement of the tropical disease voucher program, is a fantastic example. If this program is expanded to cover rare pediatric diseases, then a company that would not otherwise focus on orphan drug development will do so because it can enjoy commercial benefit while also serving a social good. This would bring additional solutions to the market quickly, which would help every child with EB and indeed any other rare disease. Corporations will follow the Government's lead. Public interest, awareness and incentives can shape private behavior. Creative solutions that provide direct or indirect incentives are effective and indispensable methods to spur the pace and likelihood of treatment developments. I—along with all other parents of sons and daughters suffering from rare diseases—urge you to consider the proposed priority voucher program. This program can improve and save the lives of millions without costing the taxpayers anything.

Beyond additional funding and private market incentives, the process for the approval of rare disease therapies must be streamlined. Achieving the delicate balance between the safety of treatments (particularly new or developing treatments) and the devastation of rare diseases remains a tremendous challenge for regulators. We need a process which deeply considers the alternative that individuals with EB or other orphan diseases face in lieu of approved treatments. A child with RDEB lives each day with tremendous pain, hoping his fingers and toes do not fuse and his esophagus does not close. With this disease, every breakdown is one step closer to a terminal cancer. Because of the horrific symptoms of this disease, individuals with EB and the parents of children with EB are more willing to accept risks that may be inherent in emerging therapies because the alternative is a painful and debilitating life. I am not advocating that safety be cast aside. I am saying that a person with EB defines safety differently than a healthy person; to a person with EB, simply living life is inherently unsafe. The CureTheProcess campaign by the Kakkis Foundation has promising ideas on how to address this issue. CureTheProcess suggests that the FDA create a new review division for rare biochemical diseases; and for the FDA to issue new guidelines to give the rarest diseases access to the accelerated approval process. We can quickly and dramatically improve the current regulatory process for rare diseases. The result should be a surge in development activity for even the rarest disorders. An improved regulatory path working together with the NIH TRND Program, Cures Acceleration Network and other new incentive programs will help ensure more patients with rare disorders will get earlier access to specific, effective treatments.

These potential treatments for which we seek funding must also be made affordable to those who need them most. A cure for EB is useless to the child shut out because he or his family cannot afford to pay for it.

One additional area that is often overlooked is that treatments for rare diseases often lead to discoveries with much wider applications. For example, Remicade—which was developed for the treatment of Crohn's disease, a population of 500,000 people—has been found to effectively treat Rheumatoid Arthritis and forms of Psoriasis, a population of over 5 million people. Rituxan, developed for non-Hodgkin's lymphoma—a group of 70,000 people per year now helps the 1.3 million Americans who suffer from Rheumatoid Arthritis. Epogen, now used for Anemia, is another illustration.

As these examples demonstrate, funding of orphan diseases can frequently have the unintended consequence of benefiting a much broader population than those suffering from the orphan disease itself. By devoting the resources to protein, stem cell and gene therapies to combat EB, we may also indirectly aide many other Americans. This potentially includes brave veterans who have suffered burns that resulted

in blistering and scarring while serving our country on the battlefield, as well as victims of other burn injuries. These individuals share many characteristics with severe RDEB children. EB is worthy of curing in its own right, but many Americans (including many of America's Finest; the men and women of our military) could benefit along the way.

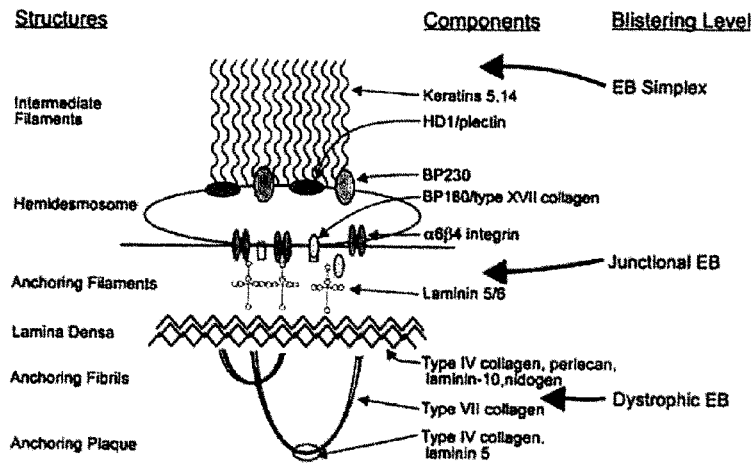
#### CONCLUSION

In closing, while there is promising research focused on helping children with EB, the current system fails them. It does not provide enough funding, sufficient private market incentives or a review process that is appropriate for the severity of the disease. The solutions are clear—more public and private funding and partnerships, a streamlined and accelerated review process and affordable treatments. We know the solutions and now, with this committee's help and support, Jackson, Joella, Megan, Leandro and every child with EB can grow up to live healthy and pain-free lives. But only if we give them that chance. Inaction is not a choice. This can be done. We can cure this disease. Let's turn hope into reality, and let's do it now. Thank you for inviting me to testify today.

#### APPENDIX

##### I. FORMS OF EPIDERMOLYSIS BULLOSA<sup>1</sup>

There are three main forms of EB: *Eli Simplex*, *Junctional Eli* and *Dystrophic EB*. These different subtypes are defined by the depth of blister location within the skin layers. Blister formation of EB simplex is within the epidermis. Sometimes EB simplex is called epidermolytic. Blister formation in *Junctional EB* is seen at the level of the lamina lucida within the basement membrane zone. *Dystrophic EB* or *dermolytic EB* is a scarring form of EB which occurs in the deeper tissue at the level of the lamina densa or upper dermis.



EB Simplex is caused by faulty proteins in the top layer of skin. This results in incorrectly formed keratins, deeming them unable to perform their normal role as a "scaffolding" for the top most layer of skin. The top layer of skin falls apart, resulting in a blister. Although EB Simplex is considered a non-scarring form of EB, secondary infection may cause scarring.

Junctional EB is caused by mutations in the genes encoding alpha 6, beta 4 integrin, collagen XVII or one of the three chains of Laminin 5. This leads to defects in the formation of hemidesmosomes or anchoring filaments. Defects within any of those components of the skin allows for the separation of tissue and blister formation whenever there is friction or trauma to an area. In many instances blistering can occur spontaneously.

<sup>1</sup>Dystrophic Epidermolysis Bullosa Research Association of America (DebRA).

Dystrophic EB is caused by mutations in the genes that carry the instructions necessary to produce the proteins in the basement membrane zone of the skin. This results in incorrectly formed anchoring fibrils, deeming them unable to perform their normal role as a “stable interweave” between the dermal and epidermal layers of the skin. Mutation occurs within the Collagen VII gene, which encodes the protein of the anchoring fibril. Anchoring fibrils hold together the two layers of skin. As a result, there is a lack of adherence and disruption of the skin when any friction or trauma occurs to an area. Where the two layers separate there is a blister. Blistering in the various types of dystrophic EB causes scarring.

To differing degrees, EB can manifest itself in the following ways:

- Generalized blistering.
- Growth retardation and malnutrition.
- Gastrointestinal tract—may include blisters in mouth, esophagus and/or anal margins.
- Pseudosyndactyly—Fusion of fingers and/or toes.
- Problems with the soft tissue inside the mouth leading to esophageal strictures.
- Squamous Cell Carcinoma.
- Ocular (eye) involvement.
- Atrophic scarring—depressions in skin as a result of thinning in epidermis or dermis.
- Nail dystrophy—presence of rough, thickened or absent finger or toenails.
- Presence of Milia—tiny skin cysts.
- Anemia—a reduced amount of red blood cells, volume of red blood cells and amount of hemoglobin.
- Granulation tissue—appearance of red fleshy tissue which is capillary formation during tissue healing.
- Dental caries (cavities).
- Enamel hypoplasia—underdeveloped enamel upon the teeth.
- Genitourinary tract involvement including scarring and/or urethral stenosis.
- Scalp abnormalities—presence of blisters on scalp and/or scarring alopecia (areas of scarring with absence of hair growth).
- Respiratory tract involvement.

Senator BROWN. Thank you very much, Mr. Silver.

Ms. Dorman.

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

Ms. DORMAN. Thank you, Senator Brown, Ranking Member, Senator Enzi, and other distinguished members of this committee, for inviting me to testify today regarding a topic that is extremely important to NORD.

In the United States, as already been mentioned, there are nearly 7,000 diseases considered rare or affecting fewer than 200,000 Americans. Some of these diseases affect only a few hundred people, or even a few dozen. There are certain challenges and issues that all people with rare diseases share, no matter where they fall in this spectrum.

Since many rare diseases are genetic, more than two-thirds of these patients are children. Rare diseases tend to be serious and lifelong. Many are life-threatening.

A recent editorial in the journal *Nature* noted that, among patients afflicted with any of the 350 most common rare diseases, 27 percent will not live to see their first birthday.

My colleagues and I have a great deal of contact with patients and their families. Over and over again, we hear about the difficult issues they face, which include diagnosis delay, too little research, too few treatments, reimbursement issues, and a general sense of having been abandoned by our Nation’s healthcare system.

I've organized my comments and subtopics reflecting the most urgent issues, challenges, and opportunities that we face.

No. 1 are preclinical challenges. Families often contact NORD just after having received a diagnosis. They are typically in a very fragile state, desperately seeking information, and hoping to find resources, medical experts, and clinical trials. All too often, we have to tell parents that there are no treatments for their child, and no one doing research.

Part of the problem is a lack of natural history data, validated animal models, patient registries, and other tools that form the foundation for clinical research. The rare disease patient community is highly motivated and resourceful, but patients can't do it alone. There must be Federal funding and Federal guidelines to establish these basic tools for research. With such support, I can guarantee that patients and patient organizations will be active partners in moving studies forward.

Then there are clinical challenges. Because patients are scattered around the globe, clinical research on rare diseases is more expensive and more challenging than other research. This must be taken into account in study requirements. Furthermore, patients with rare diseases are generally willing to accept higher levels of risk than other patients may be motivated to do.

Also, rare-disease research today is often funded by the patient community, through golf tournaments, raffles, even bake sales and car washes. As a society, it is wrong for us to expect people with devastating diseases to fund the search for their treatments. A more significant commitment is needed at the Federal level.

And there are regulatory challenges. NORD hosted a summit for 300 participants, in May 2009, to focus on accelerating the development of orphan products and ensuring patient access to them. A point made by several speakers was that industry frequently develops a second product for a disease rather than addressing a disease that has no treatment. This was attributed, in part, to a climate of regulatory uncertainty.

A few weeks ago, the chairman of NORD's board of directors addressed a public hearing hosted by FDA. Noting that only about 200 of the nearly 7,000 rare diseases have treatments, he urged FDA to implement a statement of policy on rare diseases and orphan products. His point was that, while orphan drugs are reviewed with the same standards of safety and effectiveness as other drugs, FDA does exercise a certain degree of scientific judgment in reviewing products for rare diseases.

There are reimbursement challenges, which is really devastating for families. Certain metabolic diseases, such as PKU, require specialized infant formulas and medical foods. Patients who don't get these special foods may suffer very serious consequences, including severe mental retardation. However, insurers, including Medicaid, don't always reimburse for these expenses, since these foods are not prescription drugs. Only about a third of the States currently mandate reimbursement for specialized infant formulas and medical foods. Since these foods are a necessary part of medical treatment for children with certain diseases, NORD would like to see a Federal mandate to ensure that no child is denied a needed medical food.

Another reimbursement issue is the off-label use of drugs for rare diseases. It has been estimated that 90 percent of Americans with rare diseases are treated off-label, simply because there's no FDA-approved treatment for them. But, increasingly, insurers, both public and private, are denying coverage for off-label use of drugs, biologic and medical devices, on the basis that such therapies are experimental. For people with rare diseases who have no other option, this is a serious problem.

Then there's the issue of humanitarian-use devices that Senator Franken has brought up. Pediatric medical devices are, similarly, very important. Children are not just small adults; they need both drugs and devices developed specifically for their unique needs. A member of NORD's medical advisory committee, Dr. Robert Campbell, who is a pediatric orthopaedic surgeon at CHOP, in Philadelphia, invented, developed, and brought to market a pediatric device, known as the "expandable titanium rib," that has saved the lives of hundreds of children who have a rare condition known as thoracic insufficiency syndrome. Prior to his work, there was no treatment for children with this condition. Dr. Campbell's research was begun with a small seed-money grant from NORD and later funded by FDA's Orphan Product Grants Program. The device he developed was approved by the FDA as humanitarian-use device. Because no company was interested in manufacturing it, Dr. Campbell also took it upon himself to find a small company willing to do so. It took him 14 years to do so.

This story is not unusual, and there are many children today desperately needing pediatric devices who don't have a Dr. Campbell looking after their interests. Those children need our help.

In medical education, NORD worked closely with the medical community. And we believe that our Nation is blessed with many caring, dedicated medical people in the field. However, we feel that medical education in the United States does not adequately address rare diseases and related challenges at this time. We urge greater emphasis on rare diseases and on medical education centers to prepare young clinicians.

Then there are current initiatives that we are working on. NORD believes significant progress has been made in recent months that will help to accelerate the development and treatment for children and adults with rare diseases. We urge continuation of initiatives, such as a training course for rare disease investigators, sponsored by FDA, NIH, NORD, and Duke University, that will result in development of a handbook to serve as a roadmap; a task force instituted by NORD, with NIH and FDA, collaborating to identify weaknesses in the system and ways for the two agencies to work closely together; and also, a congressional Rare and Neglected Diseases Caucus to focus on attention on these important issues.

Our recommendations were as follows: continued progress in innovative initiatives, such as a training course; Federal funding and guidelines to develop natural history data; patient registration of their basic tools; recognition that clinical trials for rare diseases represent a unique set of circumstances and needs; reduced regulatory uncertainty; and increased emphasis on rare diseases in our centers of medical education. We endorse funding measures proposed for orphan product development in the current Senate appro-

priations bill. And we urge this committee to remember that research on rare diseases often provides fundamental breakthroughs in knowledge.

In closing, I would like to reiterate several points. Among patients afflicted with any of the 300 most common rare diseases, 27 percent will not live to see their birthday. Patients and their families are willing to take on a far greater degree of risk than those affected by more common conditions. And finally, in an essay entitled “The Keys to the Kingdom,” by Dr. Fred Kaplan, the expert on one of the most rare and horrendous bone disorders, fibrodysplasia ossificans progressive, or FOP, Dr. Kaplan said,

“Research into the study of rare disorders will provide the key that unlocks the door to the treatment of the common disorders that affect the majority.”

We all stand to improve our lives and our health by promoting the development of new treatments and cures for rare pediatric disorders.

[The prepared statement of Ms. Dorman follows:]

PREPARED STATEMENT OF DIANE EDQUIST DORMAN

I wish to thank Chairman Harkin, Senator Enzi and other distinguished members of this committee for inviting me to testify today regarding a topic that is extremely important to my organization—the development of safe, effective treatments and cures for the millions of American children afflicted with rare diseases.

My name is Diane Dorman, and I am the vice president for Public Policy of the National Organization for Rare Disorders (NORD). NORD is a non-profit organization with offices in Washington, DC and Danbury, CT, that provides a voice to the nearly 30 million Americans with rare diseases. It was established in 1983 by patient organization leaders who served as the primary consumer advocates responsible for enactment of the *Orphan Drug Act*.

In the United States, there are between 6,000 and 7,000 diseases considered rare, according to the National Institutes of Health. To be classified as “rare”, a disease must be believed to affect fewer than 200,000 Americans. This is the definition used by the Food and Drug Administration and by the National Institutes of Health.

Although each individual rare disease affects no more than 200,000 people, and some affect only a few hundred or even a few dozen, rare diseases in the aggregate affect approximately 1 in 10 Americans. There are certain issues and challenges that are common to all people with rare diseases, no matter where they fall on this spectrum.

Since many of these diseases are genetic, many of the patients are children. It is believed that more than two-thirds of the individuals affected by rare diseases in the United States are children.

Furthermore, most rare diseases are serious and chronic or lifelong. Many are life-threatening. A recent editorial in the journal, *Nature*, noted that among patients afflicted with any of the 350 most common rare diseases, 27 percent will not live to see their first birthday.

My colleagues and I have a great deal of one-on-one contact with rare disease patients and their families, as well as with patient organization leaders. As you might imagine, some of the most difficult phone conversations we have are with parents of young children who have rare diseases. These families are faced with very difficult issues such as diagnosis delay, too little research, too few treatments, reimbursement or other financial issues, and a general sense of having been abandoned by our Nation’s health care system.

We very much appreciate the invitation to speak to you today. Since the topic is broad, I would like to organize my comments into the following sub-topics to reflect what we see as the primary issues and challenges through our daily contact with the families of children affected by rare diseases.

PRE-CLINICAL CHALLENGES

Families often contact NORD just after having received a diagnosis for a child. They are typically still in a very fragile state in which they are desperately seeking

information about the disease and hoping to find resources, medical experts, and opportunities to participate in clinical trials.

You can imagine how difficult it is to have to tell families, as we frequently do, that not only is there no treatment for their child's disease but there is no research in progress. The sad reality for far too many people with rare diseases is that no one—at NIH, at a teaching hospital, on a university campus, or in industry—is doing research on their disease at this time. And no research means no hope for the future.

Part of the problem is a lack of natural history data, validated animal models, patient registries and prevalence/incidence data on rare diseases. These basic tools form the foundation for clinical research, and they are a necessary first step.

The rare disease patient community is highly motivated and resourceful. Many of the few patient registries and other research resources that exist at this time have been funded or launched by patient organizations. But patients can't do it alone. There must be Federal funding and Federal guidelines and encouragement for the establishment of these basic tools for research. With such support, I can guarantee that patients and patient organizations will be active partners in moving studies forward.

#### CLINICAL CHALLENGES

Because of the small patient populations, and the fact that rare disease patients are scattered around the globe, clinical research aimed at developing treatments for the rare disease community is by its very nature more expensive and more challenging than other research. The requirements for clinical trials need to be stringent enough to provide reasonable assurance of safety and efficacy for patients, but they must also take into account the fact that these diseases present a unique set of challenges for researchers. In addition, patients with rare diseases are generally willing to accept higher levels of risk than other patients may be motivated to do.

At this time, a significant portion of rare-disease research is funded by the patient community. While NIH and particularly the NIH Office of Rare Diseases Research have made admirable strides in recent years in focusing greater attention on the need for research on these diseases, for many of the very rare diseases it is still too often the patient community that funds and drives research through golf tournaments, raffles, even bake sales and car washes. As a society, it is wrong for us to expect people with devastating diseases to fund the search for their treatments. We need to make a more significant effort at the Federal level to fund studies of rare diseases and incentivize researchers to pursue them.

#### REGULATORY CHALLENGES

NORD hosted a Summit in May 2009 at which we drew together approximately 300 participants from NIH, FDA, patient organizations and industry to focus on how to accelerate the development of treatments for rare diseases and how to ensure patient access to treatments. A point made by several speakers was that industry frequently develops a second product for a disease that already has one or more treatments rather than addressing a disease that has no treatment at all. This was attributed, at least in part, to reduced regulatory uncertainty once the first product is brought to market.

A few weeks ago, the chairman of NORD's board of directors addressed a public hearing hosted by the FDA. His recommendation, on behalf of NORD, was for FDA to reduce regulatory uncertainty and increase consistency by implementing a statement of policy on regulation of therapies for rare diseases.

Only about 200 of the nearly 7,000 rare diseases currently have FDA-approved treatments. To NORD and the patient community, it appears as if the low-hanging fruit have been harvested since enactment of the *Orphan Drug Act* in 1983, but much more remains to be done.

While orphan drugs are reviewed with the same standards of safety and effectiveness as other drugs, FDA publicly acknowledges that it exercises its scientific judgment in taking into account the special challenges of developing treatments for very small patient populations. However, without a statement of policy on rare diseases and orphan products, it is not possible to ensure consistency in that process.

Other uncertainties in the regulatory arena include the need for identification and agreement on clinical endpoints and surrogate markers, the need for greater transparency and understanding of the regulatory process, and the need to have regulators who understand the special challenges of developing orphan products. NORD applauds the recent creation of an Associate Director for Rare Diseases position in FDA's Center for Drug Evaluation and Research (CDER) and the inclusion in the

current Senate Appropriations bill of funding for staff to assist the associate director.

#### REIMBURSEMENT CHALLENGES

Certain metabolic diseases, such as phenylketonuria, require specialized infant formulas and medical foods as a very important part of treatment. Patients who don't get these special foods may suffer very serious consequences, including severe mental retardation. However, insurers (including Medicaid) don't always reimburse for the cost of these foods since they are not prescription drugs.

Only about a third of the States currently mandate reimbursement for the costs of specialized infant formulas and medical foods. Since these foods have been demonstrated to be an important part of medical treatment for children with certain diseases, NORD feels strongly that access should not be hindered as a result of inability to pay. We would like to see a Federal mandate to ensure that no child is denied a needed medical food because of failure by insurers to provide coverage.

Another reimbursement issue is the off-label use of drugs for rare diseases. It has been estimated that 90 percent of the nearly 30 million Americans with rare diseases are treated off-label simply because there is no FDA-approved therapy for them. As the cost of healthcare continues to skyrocket, insurers (both public and private) increasingly are denying coverage for off-label use of drugs, biologics, and medical devices on the basis that such therapy is experimental. For people with rare diseases who have no other options, this is becoming a serious problem.

NORD does not want to discourage pharmaceutical and biotechnology companies from conducting clinical trials to obtain FDA approval for these additional uses. However, we feel that legislation might be employed appropriately to help rare-disease patients and families obtain reimbursement for off-label treatment that is medically necessary when no FDA-approved options are available to them.

#### HUMANITARIAN USE DEVICES

While we've been speaking primarily of orphan drugs and medical foods, clearly there is a need for the development of pediatric medical devices for many children with rare diseases. And NORD feels strongly that it is important to emphasize that children are not just small adults. Sick children need medical devices and drugs developed specifically for their unique needs, taking into account their smaller size, growing bodies, and active lifestyles.

To illustrate the challenges inherent in development of medical devices for this particular population, we cite the experience of Dr. Robert Campbell, a pediatric orthopedic surgeon on NORD's Medical Advisory Committee, who is affiliated with the Children's Hospital of Philadelphia.

Dr. Campbell invented, developed and brought to market a pediatric device known as the expandable titanium rib that has saved the lives of hundreds of infants and children who have a condition known as thoracic insufficiency syndrome. Prior to his work, there was no treatment for children with this condition, and most ultimately died because there was not enough room for their lungs to expand as the children grew. (Please see attachment 1)

Dr. Campbell's research was made possible by a small seed-money grant from NORD, when no other funding was available. Later, he was able to obtain funding to continue the research through the FDA Orphan Product Development grant program. Ultimately, the device he developed—the titanium rib—was approved by FDA as a Humanitarian Use Device. Because no company was interested in manufacturing it, Dr. Campbell also took it upon himself to find a small company that would—essentially for humanitarian reasons—agree to manufacture and market the titanium rib.

The families helped by this medical device remain tremendously grateful to Dr. Campbell and his colleagues. But there are many others with other rare diseases who may not have a Dr. Campbell, and they need help, too.

A complicating factor is that, while FDA considers HUDs to be approved, they must still be reviewed by IRBs. As a consequence, insurers (both public and private) consider them experimental and may not reimburse for them. In addition, while pediatric HUD developers can now realize a profit, this is not the case for all humanitarian devices. The prohibition against developers profiting from these devices needs to be lifted.

#### MEDICAL EDUCATION

NORD works very closely with the medical community, and we know that our Nation is blessed with a caring and dedicated medical establishment. However, we feel that medical education in the United States does not adequately address issues and



challenges related to rare diseases, and is not at this time encouraging enough young scientists to engage in both research and clinical care related to rare diseases. Given the fact that approximately 1 in 10 Americans are affected by rare diseases, we believe a greater emphasis on these diseases is warranted in our centers of medical education.

One of the primary problems encountered by rare-disease patients and families is delay in obtaining an accurate diagnosis. In 2003, NORD partnered with Sarah Lawrence College on a study to replicate, on a smaller scale, an earlier study by the Federal Government of problems experienced by people with rare diseases. Sadly, our study showed that the diagnosis problem remained essentially unchanged since the Federal Government's study done in 1989.

#### SOME CURRENT INITIATIVES THAT BRING HOPE TO PATIENTS

Currently, NORD is working with FDA, NIH and others to address some of the problems outlined above and to accelerate the development of rare disease therapies. These initiatives include:

- A three-day training course for investigators from academia and small biotechnology and pharmaceutical companies involved in conducting research to develop treatments for rare diseases. This course will be taught by experienced faculty from academia, industry, NIH and FDA, and is being sponsored by NORD, FDA, NIH and Duke University. It will result in the development of a handbook for rare-disease investigators.
- A task force instituted by NORD, in which NIH and FDA have agreed to work together to examine the interface between the two agencies, identify weaknesses, and find ways to work together more effectively to facilitate the development of safe, effective treatments for patients. This task force has already had several meetings.
- A series of orphan designation workshops being hosted by the FDA Office of Orphan Products Development, in partnership with NORD and others, to de-mystify the process of getting orphan designation for a product in development as a rare-disease treatment.
- A series of focus groups, hosted and sponsored by NORD, to gather information from academic researchers, patient advocates, the investment community, and the biopharmaceutical industry to help NIH and FDA review current practices and consider possible improvements.
- An increasingly global response to the needs of rare disease patients, as evidenced by the partnership of NORD and its European counterpart, the European Rare Disease Patient Organization or EURORDIS.
- The launch of a Congressional Rare and Neglected Diseases Caucus, advocated by NORD and its partners, to help focus attention on these important issues and how to address them.

#### OUR RECOMMENDATIONS

In general, our recommendations to this committee, reflecting what we've learned over the past 27 years as well as our current assessment of the most critical needs of patients at this time, are as follows:

- Continued progress in areas such as the NORD Task Force through which NIH and FDA are identifying ways to work together more effectively; the Rare and Neglected Diseases Congressional Caucus; and the development of a handbook to serve as a roadmap for rare-disease clinical investigators.
- Federal funding and guidelines to develop natural history data, patient registries, epidemiological data and other basic tools to support research.
- Recognition that clinical trials related to rare diseases are, by their nature, different from studies of more common diseases and that they represent a unique set of circumstances and needs.
- A renewed Federal commitment to funding research on rare diseases through offices such as the NIH Office of Rare Diseases Research.
- Reduced regulatory uncertainty through steps such as greater transparency of FDA practices and creation of an FDA statement of policy on rare diseases and orphan products.
- Incentives to encourage young investigators to study rare diseases.
- Increased emphasis on rare diseases in our centers of medical education.
- Adoption of the funding proposed in the current Senate Appropriations bill for the FDA Orphan Products Research Grants Program and to staff the new associate director function in FDA CDER.
- Assessment of reimbursement issues related to medical foods and off-label treatment for children with rare diseases.

- Training in rare diseases and orphan product development for FDA reviewers and staff involved in review of orphan products.

In closing, I would like to reiterate several very important points:

1. Among patients afflicted with any of the 350 most common rare diseases, 27 percent will not live to see their first birthday.
2. Patients and their families are willing to take on a far greater degree of risk than those affected by more common conditions.
3. Understanding the pathogenesis of rare diseases will advance the scientific and medical understanding of common conditions.

Chairman Harkin and Ranking Member Enzi, thank you once again for allowing NORD to testify before you today.

Senator BROWN. Thank you, Ms. Dorman.

Mr. Crowley.

**STATEMENT OF JOHN F. CROWLEY, PRESIDENT AND CEO,  
AMICUS THERAPEUTICS, CRANBURY, NJ**

Mr. CROWLEY. Great. Thank you, Senator Brown.

Senator BROWN. Thank you.

Mr. CROWLEY. Thank you, Senator Brown—and thank you for the leadership in the Rare Disease Caucus—Senator Enzi, Senator Sanders, Senator Casey.

I come here wearing a number of hats today. I come as the chairman and chief executive officer of a small biotechnology company, Amicus Therapeutics, a 100-person company in Cranbury, NJ, developing novel medicines for human genetic diseases. I come also as a member of the board of directors of the Biotech Industry Organization. But, most importantly, I come as the father of two children with a rare disease, as you alluded to in your kind introduction, Senator, Megan and Patrick.

My whole involvement in this industry goes back to that 1998 diagnosis. My wife and I were a year out of graduate school, 31 years old, and we are recessive carriers for a gene to cause this fatal neuromuscular disease, Pompe, so there's no history of it in our family. We were told, in March 1998, that our then 15-month-old daughter, Megan, and our then 7-day-old son, Patrick, had this rare form of a muscular dystrophy. We were told that there was very little research, there was no drug in clinical development, and the doctor said, most apologetically—he said, “I’m sorry. There’s nothing we can do. They’ll live maybe another year or two.”

What has happened in the last 12 years, I think, could only happen in the United States. It was a common effort by a lot of people who worked incredibly hard, tirelessly. And I think it's representative of what is very unique about drug development in America, this virtuous circle, where it was years of academic research; it was researchers at the NIH; it was reviewers at the FDA; it was philanthropist patient advocates; a small biotechnology company that I started; more out of frustration with the pace of development than anything, to just try to move the ball a little bit; it was venture capitalists; it was eventually large biotech companies. And from 1998 to 2006, we helped to develop a drug eventually brought to market by a large biotechnology company, Genzyme. And with that, it was 8 years of clinical development, almost \$500 million of investment—almost exclusively private industry investment—to bring the medicine to just a couple thousand people in the United States and around the world.

With Pompe disease in children, there is a severe enlargement of the heart. Our kids' hearts were two to three times normal size when they went into the clinical study. Within months, their hearts shrunk back down to normal. We saw significant improvements in their muscle strength.

Years later, they still take that medicine—every other week, a 6-hour infusion. It maintains their strength. It keeps their heart healthy. It is still not a cure. It is a first-generation approach. They're still in wheelchairs. They're still on ventilators. They are now, I'm happy to report, 13 and 12 years old, going into the eighth and seventh grades—amazingly smart and vibrant and precocious little kids.

We had the incredible experience of having this movie, "Extraordinary Measures," made about our lives that came out just earlier this year. And it was a very positive experience for our family—at times, very surreal. But, in many ways, Megan and Patrick, in that film, are proxies for millions of other children, some of whom have received life-saving medicines, medicines that never would have come about without the efforts of a lot of people and the Orphan Drug Act, 27 years ago. But, probably even more significantly, I think they really represent the millions of children who still strive for therapies, who need cures, who need development, who need that virtuous cycle of development that we've put in place, in the last many decades in the United States, to not only continue, but to grow and to thrive.

And with all those different hats I wear, I can tell you I'm very concerned that, on one hand, we sit on what I think is a Golden Age of Medicine, in the next 10 or 20 years, as we look at all the technologies in development in universities, at the NIH, in private industry—so much potential to fundamentally alleviate human suffering, to cure these diseases, to provide breakthroughs that could ultimately affect much more broadly prevalent disorders, like Parkinson's and Alzheimer's, diseases that really are genetic diseases at their core.

But, as an industry, we look at things like the financial markets. For small biotechnology companies, venture capital funding is down 30 percent. Much of that doesn't go into the risk-taking enterprises that are typically involved in this development.

IPOs in our industry—there were 35—our company was one of them, in 2007. In the last 5 years, there have been five. Our company, in 5½ years, has raised \$300 million, and spent over \$200 million, to develop a handful of drugs for very rare human genetic diseases, none of which are still approved. Our lead drug has been in clinical studies now for 5 years, through phase 1; safety studies through phase 2; proof-of-concept studies; and now, in what will be a fairly lengthy time to enroll, hopefully by the end of this year, a phase-3 study to prove its safety and efficacy. All in, my guess is, it will be \$200 million to develop that drug, and that it will have taken 7 years of clinical studies for a drug that's probably going to help a couple thousand people with a rare disease called Fabry disease.

That paradigm can't continue. We can't raise that type of money. We can't do 7 years of clinical work.

In 1992, the AIDS community was very active, and they got a drug called AZT approved, the first treatment that started to check the disease, HIV. In the 20 years since, under the subpart H regulations of the FDA for accelerated approval, approval based on a surrogate endpoint, almost 20 drugs for AIDS have been approved, much, much to the benefit of that community, and rightfully so.

In those 20 years, just one drug for a human genetic disease has been approved under those accelerated standards.

I think, with that, some of the proposals that, as a dad, as an entrepreneur, and as an industry representative, we support are: urging the FDA to issue new guidance and review standards for demonstrating the efficacy and safety of rare diseases; greater use of surrogate endpoints likely to predict clinical benefit; much faster timelines; ultimately, I think, the ability to accept higher levels of risk—I think the mantra should be “approve fast and follow long.” We should look at funding the Cures Acceleration Network. I think that’s a good example of public/private partnership that can play a role for the most rare of the rare diseases. I think, too, promoting industry—in the fact that industry is the one that develops all of these drugs through capital markets incentives, extending and expanding the Qualifying Therapeutic Discovery Project Tax Credit, I think will be incredibly important.

I thank all of you for the time. This is obviously an incredibly important issue to all of us. I think it will be incredibly important going forward. And I look back to 1984, when Ronald Reagan signed the Orphan Drug Act into law. It was a very bold move, and it was with full Democrat and Republican support. When he signed that bill in the White House, he said, “I only wish, with the stroke of this pen, that I could also decree that the pain and suffering of people living with these diseases would cease, as well.” It didn’t, with the stroke of that pen, but it set in place a whole new framework, a system of incentives, the patient advocacy movement, itself, that has led to a significant number of cures. We need to take it to the next level. Maybe we need a second Orphan Drug Act to address these challenges.

But, hopefully we can get to the day where fewer and fewer parents have to sit in that doctor’s office and hear what we heard 12 years ago, a doctor saying, “I’m sorry, there’s nothing we can do.” I think we can do much better.

Thank you.

[The prepared statement of Mr. Crowley follows:]

PREPARED STATEMENT OF JOHN F. CROWLEY

INTRODUCTION

Good afternoon Chairman Harkin and members of the committee. My name is John F. Crowley of Princeton, NJ. I am the chief executive officer and chairman of Amicus Therapeutics, Inc. and I serve on the board of directors of the Biotechnology Industry Organization (BIO). More importantly, I am the father of two children diagnosed in 1998 with Pompe disease—a rare and devastating neuromuscular disorder. I appreciate the opportunity to be here today to talk about ways in which the Federal Government can encourage and speed the development of drugs, vaccines, and diagnostic tests for rare and neglected diseases.

Amicus Therapeutics is a 100-person biopharmaceutical company developing orally administered, small molecule drugs called pharmacological chaperones, a novel, first-in-class approach for treating a broad range of human genetic diseases. Amicus’ lead program is in Phase 3 testing for the treatment of Fabry disease, a rare and

severe lysosomal storage disease affecting an estimated 10,000 individuals worldwide. My involvement with the biotechnology industry stems from that 1998 diagnosis of our two youngest children, Megan and Patrick.

BIO represents more than 1,200 biotechnology companies, academic institutions, State biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

From my perspectives as both a biotechnology entrepreneur and as a father, I am most appreciative that the committee is undertaking this broad inquiry into the state of rare and neglected pediatric diseases. The time to consider change and to build on past successes could not be better. We have come a long way but we have much further to go to address the severe unmet medical needs of people who bravely live with these rare diseases, especially children. Research and drug development in this crucial field is at a precarious tipping point.

#### THE FOUNDATION OF SUCCESS: THE ORPHAN DRUG ACT

The Orphan Drug Act (ODA) of 1983 has brought unprecedented success. It contained several market-based incentives for biotechnology and pharmaceutical companies to develop and market products for rare diseases. To date, in excess of 1,000 orphan product designations have been granted by the FDA's Office of Orphan Product Development and more than 250 drugs and biologics have received approval by the FDA with Orphan designation, collectively helping millions of adults and children with rare diseases worldwide. We have come a long way, indeed. In the decade prior to enactment of the ODA fewer than 10 products for rare diseases came to market. Among these advancements are accomplishments that I have participated in professionally and, in the case of my own children, have witnessed most personally. Today, there are an estimated 7,000 rare diseases, each one affecting 200,000 or fewer individuals, but collectively affecting nearly 30 million Americans. Treatments exist for only a fraction of these devastating, life-threatening diseases leaving so many people of all ages with significant unmet medical needs. And of those treatments, the majority of approved orphan drugs are for those rare diseases with higher prevalence.

BIO believes that the lesson we can learn from the ODA is that government policies can effectively foster research and development of products for rare diseases—and create an entirely new marketplace to meet severe unmet medical needs. The challenges of developing orphan products are great and they require innovative policy and regulatory solutions. Further, many rare diseases affect far fewer patients than the 200,000 threshold in the ODA. For these diseases, the challenges are even more daunting.

#### CONTINUED UNMET MEDICAL NEED

The gap in development for pediatric rare diseases is particularly acute for the most uncommon disorders, which collectively still affect the majority of children with rare diseases. Most all rare or orphan diseases with lower prevalence remain without treatment. According to an Orphan Drug Development Trends report published by BioMedical Insights in January of this year, 83 percent of rare diseases are "ultra-rare," yet only 11 percent of orphan designations issued between 1997 and 2009 were for these ultra-rare diseases (144/1,310). What do these numbers translate to for the average patient family in the rare disease community? No treatment options and the invariable and painful words from a physician that are all too common: "I am sorry. There is nothing we can do. There are no treatment options for your child."

For most of these rare and extremely rare diseases, perhaps as many as 2/3, medical research is absent—completely. Affected patients, their families and friends strive to bring attention to their causes. For other diseases, such as Tay-Sachs, for example, medical research is just now gaining momentum, despite it being one of the most commonly known rare, genetic diseases, with one of the oldest advocacy groups in the country, and the first disease for which a carrier genetic test was perfected back in 1970. Yet it could be many more years before a safe, effective treatment is ready for the clinic, and tens of thousands of children and adults will still die from this deadly neurodegenerative disease. As a past-president of the National Tay-Sachs & Allied Diseases Association, I've seen the hope sustained by parents listening to academic researchers, while they watch Tay-Sachs ravage their young children physically and mentally. And for those rare diseases fortunate to have a

treatment, not all is perfect. As can be the case with Pompe disease, for example, many patients cannot tolerate the treatment due to immunogenicity or other significant issues. For others, the treatment may be of limited effectiveness but there are no other options. Much work remains to be done in orphan drug development to evolve the unmistakably critical work already achieved for rare diseases.

#### ABILITY TO MEET THE CHALLENGES

In the year 2010, we have the collective ability to tackle the challenges of understanding and developing viable treatment options for rare and ultra-rare diseases with unmet medical need, especially for children. Basic scientific, biomedical and preclinical research is taking place with groundbreaking technology in laboratories at colleges and universities, independent academic medical centers, at the National Institutes of Health, and in the biotechnology industry. Initiatives such as the Therapeutics of Rare and Neglected Diseases (TRND) Program at the National Human Genome Research Institute (NHGRI) have impressive capabilities and hold great promise for discovery at the level of public/private collaboration that is necessary to help address many of these challenges. In particular, this is a new and exciting approach to moving forward from screening and developing compounds through the junctures of pre-clinical and clinical work, optimizing resources and harnessing the varied expertise of collaborators along the way.

Though just getting off the ground, the TRND program has the potential to help companies bring promising products forward. Many of these products stall in development because biotech companies lack the financing to advance them. The TRND program could fill some of these funding gaps. BIO is encouraged by this effort. We pledge to work with the NIH on intellectual property concerns, technology transfer rules, and other matters to make sure the program accomplishes its goals.

Patient advocacy for pediatric rare diseases is increasingly important. Families and friends of children and adults affected by these debilitating, horrific, often fatal rare diseases no longer passively sit around sick rooms and hospital rooms. They—we, because I am one of them, are well aware of the promising developments taking place in the research labs of the biotechnology industry and at academic institutions and are confident that technology can match our sense of urgency. Patient advocates are proactive agents for changing how this research can be conducted and how quickly it gets translated to the clinic, all with the hope that it will positively influence their loved one's clinical outcome. Today's patient advocacy and disease organizations are partners in social and venture philanthropy with industry. They want the exciting and promising technology that exists for their diseases to see the light of day, and even more they want treatments and potential cures to be realities in their lifetimes. Here are just two examples.

The Cystic Fibrosis Foundation is one such health venture philanthropist. In 2000, there were few potential treatments in the CF pipeline. Today, there are more than 30 treatments in development, a few already available to patients, with a pipeline portfolio ranging from gene therapy, protein rescue, mucus alteration, restoring airway surface liquid (ion transport), anti-inflammatory, anti-infective, transplantation and nutrition. In the area of protein rescue alone, the CF Foundation invested more than \$100 million with Vertex Pharmaceuticals and \$25 million with PTC Therapeutics, both fellow BIO member companies, for two different small molecules in the past few years.

“Fight Spinal Muscular Atrophy” (FightSMA) dedicates itself to research for a cure for this group of diseases which affect the motor neurons of the spinal cord and brain stem. In its infantile form, SMA kills more babies than any other genetic disease. With grants up to \$250,000 each, FightSMA is a social philanthropy funding about 20 academic and medical institutions in the United States and internationally. The organization brings approximately 25 SMA researchers together for an annual scientific conference to encourage collaboration at the same time that SMA-affected families come to meet each other for support and learn from these researchers.

It is exactly this type of community-driven, cross-fertilization and financial support of ideas, and sharing of disease experience that has occurred at advocacy organization conferences for years that the patient community is more recently asking take place on a broader scale in clinical research and drug development. Patients are appreciative of the active role of the Office of Rare Diseases at NIH in supporting these meetings and of the Office of Orphan Product Development participation at many programs. Collaborative approaches are in the United States and abroad, originated by highly respected organizations such as NORD and now assumed by their counterparts, such as EURORDIS, CORD and ICORD. The 2010 European Conference on Rare Diseases held last month in Krakow, Poland, attracted

more than 600 participants from 43 countries, with one-third from Eastern Europe: the aim to discuss public policies and actions that will improve the lives of people with rare diseases. The rare disease community may be growing, but it represents a world that is getting smaller all the time. The demands of the diseases themselves have always been there; however, the presence of the diseases is augmented by the fast-paced technology available to researchers, the charged atmosphere of advocacy, immediate access to information about diseases, research and support groups, and connectivity through the Internet and social media for all disease stakeholders.

Collectively, these activities represent a trend toward acceleration of all aspects of orphan drug development to ultimately, and most importantly, benefit patients living with rare diseases. The Federal Government can support new policies and programs that extend, leverage and enhance these global efforts.

The biotechnology industry has made a significant contribution to this field over the years. Indeed, the mission of many biotech companies, such as my own, is to bring hope to the patients who suffer from rare diseases. Today, I would like to provide you with some thoughts about policies that will complement and advance the objectives of the ODA and facilitate the development of the next generation of orphan products for children.

#### NEW POLICIES FOR CONSIDERATION TO ACCELERATE TREATMENTS FOR RARE AND NEGLECTED DISEASES

##### CHANGING THE FDA REGULATORY ENVIRONMENT FOR PEDIATRIC RARE DISEASES

The committee must address the current regulatory environment and the FDA's review process for orphan products. For instance, the sheer size of patient populations is an important factor for consideration in clinical study design. Affected individuals are part of such small individual patient populations; they may represent disease prevalence of as many as 67:100,000 to as few as 2:100,000. No one rare disease exceeds an incidence of 200,000 in the United States. Limited individual disease experience makes it unlikely that there are organized registries from which to draw information for the majority of these diseases, and unrealistic to consider conducting natural history studies as prelude to or in parallel with clinical trials. (The topic of disease and product registries currently is a controversial one in the rare disease community and one worth exploring, as well.) Numbers of subjects for any orphan product study should be carefully considered based on current disease situations. Given that these trials, especially registration studies requiring larger numbers of subjects, typically necessitate global recruitment, protocols should be able to satisfy institutional review boards and ethics committees internationally. In the ultra-rare category, consideration also should be given to combined Phase 1/2 and Phase 2/3 studies with a Phase 4 commitment from sponsor companies making these investments. The regulatory mantra should be: Approve fast, follow long.

The committee should respectively consider enabling the FDA to focus on orphan diseases/orphan products beyond the fine work already being conducted by the Office of Orphan Product Development. The multi-systemic, complex nature of the majority of rare diseases, as genetic, metabolic, inborn errors of metabolism, further complicates a simple route forward for the guidance and development of well-designed clinical protocols. Therefore, study design guidance and review for rare diseases should also have an approach characteristically distinct from that used with common disease guidance and review. The FDA would benefit from a dedicated team of experts in the genetic and metabolic disorders that together with regulatory colleagues can offer guidance to study sponsors that will result in clinical protocols that account for limited patient numbers, the most current collective thinking on disease biomarkers, surrogate endpoints and better use of pharmacogenetics.

I suggest that the establishment of a separate Division of Genetic and Metabolic Disorders at FDA is essential and long overdue. Along these same lines, the Agency might consider having reviewers, staff other than OOPD, spend more time with rare disease patient organizations to learn from their leadership and members what they think and know of clinical trials, barriers to participation, etc. This might be mutually beneficial for educational purposes and understanding the rare disease patient experience.

Additionally, BIO urges FDA to publish further guidance regarding orphan drug development that provides interpretation of current regulations including: what are acceptable subsets of disease to meet the prevalence requirement; what is a "major contribution to patient care" that allows a drug to be found "clinically superior" even if it has the same active moiety of a previously approved drug; what is the definition of "reasonably likely to predict clinical benefit," and whether the sponsor of the original drug can also be a "subsequent sponsor."

Other regulatory changes should be pursued as well. For example, we urge that FDA review use of its standards for demonstrating efficacy of a rare disease product. The requirement for sponsors to use two adequate and well-controlled studies is the same standard used by the Agency for other drugs and biologicals. However, it is significantly harder to develop those studies for rare disease products because of the small patient populations available. This is particularly true for very rare diseases. BIO urges FDA to consider alternatives that include: approval based on a single adequate and well-controlled trial at a  $p < 0.05$ , if there have been NIH-conducted studies using the same populations; use of consortia between government, academia and industry; and use of patient registries for rare diseases as part of efficacy considerations.

In addition, we urge FDA to support greater use of surrogate endpoints for product approval, either for full approval or accelerated approval purposes. Although they currently can be used during the accelerated approval process, more guidance from the Agency is needed on use of surrogate endpoints for registration. Amazingly, in the past 20 years, only one drug for the treatment of a human genetic disease was approved under the “accelerated approval” provision of subpart H of the FDA regulations.

Moreover, BIO believes FDA can improve communications processes for rare disease stakeholders. For example, once orphan designation has been granted, there is no communication policy for sponsors as the review divisions take over. This often makes interaction with the Agency difficult. It is important that FDA encourage reviewers to establish communications processes that allow reviewers and sponsor researchers to discuss scientific issues based on real-time data more efficiently. Such real-time scientific dialogue would not take the place of the required regulatory communications and meetings with FDA but rather ensure that these required communications and meetings are utilized more efficiently. Additionally, there is no special priority given to rare disease products in current FDA practices regarding protocol assistance, communication with the Agency and other matters. Given the complexity and special challenges of developing rare disease products, these communication gaps impede development and approval.

Other regulatory changes should be pursued as well, such as greater transparency at the Agency including more meeting opportunities, and greater consistency among FDA’s review divisions. The challenges of developing rare disease products require new regulatory approaches. Also, in light of the fact that biomedical research and development is a global enterprise, we urge the FDA to work with foreign regulatory agencies, particularly in Europe, to harmonize requirements for pediatric research.

In addition, many patients suffering from rare diseases are treated by products that are labeled for another indication. Companies looking to get FDA approval for the rare disease indication are often either prohibited or severely restricted from performing a placebo-controlled trial for that indication because the commercially available (off label) product has become the clinical standard of care. In such situations, FDA should allow non-placebo controlled trials such as historical control or open label trials.

Regarding FDA’s approval of medical devices for rare diseases, the use of different threshold numbers for defining rare (“orphan”) disease for medical device (4,000) versus drugs and biologics (200,000) is illogical. The device regulations should be changed, as it is the disease incidence not the therapy that should define the population.

Finally, we note that the dual statutes governing pediatric research, the Best Pharmaceuticals for Children’s Act (BPCA) and the Pediatric Research Equity Act (PREA), have been remarkably successful in ensuring that the medications used in children are tested and labeled appropriately for their use. Together BPCA and PREA have generated a wealth of pediatric drug information for physicians and parents. BPCA rewards drug companies with 6 months of additional market exclusivity after the completion of studies in children as requested by the Food and Drug Administration (FDA). PREA requires new drugs to be studied in children and allows FDA to mandate child studies in certain already marketed drugs. However, despite a proven track record in encouraging pediatric medical research, both programs are scheduled to expire in 2012. BIO urges Congress to recognize the success of these programs, eliminate the sunset provision, and make permanent the incentives for ongoing pediatric research.

#### UNDERSTANDING AND ACCEPTING APPROPRIATE RISK TOLERANCE

The required pre-clinical and clinical safety studies and risk assessments for the development and approval of life-saving pediatric drugs for rare diseases is virtually the same in all instances as for antibiotics for common ear infections. We need to



better understand the risk/reward ratios for these rare disease drugs. Addressing the tolerance for risk in drug development in the rare disease space is also essential to advancing newer therapies. Individuals directly affected by these highly unusual disorders, or their parents, custodial family members and caregivers are experiencing unusual, almost unique and unprecedented unmet need. They have a sense of urgency few if any can understand, but this does not necessarily cloud their judgment or ability to understand the risks and benefits of clinical trial participation. There should be no less scrutiny of safety for patients with ultra-orphan diseases but many of the traditional pre-clinical and clinical safety studies typically required of most drugs need to be reevaluated in the context of the cost and time associated and the severity of the unmet need.

Certainly, the protracted timelines too often impose the ultimate cost on affected families awaiting treatment for their rare disease—the loss of their child or other loved one. It behooves the FDA to reassess the process and the extraordinary financial costs involved in developing orphan drugs. For example, the last five drugs developed and approved to treat lysosomal storage diseases have cost more than \$200 million each in research and development expenses alone to develop, while addressing populations in the United States of less than 3,000 patients. Each of these drugs were for use in children as well as adults. There is no current economic framework that exists to promote this kind of investment. While the industry is appreciative of the existing incentives established by the Orphan Drug Act 27 years ago, it is time to update these to ensure ongoing and future innovation to benefit rare diseases. Some very practical considerations are: investment tax credits, permanent R&D credits and tax grants for companies conducting research for ultra-orphan treatments, accelerated clinical studies, and special tax treatments for investments in smaller companies with fewer than 250 employees.

BIO companies believe that FDA has made great strides to make sure that safe and effective orphan products reach patients as soon as possible. For example, we applaud the FDA Office of Orphan Products Development for their sponsorship of the training program for reviewers on statistical methods for small patient populations. In addition, the “Build an Orphan”—designed to help companies properly submit the application for orphan drug designation in a timely fashion—holds promise. But more must be done.

The ODA created a grant program administered by the FDA to fund companies for development of orphan products. It's called the Orphan Drug Grant Program. This program has not had increases in funding commensurate with inflation for many years. BIO urges increased funding for the Orphan Drug Grant Program.

Similar to what FDA has done through its Critical Path initiative, we believe the Agency also needs to take affirmative steps to spur drug development for rare diseases. The regulatory approval pathway simply must be more predictable. For example, during the most recent negotiations surrounding enactment of the Prescription Drug User Fee Act (PDUFA), the FDA committed to developing a series of guidances regarding clinical trial design; adaptive clinical trials; and new methods of statistical analysis. These would be valuable for developers of rare disease products. We appreciate the publication of the adaptive clinical trial guidance and the non-inferiority draft guidances released earlier this year, and we look forward to timely publication of other pending guidances on clinical trial design.

#### FUND THE CURES ACCELERATION NETWORK

The recently enacted Patient Protections and Affordable Care Act (PPACA) includes a provision called the Cures Acceleration Network (CAN) that is intended to speed the translation and application of promising new treatments for diseases from the laboratory to the marketplace. The CAN will be placed under the Office of the Director of NIH, and is authorized to make grants through the NIH to biotech companies, universities, and patient advocacy groups to target applicants that have shown promise at the laboratory level, but have not been able to advance enough to attract investors that are willing to commit to a promising discovery.

Specifically, CAN will focus on funding the development of “high need cures”, defined as those which the NIH Director determines to be a priority to “diagnose, mitigate, prevent or treat harm from any disease and condition” **and** for which commercial incentives are unlikely to result in timely development. The functions of CAN will be to not only support research that would accelerate the development of high need cures, but to reduce barriers of getting discoveries that are in the lab into clinical trials, as well as facilitate the FDA review process.

In regards to providing assistance with the FDA review process, CAN will work to facilitate communications with the FDA on the status of a high needs cure approval and ensure activities are coordinated in a manner that would expedite their

development approval. Lastly, CAN will work to connect those developing high need cures with additional technical assistance.

PPACA authorizes \$500 million for fiscal year 2010 for the creation of two new grant programs. Importantly, these grant awards will be available to biotech companies, medical centers, universities, disease advocacy organizations, patient advocacy organizations, pharmaceutical companies and academic research institutions.

#### EXTEND AND EXPAND THE QUALIFYING THERAPEUTIC DISCOVERY PROTECT TAX CREDIT

One provision included in the health reform law that may be of enormous benefit to small life sciences companies is the Qualifying Therapeutic Discovery Project Credit program, now section 48D of the tax code. Modeled after existing tax credits for investments in advanced renewable energy efforts, this program creates \$1 billion of tax credits or grants to encourage investments in promising new therapies to prevent, diagnose, and treat acute and chronic diseases. For qualifying companies with 250 employees or fewer, this program will provide immediate funding for work on therapies for cancer and other debilitating conditions, including a number of rare diseases, while providing small firms the ability to weather the ongoing economic storm. Without help to these companies, the effects of the financial crisis and the resultant capital markets contraction threatens to halt or significantly delay the next generation of promising therapies for various diseases and afflictions that affect tens of millions of patients and their loved ones.

Today, July 21, is the deadline for applications for the therapeutic credit program. While Congress saw fit to fund this program with \$1 billion, the Treasury Department has estimated that more than 1,000 applications could easily be filed. In reality this number could be closer to 2,000. Whatever the number of applications, it is clear that there will be many more promising projects than can be funded under the initial \$1 billion.

#### CONCLUSION

I agree with President Obama's statement that,

"science is more essential for our prosperity, our security, our health, our environment, and our quality of life than it has ever been before—including [the] creat[ion of] new incentives for private innovation [to] promote breakthroughs in energy and medicine."

Change does not come easily. It was not an easy process when a group of parents led by Abbey Meyers, the founder of NORD, spearheaded the development of the Orphan Drug Act in 1983. In January 1984, when Ronald Reagan signed the Orphan Drug Act into law, with Democrats and Republicans at his side, he stated that, "I only wish that with the stroke of this pen that I could also decree that the pain and suffering of people living with these diseases would cease as well." It didn't, but the act did create an environment with a system of special incentives for industry and certain government-supported programs that spawned a new era of research and drug development. We have come very far in that last quarter of a century but we have much further to go. The change brought about by the Orphan Drug Act improved millions of lives in this country and abroad, helped launch an industry and established the global rare disease advocacy movement. It does not come easily for every family that struggles with illness and then receives a life-altering diagnosis of a rare disease with no treatment or cure. But each of us committed to orphan drug development, including the FDA and those responsible for seeing the Agency is appropriately funded, owe those families a more-than-fighting chance that their medical needs will be met and that more and more parents will instead receive a diagnosis of a rare disease in their child, followed immediately by the words: "There are, however, several treatments options for your child."

Senator BROWN. Thank you, Mr. Crowley, for your story.

Ms. Moon, welcome.

#### **STATEMENT OF SUERIE MOON, BOARD MEMBER, DOCTORS WITHOUT BORDERS USA, NEW YORK, NY**

Ms. MOON. Thank you, Senator Brown, Ranking Member Enzi, Senator Sanders, and Senator Casey.

My testimony today is based on our decades of experience as one of the only actors providing treatment and care for neglected diseases in the developing world. It's also based on our experience as

a founding member of the Drugs for Neglected Diseases Initiative, or DNDI, which is a public/private product development partnership. Our support to DNDI makes us the third-largest philanthropic funder of neglected disease research in the world.

In a nutshell, we're facing two different types of problems in addressing neglected diseases in developing countries. First, there's very limited access to the tools that already exist to diagnose and treat these diseases. But, at the same time, the tools that we have are terribly insufficient. We urgently need innovation and new and better products in order to address these diseases. We need products that are effective, that are easier to use, and that are well-adapted to field conditions in resource-poor settings.

Globally neglected diseases affect what are often called the "bottom billion," people who live in the most rural areas, who have little or no access to healthcare, and who are often living on as little as a dollar or less per day.

Therefore, it was welcome news for us, in 2008, when the Presidential Initiative on Neglected Tropical Diseases was established. However, the initiative only focused on 5 of the 14 neglected tropical diseases that were identified by the World Health Organization. It did not fund diagnosis and treatment of the deadliest neglected diseases, such as Chagas disease, sleeping sickness, and kala azar. These have been identified, in fact, as the most neglected, and are the focus of a number of MSF programs.

Many of you in this room may never have heard of these diseases. They often occur in remote areas or in countries that are undergoing political instability. Because of time constraints, I won't go through and describe each of them to you, but perhaps I could tell you a little bit more about one of them, Chagas disease, because it infects about 300,000 people in the United States today, as well as 15 million people around the world.

It's the largest parasitic killer in the Americas, and is responsible for about 14,000 deaths every year. The disease is caused by a parasite that's transmitted by what's called the "kissing bug," because the bite of the bug is so gentle that victims often don't even know that they've just been infected. Chagas disease can also be transmitted from mother to child during pregnancy, so it infects infants, through blood transfusions and organ transplantation, as well as through oral transmission. If left untreated, it eventually infects the heart and the digestive system, and kills 30 percent of those who are infected.

Despite its deadly effects, we don't have many tools to combat Chagas disease. For example, currently we only have two medicines, nifurtimox and benznidazole. Both were developed 45 years ago, and neither of them were developed specifically in research aimed at Chagas disease. Neither of these drugs are currently adopted for use in children, although, in the coming months, we hope to have a pediatric formulation of benznidazole made available.

Furthermore, there's no tests for cure for Chagas disease. So, once a patient has gone through a treatment course, we still don't know if they've actually been cured of the disease. We urgently need new diagnostic tests, better medicines, a vaccine, and a test for cure to help prevent, diagnose, and treat this disease.

Another area where we urgently need better innovation is for diagnostics for tuberculosis, or TB. In 2008, there were 12,900 cases of TB here in the United States, and 9.4 million cases worldwide. TB is one of the world's leading causes of pediatric and adult mortality, causing nearly 5,000 deaths per day.

However, the current system that we have for diagnosing TB in most developing countries is very weak. It detects less than half of all TB cases, and it detects even fewer among children and people who are living with HIV.

So, I think the question that comes up is, Why don't we have better tools available to combat neglected diseases? It's precisely because the patients that we're talking about are poor and their needs get neglected. The current system that we have to incentivize R&D to develop new drugs, diagnostics, and vaccines is driven by commercial rewards. So, generally speaking, a company will develop a drug or diagnostic tool, then they'll receive a patent that allows them to sell the product at a high price, and the high price is, in turn, expected to cover R&D costs.

But, the system fails miserably to meet the needs of people who cannot pay the high prices, either because there are too few of them, which is the case, of course, for orphan and rare diseases, or because they're too poor, which is often the case for neglected tropical diseases that affect millions of people. This is the reason why, between 1975 and 2004, only 1.3 percent of all drugs that were developed targeted tropical diseases or tuberculosis, even though these diseases account for 11.4 percent of the global burden of disease.

It's clear to me, then, that if we want new tools to combat these diseases, we need new incentive mechanisms. MSF believes that the key principle in evaluating and designing new incentive mechanism should be what we call "delinkage." And what do I mean by this term? I think this term is relatively new here in Washington, so I'll take a few minutes to explain.

Delinkage refers to the idea that we can separate the market from R&D from the market for product manufacturing. What I mean is that, on the one side, we can specify the kind of R&D that we need, generate competition amongst researchers, and then reward the best innovator, once they've solved the problem that we've set out.

On the other hand, we have a market for production of the tool, whether it's a drug or a diagnostic or a vaccine. Once the product has been developed by the innovators, there would be no need to grant monopoly rights. So, what we could do is encourage a number of different manufacturers to enter the market, and encourage robust competition, to get the lowest sustainable prices.

So, when I say "delinkage," the link that we're breaking is, in fact, the link between high medicines prices and R&D. Because if high medicines prices are the only incentive we have for R&D, we're not going to get innovation and access for the needs of the poorest patients.

Delinkage can stimulate R&D where there's no profitable market; that is, for the neglected, rare, orphan, or pediatric diseases that we've been hearing about this morning. But, because the product development process is long and uncertain, we need a range of

different funding mechanisms that allow delinkage, either to push R&D at the beginning of the pipeline or to pull R&D at the end, and make sure that the right products make it through.

One of the proposals I'd like to put on the table in front of you today is for prize funds. We believe that prize funds are an attractive pull mechanism that incorporates the principle of delinkage. A prize is essentially an award that would be provided for different stages of the R&D process. It could be provided for identifying biomarkers, for proof of concept, for product synthesis, or for the final product. Once a prize is awarded, as I mentioned before, there would be no need to give the innovator a monopoly to recoup their R&D costs, because we would have just paid for it.

A well-designed prize offers a number of benefits, including: No. 1, the ability to drive R&D based on health needs; No. 2, allowing competition to determine the path or the team that's most likely to succeed, rather than relying on government or donors to do so; No. 3, it would attract a broader, more diverse base of potential solvers for the problem that we've identified; and No. 4, it allows us to build a lot of flexibility into the—I'm sorry—it gives us a lot of flexibility to build provisions into the prize to serve the public interest. For example, we can encourage collaboration, knowledge-sharing, and affordability provisions.

A prize fund, we believe, could quickly be established for a TB diagnostic test that could be used at the point of care in resource-poor countries.

In summary, we welcome the increased political attention being paid to the needs of the most neglected patients. However, we urge the U.S. Government to include the most neglected tropical diseases, by which I mean Chagas disease, sleeping sickness, kala azar, and Buruli ulcer, within the scope of the new Global Health Initiative. We ask the initiative to provide support for improved access to existing health tools, as well as to support the development of new and improved ones.

In order to develop new and improved tools, what we need is to explore new innovation mechanisms that address the shortcomings of the existing system. The key principle to keep in mind is delinkage; that is, breaking the link between high medicines prices and the funding of R&D. We believe prize funds are one promising mechanism for generating innovation that meets the health needs of the poorest people on the planet. We ask this committee and the U.S. Government to support innovative new approaches, such as prizes, that can be established relatively quickly, such as for TB diagnostics. We also ask the committee to consider prizes for other areas of neglected innovation, such as Chagas disease. At the same time, we urge the United States to support more systematic long-term changes that are needed to improve sustainable financing for health-needs-driven R&D that ensures equitable access to the end products. And important discussions are currently taking place at the World Health Organization and the Pan American Health Organization in this regard.

In closing, there's increasingly widespread recognition that the existing R&D system is failing. I think the previous speakers on the panel illustrated that very clearly. It's failing patients with neglected tropical diseases, with orphan or rare diseases, and chil-

dren, among others. Now is the time to begin testing new approaches to generate the innovation that we need to meet global public health needs.

Thank you very much for this opportunity to share our experience.

[The prepared statement of Ms. Moon follows:]

PREPARED STATEMENT OF SUERIE MOON

EXECUTIVE SUMMARY

Doctors Without Borders/Medecins Sans Frontières (MSF) is an international independent medical humanitarian organization. For decades, MSF has been one of the only actors providing care and treatment to impoverished people suffering from neglected diseases, such as Chagas disease, kala azar, sleeping sickness and Buruli ulcer. Globally, neglected diseases target the bottom billion—those living in the most rural locations, with poor or no access to healthcare, and extraordinarily limited resources. As a founding member of the Drugs for Neglected Diseases *initiative* (DNDi), a product development partnership (PDP), MSF is also the third largest philanthropic funder of neglected disease research. The problems we face are two-fold: there is limited access to the tools that exist to diagnose and treat these diseases, but the existing tools are also terribly insufficient—new products are urgently needed.

However, the current commercially driven system for drug, diagnostic and vaccine development leaves many urgent health needs unanswered. New medicines for sleeping sickness were not developed for 50 years despite pressing needs. There is no test to determine whether patients have been cured of Chagas disease after a course of treatment. A diagnostic tool for tuberculosis (TB) does not exist in a form appropriate for resource-poor settings. The populations afflicted by these diseases are simply too poor to provide adequate commercial incentives for R&D in a system that relies almost entirely on the ability to sell products at high prices to incentivize drug and diagnostic development. New incentive mechanisms are needed.

MSF believes that de-linking the cost of R&D from the price of health products needs to be the key principle used to evaluate and develop mechanisms to stimulate R&D and ensure access. De-linkage would separate the market for R&D from the market for product manufacturing. The concept of de-linkage fully accepts that R&D costs money, but seeks alternative ways to fund it. By paying for R&D through financing rather than through product prices, de-linkage removes the need to incentivize R&D through high prices. In this way, de-linkage can also stimulate R&D where there is no profitable market—that is, for neglected, rare, orphan diseases, or diseases like pediatric HIV/AIDS. From our experience with DNDi, we know that a range of different funding mechanisms that allow de-linkage are needed, either to “push” R&D via up front funding (e.g., through PDPs) or to “pull” R&D to ensure that the right products reach the end of the pipeline.

Prizes are one attractive “pull” mechanism for de-linking the markets for R&D and product manufacturing. The key potential benefits of a well-designed prize include: the ability to drive R&D based on health needs; allowing competition (rather than governments or donors) to determine the path or team most likely to succeed; attracting a broader, more diverse base of potential “solvers” to a problem; and the flexibility to build in provisions for collaboration, knowledge-sharing, and affordability of end products. Prize designs can vary, and they can also be given for different stages of the R&D process. Prize funds would be promising, and could quickly be established, in at least two areas of urgent need: a point-of-care TB diagnostic test and new products for Chagas disease.

In 2008, the U.S. Government established the Presidential Initiative on Neglected Tropical Diseases. However, the initiative only focused on 5 of the 14 most neglected tropical diseases identified by the WHO, did not fund diagnosis and treatment of the deadliest neglected diseases, and did not provide support for the development of innovative products for these diseases. MSF urges the U.S. Government to include the most deadly tropical diseases (Chagas disease, sleeping sickness, kala azar, and Buruli ulcer) within the scope of its new Global Health Initiative, and to provide support for improved access to *existing* health tools, as well as for the development of new and improved ones.

We also urge the U.S. Government to craft its policies and mobilize its financial resources to support new incentive mechanisms that embrace the principle of de-linkage, such as prize funds, in order to generate the innovation that we need to improve the lives of the world’s poorest children and families.

Thank you, Chairperson Harkin, Ranking Member Enzi, and the Senate Health, Education, Labor, and Pensions Committee for calling for this important hearing. This is a critical moment of both need and opportunity for innovation and access for neglected tropical diseases.

My name is Suerie Moon and I am on the U.S. Board of Directors of Doctors Without Borders, known as MSF, an acronym for our French name, *Médecins Sans Frontières*. MSF is an international independent medical humanitarian organization. My experience with MSF dates back to 1999 and includes fieldwork in the Democratic Republic of Congo and China, as well as over a decade of research and analysis on access to medicines and innovation policy issues.

We are most known for our emergency responses during armed conflict or following devastating natural disasters, or for our work against medical disasters like HIV/AIDS.

Less visible is our engagement in providing care and treatment to impoverished people suffering from diseases so neglected that many in the world have never heard of them before—Chagas disease, kala azar, sleeping sickness and Buruli ulcer, to name a few. From our decades of experience running programs and conducting operational research, we know that there is limited access to the tools that exist to diagnose and treat these diseases. But we also know very well that these tools are terribly insufficient, and new products are needed.

Globally, neglected diseases can best be thought of as the diseases of the bottom billion—those living in the most rural locations, with poor or no access to healthcare, and extraordinarily limited resources. People suffering from these diseases do not represent a profitable potential market and therefore current market incentives have proven insufficient to generate the development of better tools for prevention, diagnosis, treatment, and cure for these diseases. Between 1975 and 2004, only 1.3 percent of all new drugs were specifically developed for tropical diseases and tuberculosis, even though these diseases account for 11.4 percent of the global disease burden.<sup>1</sup> In addition, even when effective tools do exist, these populations can be difficult to reach due to geographic or social marginalization. Political will is often lacking, and healthcare infrastructure can be weak.

I would like to take the opportunity to share with you today the experiences of MSF in both treating and supporting innovation in treatments and diagnostics for neglected diseases.

#### MSF EXPERIENCES WITH NEGLECTED DISEASES

Many diseases, such as tuberculosis and tropical diseases, are neglected because they primarily affect people in poor countries. Across many of the diseases that disproportionately affect developing countries, children are particularly neglected: adapted pediatric medicine formulations are missing for diseases such as tuberculosis, Chagas disease and HIV/AIDS.

The World Health Organization (WHO) has identified as neglected tropical diseases (NTDs) 14 major parasitic, bacterial and viral diseases that are the most common infections in the 2.7 billion people living on less than \$2 a day. Those affected are often marginalized and forgotten by governments, left to suffer in silence. Other diseases like tuberculosis and pediatric HIV/AIDS are also neglected but are not within the WHO list of NTDs.

MSF has for many years provided diagnosis and treatment for individuals afflicted with NTDs, primarily focusing on visceral leishmaniasis (VL, or kala azar), human African trypanosomiasis (HAT, or sleeping sickness), Chagas disease (American trypanosomiasis), and Buruli ulcer. Three of these NTDs—VL, HAT, and Chagas disease—are often fatal if left untreated and have the highest rates of death of all of the NTDs. MSF is one of the only actors in the world involved in the treatment of these diseases.

Governments and donors have continued to neglect those who suffer from these diseases. These four diseases are largely left out of control and treatment programs by health actors and donors because they are considered too difficult and costly to treat; the available tools are limited; little investment has been made into research and development (R&D); and their disease burdens are poorly understood due to inadequate screening and surveillance systems. Nevertheless, the diseases are no less devastating for the individuals and countries affected. These barriers beg greater, not less, attention for effective responses to these diseases.

In 2008, the U.S. Government established the Presidential Initiative on Neglected Tropical Diseases. However, the initiative only focused on 5 of the 14 identified by

<sup>1</sup> Chirac, P., & Torrelee, E. (2006). Global Framework on Essential Health R&D. *The Lancet*, 367(9522), 1560–1561.

the WHO.<sup>2</sup> It did not fund diagnosis and treatment of the deadliest neglected diseases, and did not provide support for the development of innovative products for these diseases. As part of the Global Health Initiative (GHI), the U.S. Government has now proposed a significant increase in funds for NTDs. MSF welcomes this increased attention to the NTDs. However, there remains an ongoing neglect of the most deadly and most forgotten diseases.

It may be impossible in an illustrious committee room in the U.S. capital to paint a picture of the diseases that affect the poorest of the poor, who often live in the most remote areas of the world, but I will try.

#### *Chagas Disease (American Trypanosomiasis)*

Chagas disease is an appropriate place to start if only because there are currently an estimated 300,000 people living with this disease in the United States today. There are 15 million people living with Chagas disease around the world. It is the largest parasitic killer in the Americas, responsible for about 14,000 deaths per year, mostly in South and Central America.

This disease is caused by a parasite transmitted by a bug (the triatome). They call it the “kissing bug” because it bites gently, and victims often do not even know they have been bitten. It also can be transmitted from mother to child during pregnancy; and through blood transfusions and organ transplantation, and sometimes through oral transmission. If untreated, it infects the heart and digestive system of one-third of those carrying the parasite—with fatal effects in 30 percent of patients over a period of time.

Diagnosis currently requires confirmation through laboratory tests. In many cases, the endemic countries do not have the necessary facilities or staff available to carry out these tests.

MSF has provided free diagnosis and treatment for Chagas disease since 1999 in countries including Honduras, Nicaragua, Guatemala, and Bolivia, which has the highest prevalence in the world. In Cochabamba, Bolivia, MSF runs free, urban and rural Chagas programs that are carried out in collaboration with the Bolivian Ministry of Health in an integrated way in five primary care centres, where children and adults up to the age of 50 are treated and diagnosed. Through 2009, MSF has screened over 60,000 people for Chagas disease and treated more than 4,000. We are also currently exploring the possibility of opening a project here in the United States to improve detection and access to treatment for people living with Chagas disease.

The tools we have at hand can be used for treatment, but are insufficient. Currently, there are only two medicines to combat Chagas disease: benznidazole and nifurtimox. Both were developed over 45 years ago through research that was not even specifically targeting Chagas disease. Presently, neither of these drugs is adapted for use in children, although a paediatric formulation of benznidazole is anticipated in the coming months. As the side effects of the treatment are more common in older patients, doctors have been reluctant to administer the medicine out of fear of the consequences. Further, there is no test for cure for Chagas disease.

Millions suffering from Chagas disease, especially in rural areas, have neither the opportunity to find out that they are infected nor the possibility of being treated. New diagnostic tests, better medicines, a vaccine, and a test for cure are urgently needed to help prevent, diagnose and treat this disease.

#### *Sleeping Sickness*

Sleeping sickness, otherwise known as human African trypanosomiasis (or HAT), is a fatal parasitic disease found in 36 countries in sub-Saharan Africa, with an estimated 70,000 annual cases and 60 million at risk. During 2009 less than 10,000 cases were diagnosed and treated, but many more are affected—the true size of the problem remains unknown. Sleeping sickness occurs in the poorest rural areas of Africa, where difficulty of diagnosis, political instability, and lack of health surveillance make diagnosis and care difficult. Sleeping sickness rapidly deteriorates into coma and death—and is fatal in 100 percent of patients within approximately 2 years if untreated.

Up to 10 years ago, patients with advanced sleeping sickness would have received an arsenic-based treatment called melarsoprol. Melarsoprol is more than 50 years old and highly toxic, with rising rates of treatment failure. No new treatments had been developed for a half-century for sleeping sickness even though melarsoprol was

<sup>2</sup>The Presidential Initiative on Neglected Tropical Diseases disaggregates one WHO identified disease into three, therefore identifying the Presidential Initiative as responding to seven neglected diseases.



killing the patient in about 5 to 10 percent of cases, and in some affected areas had only 50 percent effectiveness.

Thanks to the efforts of many partners, including MSF, the WHO, Epicentre, the Drugs for Neglected Diseases *initiative* and the Swiss Tropical Institute (STI), there is now a new treatment for patients with advanced sleeping sickness. These partners have also supported the development of research capacity in countries where sleeping sickness is endemic. Using nifurtimox-eflornithine combination therapy (NECT) has proven to be safer and more effective compared to the existing standard of care. Eflornithine is given intravenously twice a day for 7 days alongside orally administered nifurtimox. The treatment is life-saving and prevents relapse back into the sickness. In May 2009, the WHO added NECT to the Essential Medicines List (EML) for the treatment of advanced sleeping sickness.

Despite these improvements, the current treatment for sleeping sickness remains long and difficult—for both patients and health workers. Both diagnosis and staging—which requires painful lumbar punctures—demand significant technical capacities and are therefore difficult to implement in remote areas where the disease occurs. There is an immediate need to improve current diagnostic and treatment options, particularly for patients in the advanced stages of this disease.

#### *Tuberculosis*

Tuberculosis (TB) is a major public health problem, with over 9.4 million new cases and almost 1.8 million deaths in 2008 alone—or nearly 5,000 people every day. TB is a leading cause of mortality in children worldwide, with approximately 1 million cases and 400,000 deaths each year in children under 15 years old as of 2006. The most commonly used TB diagnostic test is Sputum Smear Microscopy (SSM).<sup>3</sup> It is relatively fast and easy to implement in resource-limited settings, but it has significant limitations: it detects less than half of all TB cases<sup>4</sup> and performs even worse in children and people living with HIV who either have difficulties producing enough sputum, or don't have sufficient or any mycobacteria in their sputum to be detected under the microscope. It also completely misses the extrapulmonary form of TB.<sup>5,6</sup>

A study analyzing the contribution that improving TB diagnostics could make to reducing the global burden of TB, shows that improving the performance, speed and accessibility of TB diagnostic tests are key factors.<sup>7</sup> The study calculates that 392,000 deaths or 22 percent of annual deaths due to TB in the four highest-burden WHO regions, could theoretically be avoided by the introduction of a new TB point-of-care diagnostic.

We desperately need a new point-of-care diagnostic test able to diagnose active TB in adults and children who may also be co-infected with HIV; has high sensitivity and specificity; is simple to use and can be operated without the need for extensive infrastructure. Despite the valuable work supported by grant programs administered by entities such as the Foundation for Innovative New Diagnostics (FIND), there is widespread agreement that there is insufficient progress on the development of a new test that meets these needs.

#### *MSF Experience in Innovation*

A decade ago, MSF created the Campaign for Access to Essential Medicines because of our concern about barriers to access to medicines in low- and middle-income countries. People in developing countries are dying because medicines do not exist due to inadequate incentives for their development; or because they are unavailable due, in part, to high costs.

Our work on NTDs convinced us that we wanted not only to advocate for new tools, but also to engage actively in the development of these tools. Therefore, MSF became a founding member of the Drugs for Neglected Diseases *initiative*, or DNDi, a product development partnership (PDP). We continue to contribute funding, mak-

<sup>3</sup> Sputum smear microscopy is done by staining a sputum sample with an acid-fast stain and then examining the sample with a microscope for acid-fast bacilli.

<sup>4</sup> In countries characterized by high HIV prevalence, the challenge of providing timely TB diagnosis and treatment initiation is even greater. In a study recently conducted in Rwanda, where 62 percent of the recruited patients were TB/HIV co-infected, only 18 percent of TB confirmed cases were started on treatment within 1 month and only 56 percent within 2 months.

<sup>5</sup> Perkins, MD, Roscigno, G, Zumla, A. (2005) Progress towards improved tuberculosis diagnostics for developing countries. *The Lancet* 367(9514): 942–943.

<sup>6</sup> Shingadia, D, Novelli, V. (2003) Diagnosis and treatment of tuberculosis in children. *Lancet Infect. Dis.* 3(10): 624–632.

<sup>7</sup> Keeler, E., et al., (2006) Reducing the global burden of tuberculosis: the contribution of improved diagnostics. *Nature* 444: 49–57.

ing MSF the third largest philanthropic (under of neglected disease research.<sup>8</sup> From our experience as a founding member of DNDi, we know that a critical role is played by “push” funding—that is, grants invested into promising candidates for future drugs. While push funding and PDPs play an important role, our experience also tells us that incentives are needed throughout the innovation process to ensure that the right products reach the end of the pipeline. For this reason, we also need “pull funding”—that is, incentives at the end of the product development process, such as the promise of a profitable market or other reward. While donors and governments have invested increased amounts in *push* funding, we are just beginning to see serious efforts to explore how best to put in place *pull* funding.

#### PRIORITIZATION OF ACCESS CONSIDERATIONS: THE IMPORTANCE OF “DE-LINKAGE”

The current system for drug, diagnostic and vaccine development creates both innovation and access barriers. Driven by commercial rewards, it is a system that leaves many pressing health needs unanswered—needs that we identify in our medical programs every day. New medicines for sleeping sickness were not developed for 50 years despite pressing needs. The diagnosis of sleeping sickness is complicated, and often requires a blood sample, lymph node aspiration and a painful lumbar puncture. There is no test to determine whether patients have been cured of Chagas disease after a course of treatment. A diagnostic tool for tuberculosis does not exist in a form appropriate for resource-poor settings. These populations are simply too poor to provide adequate commercial incentives for R&D in a system that relies almost entirely on the ability to sell products at high prices to incentivize drug and diagnostic development.

But what if we could separate the market for medicines production from the market for R&D? What if we could encourage robust competition in both?

MSF believes that de-linking the cost of R&D from the price of health products needs to be the key principle used to evaluate and develop mechanisms to stimulate R&D and ensure access. This principle has gained increasing acceptance worldwide. The concept of de-linkage fully accepts that R&D costs money, but seeks alternative ways to fund it. Rather than relying on high prices charged after the innovation has been developed, de-linkage would seek to stimulate innovation from many sources and consider access issues in advance. This approach would broaden incentives for innovation beyond just the profitable diseases, and remove the access barriers created by high prices.

The concept of de-linkage has been included in the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPoA), which was agreed upon in 2008 by all WHO Member States, including the United States.<sup>9</sup> In conjunction with this plan, several governments have proposed the creation of new incentive mechanisms, including prizes, based on the principle of de-linkage. Just 2 months ago, the Council of the European Union decided to explore “models that dissociate the cost of Research and Development and the prices of medicines,” as a part of its global health efforts.<sup>10</sup>

Why the broad interest in “de-linkage”? De-linkage is important because the price of the final product is critical for affordability and access, and because R&D should be driven by health priorities, not the size of the market. Innovation by itself is of little value if the tools developed are unavailable or unaffordable to the people who need them. By paying for R&D through financing rather than through product prices, and by addressing the price and availability of the product at the outset, de-linkage removes the need to incentivize R&D through high prices. De-linkage also stimulates R&D where there is no profitable market—that is, for neglected, rare, orphan diseases, or diseases like pediatric HIV/AIDS which has been all but elimi-

<sup>8</sup>Moran, M., Guzman, J., Henderson, K., Ropars, A., McDonald, A., McSherry, L., Wu, L., Omune, B., Illmer, A., Sturm, T., & Zmudzki, F. (2009). *Neglected Disease Research and Development: New Times, New Trends*. Sydney, Australia: The George Institute for International Health, p. 62.

<sup>9</sup>The Global Strategy and Plan of Action Section 5.3.a states:

“explore and, where appropriate, promote a range of incentive schemes for research and development including addressing where appropriate, the de-linkage of the costs of research and development and the price of health products, for example through the award of prizes, with the objective of addressing diseases which disproportionately affect developing countries.” World Health Assembly. (2008). Global Strategy and Plan of Action on public health, innovation and intellectual property. Resolution 61.21. Geneva. Available: [http://www.who.int/gb/ebwha/pdf\\_files/A61/A61\\_R21-en.pdf](http://www.who.int/gb/ebwha/pdf_files/A61/A61_R21-en.pdf).

<sup>10</sup>Council of the European Union. (2010) “Council conclusions on the EU role in Global Health.” 2011th Foreign Affairs Council meeting. Brussels. 10 May 2010. Section 18.c. Available: [http://www.consilium.europa.eu/uedocs/cms\\_Data/docs/pressdata/EN/foraff/114352.pdf](http://www.consilium.europa.eu/uedocs/cms_Data/docs/pressdata/EN/foraff/114352.pdf).

nated in rich countries even as a rich country market continues to exist for adult HIV/AIDS medicines.

De-linkage is not just about breaking the link to high prices, but is also about pro-actively designing into any new incentive mechanisms ways to ensure that the affordability and availability of any new health tool are incorporated from the outset of the R&D process. A range of different funding mechanisms that allow de-linkage are needed, either to “push” R&D via up front funding (e.g., through PDPs) or to “pull” R&D via incentives that focus investment efforts on products needed in developing countries (such as prize funds).

Once the market for R&D is de-linked” from high medicines prices, we can encourage robust competition among producers of the end product. Our experience shows that competition is the most effective way to achieve reliable price reductions and sustainable, affordable prices. Intellectual property can and should be managed in a way that ensures that a new health tool can be manufactured by other producers, fostering competition and access. A recent example is the patent-free development of the anti-malarial fixed-dose combination of artesunate and amodiaquine by DNDi, in collaboration with the pharmaceutical company Sanofi-Aventis. (In cases such as vaccine development where competition may not be technically feasible in the immediate term, even when favorable licensing terms exist, a pathway to facilitate access is needed, including technology transfer.)

#### BREAKING THE INNOVATION BARRIERS

Prizes are one attractive option for de-linking the markets for R&D and product manufacturing. Prizes can act as powerful incentives for innovation, but need to be designed carefully in order to maximize the sharing of knowledge, access to end products, and overall return on the public’s investment. Prize designs can vary, and they can also be given for different stages of the R&D process, such as identifying biomarkers, proof of concept, product synthesis, or developing a finished product all the way through the registration process. The key potential benefits of a well-designed prize include some of the following<sup>11</sup>:

1. It would allow R&D efforts to be driven by health needs.
2. It would establish a bold and important goal without having donors or governments pick winners by choosing in advance the path or team that is most likely to succeed in reaching it.
3. Payment would only be made when results are achieved. The prize is only paid if the challenge has been met, i.e. if donors can see a direct connection between their funding and the outcomes.
4. With the right backing, a prize can create a “lighthouse” effect by highlighting a problem to a whole new range of potential innovators, who may have previously been unaware of the problem. This increases the number and diversity of potential “solvers” for a problem, which could include, for example, both commercial enterprises and academics. An even wider range of participants could be sought through the award of intermediate prizes for solutions to specific technical challenges.
5. A prize could include incentives for collaboration and knowledge-sharing.
6. By including affordability criteria, the prize could promote both innovation and access.

Two specific examples of urgent needs that we’ve identified in our programs—and for which there will be little engagement from the major R&D players without novel innovation mechanisms—are related to TB and Chagas disease.

Millions would benefit from the creation of a point-of-care (POC) test that would allow the diagnosis of TB at local health centers in resource-poor contexts. The dearth of R&D in TB diagnostics is demonstrated by the chronic lack of investment in this area, particularly from the private sector. Only U.S. dollars—41.9 million was directed towards TB diagnostics R&D—a mere 9 percent of total resources spent on TB product development, which is already an under-funded field. Of this amount, only U.S. dollars—2.5 million came from the private sector. A TB diagnostic test designed for use in resource poor areas, which necessarily has to be low cost, requires a different form of incentive that would allow for the cost of the final product to be de-linked from the cost of R&D. A prize competition would create the incentives for R&D in this neglected area.

As noted above, a prize fund would allow for many different approaches to be pursued without deciding at an early stage which is the most promising. This is particularly important in the field of TB POC diagnostic development since there are several approaches that could potentially lead to the delivery of the right test, but

<sup>11</sup>See, e.g., Love, James and Hubbard, Tim (2009). “Prizes for Innovation of New Medicines and Vaccines,” *Annals of Health Law*, 18 (2): 155–186.

it is not clear which angle will be the most successful. Current R&D in different areas of the POC diagnostic market, such as bioterrorism, pandemic influenza, and HIV viral load testing, holds the potential for breakthroughs in the area of TB diagnosis. The governments of Bangladesh, Barbados, Bolivia and Suriname have proposed a prize fund of \$100 million or more for a TB POC diagnostic.<sup>12</sup> By providing a sizeable incentive, the prize would attract many developers to the neglected area of TB.

Prizes are not a new mechanism, but have successfully been used in the past to induce innovation. For example, recently the Global Alliance for TB Drug Development (a PDP) and the Rockefeller Foundation awarded two prizes for more efficient ways to synthesize a new tuberculosis drug candidate, PA-824. Prizes are also receiving renewed attention in policy circles because of their potential to help address our most pressing public problems. Just this past spring, the White House issued guidance on the Open Government Directive, supporting the use of prizes to encourage innovation in a range of areas, including climate change technology and promoting open government.<sup>13</sup>

While individual initiatives that can be established quickly, such as a TB POC diagnostic prize fund, are important, others are exploring how prizes could be used as part of longer-term systemic changes that are needed to provide sustainable financing for health needs-driven R&D that ensures equitable access.

Similarly, we need innovative tools for the diagnosis, treatment, and test of cure for Chagas disease. The governments of Bangladesh, Barbados, Bolivia and Suriname have proposed creating a \$250 million prize fund to reward the development of new products that would decrease the burden of disease from Chagas.<sup>14</sup>

Prizes are also flexible tools. There is not just one model, and they can be designed to fit the medical, scientific, and technical problems that need to be addressed and the specific access issues for a disease area. In some areas it may be more appropriate to have a prize that rewards the development of the final product. In others, it might be more effective to support a prize that can be focused on a critical milestone that could overcome a key barrier to further development. In all cases, however, it is critical that methods to ensure affordable access must be part of the prize design at the start.

DNDi has been considering milestone prizes for Chagas drug development. Substantial rewards for attaining specified milestones along the path to a new drug or other health technology could be a useful supplement to grants for diseases for which market incentives are deficient and where patents are not an effective incentive. Milestone prizes promise earlier pay-outs and are likely to attract new actors such as biotechnology firms, which cannot make major investments in pursuit of rewards that may be many years away.

Several discussions to explore de-linkage mechanisms for the technological needs of Chagas are also ongoing at the regional level as part of the Pan American Health Organization's (PAHO) regional implementation of the GSPoA. These discussions provide a framework for agreement on new incentive mechanisms, including appropriate prize designs to stimulate innovation for Chagas disease.

#### CONCLUSION

MSF welcomes the growing attention to patients who suffer from neglected diseases around the world. We ask the U.S. Government to include the most deadly tropical diseases (Chagas disease, sleeping sickness, kala azar, and Buruli ulcer) within the scope of its new Global Health Initiative, and to provide support for improved access to *existing* health tools, as well as for the development of new and improved ones. We also urge the U.S. Government to craft its policies and mobilize its financial resources to support ambitious, visionary approaches to generating medical innovation that can improve the lives of the world's poorest children and families. In particular, the United States should support relevant discussions at the WHO and PAHO, and the efforts of the Consultative Expert Working Group that

<sup>12</sup> Governments of Bangladesh, Barbados, Bolivia and Suriname. (2009) Prize Fund for Development of Low-Cost Rapid Diagnostic Test for Tuberculosis. 15 April. Contributions from Member States. WHO Secretariat on Public Health, Innovation and Intellectual Property. Available: [http://www.who.int/phi/Bangladesh\\_Barbados\\_Bolivia\\_Suriname\\_TBPrize.pdf](http://www.who.int/phi/Bangladesh_Barbados_Bolivia_Suriname_TBPrize.pdf).

<sup>13</sup> Executive Office of the President: Office of Management and Budget. (2010) "Memorandum for the Heads of Executive Departments and Agencies (M-10-11)." Washington, DC. 8 March. Available: [http://www.whitehouse.gov/omb/assets/memoranda\\_2010/m10-11.pdf](http://www.whitehouse.gov/omb/assets/memoranda_2010/m10-11.pdf).

<sup>14</sup> Governments of Bangladesh, Barbados, Bolivia and Suriname. (2009) Chagas Disease Prize Fund for the Development of New Treatments, Diagnostics and Vaccines. 15 April. Contributions from Member States. WHO Secretariat on Public Health, Innovation and Intellectual Property. Available: [http://www.who.int/phi/Bangladesh\\_Barbados\\_BoliviaSuriname\\_Chagas\\_prize.pdf](http://www.who.int/phi/Bangladesh_Barbados_BoliviaSuriname_Chagas_prize.pdf).

will be formed in the coming months to analyze new innovation mechanisms in depth.<sup>15</sup>

I have outlined today just two promising possibilities—the potential of a prize fund for TB diagnostics and for Chagas disease—but there are many others. We need strong political commitment and financial support from governments and other donors if we are to make new incentive mechanisms work. There is increasingly widespread recognition that the existing R&D system is failing—failing patients with neglected tropical diseases, with orphan diseases, and children, among others. Now is the time to begin testing new approaches to generate the innovation that we need to meet global public health needs.

Thank you very much for this opportunity to share our experience with you.

Senator BROWN. Thank you, Ms. Moon.

Dr. Frattarelli.

**STATEMENT OF DANIEL A.C. FRATTARELLI, M.D., FAAP, CHAIR,  
COMMITTEE ON DRUGS, AMERICAN ACADEMY OF PEDIATRICS,  
DEARBORN, MI**

Dr. FRATTARELLI. OK. All right.

Senator Brown, Senator Enzi, Senator Sanders, Senator Casey, on behalf of the AAP, I'd like to thank the committee for holding this important hearing on treatments for children with rare and neglected diseases.

I want to let you guys know this testimony is also supported by the American Pediatric Association, the American Pediatric Society, the Association of Medical School Pediatric Department Chairs, and the Society for Pediatric Research.

Pediatricians often say that children are therapeutic orphans because they lack the breadth of available therapies that are offered for adults. That's not just for rare diseases, that's across the board. Lower financial incentives and greater clinical-trial obstacles have resulted in fewer drugs being developed specifically for children.

There are significant barriers to the development of therapeutics for children, in general. These obstacles are magnified for children with rare diseases.

As we've already heard, most of the rare diseases are pediatric. And because most of these are genetic, they're present from birth into adulthood. Pediatricians play an important role in the care of children with rare diseases, but, as we've already heard, really, so eloquently from Mr. Silver and Mr. Crowley, a lot of the time, we're left without proven therapies to treat them, or with existing therapies that just aren't sufficient for taking care of children.

The American Academy of Pediatrics have been working for decades to improve medicines for children by ensuring that the drugs used in children are studied in children. As we've heard so many times here, children are not just little adults. I'm so glad to hear that, so many ways, here, because that used to not be the case. Many people used to think that, in fact, they were; and that distinction hadn't been made. Children need drugs that are safe, effective, and developed just for them, and drugs which meet the same standards as we have for adults.

Because rare diseases are often so serious and so life-threatening, physicians must think differently about how they balance

<sup>15</sup> See the mandate given to WHO by the 2010 World Health Assembly. (World Health Assembly (2010). "Establishment of a consultative expert working group on research and development: financing and coordination." Resolution 63.28. Geneva. Available: [http://apps.who.int/gb/ebwha/pdf\\_files/WHA63/A63\\_R28-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R28-en.pdf).)

therapeutic risks and benefits in treating them. When therapeutic gaps exist for children, drugs are frequently used off-label without the benefit of the same drug labeling information that we've come to expect for adults. The outcomes of these off-label treatments, however, all too often stay with the physician and fail to benefit other patients. We need a greater capacity to capture and interpret data from what are essentially a bunch of small studies which are being conducted independently every time we treat one of these children off-label.

One possible mechanism for this would be the creation of a central repository for data generated on these individual treatment basis, to establish the efficacy and the safety of medications for rare diseases.

Now, two laws—the Best Pharmaceutical for Children's Act, BPCA, and the Pediatric Research Equity Act, PREA—have made historic progress in improving the information available to pediatricians and families for drugs used in children. Together, these laws have resulted in 385 drug labels revised with new safety, new efficacy, and new dosage information. And we can now say, with confidence, that BPCA and PREA have changed pediatric practice for the better.

Senator Chris Dodd—I was hoping he was going to be here to hear this—but, really, in particular, deserves great credit for his passionate leadership, over the course of his career, to improve the health of children. BPCA and a more recent initiative, the Pediatric Medical Devices Safety and Improvement Act, from 2007, will stand as long-lasting legacies to his dedication to child health and well-being.

BPCA and PREA have been important for children as a whole, and also for children with rare diseases. The laws greatly complement the Orphan Drug Act, which has done a remarkable job in stimulating new therapies for rare diseases. And of those 385 drug labels resulting from BPC and PREA, 56 have also received an orphan designation.

BPCA, PREA, and the pediatric devices law must be authorized in 2012, and the AAP looks forward to working with this committee on reauthorizing and strengthening these important programs.

Studying drugs in children is difficult and requires specialized skills. However, we still lack a number of qualified experts which are needed to actually do the work. We're training far too few new pediatric clinical pharmacologists. And if more is not done to reverse this trend, children will be left behind.

Finances, as we've already heard, can also be a barrier to effective therapies. New and novel drugs for children with rare diseases, which are usually expensive or often deemed experimental by insurance programs and are not reimbursed, and paying out-of-pocket for these drugs is simply not possible for many families. The promise of healthcare reform for children with rare diseases can only be realized if life-saving and life-improving therapies are paid for by insurance programs.

Along with drugs, medical and surgical devices are also important components in the treatment of many pediatric rare diseases. The development of pediatric devices shares the same obstacles, or at least similar ones, to pediatric drugs. And the Pediatric Medical

Device Safety and Improvement Act was a first legislative step to ensuring that children will have access to devices that are safe, that are effective, and that are made with their unique characteristics in mind. Children deserve a continued sense of urgency around medical devices, though, and we look forward to working with the FDA to fully implement this law.

Finally, regarding the neglected diseases, it's unacceptable for any of us, from regulatory agencies to manufacturers, for the medical community to neglect to treat diseases for which effective therapies are within reach. And the AAP encourages ongoing work focused on the identification, prioritization of clinical conditions which affect a sizable number of children, but which have, for whatever reason, been neglected.

Thank you for allowing the Academy of Pediatrics to share its views on this important issue.

[The prepared statement of Dr. Frattarelli follows:]

PREPARED STATEMENT OF DANIEL A.C. FRATTARELLI, M.D., FAAP

Mr. Chairman, members of the committee, I am Daniel Frattarelli, M.D., FAAP, a practicing pediatrician who has taken care of infants, children and adolescents for 13 years. I am chair of Pediatrics at Oakwood Hospital and Medical Center in Dearborn, MI and chair of the American Academy of Pediatrics (AAP) Committee on Drugs. On behalf of the AAP, I would like to thank the committee for holding this important hearing on new treatments and cures for children with rare and neglected diseases.

Pediatricians often say that children are therapeutic orphans because they lack the breadth of therapies available to adults. Lower financial incentives and greater clinical trial obstacles have resulted in fewer drugs developed and studied specifically for children. When a disease population is small, there is a lower likelihood that pharmaceutical companies can recoup the costs of developing new drugs. It is also difficult to recruit sufficient numbers of participants for a robust clinical trial. Both children and rare disease populations suffer from these similar small market problems. There are significant therapeutic obstacles for children in general, and these obstacles are greatly magnified for children with rare diseases.

Most of the approximately 7,000 rare diseases are pediatric diseases. Because most rare diseases are genetic, they are present from birth, through childhood, and into adulthood. Pediatricians play an important role in the care of children with rare diseases from diagnosis to treatment and care. For many of these patients, however, pediatricians are left without proven therapies to treat them or with existing therapies that are not sufficient.

The American Academy of Pediatrics has been working for decades to improve therapeutics for children by ensuring that drugs used in children are studied in children. In 1977, AAP said for the first time that not only is it not unethical to study drugs in children, but that it is unethical not to. Children are not little adults. They need drugs that are developed just for them and they deserve the same level of safety and effectiveness in drugs that is assured for adults.

Because rare diseases are so often serious and life threatening, physicians must think differently about how they balance therapeutic risks and benefits when treating them. When therapeutic gaps exist for children—and in particular for children with rare diseases—drugs must frequently be used “off-label,” or without the benefit of the same drug labeling information that we have come to expect for adults.

As doctors we know that better medical evidence is based on trials with a larger “N,” or a larger number of patients. But when this evidence is not available for children, the standard of care is off-label treatment. We call this a trial with an “N of one.” Physicians must monitor their young patients and try additional therapies, combinations, or dosages depending on the results. The outcomes of these “N of one” trials too often stay with the treating physicians. For other children to benefit from these studies, new tools are needed to collect and interpret the clinical results of off-label treatments.

One possible mechanism for the collection of these data is the creation of a central repository for data related to the safety and efficacy of treatments in rare conditions. Consensus on the specifics of the data collected can be reached by the combined efforts of physicians trained in pediatric research and those physicians in the

trenches who care for these children day in and day out. The most apparent benefit from this approach is the ability to capture and meaningfully interpret the data from what are essentially a bunch of small studies being independently conducted across the country. But another significant benefit to this approach would be a standardization or leveling of the risks to these children, as by virtue of their being enrolled in a study there is a greater, more formal, more clearly defined awareness of and attention to possible risks, which would come to light more fully through the consensus process than is possible for an individual physician.

Two laws, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), have made historic progress in improving the information available to pediatricians and families on drugs used in children. PREA provides FDA the authority to require pediatric studies of drugs when their use for children would be the same as in adults. BPCA provides a voluntary incentive to drug manufacturers of an additional 6 months of marketing exclusivity for conducting pediatric studies of drugs that the FDA determines may be useful to children.

Together these laws have resulted in 385 drug labels revised with new safety, effectiveness, and dosage information. We can now say with confidence that BPCA and PREA have changed pediatric practice for the better. They have also changed the way drugs are developed by Industry and regulated by FDA. Pharmaceutical companies have invested in greater internal pediatric infrastructure, so that pediatricians can be considered at each stage of drug development. At FDA, with the help of the new BPCA-created Pediatric Review Committee (PeRC), pediatrics has been integrated across the review divisions in a consistent and productive way for the benefit of children. The pediatric efforts at FDA would not have been possible without the leadership of Dr. Dianne Murphy and the Office of Pediatric Therapeutics (OPT).

Senator Chris Dodd in particular deserves great credit for his passionate leadership over the course of his career to improve the health of children. BPCA and a more recent initiative, the Pediatric Medical Devices Safety and Improvement Act of 2007, will stand as lasting legacies to his dedication to child health and well-being.

BPCA and PREA have been important both for children as a whole and for children with rare diseases. The laws greatly complement the Orphan Drug Act, which has done a remarkable job stimulating the development of new therapies for rare diseases. Of the 385 drug labels resulting from BPCA and PREA, 56 have been for drugs that have also received an "orphan" designation.

BPCA, PREA, and the pediatric devices law must be reauthorized in 2012 along with the Prescription Drug User Fee Act, and the AAP looks forward to working with this committee on reauthorizing and strengthening these important programs for children.

As effective as these laws have been, there is still a great need for more progress. The majority of drugs still lack pediatric information and many rare and neglected pediatric diseases lack effective therapies. New creativity in overcoming the obstacles to small market therapies, coupled with renewed resources for research and incentives for development, will be needed to continue making progress.

Advances in basic research must be a fundamental part of any strategy to develop new cures for children with rare diseases. We must work to find new drug targets for rare diseases and develop appropriate endpoints to evaluate potential therapies. The National Institutes of Health (NIH) and the National Institute of Child Health and Human Development (NICHD) are key partners in this effort and we must continue to give them the resources necessary to accomplish this essential work.

Studying drugs in children is difficult and requires specialized skills. Each stage of the pediatric drug development process comes with unique challenges. Early phase clinical trials are particularly difficult in pediatric populations. Recruitment is frequently a problem throughout the process. Trials must be designed with the vulnerabilities of children in mind, and these challenges are even greater for the smallest of children, neonates. FDA approval of drugs is also challenging, often complicated by vastly different indications for pediatric and adult use.

All of these difficulties necessitate trained pediatric investigators, and we still lack the number of qualified experts to actually do the work. Pediatric pharmacology studies require a very different level of skill to appropriately conduct and analyze, skills which are not often needed in adult studies. We are training far too few new pediatric clinical pharmacologists and if more is not done to reverse this trend, children will be left behind. BPCA made initial progress in this effort by expanding access to loan repayment for physicians who study pediatric pharmacology, but this alone will not be sufficient.



Barriers to access unfortunately do not stop at the development of an effective therapy. New and novel drugs for children with rare diseases are often expensive. Comprehensive insurance coverage is essential for these children and their families. The Affordable Care Act has taken great steps forward in ensuring that all children have access to health insurance regardless of family income, pre-existing conditions, or exceeded lifetime and annual benefit caps. Therapies for rare diseases, however, are often deemed experimental by insurance programs and not reimbursed. Paying out-of-pocket for these drugs is simply not possible for many families. The promise of health care reform for children with rare diseases can only be realized if life-saving and life-improving therapies are paid for by insurance programs.

Most of our discussion so far has focused on rare diseases, but we also would like to say something about neglected diseases as well. While development of safe and effective treatments for rare diseases is constrained by their low prevalence, the same cannot be said for those conditions which have been neglected. It is unacceptable for any of us, from regulatory agencies to manufacturers to the medical community, to neglect to treat diseases for which effective therapies are within reach. The AAP encourages ongoing work focused on the identification and prioritization of clinical conditions which affect a sizable number of children but which have, for whatever reason, been neglected.

Along with drugs, medical and surgical devices are integral components of the treatment of many rare diseases. The development of pediatric devices shares obstacles similar to pediatric drugs. The Pediatric Medical Device Safety and Improvement Act, passed in 2007, was a first legislative step to ensuring that children have access to devices that are safe, effective, and made with their unique characteristics in mind, which include smaller sizes, growing bodies, and different biology. It is important that FDA proceed quickly to realize the promise of this legislation for children and take bold steps to improve representation of pediatric expertise with the Center for Devices and Radiological Health (CDRH). We are encouraged by the approach new leaders in CDRH and FDA have taken but children deserve a continued sense of urgency.

When fully implemented, the pediatric device law will increase the tracking of pediatric device approvals and the postmarket surveillance of these devices. It will also help incentivize pediatric device development. The law modified the humanitarian use device (HUD) program to remove the profit cap for pediatric HUDs. This year, the first pediatric HUD was approved under this revised program. FDA's Office of Orphan Products Development is successfully administering a new grant program authorized by the law to fund consortia to encourage the development of new pediatric devices. We look forward to working with FDA to continue the implementation of this law, including provisions that require device applicants to submit "readily available" information on potentially affected pediatric populations.

Thank you for allowing the American Academy of Pediatrics to share its views on therapies for children with rare diseases and for raising awareness of this important issue. We look forward to working with the committee to improve the health and well-being of all children. I am happy to answer any questions from the committee.

Senator BROWN. Thank you very much, Dr. Frattarelli.

I'll start with Mr. Silver. Tell us about the difficulties, if any, that you were faced with, with insurance, in paying for your son's illness. And not just for you, who appear to have a good-paying, decent job, probably with good insurance. Talk to me about others that you know from your dealings with EB and what you've seen with insurance.

Mr. SILVER. Absolutely. Starting from my own perspective, when our son was born, we were told his disease was anywhere from mild to fatal. And they took him away within 12 hours of his birth. And the first thing I did, actually, was e-mail someone who deals with our health insurance, and had him listed as soon as possible. The reason I bring that up is one of the people, who's in the audience today, who shared this story with me just before we started. This is Kati Ward. She doesn't have her bandages covered, because it was deemed a preexisting condition.

Now, to give you a sense of what bandage costs for EB are like, they can be as high as \$14,000 a month—\$14,000. Our son, who has a severe form of EB, but a more moderate case, his bandages

run about \$6,000 a month. You add, on top of that, medical bills for doctors' visits, so forth, you easily get into 2-, 250, as a category.

Another person in this room is limited to the number of types of bandages she can have per month. So, what does that mean? That means there are certain bandages which are relatively high-tech that enable you to manage the disease better, and you're told, "Well, we will only give you five." And there's no particular reason why five is selected.

This is a long way of saying that it has been a difficult battle, a very difficult battle. And for someone with fortune to have resources, we went to battle with our insurance company, and ultimately they honored that contract, mostly because we had the contract, and we were fortunate to do so.

For those who are struggling, day-to-day, who may have insurance, the hoops you have to jump through are unbelievable. There are a number of other examples we can point to, actually just in this audience, again. Michelle, who's here, who came down, she is also limited to the number of bandages she gets.

This has to be an easier process to deal with. What you deal with when you have a child who has a disorder like this is, in so many ways, crushing, and changes your life. To add on top of that having to fight, tooth and nail, just to get your son or daughter the coverage that is, in many ways and certain cases, actually already under contract, or that you have to fight so much just to help get them through the day, needs to change.

Senator BROWN. Thank you.

Dr. Frattarelli, what is the single most significant barrier to R&D for rare and neglected diseases?

Dr. FRATTARELLI. I think one of the biggest ones is that there's often not enough children out there that you can actually get them together, get them enrolled in a clinical study, and have this conducted so that you can meet the same criteria that we would use, let's say, if we were doing a new antibiotic or something that affects a broader part of the population.

The other thing that we really don't have right now is a well-enough-developed pediatric research infrastructure. I was mentioning, before, that there's just not enough well-trained general pediatric clinical pharmacologists out there to actually design and conduct these studies properly.

I think those are probably the two biggest obstacles we're seeing right now.

Senator BROWN. OK.

Ms. Dorman, how do we attract more young scientists to this field? If we're going to do what pretty much everybody has said here, the work Mr. Crowley's doing, the work that Ms. Moon and Mr. Silver advocate, do you have any special thoughts on how we attract young people into this research?

Ms. DORMAN. You know, the NIH has been doing some really important work—the Office of Rare Disease Research. They've been going into junior high schools and talking about rare diseases, and getting them really interested in the science of rare diseases.

I also think that the medical colleges and schools don't really focus on rare diseases. It's basically just an afterthought. And I

think there needs to be an increased interest in the study of rare diseases.

Also in the academic community—a lot of times they're not willing to do any of these type of studies because, in many cases, it's publish or die, and to do very limited studies on rare diseases, it doesn't work for them. So, that's really a big problem.

I think greater outreach into the medical community and medical schools are going to be really important.

But, there is an increased interest. We're working with Duke University. We're working with Notre Dame. We're also working with the Manton Center, in Boston. So, there's an increased interest into the study of rare diseases because I think many of them are beginning to realize that understanding the pathogenesis of rare diseases is going to advance society's understanding of diseases that affect far wider populations. So, we're very excited about that, that there is an increased focus.

Senator BROWN. Senator Sanders.

Senator SANDERS. Thank you, Mr. Chairman, for holding this very important hearing today. And thank you, Senator Brown, for the leadership role you've played on this critical issue. I appreciate the committee's holding this hearing today.

It seems to me that the problem that we're having—and I want to hear responses from the panelists, and perhaps starting off with Ms. Moon—is the following, Mr. Chairman.

If you have a disease, and if you have the money—no matter how serious or nonserious that medical problem may be—but, if you have the money to pay for the medicine or the drug to treat that problem, the drug companies will provide that medicine to you. On the other hand, if you or your child is one of a relatively small number of people who have a disease which could be fatal or cause a whole lot of suffering, but there's not a whole lot of money to be made from that, the drug companies are not going to gravitate toward that issue.

The function of a drug company, as I understand it, is to make as much money as possible. That's what the market is about. So, if you have an illness that one can make money from, you will see that advertisement on television, telling you to run out to your pharmacy to buy a drug for a disease you may not even know that you had. But, you're certainly going to run out and get that drug. On the other hand, if, as Ms. Moon indicated, you're living on a dollar a day in Africa and your child may be dying of a disease that, if diagnosed, might be cured, no one's going to get that medicine to you. Because, how do you make money from people who are living on a dollar a day? That's not a very good group of folks from which you can make money.

So, I think we have a dual problem. No. 1, diseases in which there are relatively few people who are suffering from it, and, second of all, diseases where millions may be suffering, but they don't have the money to pay for the treatment or the diagnosis.

Ms. Moon, I agree with you. I think we've got to move to a new concept, in terms of funding, research, and development, and it shouldn't be simply a market mechanism.

Can you talk a little bit about the concept of the prize, and how that differs from where we are right now?

Ms. MOON. Thank you very much for the question, Senator Sanders.

The concept of the prize, and the reason why we think it's such a promising mechanism, is that we would still reward innovation. We would still pay for R&D, but we would do it in a way that would not rely on high prices. As we just heard from Mr. Silver, and as I think many people in the room have experienced personally, the high prices of medicines is something that people all over the world struggle with—in developing countries, in particular, but, of course, also here in the United States, with escalating healthcare costs.

So, the idea of the prize is that we could specify, based on public health concerns, What is the goal that we want? What is the new product, medicine, diagnostic tool, vaccine, whatever it may be that we want? And set out a number of criteria for what types of characteristics of that—What would be the characteristics of that product? And then put that out there and basically allow any innovator in the world who might be able to tackle this problem and come up with a solution, to propose a solution.

Once a product had been developed and the solution was brought to the table, a certain amount of money from the prize fund would then be paid to reward that innovator. And so, the R&D would be paid for.

What we could do after that is allow a number of different companies to produce that drug.

Senator SANDERS. Well, the point here is, we are rewarding and incentivizing the research.

Ms. MOON. Absolutely.

Senator SANDERS. Once we have a product, we're allowing a competitive and generic market out there, by definition.

Ms. MOON. That's exactly right.

Senator SANDERS. And the price will be affordable to people.

Ms. MOON. That's exactly right.

Senator SANDERS. It will not be controlled by one company, who can then charge a very, very high price.

Ms. MOON. That's exactly right.

Senator SANDERS. Would others like to comment on that concept? Does that make sense? Fairly radical concept, but what do you think? People have any familiarity with that?

Sir. Dr. Frattarelli.

Dr. FRATTARELLI. You know, one other option I'd like to mention here—it's not always the case that we have to go ahead and actually develop a whole new drug from scratch. A lot of what's going on right now is that people are using these drugs off-label, basically on an individual-case basis. All right? And, as I was mentioning earlier, we're not doing anything, collectively, to capture all that information right now. I think we could get a lot of benefit by taking these children, who are already being exposed to the risk of this therapy—right?—they're already taking these drugs off-label, and they're getting some of the benefit here, but we're getting that benefit on an individual label, not as a global sort of understanding of medicine-as-a-whole level. So, if we can go ahead, take this information, centralize it all in one place.

Another advantage I see of doing something like this would be that, while we're deciding what information we need to centralize, instead of having one individual physician doing this, you may have a group of, you know, 20 or 30 smart people, here, who can all say, "Well, you know, if you have this treatment, these are really the things you want to focus on, in terms of what a side effect might be." And so, I think it's going to step up everyone's game, in terms of following the safety for these things.

Senator SANDERS. OK, let me just jump in, because my time is running out.

First of all, I want to really applaud every single one of you for the outstanding work that you have done in your areas. And again, we're dealing today with rare diseases, and we're dealing with neglected diseases. So, some of these diseases are not necessarily rare—they may be impacting millions of people—but those folks are not getting the treatment.

Ms. Moon, in general, do you think the industry and government—and this is not just in the United States, it's internationally—have the developed countries played the kind of appropriate role that they should be playing, in terms of getting the medicines and the diagnosis to people in the Third World, in developing countries, that they require?

Ms. MOON. If I understand—the question is, Are industry and government playing the roles that they should be?

Well, of course industry and government can always do more. And that's why we would ask that the new Global Health Initiative include some of the deadliest tropical diseases that I mentioned earlier.

But, I do think that industry responds to the public policies that government puts in place. And this is why this hearing, and others like it, are so important. But, if we can put in place the right new incentive mechanisms, we're quite confident that industry would respond by delivering the types of innovation that we need, that would respond to the public health needs of people with orphan diseases, as well as neglected diseases.

Senator SANDERS. But, my guess is that government is going to have to play a strong role here, because, left alone, industry is not going to make a whole lot of money in providing a product to people who make a dollar a day.

Ms. MOON. In the current system, we would not expect industry to respond that way. It doesn't make sense, with the current rules. But, if we can change the rules and put in place new incentive mechanisms, we do think they would respond. And that's what we've heard in private conversations with people from some of the largest drug companies.

Senator SANDERS. Which brings us back to the prize concept.

Thank you very much, Mr. Chairman.

Senator BROWN. Thank you.

Ms. Moon, we are going to just ask Mr. Crowley a question, in closing, but in our list for the priority review voucher, we had 16 rare diseases or neglected diseases, around the world, as you know. We want to add the rare pediatric diseases in this country, but we also plan to, in this legislation, do that, add Chagas. It was an oversight in those 16. I think most of the other ones you mentioned

are included in the 16, I believe. But, if they're not, certainly come to us, as we work on this.

This is the last question, Mr. Crowley. I asked Dr. Frattarelli the same question. What do you think the most significant barrier to research and development for rare and neglected pediatric diseases is?

Mr. CROWLEY. I think the most significant barrier, Senator, is uncertainty. When we go to start new biotechnology companies—and they're all started virtually the same way—with the technology, with patents, usually out of a university—and we meet with a venture capitalist, and they ask us questions about the technology and the patents, but they want to know, What's the regulatory path? How long is it going to take? What's it going to cost? And, once you're on the market, are insurance companies going to pay for these drugs? What's the size of the market?

And right now, those answers are so incredibly variable and increasingly uncertain that a lot of adventure investors, a lot of other players in the field—although for the last 10 or 15 years, there's been a lot of excitement about rare diseases, I still think the excitement is there, but the barriers have actually risen. And I think the more that we can do to reduce that uncertainty through different pronouncements, better guidance, more use of surrogate endpoints, the biostatistics, potentially even the division—and one of our recommendations is the creation of a review division at FDA focused specifically on rare genetic metabolic disorders. I think anything that we can do to take the middle part of that funnel—you've had a lot of patients on this side, you've got a lot of technologies in the early stage of development here—they tend to get squeezed in the middle, through the clinical development—the more that we can do to reduce that uncertainty, to drive it forward, partly through different regulations and pronouncements, and also, too, through increased capital available to companies like ours, I think will go a long way to solving the problem.

Senator BROWN. Well, thank you.

Thank you all for your commitment, your activism, and your work that you do for so many around the country whom you don't know, and around the world. I thank you all for that, especially this panel.

I thank Bill, with Senator Harkin's staff, and Amy and Hayden, with Senator Enzi's staff. This is a hearing that shows a good side of the U.S. Senate, with the kind of bipartisan cooperation that Senator Enzi is known for around here. And I appreciate working with him on this. And, Senator Sanders, thank you for your question, too.

The record will remain open for 10 days for statements to be submitted. If you have anything that you left out today, if you want to add, or any requests of us, certainly make those available to the committee in the next 10 days. As I said, the record will be open until then.

Thank you, again.

This Committee on Health, Education, Labor, and Pensions will be adjourned.

Thank you.

[Additional material follows.]

## ADDITIONAL MATERIAL

## PREPARED STATEMENT OF SENATOR MURRAY

Thank you, Senator Harkin, for holding this hearing.

Rare diseases, particularly rare pediatric diseases, are very challenging for research funding and drug therapies. They tend to have less money dedicated to research and treatments, but there are still patients across the country who desperately need for cures to be found. So we need to find ways to encourage investments and find a safe way to streamline the approval process for life-saving drugs.

I am pleased that through the passage of health care reform, we authorized the Cures Acceleration Network (CAN). This initiative seeks to cut the time between discovery and development of drugs and therapies through new grant-making mechanisms at the NIH. It will establish CAN within the Office of the Director of NIH and authorize grants expected to speed the move from discoveries in the lab to the next generation of therapies. In addition, CAN will help coordinate the efforts of all stakeholders in the drug development process in order to help move discoveries forward.

The biomedical and life science industry has been a leader in the quest to find cures for rare diseases, and we need their great work to continue. This industry has the remarkable ability to create new and breakthrough medicines, allowing us to treat diseases that were previously untreatable and give hope back to families that had thought there was none.

That is why I am so proud that my home State of Washington is a leader in the life science industry, with universities and biomedical firms doing fantastic work finding innovative cures and medical therapies for a vast array of diseases.

Not only are Washington State companies on the cutting edge of biomedical research, they are also a major driver of economic development in my home State. According to a study published last fall by the Washington Biotechnology and Biomedical Association, the life sciences industry in Washington State directly employs over 22,000 people, and an additional 55,000 jobs in the State depend on this sector. It is also important to note that while employment has been declining in many sectors, the life sciences industry has continued to add jobs despite the economic downturn.

Once again, I am pleased that the HELP Committee held this hearing to bring more attention to this critical issue. I look forward to continuing to work to support this industry and their important work, and to help families and patients across the country by supporting the quest for cures to rare and neglected pediatric diseases.

PREPARED STATEMENT OF THE ADVANCED MEDICAL TECHNOLOGY ASSOCIATION  
(ADVAMED)

## SUMMARY

## ADVAMED ORPHAN AND PEDIATRIC DEVICE DEVELOPMENT RECOMMENDATIONS

*Humanitarian Use Device Program*

- Provide the Secretary with authority to selectively raise the annual population cap for specific pediatric conditions when FDA determines the health of pediatric or orphan patients requires an increase.

- Ensure parity with the orphan drug program by creating a tax credit for orphan and pediatric device research and to help offset high R&D costs associated with small populations.
- Develop guidance on level of evidence needed to meet the HUD standard of safety and probable benefit.
- Develop guidance to clarify for payors that HUDs are FDA-approved devices for reimbursement purposes.
- Remove HDE limitations placed on diagnostic devices that limit development of diagnostic tests for rare diseases.

*Make Better Use of Existing FDA Regulatory Tools and Valid Scientific Evidence*

While maintaining the existing standard of safety and effectiveness, where appropriate FDA should:

- Use objective performance criteria (OPCs), historical controls or well-documented case histories as endpoints to show effectiveness.
- Allow the extrapolation of clinical data between different sizes of the same device based on engineering testing and other non-clinical data.
- Rely on non-clinical data for modifications of devices specifically approved for pediatric patient populations when such modifications are unrelated to changes in intended use.
- Allow the acceptance of 510(k) devices intended for adult populations with the same use as a pediatric device as predicates for the 510(k) pediatric device.
- Allow the acceptance—as an appropriate control for investigational pediatric devices—of devices intended for use in adult populations when such devices provide the only device-related means for treating, diagnosing or preventing diseases or conditions in pediatric patients and have become the standard of care for such patients.
- Allow use of general device claims where appropriate rather than requiring specific device claims for each pediatric age bracket to respond to the broad definition of pediatric (from neonate to age 21).

OTHER FDA AND NIH-RELATED RECOMMENDATIONS

- Establish *Compassionate Use Orphan/Pediatric Device Program* to allow manufacturers to distribute no more than 100 unapproved devices annually to pediatric patients when such patients are afflicted with diseases or conditions that affect too few patients annually to justify the expense necessary to achieve an approved device under the HDE program. Appropriate controls would be specified.
- Develop adaptive clinical trial designs and regulatory models to respond to regulatory barriers and small population sizes.
- Create Orphan and Pediatric Ombudsman in CDRH to assist manufacturers in how to use existing and new regulatory pathways to achieve on-label indications.
- Develop custom device guidance to clarify the number of custom devices that can be manufactured.
- Ensure collection and prioritization of data on unmet pediatric needs through NIH to identify and assist basic research needs, offset R&D costs associated with small populations, and spur technology transfer and commercialization of devices.
- Create NIH Office of Orphan and Pediatric Diseases to conduct and coordinate data collection, establish priorities and research needs and coordinate with Orphan and Pediatric Ombudsman.

On behalf of AdvaMed, thank you for the opportunity to submit written testimony for the record to the Committee on Health, Education, Labor, and Pensions. This testimony includes our recommendations on ways to promote the development of new treatments and cures for treating rare and neglected pediatric diseases.

AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed's members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent of the health care technology purchased annually around the world. AdvaMed members range from the smallest to the largest medical technology innovators and companies. Nearly 70 percent of our members have fewer than \$30 million in sales annually.

INTRODUCTION

It is important to understand the device regulatory context with respect to rare diseases. The Orphan Drug Amendments of 1988 created the orphan products grant program. For this purpose, rare is defined as a prevalence of fewer than 200,000



patients in the United States. The related humanitarian use device program, authorized in the Safe Medical Devices Act of 1990, is a special product approval pathway to market for devices that treat or diagnose diseases and conditions that affect fewer than 4,000 patients per year in the United States, including pediatric populations and subpopulations. Although medical device companies are authorized to apply for grants under the orphan products program to support device research and development for rare diseases, device manufacturers can only use a Humanitarian Use Device (HUD) to treat rare diseases or conditions of less than 4,000 patients per year. FDA approval of a Humanitarian Device Exemption (HDE) authorizes a manufacturer to market a HUD.

In contrast to pre-market approval (PMA) requirements which necessitate that manufacturers demonstrate their products are both safe *and* effective, the review standard for HDEs requires manufacturers to demonstrate the safety of the device, the likelihood of effectiveness (termed “probable benefit”), and to demonstrate that the device will not expose patients to significant or unreasonable risk. This standard recognizes the challenges of fully establishing efficacy via clinical trials in very small populations but strikes an important balance by requiring demonstration of safety. Device manufacturers are prohibited from making a profit on the marketing of HUDs although they are permitted to recoup the costs of research and development, manufacturing, packaging and distribution.

Importantly, to spur pediatric device development and under the leadership of Senator Christopher Dodd, the Food and Drug Administration Amendments Act of 2007 (FDAAA 2007) amended the humanitarian use device program to permit a device manufacturer to make a profit for HUD devices designed to meet a pediatric device need. FDAAA 2007 also created the Pediatric Device Consortia Grant Program under the FDA Office of Orphan Products Development (OOPD) to develop nonprofit consortia to facilitate pediatric medical device development.

Much of AdvaMed’s testimony will focus on pediatric device development issues because they are an important orphan “sub-population” and the issues involved in pediatric device development exemplify many of the challenges associated with orphan diseases and conditions.

#### NEED TO COLLECT DATA ON UNMET NEEDS

A key to addressing unmet orphan and pediatric device needs is to *methodically collect data* on unmet pediatric device needs including the number of patients with a particular disease or condition, age ranges, and current treatment and diagnostic options and health outcomes. At an October 2009 FDA workshop on pediatric clinical trial design, pediatric cardiovascular physician panelists pointed out that there are still many unanswered basic pediatric research questions. As the physicians noted, failure to answer or address certain basic pediatric research issues resulted in corresponding challenges in the FDA regulatory process (e.g., making it difficult for manufacturers and FDA to select and agree on appropriate surrogate or other clinical trial endpoints). Thus, attempting to understand the associated basic research questions related to unmet medical device needs should also be an important part of any data collection effort. We understand the National Institute of Child Health and Human Development (NICHD) has recently undertaken an effort to collect information on a pediatric research agenda that includes devices. A similar process should be utilized for orphan diseases although it is our understanding that the National Organization of Rare Diseases (NORD) has already collected or conducted a considerable amount of research with respect to many rare diseases.

In addition to directed specialty evaluations, participants in previous National Institute of Health (NIH) conferences devoted to pediatric device development issues have suggested that existing hospital discharge databases could assist in identifying specific device needs for pediatric patients. Efforts to collect pediatric data through the establishment of registries [e.g., the American College of Cardiology IMPACT Registry™ (IMProving Adult and Congenital Treatments)] may be another important source of such data.

AdvaMed believes the primary responsibility for data collection efforts and basic research questions associated with unmet orphan or pediatric medical device needs should reside with the National Institutes of Health (NIH). NIH is the only entity with the breadth and depth of knowledge, funding and resources to conduct such research. Once such data is collected and prioritized, it should be made public (e.g., through a public NIH Web site or clearinghouse or for registries, via the Agency for Healthcare Research and Quality’s proposal to create a registry of patient registries) to enable all interested stakeholders, including pediatric device consortia and device manufacturers to understand potential orphan and pediatric device development opportunities.

It will also be important to *prioritize* orphan and pediatric needs, perhaps based on criteria such as size of patient population, public health need, and recognition that some small markets may not be commercially viable, or by targeting needs that are cross-cutting in nature and provide benefits beyond one subpopulation. Prioritization of needs is important to help determine and assess basic pediatric research requirements that may be beyond the resources or financial scope of any one device company and that should be conducted by NIH. Such activities may for example include assessing existing biomaterials for their effects in pediatric populations; identifying new biomaterials that are safe and effective for use in pediatric populations; or assisting in the basic research and development of key, priority research questions for devices and their related clinical trials. The latter activities could significantly reduce the development costs linked with the small markets associated with many orphan and pediatric disease device needs—a key barrier to device development—thus enhancing chances that such devices would get to market.

There is a significant need to utilize government funding in more efficient ways to address questions that are faced by all developers of orphan or pediatric-focused technologies. Although the deficit may make it challenging to significantly increase funding for orphan and pediatric research, *better coordination of existing or future research* at the National Institute of Child Health and Human Development (NICHD), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute for Biomedical Imaging and Bioengineering (NIBIB) or other relevant Institutes that target specific orphan or pediatric device needs could:

1. Help spur the basic research needed for areas where breakthrough devices are desired;
2. Help offset the tremendous expense associated with early orphan device research and development, thus enhancing commercialization opportunities for interested stakeholders such as device manufacturers or pediatric consortia; and
3. An enhanced technology transfer program between the relevant Institutes and the device industry could help assure the development and manufacture of the needed breakthrough medical devices.

#### *NIH Office of Orphan and Pediatric Diseases*

AdvaMed also recommends that the NIH develop an office of orphan diseases and conditions including pediatric populations. Such an office would presumably be aware of ongoing orphan or pediatric research issues being conducted within each institute and could also serve an important coordinating function with stakeholders to ensure that priority needs and research issues are being addressed. An office of this nature would be an automatic touch point for interested parties and stakeholders. For example, pediatric stakeholders attending FDA co-sponsored pediatric stakeholder meetings in 2004 learned—many for the first time—that the National Heart, Lung and Blood Institute (NHLBI) was developing a number of left ventricular assist device (LVAD) prototypes for commercialization, an important pediatric cardiovascular priority. Such an office would make sure that ongoing NIH research of this nature received the needed attention by relevant stakeholder groups. Further, an NIH office that could delineate and prioritize orphan and pediatric device research and development needs would create a readily understood roadmap for congressional authorizers and appropriators and other stakeholder advocates to improve congressional funding for new orphan device development projects.

#### RECOMMENDED IMPROVEMENTS IN THE HUD/HDE PROGRAM

##### *Need for Guidance on Level of Evidence Needed to Meet Standard of Probable Benefit*

As outlined at the start of our testimony, Section 520(m)(2)(C) of the Food Drug and Cosmetic Act (FDCA) establishes the standard for FDA approval of HDE applications, specifically that “the device will not expose patients to an unreasonable or significant risk of illness or injury” and that “the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternate forms of treatment.” This is clearly a different standard than the pre-market approval (PMA) requirement of reasonable assurance of safety and effectiveness which typically requires full-scale prospective randomized clinical trials because you cannot reasonably conduct such a trial in small populations. However, FDA has provided no general guidance to manufacturers regarding the type or level of evidence that must be developed to demonstrate that an HDE meets the probable benefit standard. This lack of guidance ultimately hinders the use of the HUD program as a pathway to market for devices that treat or diagnose diseases and conditions that affect fewer than 4,000 patients, including pediatric populations and subpopulations. Further, without clear FDA guidance, demands for evidence can continue to drift

upward, until they begin to resemble the expectations for a PMA filing, as has been reported by some manufacturers.

For this reason, AdvaMed recommends that FDA develop general guidance on appropriate types and levels of data necessary for HDE approval. Such guidance should provide examples of what FDA believes are the appropriate types and levels of data needed to demonstrate probable benefit. AdvaMed believes that prospective randomized controlled clinical trials generally should not be necessary to demonstrate probable benefit to health, and that FDA should consider non-clinical data, published literature, historical data and patient records, surrogate endpoints and statistical methods and evidence from experience with similar devices.

*FDA Guidance on HUD as an Approved Device Needed for Reimbursement Purposes*

On a related point, during FDA-sponsored pediatric stakeholder meetings on pediatric device development in 2004, numerous participants pointed out that private insurers typically refuse to reimburse for pediatric HUDs. The statute requires that HUDs can only be administered in facilities with properly constituted and functioning IRBs. Insurers thus assume the HDE must therefore be an investigative device that is not eligible for private insurer reimbursement. As a result, many times, costs associated with HUDs are out-of-pocket. While payment issues are not within the normal purview of FDA, in this instance, inclusion of an additional Question and Answer in FDA's HUD/HDE guidance that explicitly states that a HUD has FDA approval could be a useful addition to the guidance, assisting facilities and physicians in seeking reimbursement, improving patient access to needed HUDs, and importantly, helping patients avoid unnecessary out-of-pocket costs. For this reason, AdvaMed recommends that language be added to the guidance that explains that an HUD constitutes an explicit approval from FDA. Similarly, the Centers for Medicare and Medicaid Services (CMS) should have a process to cover and reimburse HUDs. Insurers frequently follow the lead of CMS with respect to coverage and reimbursement decisions.

*Provide Flexibility on the HDE Cap*

AdvaMed also believes that because there continues to be so little information on the size of certain orphan and pediatric populations associated with specific conditions (due among other reasons to the lack of data on unmet pediatric device needs), it is unknown what affect applying the general HDE population cap of 4,000 to children's devices may have on the availability of devices to treat pediatric conditions. AdvaMed recommends that the Secretary be given authority to selectively raise the cap for specific conditions when FDA determines the health of orphan or pediatric patients requires an increase in excess of the annual distribution number—based on medical, demographic and scientific information provided by a petitioner. As an example, it is unlikely manufacturers will be incentivized to develop devices for an orphan disease that affects 4,500 patients annually and is under full PMA requirements, yet because the population is only 500 patients over the 4,000 cap, it is ineligible for the HUD program.

*Remove HDE Limitations Placed on Diagnostic Devices for Rare Diseases*

A significant obstacle to using the HDE process for development of diagnostic devices for rare diseases is the HDE requirement to demonstrate the number of patients that would be subject to diagnosis by the device, rather than the number of individuals affected or manifesting the rare disease. Unlike other medical devices, where a demonstration by authoritative references that the disease or condition affects or is manifested in fewer than 4,000 people in the United States per year, for a diagnostic device it is necessary to demonstrate by authoritative references that the number of patients per year *who would be tested* by the device is fewer than 4,000. Because such data is generally unavailable, the identification and presentation of authoritative references to support this requirement essentially renders the HDE process unavailable for diagnostic devices. In short, if a diagnostic test were developed to diagnose patients with a condition that manifests in 4,000 people or less per year, it is quite likely that physicians would prescribe the test more than 4,000 times a year in order to diagnose those with the referenced rare disease. To address this limitation, we recommend removing this requirement and requiring the same demonstration of diagnostic devices as is required for other medical devices.

*Proposals to Help Offset Costs of R&D and Commercialization Risks*

In addition to the proposals and comments outlined above, AdvaMed has a number of other recommendations to improve orphan and pediatric device development. Many of these programs would help offset the costs of orphan or pediatric device research and development and address small market size and commercialization risks. These include:

- A strong orphan and pediatric device research and development tax credit program,
- A tax credit for orphan and pediatric HDEs similar to the tax credit that currently exists for orphan drugs,
- Minimization of governmental costs associated with developing products for orphan and pediatric populations such as restrictions on user fees,
- Expedited FDA clearance or approval of orphan or pediatric device applications, and
- Clear pathways for reimbursement once such products are cleared or approved.

*Orphan and Pediatric Ombudsman in the Center for Devices and Radiological Health*

AdvaMed also recommends the creation of an orphan/pediatric ombudsman in the Center for Devices and Radiological Health (CDRH). Currently, no one person or entity within CDRH has either the responsibility or the expertise to assist and counsel manufacturers or other interested stakeholders in how to utilize existing regulatory pathways (510(k), PMA or HDE) to achieve on-label indications for orphan and pediatric diseases and conditions. This individual could also serve as the liaison with an NIH office of orphan and pediatric diseases and conditions.

ADVAMED RECOMMENDATIONS TO RESPOND TO CHALLENGES TO ORPHAN AND PEDIATRIC DEVICE DEVELOPMENT

A key challenge in orphan and pediatric conditions and diseases is that failure to overcome certain regulatory or other barriers to on-label use consigns certain devices and the diseases and conditions they treat to an unending cycle of “jerry-rigging” or off-label use. As a result, data that could be used to improve device research and development, obtain on-label indications, or improve patient outcomes is never collected. It is not clear that orphan or pediatric populations are well-served by this un-ending cycle. While it may not be feasible for all orphan diseases or conditions and their associated devices, a concerted effort must be made to find ways to break this cycle and enable companies and clinicians to begin to obtain and to collect the data that will allow devices for orphan and pediatric diseases and conditions to be on-label.

SMALL MARKET SIZES

A related and significant obstacle to pediatric device development for devices ineligible for HUD is that the annual market associated with specific diseases and conditions may not be commercially viable (for either large or small device companies). Secondly, orphan diseases and conditions are difficult to study because patients with the affected conditions are widely dispersed making it extremely difficult to accrue sufficient numbers of clinical trial participants over a reasonable timeframe and within a manageable number of investigational sites and to assure an adequately powered clinical trial to meet FDA requirements. AdvaMed has a number of recommendations below that are responsive to small market size and failure to overcome regulatory barriers to on-label use.

*General versus Specific Device Claims*

FDA requirements for limited and very specific claims and their associated data can be an important barrier to device development for small and dispersed orphan and pediatric populations. For example, FDA may require 100 patients in each pediatric age group to demonstrate device safety and effectiveness. FDA should consider and allow for more general claims to enable device approval. Subsequent condition of approval requirements, such as requirements for a registry, could then be used to ascertain whether there are particular issues associated with specific age ranges.

*New Regulatory Models and Adaptive Clinical Trial Designs*

To address small market issues, FDA must develop regulatory models and adaptive clinical trial designs that take into consideration the reduced sample sizes associated with orphan diseases and conditions. For example, FDA could approve certain devices based on smaller confirmatory trials in conjunction with a long-term registry requirement either for an individual device or for certain device types. This would enable the collection of essential data to better understand patient outcomes and provide FDA with better data for future device approval decisions. Related to this, to facilitate pediatric device development by interested stakeholders (e.g., manufacturers or pediatric consortia), FDA should post on its Web page, examples of adapt-

ive clinical trial designs<sup>1</sup> that have already been successfully used to obtain on-label orphan or pediatric indications.

*Valid Scientific Evidence Other Than Well-Controlled Trials*

Section 513(a)(3)(A) of the Federal Food Drug and Cosmetic Act and 21 CFR 860.7 give FDA authority to utilize valid scientific evidence other than well-controlled trials.

Importantly, the standard of reasonable assurance of safety and effectiveness is the same no matter what type of scientific evidence is required. While FDA relies on many types of valid scientific evidence (other than well-controlled trials) in other areas, it is our sense that FDA has been reluctant to take advantage of this statutory authority in the case of pediatric devices.

FDA should be encouraged to make better use of all forms of valid scientific evidence which could help address the problems associated with the extremely small numbers of orphan or pediatric patients that are afflicted with any one condition or disease state. For example, what may have evolved as the pediatric standard of care may be off-label (e.g., a minimally invasive procedure supersedes a surgical procedure and becomes the standard of care). Doctors will be reluctant to randomize pediatric patients to a surgical control arm if the minimally invasive procedure is the standard of care. Parents will also be reluctant to have their child participate in such trials. In this instance, an FDA requirement to randomize pediatric patients to the surgical procedure creates a barrier that prevents the off-label use of the device from ever becoming on-label. Where numerous articles document the effectiveness of a particular off-label use of a device and it has become the standard of care, FDA should be encouraged to develop mechanisms that make use of this data.

AdvaMed has a number of recommendations that are intended to make better use of existing FDA regulatory tools *and* enhance orphan or pediatric access to medical devices. To help break down barriers to orphan and pediatric device development, FDA should provide examples of these or other types of valid scientific evidence that FDA has in FDA guidance. Importantly, the proposals below retain the existing standard of reasonable assurance of safety and effectiveness although some of the recommendations may be applied to the HUD standard of safety and probable benefit.

**1. Proposal:** Where appropriate FDA should use objective performance criteria (OPCs), historical controls or well-documented case histories as endpoints to show probable benefit or to demonstrate effectiveness.

**Background:** Reliance on well-documented case histories and historical controls would take advantage of the existing literature, respond to the extremely small numbers of orphan or pediatric patients with any one condition (which makes it difficult to run statistically valid clinical trials in a timely fashion—as one person put it “20 years of literature vs. years to put together a control group”) and help minimize the use of surgical interventions as the control where devices have been established as the standard of care.

**2. Proposal:** Extrapolation of clinical data between different sizes of the same device based on engineering testing and other non-clinical data.

**Background:** Currently, FDA requires clinical evidence on the full range of device sizes for a particular device and it can be difficult to assemble enough patients at either end of the size ranges to be valid. It is often extremely challenging to get significant data on the smallest and largest sizes. This proposal would allow the use of non-clinical and bench data as well as the potential to do post-market clinical work to approve the full range of sizes.

**3. Proposal:** Reliance on non-clinical data for modifications of devices specifically approved for pediatric patient populations, when such modifications are unrelated to changes in intended use and do not affect safety.

**Background:** Modifications made to an already cleared or approved device to improve its performance or safety require that the device be cleared or approved again. For devices, much of the data about a product’s function can be established non-clinically (e.g., relying on animal, bench and/or reliability testing). Every time a minor modification is made (e.g., material changes or minor design changes), FDA often requires that the device be cleared or approved again. The requirements for clinical data in the modification process create a challenge and limit improvements for pediatric devices. Due to the barriers associated with gathering clinical data for pediatrics (small populations, widely dispersed populations, parental unwillingness to have children participate, timeliness, etc.), the intent of this provision—for devices specifically approved for pediatric use—is to enable use of engineering and

<sup>1</sup> FDA must take care not to reveal proprietary or trade secret or confidential commercial or financial information when sharing trial designs.

bench testing, rather than clinical testing for minor device changes when the changes are not related to changing the intended use of the device and do not affect safety. FDA has the flexibility to do this—and allows it for adult devices—but should be specifically encouraged to do so in the case of pediatric products.

**4. Proposal:** The acceptance of 510(k) devices intended for adult populations with the same use as a pediatric device as predicates for the 510(k) pediatric device.

**Background:** Similar to the language proposed in the FDAAA 2007 pediatric device law which allows FDA to use adult data to support a reasonable assurance of safety and effectiveness in pediatric populations and to extrapolate data between pediatric populations, FDA has authority, where the course of the disease or effect of the device is the same in adults and in pediatrics, to use the adult 510(k) device as a predicate for the pediatric device. Doing so would be responsive to the extremely small numbers of pediatric patients—particularly of a given age range—with any one condition (which makes it difficult to run valid clinical trials in a timely fashion) and would help limit the number of children exposed to surgical controls. FDA could still require a clinical trial for a 510(k) device but the trial would be smaller and pediatric access to the device would be faster.

**5. Proposal:** The acceptance—as an appropriate control for investigational pediatric devices—of devices intended for use in adult populations when such devices provide the only device-related means for treating, diagnosing or preventing diseases or conditions in pediatric patients and have become the standard of care for such patients.

**Background:** Similar to the language proposed in the new pediatric device law which allows FDA to use adult data to support a reasonable assurance of safety and effectiveness in pediatric populations and to extrapolate data between pediatric populations, FDA has authority to utilize as the control for studies under the Investigational Device Exemption process, devices that are not approved for pediatric use but that are already being used in pediatric populations. This would enable the adult data on already approved devices or these devices themselves to serve as the “control” for the pediatric trial, responding to the limited number of pediatric patients available for pediatric trials and reducing the number of children exposed to a surgical control.

#### *Development of Custom Device Guidance*

Section 520(b) of the FDCA and 21 CFR 812.3(b) provide for the manufacture of custom devices that are intended for use by an individual patient in response to a clinician’s order. In the ongoing pediatric stakeholder dialogue, clinicians have repeatedly reported that they feel compelled to “jerry-rig” or modify existing devices to treat pediatric patients. Dr. Jon Abramson (representing the American Academy of Pediatricians) reiterated this point at a July 23, 2008 NIH workshop. Pediatric patients may also suffer more congenital deformities which may require customized devices. AdvaMed recommends that FDA develop guidance for custom devices that clarifies the number of devices manufacturers may customize for orphan and pediatric populations, a recommendation that was echoed by former Center for Devices and Radiological Health Director, David Feigal, Jr., M.D., at a July 23, 2008 NIH pediatric device workshop.

Manufacturers have been reluctant to develop custom devices because the rules are unclear. Anecdotal evidence suggests that FDA limits manufacturers to just one or a few custom devices although this has not been articulated in FDA guidance. AdvaMed has heard from manufacturers that they, on occasion, are compelled to choose between complying with FDA requirements *and* pediatric patients’ needs with the knowledge and heavy burden that their decision to adhere to FDA requirements may result in a dire outcome for the child. Given that FDA’s formal definition of pediatric is from neonate to age 21, that so many different device sizes are required to treat this wide age range, and the small market sizes that may be associated with this wide size-range, custom devices may be the only alternative for some medical devices. FDA guidance on custom devices that relaxed the current limitation on manufacturing (which we believe is just one or two custom devices) and that specified the number of orphan or pediatric custom devices that *could* be manufactured and distributed would be helpful. Envisioned here is a special program for unique devices for very small orphan or pediatric populations or very early device modeling that could encourage development of these therapies.

#### *Proposal of a Compassionate Use Orphan/Pediatric Device Provision*

Finally, AdvaMed recommends the creation of a New Compassionate Use Orphan/Pediatric Device Provision to be applied in situations where even the HUD pathway makes little sense. As mentioned elsewhere in our testimony, clinicians have repeatedly reported that they feel compelled to “jerry-rig” or modify existing devices to

treat pediatric patients. Rather than having pediatric clinicians across the country individually jerry-rig devices during surgery, AdvaMed proposes a well-regulated mechanism to provide device access for super-small, orphan or pediatric populations that are not likely to be served by the HUD program or the FDAAA 2007 pediatric HUD program. AdvaMed recommends that FDA be required to develop regulations that would allow manufacturers to distribute no more than 100 unapproved devices annually for patients when such patients are afflicted with diseases or conditions that affect too few patients annually to justify the expense necessary to achieve an approved device under the HUD program. Appropriate controls would be statutorily mandated including: (1) compliance with quality system, labeling, adverse event reporting, device tracking and postmarket surveillance regulations; (2) device promotion would be limited to medical professionals and no claims of safety or effectiveness could be made; (3) the manufacturer would be required to notify the Secretary upon the first shipment of such a device; (4) maintenance of records of each shipment of such a device; (5) limitation of distribution to prescription use only; (6) institutional review board approval would be required for each use of such a device; and (7) informed consent prominently informing the patient and the patient's parent or legal guardian that the device is not approved by the Food and Drug Administration would be required.

In closing, AdvaMed greatly appreciates this opportunity to provide our thoughts and recommendations to the Committee on Health, Education, Labor, and Pensions on rare disease and pediatric device development issues.

PREPARED STATEMENT OF PETER J. HOTEZ, M.D., PH.D., PRESIDENT,  
SABIN VACCINE INSTITUTE

On behalf of the Global Network for Neglected Tropical Diseases and the Sabin Vaccine Institute, our organization welcomes the opportunity to submit a written statement affirming two specific issues raised during the committee's hearing on July 21, 2010 entitled, "*Treating Rare and Neglected Pediatric Diseases: Promoting the Development of New Treatments and Cures.*"

Before outlining the specific issues we would like to address, we thought it would be best to provide the committee with some background on the Sabin Vaccine Institute and two of its important initiatives. Founded in 1993, the Sabin Vaccine Institute is a non-profit 501(c) (3) organization dedicated to preventing and curing infectious and neglected tropical diseases worldwide and eliminating the tremendous human suffering they cause. An essential element of the Sabin Vaccine Institute's mission to reduce human suffering caused by infectious and neglected tropical diseases (NTDs) is our vaccine development program conducted in collaboration with the George Washington University and other international organizations, including the Oswaldo Cruz Foundation and Instituto Butantan (Brazil), Queensland Institute of Medical Research (Australia), the London School of Hygiene and Tropical Medicine (United Kingdom), and The Institute of Parasitic Diseases Chinese Center for Disease Control and Prevention (China).

In 2000, Sabin established an innovative non-profit Product Development Partnership (PDP) to develop new vaccines for human hookworm infection, schistosomiasis and other NTDs. Our vaccine development program is the first and only PDP with a mission to develop a vaccine to confer preventive immunity against human hookworm infection ("hookworm"), an NTD that threatens vulnerable populations around the globe. An estimated 576 million people suffer from hookworm, primarily in the most impoverished communities of sub-Saharan Africa, Asia, and Latin America. In these countries, hookworm is a leading cause of anemia and malnutrition. Children are among the most vulnerable populations, and suffer from severe growth and cognitive delays as a result of this disease. Women of reproductive age, including pregnant women, are also highly susceptible.

We have established a vaccine development pipeline that contains multiple antigens at various stages of development. Our vaccines undergo clinical testing in Brazil, a country where large numbers of people are affected by hookworm infection. In addition, Sabin Vaccine Development is pioneering the creation of some other vaccines that have no traditional commercial market. The diseases represent the most common scourges of the world's poorest people, including hookworm, schistosomiasis, and malaria. Our vaccines enter into clinical trials following regulatory submissions to the U.S. FDA and ANVISA, the national regulatory authority in Brazil.

The Global Network for Neglected Tropical Diseases is another initiative of the Sabin Vaccine Institute dedicated to raising the awareness, political will, and funding necessary to control or eliminate the most common NTDs—a group of disabling, disfiguring, and sometimes deadly diseases affecting more than 1.4 billion people worldwide living on less than \$1.25 a day through mass drug administration cam-

paigns. The seven most common of these NTDs—ascariasis (roundworm), trichuriasis (whipworm), hookworm, schistosomiasis (snail fever), lymphatic filariasis (elephantiasis), trachoma (blinding trachoma), and onchocerciasis (river blindness)—account for 90 percent of the NTD burden around the globe. Research has shown that some of these diseases, such as LF, onchocerciasis, and trachoma can be eliminated through mass drug administration, while others such as hookworm can be controlled temporarily until the vaccine is developed. These mass drug administration treatments can allow millions to climb out of poverty through increased access to education and improving economic performance.

Because of the Sabin's commitment to drug development and its fight to control and eliminate NTDs globally, we affirm the steps the Food and Drug Administration (FDA) is taking in implementing Section 740 of the fiscal year 2010 Appropriation Act (Agriculture, Rural Development, Food and Drug Administration, and Related Appropriation Act, 2010, Public Law 111-80) to establish expert review groups and issue guidance related to rare and neglected diseases. This work conducted by the FDA will further enhance the work of those in the research and development field and streamline product availability. In particular, it should allow for clarity in the review process for products, such as new vaccines for NTDs that would not necessarily be used within the United States but could have significant impact on the disease burden resulting from neglected diseases around the world. Furthermore, the use of the Priority Review Voucher process to provide incentive for the development of new products targeting the NTDs is welcomed.

Additionally, Sabin and the Global Network will look forward to participating in the Part 15 hearing to be held this fall, which will focus on the development of medical products used in the prevention, diagnosis, and treatment of neglected tropical diseases and assist the FDA in the collection of stakeholder comments to update its development and approval guidance.

Another important issue discussed before the committee is the need for new incentive mechanisms to de-link the cost of research and development from the eventual revenues to be obtained from the sale of new health products or medicines. The concept of de-linking would help ensure that the right products for NTDs reach the end of the development pipeline despite the lack of a commercial market. Alternative incentives, such as prizes or other forms of "pull funding," are essential to stimulate the development of new vaccines, drugs, and diagnostics for the NTDs. This concept is something that Sabin strongly supports.

Again, we appreciate the opportunity to share our views and contribute to this important global health discussion and the work of this committee to streamline the development and approval of medicines and treatments that target rare and neglected diseases. If the committee should have any further questions about this statement or programs of the Sabin Vaccine Institute Diseases, please do not hesitate to contact me.

Thank you.

PREPARED STATEMENT OF THE HUNTINGTON'S DISEASE SOCIETY  
OF AMERICA (HDSA)

Chairman Harkin and Ranking Member Enzi, on behalf of the Huntington's Disease Society of America (HDSA), we applaud you for holding this important hearing to discuss treating rare and neglected pediatric diseases. We appreciate the committee's commitment to this issue and hope that through increased awareness and Federal research dollars we can find a cure for Juvenile Huntington's Disease (JHD).

Huntington's Disease (HD) is a rare, genetic, neurodegenerative disease that causes total physical and mental deterioration over a 10- to 25-year period. HD affects 30,000 Americans while another 200,000 are considered "at risk" of inheriting it from a parent. Even more rare is JHD, which affects only 10 percent of individuals with HD.

Early signs of JHD include rigidity, slowness and stiffness, clumsiness of arms and legs, behavioral changes, decline in cognitive function, seizures and more. There is no cure for JHD or adult HD. Today, physicians prescribe a number of medications to control emotional and movement problems associated with the disease but there is no treatment to stop or reverse the course of HD or JHD.

Increasing awareness of rare, orphan diseases is one way that we can find a cure for diseases like JHD. Currently, there is legislation in the House and shortly to be introduced in the Senate, the *Huntington's Disease Parity Act (H.R. 678)*, which has received the support of nearly 140 Members of Congress. Current Social Security Administration (SSA) guidelines for determining disability for individuals with HD is more than 30 years out-of-date. Even more alarming is that the SSA has failed to acknowledge the existence of JDH. H.R. 678 not only updates the medical



criteria and guidelines for HD, but also directs the SSA Commissioner to include JHD in its list of Pediatric-Neurological diseases. Further, the bill also removes the 2-year waiting period for those with HD to receive critical Medicare benefits.

Another way Congress can promote the development and treatment of rare diseases is through the expansion of Federal research dollars. Current HD research examining the processes of HD is helping scientists and researchers identify new therapies and tools that are applicable to other neurodegenerative and genetic diseases. While most of the current research is focused on adults, the symptoms of JHD appear much earlier and the progression of the disease is much more rapid from symptomatic onset. Therefore JHD's biological, chemical, metabolic and molecular processes may be easier to identify and flag—and thus our understanding of Huntington's disease, other juvenile neurodegenerative and genetic illnesses, and the means to thwart their progression.

We were also especially pleased to see that the Senate Appropriations Committee included funding for the Office of the Associate Director for Rare Diseases at the FDA and increased funding for Orphan Product Development Grant program in the fiscal year 2011 Agriculture, FDA, and Rural Development Appropriations bill. These two funding opportunities will further the clinical development of products used to treat rare diseases.

In conclusion, we thank you for your support for pediatric orphan diseases and congressional funding for research. We also ask that you consider reviewing the Social Security Administrator's characterization of HD and JHD to ensure that the medical guidelines are accurate and up to date so that people with these diseases can have much-needed access to Social Security disability and Medicare.

#### PREPARED STATEMENT OF THE NATIONAL VENTURE CAPITAL ASSOCIATION (NVCA)

The National Venture Capital Association (NVCA) appreciates the opportunity to submit a statement on the role of venture capital investment in the treatment and cure of rare and neglected pediatric diseases. The NVCA represents the interests of more than 425 venture capital firms which comprise more than 90 percent of the capital under management in the United States. NVCA's mission is to foster greater understanding of the importance of venture capital to the U.S. economy, and to support entrepreneurial activity and innovation.

For decades, the U.S. venture capital industry has committed itself to bringing groundbreaking medical innovation to the American people. Since the early 1970s, venture capital firms have identified the most promising breakthroughs in labs across the country, built companies around these innovations, and worked alongside scientists and entrepreneurs to safely commercialize these products—improving and saving millions of lives along the way. In fact, according to Thomson Reuters, venture capitalists have invested more than \$81.5 billion in over 4,000 start-up life sciences companies in the last four decades. This represents approximately 30 percent of total venture capital investment over the same period.

Venture capital-backed companies have pioneered the development of important new treatments for a wide range of serious diseases, such as cancer (including many rare pediatric cancers), cystic fibrosis, lysosomal storage disorders and other inborn errors of metabolism, and many more. These kinds of rare diseases represent relatively small markets that frequently attract little interest from large, established pharmaceuticals. Venture capital-backed companies have been the engine of innovation when it comes to breakthrough treatments for rare pediatric diseases.

NVCA wants to promote greater investment in this important area. However, the incentives for investment in rare diseases are at risk in a number of ways, and we must act now to ensure that the venture capital-backed innovation engine can continue to deliver important new therapies for rare diseases. Among other issues, we must ensure that the regulatory environment is conducive to investment in this area. Development of novel therapies for rare diseases is inherently difficult and risky. Patient populations are small, and it is frequently impossible to complete the kind of large clinical trials that FDA demands. It is essential that regulators recognize the unique challenges of developing treatments for rare diseases, and show appropriate flexibility in the application of regulatory standards, to promote the continued development of new therapies for rare diseases while continuing to ensure the safety and efficacy of new treatments.

Over the years, the venture capital investment process has remained largely unchanged—largely because it works. Venture capitalists invest pools of funds in start-up companies across the country with the goal of making a significant return for their investors. Historically, these investments are made in scientific discoveries and novel technologies that address emerging or complex economic and social needs. This characteristic adds significant risk to the process, but also enhances the re-

turns on successful ventures for investors, who are commonly State pension funds and educational endowments. Because of the high-risk and long-term nature of the investment, no other asset class is positioned to invest in these types of companies. Without venture investment, most of these medical breakthroughs would remain in the lab and never reach the public.

It is important to understand that venture capital investment involves more than just money. Venture capitalists invest a significant amount of time, energy and expertise in each of the companies in their portfolios. The life cycle of a venture investment typically follows the same path. Venture capitalists seek out the most promising medical breakthroughs in their early stages—looking for products or processes that are ready to move on to the commercialization phase. Most often, these innovations spring from government-funded basic research conducted at universities and government labs. Venture capitalists typically do not fund this basic research, but rather use their funds to apply the products of basic research to solving real-world problems.

Once an idea is identified by a venture capitalist, the investment is vetted by the entire firm and the most promising ideas are funded. Venture capitalists, who are often scientists, engineers or doctors themselves, will work closely with a company's founders to build the business by taking a seat on the board of directors and offering strategic counsel as the company matures. Usually, a venture capitalist will invest several rounds of financing into a company over a period of time. The average round of financing into a biotechnology company in the first half of 2010 was just under \$9 million. Companies must reach specific, pre-determined milestones in order to earn their next rounds of funding. If a company fails to achieve these goals, the venture firm may decide that the risk is too great and the chance of success is too small to continue funding it. In such instances, the company will likely go out of business.

The goal of the venture capitalist is to one day sell the company to a larger player or have the company go public, generating a significant return on the total amount invested. In fact, many venture-backed life sciences companies are sold to larger pharmaceutical corporations because it is often the optimal way for large corporations to acquire innovation. However, the largest returns are realized when a company goes public. Venture capitalists look for returns that are at least four times their original investment. Because many venture-backed companies will fail, the returns generated by the successes must significantly outweigh the cost of the failures for the venture capitalist to be successful.

To wit, venture capital investment in life sciences is not for the faint at heart. It requires tremendous patience and an appetite for considerable risk. Due to the substantial regulatory path that medical innovations must travel, investment in life sciences has a significantly longer time horizon than other industries. Whereas a venture investment in a software company might last 5 to 7 years, a biotechnology investment typically lasts 15 years on average and can cost up to \$800 million. Additional regulatory hurdles add to the length of the investment and the scope of the challenges. Not only do these small companies face technological and market risk (i.e., will it work and will it sell?) but also regulatory and pricing risk (will it be approved by the FDA and receive a fair price by CMS?). Over the years, the uncertainty surrounding the regulatory process has added additional risk to an already tenuous path.

Given the role venture capitalists play in guiding life sciences companies through their start-up and expansion phases, they have a valuable perspective on the hurdles that emerging businesses confront and the environments that promote or stifle growth and innovation.

Our members tell us that it is becoming increasingly difficult to build an investment case for new investments in novel therapies targeted at rare diseases, including pediatric diseases. The low-hanging fruit is gone, and new therapies are inherently risky to develop. Venture investors report that FDA regulation is becoming increasingly inflexible. Whereas in the past, FDA appeared to show greater flexibility in evaluating therapies for serious, rare diseases, recognizing the challenges of developing these therapies, our members report that FDA is increasingly painting novel therapies for rare diseases with the same regulatory brush as other kinds of treatments for more common diseases. If FDA fails to apply flexible standards that reflect the unique challenges presented by rare diseases, then investment in these therapies will grind to a halt.

Regulatory uncertainty and inconsistency can delay approvals to the point of bankrupting innovative companies. This trend is impeding patient access to critical therapies and medical technologies and is disrupting critical U.S.-centered research and development. This in turn greatly reduces the willingness on the part of venture capitalists to invest in disruptive medical therapies. Strikingly, venture capital investors are noting with alarm that novel therapies for rare diseases are increas-

ingly coming to market in Europe, Japan and other parts of the world before they do in the United States. This points to a serious risk that the United States could lose its leadership position in medical innovation and the risk that patients with these diseases may suffer without access to treatments that are benefiting patients in other parts of the world.

Today's hearing provides an important opportunity for NVCA to offer our suggestions on what can be done to create the proper incentives for investment in the development of new treatment and cures for treating rare and neglected diseases, including the pediatric population. NVCA believes that the following suggestions will help alleviate the challenges facing investors and innovators generated by the U.S. regulatory framework and will promote the advancement of critical life-saving therapies, a common goal of the NVCA, the FDA, and patients.

NVCA believes that innovative companies need:

- The application of flexible regulatory standards that reflect the unique challenges of drug development for rare diseases;
- A special well-defined regulatory pathway for truly “novel therapies” which include therapies for rare and neglected diseases that is robust, collaborative and flexible, but also predictable;
- A process to assemble a senior team of highly qualified regulatory reviewers and expert advisory panel members well-versed in the current science and current safety and efficacy of novel therapies;
- FDA approval requirements based on actual risk; and
- A reasonable and predictable review regimen for all medical therapies, including “novel therapies.”

FDA approval of a company's innovative product can mean the difference between success and failure for the business. Moreover, investment in emerging companies will further decrease if the regulatory environment remains so uncertain and burdensome as to jeopardize final clearance of the product. This situation prevents U.S. patients' access to the most innovative technologies. Unclear regulatory requirements, inconsistent application of regulatory requirements and high staff turnover can all lead to lengthy delays in product review times, costing the emerging company hundreds of thousands of dollars, or even millions of dollars, and risking future venture investment in the start-up. These concerns are compounded during the review of “novel therapies” which often raise issues of first impression for the Agency since new therapies rarely fit into the normal regulatory pathway.

NVCA believes that creating a special regulatory risk-based pathway for “novel therapies” that is flexible, but predictable, would mitigate some of these problems, particularly if such a system were to focus dedicated resources and senior staff on expediting the review of these therapies and technologies. We suggest that the following specific changes relative to novel therapies at the FDA.

- **Clear Definition of “Novel.”** The term “novel” is not defined by the FDA.
- **Dedicated Resources for Novel Therapies.** NVCA suggests that the FDA dedicate a pool of cross-disciplinary, highly experienced staff, and significant resources to the review (including expedited review) of “novel therapies.” NVCA believes that it is important for the FDA to continue to hire and retain qualified medical reviewers who are well-versed in the current science and are up-to-date in the practice of medicine in the specialties by which the therapies and technologies they are evaluating will be used. A dedicated pool of qualified reviewers will ensure that the Agency focuses precious resources on truly innovative products, and that these therapies receive appropriate and timely attention from experts at the Agency. Moreover, by offering high-performing staff the opportunity to work with cutting edge therapies, it may also aid the Agency in retaining top reviewers, and will reduce delays due to staff turnover. Special fees could be required for products designated for novel technology review.
- **Well-Defined, but Flexible, Review Process for Novel Therapies.** Because novel products often raise new issues of safety and effectiveness for the Agency, a clear review process and a clear path for resolving disputes during the review process will provide added regulatory certainty and additional security for venture investment. For example, early, pre-clinical discussions with Agency reviewers to design appropriate study requirements are invaluable to start-up companies. In addition, continued discussions and an open dialogue with the Agency during the review process is essential, as is the ability to use new methods of statistical modeling and cutting-edge clinical trial designs to speed the review process. All of these items will increase transparency between the Agency and the sponsor, and reduce regulatory risk for VC investors in novel therapies.
- **Regulatory standards that reflect the unique challenges of drug development for rare diseases.** As discussed above, it is essential that FDA apply

standards that reflect the realities of drug development for rare and neglected diseases. We believe that FDA has statutory authority to apply its judgment and discretion in the evaluation of novel therapies for rare diseases. What is needed is clear direction and leadership from senior FDA officials who recognize these issues, leading to the articulation of a regulatory policy that encourages an appropriate balancing of benefit and risk in the context of the realities of drug development for rare diseases.

- **Regulation based on risk classification.** The level of approval standards should be based on the risk. Higher levels of evidence of efficacy and safety would be required for therapies and technologies which present greater risk concerns.

- **Ensuring Appropriate External Expertise to Support Reviews of Novel Therapies.** As stated above, the potential for inadequate expertise at the Agency and on advisory panels to review and rule upon novel products is a real problem because persons who can provide the day-to-day input to ensure a knowledgeable, effective and efficient review are often excluded from the process due to conflict of interest concerns. Although they can participate at selected moments as part of the sponsor's team, their value is greatly reduced in that capacity. NVCA strongly believes that the advisory committee review process must have persons with intimate knowledge of novel therapies if these panels are going to properly advise the FDA. Accordingly, we propose that the FDA request that its legal counsel determine transparent processes and standards to permit persons with an interest in a novel therapy and technology to participate in the advisory panel process as an advisor or a non-voting panel member with adequate disclosure of any conflicts or potential conflicts. If there are ownership interests, functioning as a scientific advisor to a panel could be inappropriate. However, if there are no financial interests, but the individual does have a financial interest, participation as a non-voting panel member may be appropriate, again with adequate disclosure of the person's association or interest in the device. Medical advisory committees must be able to recruit the most qualified experts in the field in order to provide meaningful recommendations to the Agency on product approvals. NVCA believes that the current conflict of interest policies prevent the best academic researchers and physicians and those from industry from serving on advisory committees, to the detriment of patients and innovation.

#### CONCLUSION

NVCA believes that these suggestions will stimulate innovation and the development of "novel therapies" without compromising the safety or effectiveness of cleared or approved therapies and will provide the appropriate incentives that will lead to the development of critical treatments for rare and neglected diseases. NVCA looks forward to working with the committee to help accomplish this important goal.

RESPONSE TO QUESTIONS OF SENATOR HARKIN, SENATOR ENZI, SENATOR CASEY, SENATOR HAGAN, AND SENATOR FRANKEN BY THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

#### SENATOR HARKIN

*Question.* Some suggest that FDA should create a separate division of rare and neglected diseases within the Center for Drug Evaluation and Research to bring the proper expertise to bear on the analysis of drug applications intended to treat such maladies. Can you please comment on the merits of this idea?

*Answer.* FDA shares the goal of encouraging and speeding the development of drugs, vaccines, biologic medical products, and diagnostic tests for rare and neglected diseases and appreciates efforts by Congress to achieve these goals. FDA is aware of proposals to establish a specific review group in the Center for Drug Evaluation and Research (CDER) for products to treat rare diseases. This approach may have some challenges that would be important to carefully consider so as to avoid potential unanticipated consequences. For example, rare diseases cut across all medical disciplines, from oncology to obstetrics to rheumatology to infectious diseases to neurology to inborn errors of metabolism, etc. The scientific and practical challenges posed by these products require input from our most experienced scientists and clinicians. Expertise in particular rare diseases, including expertise in defining appropriate endpoints and employing flexible clinical trial designs, is currently embedded within the medical disciplines that also embrace more common diseases.

In February 2010, FDA created a position of Associate Director for Rare Diseases (ADRD) in CDER. The ADRD coordinates the development of policies and procedures for the review and approval of treatments for rare diseases throughout CDER,

ensures appropriate training of staff, establishes consistent processes for providing advice to sponsors, and advocates for and oversees the efficient development of products for rare diseases across multiple scientific disciplines. The ADRD is actively addressing challenges related to rare diseases through enhancing coordination and identifying and promoting best practices among FDA's experts in the specific disease areas of interest, bringing detailed knowledge of flexible approaches to development and review of drugs to treat rare diseases. In conjunction with the Office of Orphan Products Development (OOPD) and the Office of the Chief Scientist (OCS), the ADRD 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.

Thank you again for your interest in rare and neglected pediatric diseases. If you have further questions, please let us know.

SENATOR ENZI

*Question 1.* Looking at these different programs at different agencies, is there any entity that acts as a shepherd for a company or product along the entire development process, or does each agency just monitor its own program?

Answer 1. In February 2010, FDA and the National Institutes of Health (NIH) established a Joint NIH-FDA Leadership Council to spearhead collaborative work on important public health issues. The Joint Leadership Council works together to help ensure that regulatory considerations form an integral component of biomedical research planning, and that the latest science is integrated into the regulatory review process. The collaboration will advance the development of new products for the treatment, diagnosis, and prevention of common and rare diseases and enhance the safety, quality, and efficiency of the clinical research and medical product approval enterprise. The formation of the Leadership Council represents a commitment on the part of both agencies to forge a new partnership and to leverage the strengths of each agency toward this common goal.

In addition to the Leadership Council, FDA collaborates with NIH on multiple levels. FDA's Office of Orphan Products Development (OOPD) works closely with NIH's Therapeutics for Rare and Neglected Diseases (TRND) program and the NIH Office of Rare Disease and Research (ORDR), integrating activities across agency boundaries. OOPD acts as an ombudsman throughout the drug development process, meeting with sponsors from the earliest idea all the way through the drug development process. OOPD has a formal role in granting orphan status designation and awarding grants and regularly attends review division meetings, providing overall regulatory advice to all companies that aspire to make new therapies for people with rare diseases.

FDA's Center for Drug Evaluation and Research (CDER) recently established a new position of Associate Director for Rare Diseases (ADRD), which is intended to serve as a focal point within CDER for communication with rare disease stakeholders, including partner offices at NIH. In conjunction with OOPD, the ADRD also 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.

Finally, FDA's Office of Pediatric Therapeutics (OPT) works closely with NIH's Eunice Shriver National Institute of Child Health and Human Development to shepherd pediatric products through the development pipeline.

*Question 2.* I am glad to hear that you are focused on training FDA reviewers in the science of conducting and analyzing small clinical trials. Is there a corresponding effort to provide regulatory certainty via guidance to industry for clinical trial design for these small populations?

Answer 2. FDA is exploring the development of guidance documents for rare disease research programs; however, because these trials often have unique circumstances, guidance will not answer all of the questions that industry may have. For this reason, FDA is working to educate industry and other stakeholders about the possibilities for the science of conducting and analyzing small clinical trials. The FDA annual course entitled, "The Science of Small Clinical Trials" was originally limited to FDA and NTH participants but was recently opened to a wider audience. Last year more than 1,500 registrants participated, many of whom were from industry. In addition, FDA and NIH, in collaboration with the National Organization for Rare Disorders (NORD) and Duke University Medical Center, are co-sponsoring a training course for rare disease investigators, scheduled to take place in October 2010. The course will focus on special considerations and regulatory requirements for research on rare diseases and orphan products. FDA plans to repeat this course annually.

*Question 3.* Both the orphan drug and Humanitarian Device Exemption programs are designed to incentivize developing treatments for rare diseases. The population limit for orphan drug designation is 200,000 people. However, the limit for the Humanitarian Device Exemption is 4,000 people. Do you believe the difference is appropriate? If so, why?

Answer 3. These statutory limits were determined by Congress, not FDA; however, FDA recognizes that there are reasons why these numerical differences may exist. The Humanitarian Use Device/Humanitarian Device Exemption (HUD/HDE) program and the Orphan Drug program are vastly different in terms of the incentive that they offer. The HUD/HDE program offers as its major incentive an exemption from the otherwise applicable effectiveness requirements. To qualify for this exemption, certain criteria must be met, including a determination by FDA that the probable benefit outweighs the risk of injury or illness from use of the device. Arguably, one might wish to be especially restrictive of the population to which one exposed less well-established therapies. In contrast, the Orphan Drug Act offers market exclusivity (and other financial rewards) as its major incentive, but maintains the same requirements for safety and efficacy as any other drug/biologic.

While FDA has no position on changing the limit for the Humanitarian Device Exemption, the Agency strongly urges Congress to ensure that, if a change is made, the population limit is clearly defined, not variable. Any variation in the system will lead to unnecessary confusion and may unintentionally disincentivize innovation in this area.

SENATOR CASEY

*Question 1.* What sort of data exists on post-marketing surveillance for children's use of pharmaceuticals and medical devices?

Answer 1. FDA's Adverse Event Reporting System is a computerized information database designed to monitor new adverse events and medication errors that occur in marketed, FDA-regulated products. The system includes data on adverse events experienced by children, though it is incomplete because reporting of adverse events from the point of care is voluntary in the United States. Recognizing the need to improve post-marketing surveillance for children's products, Congress enacted legislation to address this issue. The Food and Drug Administration Amendments Act of 2007, which included the Pediatric Research Equity Act, the Best Pharmaceuticals for Children Act, and the Pediatric Medical Device Safety and Improvement Act of 2007, requires FDA's Pediatric Advisory Committee (PAC) to review all adverse events in the year after a product receives new pediatric labeling resulting from pediatric studies. Because the legislation increased the number of pediatric clinical trials, and subsequently, the number of products with pediatric information in labeling, the number of products up for pediatric-focused safety review has steadily increased from approximately 8 products annually to over 40 products per year. As of June 2010, the PAC reviewed 135 products and recommended labeling changes on 32 (24 percent) of those products. In addition, the PAC recommended additional studies for seven products. These products include both pharmaceuticals and medical devices.

*Question 2.* Would it be advisable for FDA to better understand the frequency and practice of "off-label" use in children—particularly those with rare diseases? If so, what should be done?

Answer 2. Off-label use of commercially available drug and biological products is a concern for both pediatric and adult rare-disease populations. Products that are approved for other indications are frequently prescribed off-label for rare diseases, usually in situations where no other specific treatment for the rare disease is available. The frequency of off-label prescribing in rare diseases has not been quantified, though we are aware of the practice through communication with patient groups and treating physicians. We recognize that in some cases limiting off-label use would leave patients with few, or no, treatment options. The best approach for patients would be to study these products—in children and adults—in the conditions for which they are being used in order to adequately inform patients and physicians of their safety and effectiveness. FDA is currently working to encourage such studies through the work of its OOPD, OPT, and the Associate Director for Rare Diseases in CDER.

SENATOR HAGAN

*Question.* One challenge that many of the witnesses today spoke of is the need to incentivize the device and drug/biotech industry to develop therapeutics for rare, pediatric diseases. Assuming a device or compound gets to the clinical trial stage,

how long does it take to conduct the adult trials and then the follow-on clinical trials in children? Is there a way to speed up this process?

Answer. The time required to conduct clinical trials in adults and children varies greatly as the Agency must review and evaluate each device or compound on a case-by-case basis. Although pediatric trials are usually smaller in size and for some studies, such as pharmacokinetics, can be completed fairly quickly (weeks), the smaller number of children with the disease may result in prolonged enrollment periods.

There are many factors that contribute to the length of the trial. The condition being studied and the proposed effect of the intervention on the disease (i.e., endpoints and outcome measures) will be major determinants for the length of the trial, and will vary considerably depending on disease, treatment and outcome. Additional considerations specific to clinical trials conducted in children include the prevalence of the disease in children, ineligibility to volunteer to participate in trials, and the fact that trials should not be conducted in children without the condition are important factors that impact the availability of children for trials and thus the length of the trial. Other factors, such as the need or specialized equipment, variable treatment affect, issues related to individual growth and development, specialists/nurses, labs, and pediatric-friendly facilities, directly contribute to the complexity and technical difficulties of pediatric trials.

One approach that does facilitate the conduct of pediatric trials is the ability to extrapolate efficacy when the course of the disease and the response to therapy are thought to be “sufficiently similar” in adults and older children. In some cases, the ability to extrapolate could eliminate the need to replicate efficacy trials, shaving years off the development process. We also encourage companies to interact with the Agency in the early stages of product development to identify a potential use of the product in a pediatric population. Early dialogue with the Agency may allow the company to obtain approval for pediatrics close to or concurrent with the adult approval. This is particularly true when there are limited or no other therapeutic options and the condition is serious or life-threatening. One should note, however, when the product is novel or a new molecular entity with little or no adult experience, it is considered prudent to wait until a more robust understanding of its effectiveness and safety has been established before enrolling a population that is as vulnerable and variable as the pediatric population.

SENATOR FRANKEN

*Question 1.* A key stipulation for a humanitarian device exemption is that “the probable benefit to health from using the device outweighs the risk of injury or illness from its use.” How exactly does FDA determine what constitutes “probable benefit to health?” Would FDA be willing to offer guidance on this topic so device companies can more easily navigate the humanitarian device exemption process?

Answer 1. The Federal Food, Drug and Cosmetic Act requires that applicants for Humanitarian Use Device (HUD) designation provide an explanation of how the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. This requirement allows FDA to examine applications on a case-by-case basis, taking into account the specific circumstances related to the device and its use. We recognize the challenge that the terminology presents and appreciate the desire for guidance on this topic, and we will be considering that in determining future guidance to make this issue clearer.

*Question 2.* We’ve heard stories of pediatric patients in Minnesota who are unable to get the humanitarian use devices they need because insurance companies consider these devices to be “investigational.” Does FDA consider these devices to be investigational?

Answer 2. FDA considers a device that has been approved as a HUD to be an approved device. FDA’s role is to make decisions about safety and effectiveness, not coverage and payment; however, we view our recent agreement to establish a memorandum of understanding with the Centers for Medicare and Medicaid Services (CMS) entitled “Parallel Review of Medical Products by the FDA and CMS Agencies” as an opportunity to better share information with our sister Agency about HUDs and other approved products in the future.

FDA staff handle many inquiries from private payers on this issue. We work directly with the payers to help them understand that an HDE is an approved product and is not under investigation. We also work with payers on individual cases to help secure coverage for individual patients. FDA staff regularly conduct outreach to help the health care industry and those who make payment decisions understand the

status of HDEs and issue guidance in which it was made clear that an HDE is an approved product. Recently, FDA issued an updated HDE guidance that provides additional information and clarity to interested parties.

RESPONSE TO QUESTIONS OF SENATOR ENZI, SENATOR BROWN, SENATOR CASEY, AND SENATOR HAGAN BY ALAN E. GUTTMACHER, M.D.

SENATOR ENZI

*Question 1.* What strategy has the NIH established to ensure the TRNDs program is successful?

Answer 1. The Therapeutics for Rare and Neglected Diseases program (TRND) is explicitly intended to tackle a phase within drug development well-known to be fraught with failure and unpredictability; hence its moniker in the biopharmaceutical industry as the “Valley of Death.” To ensure that the program is successful, NIH has established a number of strategies to achieve TRND’s twin goals of: (1) producing drugs for rare and neglected diseases ready for clinical research testing; and (2) developing new paradigms and technologies that will increase success and decrease costs in this extremely challenging arena. Many programmatic features integral to TRND are unique and made possible because TRND is being conducted through NIH. Such features include:

- Establishing a project selection and ongoing review process that utilizes world experts in drug development from the academic, biotechnology, pharmaceutical, venture capital, and foundation sectors;
- Establishing a diversified portfolio within the drug development pipeline that includes projects at various stages and with various degrees of difficulty;
- Selecting projects (after a rigorous review process) on the basis of scientific opportunity and medical need rather than anticipated financial return;
- Choosing projects potentially applicable to multiple diseases, thus increasing the utility of each drug developed;
- Hiring the best talent from the biopharmaceutical industry to support in-house activities in addition to convening consulting scientists from all sectors to develop the best strategies for individual projects;
- Focusing activities on technology, paradigm, and systems engineering development to continuously increase efficiency of processes within the drug development pathway.

*Question 2.* How could increasing funding for the Common Fund help support research for rare and neglected diseases?

Answer 2. Many rare and neglected diseases are multisystem diseases; that is, they involve multiple organ systems and parts of the body. Thus, full understanding of their underlying biology and the development of effective therapeutic and preventive strategies often require the expertise and perspectives of many NIH Institutes and Centers and their communities of researchers. The NIH Common Fund supports programs that require just such multi-Institute expertise and that go from the most basic science to translational and clinical research. Supporting the fiscal year 2011 Budget request for the Common Fund would therefore support rare and neglected diseases in several ways.

For example, the new Common Fund program entitled Knock-Out Mouse Program Phenotyping (KOMP2) seeks to build upon an existing resource of mouse mutant strains to determine their physiological characteristics (phenotypes). These mutant strains are intended to provide animal models of genetic disorders, and they therefore provide basic science tools to understand rare disease etiology as well as translational tools to study potential therapeutic approaches.

The Interdisciplinary Research Program provides funds for teams to develop comprehensive approaches to complex health problems, including provision of core facilities, research projects, and interdisciplinary training programs focused on the health problem. One consortium funded through this program addresses Fragile X-Associated Tremor/Ataxia Syndrome. It focuses on the critical periods of development when mutations are most problematic, seeking to identify the molecular targets where therapies might be most effective and to determine mechanisms of cognitive dysfunction in the disease.

The Human Microbiome Program is designed to identify and characterize all the microbes that live on and in us, and to determine their contribution to health and disease. Current projects funded through this program address the role that microbes play in maintenance of health and in development of a variety of disorders.

Neglected diseases in Africa are an emphasis area for the Human Heredity and Health in Africa Program, a new program to be launched in the Common Fund this



year. In conjunction with the Medical Education Partnership Initiative which is also funded via the Common Fund, this program provides support to develop research capacity in Africa so that neglected diseases can be studied in the areas where they are most common. The funds currently planned through the Common Fund are intended to facilitate the study of genetic and environmental traits that underlie differential susceptibility to such diseases.

*Question 3.* How many therapies or research projects will the Agency be able to conduct and complete with \$24 million? On average, how much is necessary to successfully develop a candidate compound that is ready to be tested in patients and licensed to the private sector?

*Answer 3.* While the cost of developing a project from a “lead” stage through an Investigational New Drug (IND) application or a proof-of-concept study in humans varies widely, the industry standard for entirely novel targets and diseases (those TRND will work on) is approximately \$10 million over 2 to 5 years. Even with this substantive financial investment, industry-standard success rates for candidate drugs targeting diseases of this sort are approximately 1 in 10. Therefore, with the current budget of \$24 million, TRND is initiating five pilot projects that enter the 2- to 3-year preclinical development process at various points; those entering later in the process cost less. Through the pilot projects, TRND is building infrastructure necessary to support these and future projects, while also working on several small-scale technology development projects, since each of these areas will be critical to TRND’s long-term success. With over 6,000 rare and neglected diseases at the heart of its mission, TRND cannot, and will not, simply adopt current industry best practices, because their cost and failure rates are just too high. Technology development—the **science** of preclinical drug development—is critical to TRND’s long-term impact, both for the diseases it works on, and for the drug development enterprise generally. In fiscal year 2011, TRND expects to launch an additional three to five projects.

*Question 4.* Can you provide an overview of the Bench-to-Bedside Program? How much funding does the program provide for research focused on rare and neglected diseases?

*Answer 4.* The Bench-to-Bedside Program was established in 1999 to integrate the work of basic and clinical scientists on the NIH campus, aimed at creating collaborations based on high quality science that has the strong potential to result in new understanding of a disease process or lead to new therapeutic interventions. The program expanded in 2006 to encourage partnerships between intramural and extramural programs. Grants are funded for 2 years of up to \$135,000 per year. In recent years, the Office of Rare Diseases Research (ORDR) has set aside up to \$1 million annually, with matching co-funding from one or more NIH Institutes. In 2010, ORDR provided \$931,412 for 12 projects, six of which were in their second year. The ORDR contribution was matched by 10 Institutes thereby raising the total for rare diseases to almost \$2 million annually. To date, about 600 primary and associate investigators have collaborated on nearly 200 funded projects with approximately \$40 million distributed in total bench-to-bedside funding.

*Question 5.* How much funding does the Agency spend on rare and neglected diseases? How does that compare to the Agency’s overall budget? What percent of funds targeted for rare and neglected diseases are spent on rare and neglected cancers?

*Answer 5.* Since the NIH has not collected information on rare and neglected diseases as a single category, there are many specific rare diseases for which total NIH investment cannot currently be reported, but which are supported by and tracked by individual NIH Institutes and Centers. For example, the National Cancer Institute reports spending \$192.8 million on childhood cancer research in fiscal year 2009.

Currently, the NIH does not collect information on funding for rare and neglected diseases research *per se*. However, three major programs in recent history have greatly increased NIH’s focus on rare diseases diagnoses and treatments. In 2003, the Office of Rare Diseases Research (ORDR) partnered with several NIH Institutes and Centers to fund the Rare Diseases Clinical Research Network (RDCRN). In 2008, at the conclusion of the first 5-year funding cycle of 10 consortia, the ORDR, in collaboration with NIH Institutes funded 19 consortia. For the 10-year duration of the RDCRN, NIH has committed almost \$200 million.

In addition, the NIH has committed \$24 million annually for fiscal year 2009 and fiscal year 2010 to the Therapeutics for Rare and Neglected Diseases (TRND), a new collaborative drug discovery and development program. The fiscal year 2011 Budget requests \$50 million to expand TRND activities.

The Undiagnosed Diseases Program (UDP) is another effort that focuses by its very nature on rare diseases. Using a unique combination of scientific and medical expertise and resources at the NIH, the UDP provides answers to patients with mysterious conditions that have long eluded diagnosis. The fiscal year 2011 Budget includes \$3.5 million for this effort.

*Question 6.* Specifically, how is the Agency working with the FDA and industry to develop a more seamless process in drug development?

Answer 6. Historically, the NIH and the FDA have established collaborations largely according to scientific disciplines in order to address specific research areas and needs. In February 2010, the two agencies announced an unprecedented effort to work together to help ensure that regulatory considerations form an integral component of biomedical research planning and that the latest science is integrated into the regulatory review process. A joint NIH-FDA Leadership Council (LC), composed of the NIH Director and FDA Commissioner and senior leadership from each agency, was formed. The collaboration will advance the development of new products for the treatment, diagnosis and prevention of common and rare diseases and enhance the safety, quality, and efficiency of the clinical research and medical product approval enterprise. The formation of the Leadership Council represents a commitment on the part of both agencies to forge a new partnership and to leverage the strengths of each agency toward this common goal.

In addition, at the program level, the recently launched Therapeutics for Rare and Neglected Diseases (TRND) program within the NIH Intramural Research Program has established monthly working group meetings with representatives from the FDA Office of New Drugs and its Office of Translational Science. The aim of these meetings is to focus on conceptual issues presented through TRND projects and develop potential ideas to address any roadblocks identified in the drug development process. Furthermore, TRND leadership is working closely with the FDA Office of Orphan Product Development to coordinate activities and leverage existing programs to advance mutual goals.

The NIH Office of Technology Transfer serves as one of the NIH's primary interfaces with both industry and academia in pursuing common research goals. Government scientists can leverage their own research resources to facilitate the development and commercialization of health care pharmaceuticals and products, while private companies can leverage their own research efforts while collaborating in cutting edge NIH research. One of the primary tools is a Cooperative Research and Development Agreement (CRADA), which can make government facilities, intellectual property and expertise available for collaborative interactions to turn scientific knowledge into useful, marketable products through licensing agreements. For products that may be used to treat rare conditions, this arrangement can prove especially useful by allowing the NIH to support the initial research on a drug or device (often the riskiest and most time-consuming part of the process), and then turning it over to a private company for final testing, FDA approval, and marketing.

*Question 7.* What types of research do you support to assist FDA in establishing guidance to further clarify the requirements for drug approval?

Answer 7. In February, 2010, the NIH released a new Request for Applications (RFA), jointly funded with the FDA, titled Advancing Regulatory Science Through Novel Research Technologies. The purpose of this funding opportunity is to foster the development, evaluation and availability of new or improved tools, methods, standards, and applied science that support a better understanding and improved evaluation of product safety, quality, effectiveness, and manufacturing throughout the product lifecycle. The science may range from nanotechnology to the development of novel experimental models, such as a biological system on a chip for assessing safety and toxicity, to innovative research on clinical trial design. By the end of fiscal year 2010, NIH expects to be supporting several novel cooperative grants in cross-cutting areas of science.

Research results from investigator-initiated basic and clinical research supported across the NIH inform and clarify requirements for drug and device development. Much of this research is focused on individual diseases and conditions; however, the characterization and standardization of new and emerging technologies, such as stem cells, genomics and related technologies, and nanotechnology, is cross-cutting and serves all research communities and the FDA in establishing guidance and requirements for development and subsequent approval. For instance, the NIH funds both intramural and extramural research directed toward the examination of the fundamental principles of nanotechnology and their application to the development of diagnostics and interventions. This research augments existing knowledge and helps to assess what data are still needed to approve specific drugs and medical de-

vices. Another cross-cutting type of research is in the area of clinical trial design. As clinical trials are becoming more complex, and trials are being conducted in sometimes small sample populations, investigators are looking to adaptive design methodologies. The NIH supports biostatistical research projects through a variety of grant-related mechanisms that informs study design and analyses.

*Question 8.* Can you provide a specific example of NIH funded research associated with FDA guidance or overall improvements in the drug review process?

*Answer 8.* The NIH and the FDA traditionally have established collaborations largely according to scientific discipline in order to address specific research areas and needs. One example of an intramural-funded collaborative effort that resulted in a guidance document and associated improvements in the drug development process can be found in the FDA/NCI Interagency Oncology Task Force (IOTF). The IOTF was formed in 2003 as an interagency effort to enhance the efficiency of clinical research and the scientific evaluation of new cancer medications. Through it, the two agencies share knowledge and resources to facilitate the development of new cancer drugs and speed delivery to patients. As a direct outcome of the collaborative effort, in January 2006 the FDA released its Guidance for Industry, Investigators, and Reviewers on Exploratory Investigational New Drug (IND) Studies. Exploratory IND studies enable a sponsor to proceed more efficiently with the development of promising candidates by allowing a new drug candidate to provide clinical information at a much earlier phase of drug development. The guidance document addressed what preclinical and clinical approaches, including chemistry, manufacturing, and controls information, should be considered when planning exploratory studies in humans. This tool enables a faster, more cost-effective path to early clinical development.

The Patient Reported Outcomes Measurement Information System Program (PROMIS), an extramural project funded through the NIH Common Fund, is designed to develop a precise, efficient and valid assessment of patient outcomes, such as fatigue, that are the result of disease or treatment. The NIH is working with the FDA in this program to ensure that the work done with the system takes into account FDA guidance and perspectives for the assessment of efficacy and safety of new drugs/treatments. This is critical for the many diseases/conditions where patient reports are a primary assessment of improvement, including pain and depression.

*Question 9.* Can you elaborate on why the Human Genome Project and why genetic research in general is so important for rare and neglected diseases?

*Answer 9.* Fundamentally, approximately 80 percent of rare diseases are genetic diseases—that is, they are caused by the malfunction of one or more specific genes. For this reason, the Human Genome Project has been enormously beneficial to the rare disease community; the genetic causes of over 2,000 different rare diseases are now known. While knowledge of the genes involved in a disease is critical information to developing targeted drugs, it is just the start. Many diseases whose genetic cause(s) have long been known are still without sufficiently effective treatment (e.g., Huntington's disease and sickle cell disease). This difficult reality is why the TRND program is so critical.

*Question 10.* I understand the Agency has been working to provide basic tools to researchers that were previously not available to reduce barriers for investigators. Can you provide an example of a specific tool and academic institution or other type of research entity that benefited from the tools? Who has access to these tools? Are the tools only accessible to NIH grantees or all public and private research institutions?

*Answer 10.* The NIH provides basic research tools, including genome sequences, gene libraries, knockout mice, and informatics databases of various kinds, to researchers from all sectors without restriction. For example, the National Centers for Biomedical Computing program develops informatics tools for a wide variety of research areas and makes them publicly available. Among the newest types of tools to be made available are small molecule tools, which are “drug-like” chemicals that can be used to study diseases in cell and animal models. NIH began a large-scale program to produce small molecule research tools, and data on them, in 2003 with the launch of the Molecular Libraries Program, as part of the original NIH Roadmap. That program has been enormously successful and has produced hundreds of compounds to study genes, pathways, and cells in collaboration with researchers throughout the country and the world. These tool (or “probe”) compounds are readily available to any researcher (over 300 investigators have used the Molecular Libraries resources to date), irrespective of whether the researcher is an NIH grantee or works within the public or private sectors. Detailed reports on the research (and

tools) are made publicly available through the NIH Web site, and all the data generated are made publicly available via the NIH PubChem database, which enables investigators to see the chemical structures of all compounds that have been shown to be active in various assays (tests).

One example of the success possible through the access to these tools is a new compound for studying the cause and treatment of schistosomiasis, a parasitic disease highly prevalent (affecting more than 250 million people) in Africa and South America. The NIH Chemical Genomics Center (NCGC), part of the Molecular Libraries Program, collaborated with Dr. David Williams at Rush University in Chicago, an NIH grantee and expert in schistosomiasis, to produce new tool compounds and then prove that the enzyme inhibited by a particular tool compound was required for the parasite to live. The tool compound very effectively kills schistosomiasis worms both in cultures and in mice, and the work was published in major scientific journals. This work is also an example of the catalytic effect these kinds of tools can have, because as a result of the publications, a different researcher—Dr. Michael Cappello at Yale University—contacted Dr. Williams and NCGC, who provided Dr. Cappello with the tool compound. Dr. Cappello then showed that the compound is also very effective at treating a completely different parasitic infection, hookworm. Dr. Williams, Dr. Cappello, and the NCGC scientists are now working together to develop these compounds further, so that they can be tested in humans with these devastating diseases.

SENATOR BROWN

*Question 1.* As was discussed in depth at the HELP committee's hearing, rare pediatric diseases pose a number of challenges. One barrier is that the number of patients available for clinical trials is small. As such, the need for sharing and collaboration is all the more critical for rare pediatric diseases. I have been working with Senator Bond to advance legislation—the *Pediatric Research Consortia Establishment Act*—that envisions a networked consortium of leading pediatric biomedical research entities that would be competitively selected by NIH. By operating in such a model, the project would foster resource sharing, collaboration, and help pool patients to ultimately develop treatments and therapies for diseases and disorders of both childhood and adulthood. What are your thoughts on the challenges associated with pediatric research and the ability to use a networked consortia approach to overcome these issues and permit a more robust pediatric biomedical research enterprise? I'd like to ask that NICHD provide a full written assessment as to the merits of this proposal.

*Answer 1.* In fiscal year 2009, the NIH, through 22 Institutes and Centers (ICs), awarded approximately \$3.4 billion, including funds from the American Recovery and Reinvestment Act, in support of pediatric research activities across the country. This funding was distributed to the research community through the full range of available funding mechanisms, including investigator-initiated grants, contracts, and research networks. This flexibility allows the extensive scientific expertise at the NIH and across the extramural scientific research community to judge which mechanism(s) might be best suited for the specific research needed to answer questions about children's health and development and pediatric diseases and conditions. Less commonly, but where the scientific challenge warrants and funding permits, NIH ICs (often in trans-Institute collaboration) have created multidisciplinary centers of excellence or research networks for specific pediatric populations, specialties, or conditions, such as autism, pediatric oncology, neonatology, and adolescents with HIV/AIDS, to name a few.

For example, the NIH Office of Rare Diseases was directed by Congress in the Rare Disease Act of 2002 (P.L.107-280) to establish a clinical research network focusing on rare and neglected conditions. Since 2003, the Rare Disease Collaborative Research Centers network of investigators and patient groups, in partnership with technology leaders, has been working to develop biomarkers and new approaches to diagnosis, prevention, and treatment, provide content for a web-based resource site about rare diseases, and train new clinical investigators in rare disease research. Of the 19 current member sites of the network, three are focused on pediatric rare diseases. These three main sites and their 33 affiliate sites (many located at children's hospitals) are managed by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) on behalf of the NIH.

In addition, a number of the Clinical and Translational Science Awards (CTSAs) sites include a strong emphasis on creating infrastructure to conduct pediatric clinical trials, which will allow pediatric researchers who focus on a wide variety of conditions to utilize this new resource and to conduct clinical trials efficiently and effectively.

The NIH may provide only technical assistance on legislative proposals on which the Administration has not yet taken a position. However, in evaluating what mechanism or infrastructure to use to address any question about health or disease, important considerations include whether the proposed mechanism provides the range of scientific expertise required to answer that question, the availability of a sufficiently sized study population, and whether a currently existing mechanism might adequately meet these needs. The impact of creating a new infrastructure on investigator-initiated proposals also must be weighed.

SENATOR CASEY

*Question 1.* How is our emerging knowledge of genetics helping us understand rare childhood diseases—and bring new cures and treatments to children faster?

Answer 1. Since approximately 80 percent of known rare diseases, a substantial proportion of which occur in children, are thought to have a genetic basis, increasing understanding of the role of genetics in rare diseases will unquestionably have a considerable impact on their diagnosis, prevention, and treatment. However, a few decades ago, many scientists assumed that once causative genes were identified, treatments would be imminent, an assumption that has proven overly optimistic. Rare diseases are very complex and often affect multiple organ systems, and phenotypic (physiological characteristics) expressions of these genes in individuals can be quite diverse. Nevertheless, by continuing to increase the knowledge base about the origins of pediatric diseases, and the impact of those diseases over a lifespan, targeted treatments can be developed that can reduce morbidity and mortality, and improve the quality of life of children and their families.

*Question 2.* Have we made appropriate public investments in understanding rare childhood diseases?

Answer 2. The NIH spends a substantial amount on research on various rare diseases, including those affecting children, but with over 6,000 known rare diseases, not every one has been fully addressed. Different types of research also are required, including basic, translational, clinical and natural history studies, which are essential to understanding the expression of a genetic illness. With the Rare Diseases Clinical Research Network, the NIH has developed a model to help move this research forward.

SENATOR HAGAN

*Question 1.* In your testimony, you mention there are now 29 conditions that States screen newborns for. How many of these are rare diseases? Is there any effort underway to expand the number of diseases we screen for? Why or why not?

Answer 1. Newborn screening has the potential to prevent or ameliorate many serious heritable conditions. The HHS Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children is responsible for assessing the scientific evidence on potential conditions eligible for newborn screening and making recommendations to the Secretary about the addition of such tests to the 29 (all considered rare by definition) already on the screening panel that most States have adopted. The committee recently recommended the addition of Severe Combined Immune Deficiency (SCID), a rare condition, and the recommendation was accepted by Secretary Sebelius. Currently under consideration by the committee are severe critical heart disease and hyperbilirubinemia.

The NIH has supported research for many years that has produced the evidence necessary to determine the efficacy of screening. One of the early successes occurred in the 1960s, when NIH-supported researchers discovered techniques for detecting phenylketonuria (PKU), a metabolic disorder that was a primary cause of intellectual and developmental disabilities. PKU, which could be readily treated with dietary therapy (medical foods), was the first disorder for which newborn screening became mandatory. While not all diseases detectable through newborn screening are as manageable, detecting disabling and potentially fatal conditions provides an opportunity for critical early treatment, often before an infant shows symptoms of a condition, having a profound impact on how severe the condition becomes, and improving the quality of life, usually dramatically, for affected individuals.

In early 2008, the Newborn Screening Saves Lives Act was signed into law, providing direction to the Secretary's Advisory Committee on its work, and establishing the Hunter Kelly Research Program within the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The new law directs the NICHD to support research to identify, develop, and test promising new screening technologies, which will lead to the expansion of conditions for which newborn screening can be done. Along with other Institutes at the NIH, the NICHD is cur-

rently supporting research in newborn screening for spinal muscular atrophy, Fragile X syndrome, Krabbe disease, and other conditions.

*Question 2.* In your testimony, you discuss spinal muscular atrophy—a terrible disease that is the leading genetic killer of infants. I met with a family in North Carolina whose 18-month old daughter was diagnosed with SMA a few months after birth. While she is progressing like a normal toddler in many ways, she is now confined to a wheelchair and can no longer sit or roll over on her own. I understand that NIH through the National Institute of Neurological Disorders and Stroke (NINDS) has some promising treatments for SMA in the pipeline. Industry working with advocacy groups has also been interested in developing therapeutics.

*Answer 2.* Because the failure rate at each stage of therapy development is very high for all diseases, the NIH is pursuing multiple avenues to prime the therapy development pipeline for treatments for spinal muscular atrophy (SMA). In 2003, the NINDS recognized that advances in understanding SMA had unlocked the possibility of rationally developing treatments, and the Institute chose SMA as the disease on which to test an aggressive new approach to expedite preclinical therapy development. The SMA Project developed a detailed drug development plan with the guidance of a steering committee that included expertise in drug development from academia, industry, and the FDA. The Project is implementing the plan through a “virtual Pharma” organization that engages the expertise and resources to carry out industry-style drug development via contracts. This allows rapid response to opportunities as results emerge. The SMA Project is making encouraging progress, with two patents applied for on new compounds that show promise against SMA in laboratory models. Advanced preclinical safety testing of the most promising compounds is underway with the goal of beginning clinical trials in 2011, and the Project is also continuing to develop other drug candidates.

The SMA Project is being supported in addition to, rather than instead of, other therapy development efforts. The NIH supports several other preclinical therapy development projects for SMA through investigator-initiated research programs and through SMA-targeted solicitations. Ongoing projects at the NINDS and the NICHD include research on gene therapy, stem cells, and drug development. This area of research received a substantial boost from American Recovery and Reinvestment Act (ARRA) funds. ARRA-funded projects include Grand Opportunity (GO) and Challenge grants on gene therapy and on induced pluripotent stem cells (a type of stem cell derived from adult cells), as well as research on small-molecule drugs. Industry and patient voluntary organizations also are interested in working with the NIH on therapeutics development for SMA. The NIH is supporting substantial academic-industry collaboration on SMA through an NINDS milestone-driven therapy development program, and the NIH is convening a meeting in the fall of 2010 that will bring together the various public and private groups to discuss SMA therapy development.

*Question 3.* However, I understand that one of the main obstacles going forward is identifying a sufficient number of children to participate in the clinical trial. Can you comment on the Agency’s plans to support the implementation of clinical trials for SMA?

*Answer 3.* Because therapies for SMA and for several other rare neurological diseases may be ready for clinical testing in the next few years, it is important that the NIH be prepared to conduct clinical trials. Thoughtful selection of the best candidate therapies for testing is one essential aspect of conducting trials for rare disorders, and multi-site clinical networks are another important answer to the need for rapidly recruiting sufficient numbers of patients. Rather than developing separate clinical networks for each disease, the NINDS is developing a clinical network that will serve SMA and other neurological diseases. The program will be open to the best candidate therapies, regardless of whether they arise from NIH programs or other sources. For many reasons, this combined network will be not only more cost efficient but also more effective for SMA and other diseases. For example, this network will offer expertise in a range of disciplines, including pediatrics, and provide a breadth of experience in running clinical trials that will help inform the SMA clinical research field.

*Question 4.* Could you also comment on whether SMA could be a candidate for newborn screening? It seems to me that that might help identify patients to participate in clinical trials and accelerate approval of a therapeutic.

*Answer 4.* The NICHD is currently funding research to pilot test newborn screening for SMA. While there is no available treatment for SMA (usually a prerequisite for a Secretary’s Advisory Committee recommendation to add to the newborn screening panel), the NICHD also is supporting research on potential treatments. As men-

tioned in an earlier response above, the NICHD (as well as the NINDS, as described in the previous response) is cosponsoring an important scientific conference in October 2010, entitled “NIH Therapy Development Conference in SMA.” The main purpose of this meeting is to review and address the needs of the research field and the scientific opportunities for moving forward on the development of SMA therapeutics.

RESPONSE TO QUESTIONS OF SENATOR ENZI BY ALEXANDER J. SILVER

*Question 1.* Do you think that Congress should fund research at the NIH by specifically providing funds for each disease, or do you think Congress should provide funds categorized broadly for different types of research and allow the Agency to allocate those funds based on research grants that have scientific merit?

Answer 1. I do not believe that Congress should mandate specific disease research at the NIH. The NIH needs to maintain ultimate decisionmaking in determining whether research is of high enough quality to fund. However, given Congress’ close relationship with the American public, it can and should play a pivotal role in promoting treatments and cures in a timely manner for the devastating diseases that inflict its constituents. Citizens can advocate for themselves but also rely on those they elect to do so when needed, especially when simply caring for a loved one who has a disease consumes all aspects of life such as Epidermolysis Bullosa (“EB”). For example, when rare disease research funding composes just a fractional piece of NIH funding—according to figures provided by the NIH, it provided \$118 million in research funds for orphan diseases out of its \$30 billion budget in 2009 or 0.3 percent—even though approximately 10 percent of the American population suffers from rare diseases, Congress can highlight this discrepancy and suggest that it be examined. Furthermore, when private market incentives are not adequate to attract funding to advance rare disease treatments and cures, Congress should simultaneously design the correct incentives as well as use all current tools possible to encourage rare disease treatment and cure development. In the case of children with EB, parent advocacy coupled with congressional leadership can lead to a cure.

Another important factor to consider when allocating resources to fund EB or other orphan disease research is that many medical breakthroughs impacting a larger group of Americans start with rare disease research. As I wrote in my testimony, Remicade—which was developed for the treatment of Crohn’s disease, a population of 500,000 people—has been found to effectively treat Rheumatoid Arthritis and forms of Psoriasis, a population of over 5 million people. Rituxan, developed for non-Hodgkin’s lymphoma—a group of 70,000 people per year now helps the 1.3 million Americans who suffer from Rheumatoid Arthritis.

Most recently, the University of Minnesota released the results of its current stem cell trial for EB; specifically, the procedure involves transplanting the bone marrow from a donor who can make the protein needed to adhere the layers of skin together to an individual who has EB and lacks this protein. The initial results are extremely promising. Importantly, this is the **first time stem cells have been used to repair skin**. The wider implications are potentially enormous—this could help Americans with burns, diabetic ulcers, wounds or practically any other skin disorder. Congress can make sure that the allocation of resources takes both the immediate and bigger pictures into account. Helping a child with EB also will help other Americans.

While the NIH must maintain autonomy, Congress also must play a pivotal role in the conversation about the allocation of publicly funded research resources. If not, telling a child with EB that he or she needs to wait until we have the perfect incentives in place to help him or her is equivalent to a death sentence in many cases.

*Question 2.* What types of treatments are currently available for your son? How many of them are just to alleviate symptoms?

Answer 2. Currently, the only treatments available, if any, to those who have EB address the symptoms as they occur. When Jackson, our son, falls and tears the skin off his palms, we can wrap them with bandages and hold him through the pain. When the skin in his throat sheers off from eating, we have to wait days until he starts to drink and eat again. When Jackson’s knee blisters and fills with blood, we can only lance it with a large needle and painfully compress the blood out of the wound. When an EB child’s fingers and toes fuse, their parents are powerless to stop their child’s lifelong physical deformity and pain. Children who suffer from EB live in daily agony as their bodies disintegrate.

There are no approved treatments available that prevent injury or systematically cure EB. *However*, researchers know exactly what causes EB and have extremely encouraging knowledge of how to fix it. The key factors hindering this dream from becoming reality are sufficient funding and a streamlined approval process.

As an example of a cure's proximity to becoming a reality, I have attached the recently published study in *New England Journal of Medicine*, a review of the study<sup>1</sup> and the lead article from CNN on August 12, 2010 about the stem cell bone marrow transplant study for children with EB ongoing at the University of Minnesota. As you can see, the results suggest a cure is within reach. There are more questions to answer and to do so one needs to conduct more trials. In order to conduct more trials, one needs more funding. Even with additional funding, an improved approval process that balances the safety of treatments and the devastation of EB is necessary to ensure children are helped before it is too late. In addition to stem cell therapies, as discussed in my written testimony, protein replacement and gene therapies are close to the clinical trial stage but again lack adequate funding and approval in a timely manner. The unifying theme among all treatments and cures is that they currently only help to cope with EB's superficial symptoms *but it does not have to be this way*. Viable treatments and cures are just a few inches from our fingertips with the proper support.

*Question 3.* Can you provide more detail about the Jackson Gabriel Silver Foundation? How successful have your fundraiser efforts been? Are there other EB foundations that you partner with? How do you invest the funds you have raised?

*Answer 3.* The Jackson Gabriel Silver Foundation ("JGS Foundation") is a recently formed non-profit dedicated to supporting research focused on curing and treating EB. Given its very recent Federal approval, the JGS Foundation has not held an official fundraiser yet. The Foundation plans to hold several major events a year and has raised over \$55,000 without an official campaign in its few months of existence. We believe the JGS Foundation can become a significant fundraising vehicle to help children with EB. All funds raised are kept in FDIC insured checking or savings accounts. Just shy of 100 percent of every dollar raised is provided to researchers to advance their work on EB treatments and cures. However, given the small number of children with EB, raising the funds that are needed to advance EB treatments and cures *to help today's children* will not be possible without both direct and indirect Federal assistance.

I am also a trustee of the Dystrophic Epidermolysis Bullosa Research Association of America ("DebRA"), which is the largest EB patient care non-profit in the United States. Within DebRA, my family and I have raised over \$150,000 during the previous 2 years to help children with EB. The Epidermolysis Bullosa Medical Research Foundation ("EBMRF") is the other significant American non-profit focused on curing EB. The EB community is small; the JGS Foundation, DebRA and the EBMRF have and should continue to work together to accomplish our goals.

I estimate that in aggregate, these foundations have raised approximately \$4 million over the last 3 years. To put this in context, inexpensive clinical trials are in the tens of millions. The cost of a child to participate in the University of Minnesota stem cell trial is \$1 million. While I do believe the community can and will do a better job fundraising, we need the leadership of our Federal Government. Children with EB need both direct Federal support as well as private market incentives, such as the recently introduced Creating Hope Act of 2010 (refining the rare tropical disease voucher program to include rare pediatric diseases), if these children are to have a chance of leading pain free and full lives. While the amount of funding needed to cure this disease is not small in absolute terms, it is quite small compared to Federal and private expenditures in every comparison. EB can be a curable disease and EB research can help other Americans with wounds and burns lead better lives; we just need to make it a higher priority.

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[CNN Article, August 12, 2010]

#### A MOTHER'S PLEA: HEAL MY CHILDREN'S SKIN

(By Madison Park)

#### STORY HIGHLIGHTS

- Epidermolysis bullosa is a terminal genetic condition that causes persistent skin problems.
- Patients lose their skin with the slightest friction because of the lack of a protein.

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<sup>1</sup>The review of the study referred to may be found at [www.nejm.org/doi/pdf/10.1056/nejmoa0910501](http://www.nejm.org/doi/pdf/10.1056/nejmoa0910501).



- Bone marrow transplant recipients show improvement in collagen levels and skin.

For years, Theresa Liao heard there were no cures, no treatments, no hope to help her son Jake.

“When he was born, his hands looked like they had been boiled in oil,” said his mother. “It looked like someone had taken a potato peeler and skinned him down to muscle.”

At the slightest friction, Jake’s skin would shed, leaving the newborn wailing in pain. When Jake rubbed his eye, a chunk of his eyelid would come off in his fingers. He was born with recessive dystrophic epidermolysis bullosa, a terminal genetic condition in which persistent skin problems lead to crippling deformities and, eventually, skin cancer.

Liao’s crusade led to the first stem cell treatment for epidermolysis bullosa, also known as EB.

New research findings, published in *The New England Journal of Medicine* this week, show that bone marrow transplants can help repair wounds and regenerate skin in EB patients. Doctors say it’s an important step in stem cell science.

“I’m not saying this is a cure,” said co-author Dr. Jakub Tolar, an associate professor of pediatrics at the University of Minnesota. “This is a critical step on the road to make this a disease of the past.”

EB patients lack a protein called collagen 7 that acts as a Velcro, hooking the layers of skin—the epidermis and the dermis—together.

The transplanted bone marrow contains stem cells that can turn into skin cells. These new skin cells could produce the missing collagen 7 to stitch the skin layers, gradually healing the blisters and improving the patient’s condition.

The transplant appears to be effective, but doctors don’t know exactly what type of stem cells are responsible for the change.

EB patients have often been called butterfly children, because their skin is so sensitive. They have also been likened to permanent second-degree burn victims.

The graze of a diaper can sheer off skin from their waist and inner thigh. Putting T-shirts over their heads can cut skin off their ears. In severe cases, children live in the bondage of bandages, like little mummies, to protect their fragile skin from wounds and infections.

The constant inflammation and blisters can fuse fingers and toes, creating a webbed look. EB also irritates the lining of the esophagus, so that many children with the condition get stomach feeding tubes.

The Netherlands allows for euthanasia for patients of this rare condition. The ones who survive to their 20s usually succumb to skin cancer.

EB patients require daily bandage changes to protect their skin in an intensive process that takes about 4 hours. Liao likened it to “controlled torture.”

For years, Liao, of Princeton, NJ, scoured the Web, and called companies, dermatologists, hematologists and nurses until one doctor mentioned that perhaps a stem cell treatment could reboot Jake’s entire body to help him produce the missing collagen.

Liao pounced after learning that Dr. John Wagner, director of pediatric blood and marrow transplantation and clinical director of the Stem Cell Institute at the University of Minnesota, would be in New York for a meeting in 2004. He had a long track record of working on stem cell and cord blood issues.

Liao approached Wagner with her then-2-year-old Jake in her arms. Jake had thrown up parts of his esophagus a few days before, and was still moaning in pain.

“She held him up in front of me and said, ‘Please, save my child,’” Wagner recalled.

The pediatrician was horrified.

He told Liao that he couldn’t just start a stem cell treatment—there had to be animal models, money for research (orphan diseases like EB are notoriously hard to fund), approval from regulatory bodies, and he needed to have a track record of treating the disorder. There were many complicated, time-consuming steps and millions of reasons to listen politely and walk away.

“Little by little, he tried to avoid me. I kept e-mailing him and calling him,” Liao said.

“What affected me more was this mother pleading with me, saying ‘You can’t say no. Everyone else says no. Everyone else says it’s incurable.’” Wagner said. “I was both horrified and feeling horrible that I can just walk away from this and say, ‘I’m sorry. I take care of leukemia patients. I don’t want to choose this one.’”

“My research is developing stem cell-based therapies for kids who are destined to die. So I deal with many sad cases, but this one is over the top,” he said.

Though they had no experience in skin diseases, Wagner and Tolar, the study co-author, started examining stem cell possibilities for EB.

They implanted several different types of stem cells into mice. After trial and errors, they eventually found that bone marrow transplants somehow helped heal wounds and regenerated skin in mice.

In 2007, they started the first human clinical trial with seven EB patients.

The transplants were risky because they require chemotherapy to wipe out the recipient's immune system to prevent rejection of the bone marrow.

Liao knew the risks but said she felt Jake and a younger brother were "going to die, relatively painfully and have a difficult existence" until passing away from malnutrition or cancer with the disease.

"Before anyone judges me or my family, I'm not going to ask them to walk a mile in my shoes, I would say take about three steps," Liao said. "Somebody had to go first. Somebody had to make a difference."

By that time, Jake was 5 years old and had a 16-month-old brother, Nate, who also had EB.

In November 2008, Nate went first in the trial, receiving a bone marrow transplant from a perfect match—his older brother, Julian.

When doctors examined Nate months after the surgery, the contrast was striking. Nate was also producing more collagen 7.

"The differences in the way the skin healed, he was very different," Wagner said. "He gave us hope."

Seven months later, Jake was patient No. 3 in the trial, receiving a bone marrow transplant from a cord blood match.

But Jake struggled. Stricken with complications of the transplant and an infection, he died 183 days after the procedure.

Out of seven children in the trial, two died. The other child had died in the clinical trial before the transplant. The transplant has inherent risks, the authors said.

"This is bone marrow transplantation, it's not a trivial procedure," said Dr. Jouni Uitto, professor and chairman of dermatology and cutaneous biology at Thomas Jefferson University, who was not part of the study. "It's a major procedure that has a high risk component."

The five participants who survived have all improved. One boy bought a trampoline and can enjoy activities he never imagined before the transplant.

"It's an exciting study in the sense it raises cautious optimism that bone marrow transplantation may be a way of treating the condition," Uitto said.

More research is under way to better minimize risks. Since the study was published, six more children with EB have received transplants, and all have shown improvements, doctors said.

Hundreds of EB patients have come to Minnesota hoping to take part.

It's bittersweet for Liao, as she closely monitors Nate's health, but also grieves for Jake.

"I'm still involved because of Nate. There's a lot more work. I really want this disease wiped off the planet. It wiped my son off the planet. It's fair play."

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NATIONAL ORGANIZATION FOR RARE DISORDERS (NORD),  
August 19, 2010.

Hon. TOM HARKIN, *Chairman,*  
*Health, Education, Labor, and Pensions Committee,*  
*U.S. Senate,*  
*Washington, DC 20510.*

DEAR MR. CHAIRMAN: On behalf of the millions of men, women and children affected by one of the thousands of rare diseases, the National Organization for Rare Disorders thanks you for the opportunity to testify before your committee on July 21, 2010.

Below are the answers to the questions posed by Senators Enzi, Casey and Franken. Rather than answer each question individually in some cases, attached please find NORD's testimony before the FDA's Part 15 hearing on June 29, 2010. Frank Sasinowski, who delivered the statement, is Chair of NORD's Board of Directors. He delivered the statement before the FDA hearing on "Considerations regarding FDA review and regulation of articles for the treatment of rare diseases."

Respectfully Submitted,

DIANE EDQUIST DORMAN,  
*Vice President, Public Policy.*

RESPONSE TO QUESTIONS OF SENATOR ENZI, SENATOR CASEY AND SENATOR FRANKEN  
BY DIANE EDQUIST DORMAN

SENATOR ENZI

*Question 1.* Are existing incentives sufficient to support the development of therapies for rare diseases? How might these incentives be improved or increased?

Answer 1. Please see attached document.

*Question 2.* Some of the incentives available for pediatric and rare and neglected diseases are stackable—a business can get more than one for a given product. Do the different programs work well together? Could they be more coordinated?

Answer 2. NORD agrees with the American Academy of Pediatrics that “the orphan drug exclusivity provided by the Orphan Drug Act and the pediatric exclusivity offered by the Best Pharmaceuticals for Children Act (BPCA) work well together to improve access to safe and effective drugs for children and patients with rare diseases.

The Orphan Drug Act incentivizes the development of drugs for rare diseases and BPCA incentivizes the study of drugs in pediatric populations. Pediatric exclusivity under BPCA is only granted in response to fulfilling the requirements of a written request issued by FDA and is not given in conjunction with any other incentive program.

Both incentive programs are necessary and serve distinct purposes. Whereas BPCA may be used to add pediatric labeling information to a popular adult drug, the Orphan Drug Act may be used to incentivize the development of that same drug to treat an entirely different condition that classifies as a rare disease.”

*Question 3.* Given the genetic basis of many rare diseases, has the Human Genome Project helped rare disease research and development of treatments?

Answer 3. Yes. NORD believes that the National Institutes of Health has made important strides towards increased research into rare diseases and the development of treatments for them. The NIH recently announced the establishment of the Therapeutics for Rare and Neglected Diseases (TRND) initiative. It was recognized that of the 7,000 human diseases, fewer than 300 are of interest to the biopharmaceutical industry, due to limited prevalence and/or commercial potential. More than 6,000 of these diseases are rare (defined by the Orphan Drug Act as <200,000 U.S. prevalence), and the remainder are neglected because they affect impoverished or disenfranchised populations. 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 (RND) (<http://rarediseases.info.nih.gov/Resources.aspx?PageID=32>).

*Question 4.* Can you elaborate on striking the correct balance between the safety and risk of treatments for patients suffering from rare diseases versus for patients with more common conditions?

Answer 4. Please see attached document.

SENATOR CASEY

*Question 1.* In your testimony, you talked about how FDA reviews safety and efficacy data for orphan diseases and say that “without a statement of policy on rare diseases and orphan products, it is not possible [for the FDA] to ensure consistency in that process.” Can you elaborate on why this is necessary and what sort of information you would like to see in such a policy statement? How should such a statement take children with rare diseases into consideration?

Answer 1. Please see attached document.

*Question 2.* Can you comment on the balance between public investment and private investment in finding cures for rare and neglected diseases?

Answer 2. Unlike patients with conditions that affect very wide populations, the rare disease community has always taken a pro-active approach towards rare disease research and the development of orphan therapeutics. Patients and the organizations and foundations that represent them attempt to raise small sums of money with the hope of raising sufficient funds to interest an academic researcher in conducting the needed basic research on their particular rare disease. But progress can be very slow. For that reason alone, the rare disease community is very dependent on the cutting-edge basic and translational research being conducted at the National Institutes of Health and other healthcare-related Federal agencies.

In order to move the basic and translational research to actual treatments, there must be increased coordination of efforts between Federal agencies, the biopharmaceutical and medical device industries, as well as patient organizations.

For this reason, NORD is working closely with the NIH, FDA, academic investigators and industry to find better pathways to orphan product development. More detailed information is included in the attachment.

Attached you will find the ORDR Newsletter on Rare Diseases (May 2010) providing information about all programs and initiatives related to rare diseases within the NIH. NORD is unable to estimate the funding for these programs.

SENATOR FRANKEN

*Question 1.* I recently heard about a 14-month old boy who's being treated at the University of Minnesota. He was ill as an infant, has intestinal problems, and can't eat normally. He survives with IV nutrition and an investigational drug that's approved in Germany. This drug enables him to absorb nutrients so he can survive beyond the age of 3. At first, his mother's insurance covered the investigational drug. Then his mom lost her job and his father's insurance refused to cover the monthly cost of \$1,200. The family can't afford the cost and so this child will stop receiving the treatment, which will lead to liver disease or liver transplant, and very possibly, his death, even though the treatment is working for him! This is just not right. What can we do to encourage insurers to cover treatments in such cases?

*Answer 1.* Unfortunately, Senator Franken, this scenario is one NORD hears many times a day. If a therapy is considered "experimental" by insurers, they may refuse to pay for it, leaving patients and their families few alternatives. When families contact NORD with these types of situations, we often refer them to the insurance commissioner in their State, who is sometimes able to intervene. One part of the solution is increased cooperation between European and U.S. regulators, and NORD is working with FDA and EMA in Europe to encourage that. Also, in very serious situations where there is no FDA-approved alternative for the patient, it may be possible for advocates such as NORD to help patients obtain life-saving medications through Expanded Access Programs. FDA has an Office of Special Health Issues that is sometimes able to help individuals obtain access to investigational drugs. Today, these scenarios are addressed on a case-by-case basis but it would be wonderful if insurers could be required to pay when patients face severe consequences and have no approved alternatives.

ATTACHMENT 1.—PREPARED STATEMENT OF THE NATIONAL ORGANIZATION  
FOR RARE DISORDERS (NORD)

(PRESENTED AT THE U.S. FOOD AND DRUG ADMINISTRATION PART 15  
PUBLIC HEARING—JUNE 29, 2010)

Good morning. The National Organization for Rare Disorders (NORD) welcomes this opportunity to be the initial presenter at the FDA's first public hearing on rare disorder therapies. I am Frank Sasinowski, Chair of the Board of NORD, and we want to share our views on the FDA's exercise of its responsibilities for regulating therapies for Americans with rare disorders.

NORD is the leading advocate for the 30 million Americans with rare disorders. NORD is justifiably proud of our history as the principle force behind the effort that culminated in the 1983 Orphan Drug Act. And, NORD is just as equally proud of our current activities to advance the interests of Americans who have 1 of 6,000 rare disorders. I only have time to merely list some of NORD's major initiatives over the past 13 months.

1. NORD organized a full-day Summit on orphan disorders at the Willard Hotel in May 2009 which was chaired by former FDA Commissioner Kessler and key participants which included Dr. Janet Woodcock and Dr. Francis Collins. A summary of this Summit is available on the NORD Web site.

2. NORD, with the assistance of John Crowley, CEO of Amicus, one of NORD's Corporate Council members, was responsible for organizing a Congressional Caucus on Rare and Neglected Diseases this year.

3. NORD was a key player involved in Section 740 of the fiscal year 2010 Appropriations Act (the so-called Brownback/Brown amendment) which is the impetus for this hearing.

4. NORD suggested and supported that the FDA and the Center for Drug Evaluation and Research (CDER) establish its first position dedicated to issues related to the regulation of medicines for those with rare disorders, and in February FDA created the post of CDER Associate Director for Rare Diseases.

5. NORD worked for the passage of comprehensive health care reform, and in particular, those two provisions of vital interest to those with rare disorders: eliminating pre-existing conditions and eliminating lifetime and annual insurance caps. To see that what was gained in Congress is not lost in the courts, NORD is currently participating in an amicus brief to defend the constitutionality of the health care reform law.

6. NORD, with the involvement of FDA Commissioner Hamburg and NIH Director Collins, set up a Task Force on rare disorders in January. In several meetings at which senior FDA and NIH officials participated, NORD has explored ways to facilitate the development of therapies for rare disorders, including holding a series of four focus groups, each separately meeting with representatives of patient organizations, the medical and scientific research community, the pharmaceutical industry and the financial investment community.

7. And, finally, on the seventh day, NORD rested.

Both at the NORD Summit last May and at the NORD Task Force meetings, including focus groups, NORD has learned much and we want to share some of those key findings with FDA today.

First, over the 27 years since its enactment the Orphan Drug Act has proven a resounding success. This is best seen in the over 350 new medicines for more than 200 different rare disorders approved by FDA over the first quarter of a century of the law's existence. However, what NORD learned at its Summit and in its Task Force proceedings is that there are still about 5,800 disorders for which there are no FDA-approved therapies. Perhaps most discouraging is that many affected with these rare disorders do not even see any research being conducted in their conditions. To NORD, this seems as though the proverbial low hanging fruit have already been harvested in the first quarter of a century of the law's existence, while the vast majority of therapies are currently out of reach of those in need of an FDA-approved medicine. In sum, much has been accomplished by FDA, by NIH, by medical and scientific researchers, by the pharmaceutical industry, by the financial community and by patient advocates in these first 27 years, but much, much, much, much more beckons each of us to respond to the needs of those with rare disorders.

Second, how best can each of us respond to those in need of therapies? As part of the NORD Task Force, NORD—with senior FDA and NIH officials—in April held a series of four focus groups to listen and learn what are the barriers slowing or barring the development of new therapies for rare diseases, especially the 5,800 rare disorders for which there are no FDA-approved medicines. We had a separate focus group with each of the four major stakeholders involved in developing new therapies—the patient community, the academic research community, the pharmaceutical industry and the financial investment community. In those Task Force proceedings and at the NORD Summit, we heard many ideas. Several of those ideas would require new legislation and so those are beyond the scope of today's hearing.

What we at NORD heard which can be addressed by FDA is the benefit that would be gained from FDA action on the following two NORD recommendations:

I. For a clearer, more granular expression of FDA's historic commitment to exercise flexibility in its review of therapies for rare disorders; and

II. For an FDA expression of ways to reduce regulatory uncertainty in the development and review of orphan disorder therapies.

Let's explore each of those.

NORD RECOMMENDATION #I—FOR AN FDA STATEMENT OF POLICY ON FDA'S HISTORIC FLEXIBILITY IN REGULATING ORPHAN DRUGS

NORD heard, especially from the investment community and the pharmaceutical industry, that FDA delivers a consistent, repeated message that the statutory standards for safety and efficacy are the same for both rare disorders and prevalent diseases. What is not often heard is the companion portion that completes that statement which is that, while the statutory standards are the same, the FDA interpretation and application of those same standards have historically been tailored by FDA to the unique facts of each particular medicine under FDA review. Moreover, there are FDA regulations and guidances that express this flexibility. In addition, FDA actions on marketing applications eloquently embrace and express this concept of flexibility. This exercise of FDA scientific judgment in applying these statutory standards flexibly to various situations apparently is not being heard by some of the key stakeholders in this system.

So, today NORD is asking the FDA to develop and issue a specific Statement of Policy on FDA's role in regulating therapies for rare disorders which includes an explanation and affirmation of the FDA's historic position that FDA flexibly applies the standards of safety and effectiveness with respect to therapies for those with

rare disorders. What we, NORD, have heard is that the investment community and pharmaceutical industry may benefit from such a formal, explicit statement of policy that will encourage investment in, research of and development of medicines for those with rare disorders, especially for those 20 million Americans with one of the 5,800 rare disorders for which there still is not a single FDA-approved therapy.

#### 1. FDA REGULATIONS AND GUIDANCES

A. In responding to the AIDS crisis that was becoming apparent around the same time that FDA was implementing the Orphan Drug Act in the mid-1980s, FDA promulgated Subpart E of the IND regulations for “drugs intended to treat life-threatening and severely-debilitating illnesses.” FDA stated that the purpose of Subpart E is,

“to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated [in section] 314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand **FLEXIBILITY** in applying the standards. The FDA has determined that it is appropriate to exercise the broadest **FLEXIBILITY** in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. ***These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated.***” (Emphasis added.)

B. The regulation that was referenced in the Subpart E regulation is section 314.105(c) which even predates the Subpart E regulation and illustrates again FDA’s historic position on applying the same statutory standards in a flexible way depending upon the circumstances. Section 314.105(c) states that:

“FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to them and the wide range of uses for those drugs demand **FLEXIBILITY** in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet them. FDA makes its views on drugs products and classes of drugs available through guidelines, recommendations and **statements of policy**” (emphasis added).

C. An example of a formal regulatory policy or guidance that expresses this concept of “flexibility” in FDA’s application of the statutory standards of safety and efficacy is seen in the ICH E1A guidance. That FDA-adopted international guidance stipulates the minimum quantum of safety exposures necessary for FDA to even accept a marketing application for review when the medicine is intended for a chronic condition. Most rare disorders are chronic in nature and not acute, and so this guidance applies to most rare disorder therapies. The guidance states that the minimum number of safety exposures to meet the statutory standard for safety are 1,500 persons exposed to the investigational therapy with 300 to 600 of those exposed for at least 6 months and with at least 100 exposed for 1 year. However, the guidance states that these minimum safety thresholds do not apply to therapies for rare disorders. Importantly, the guidance then does NOT state what is required in the alternative whereas it could have stated an algorithm such as at least 1 percent of the U.S. population with the rare disease must be exposed with half of them for at least 1 year. No, instead the guidance relies upon the exercise of FDA’s scientific judgment to determine what is appropriate to meet the statutory standard for safety in each particular rare disorder therapy.

#### 2. FDA ACTIONS ON RARE DISORDER THERAPY MARKETING APPLICATIONS

Instead of reviewing many such precedents, NORD refers to but one recent example as illustrative. In March of this year, FDA approved Carbaglu for NAGS deficiency, the rarest urea cycle disorder, with only 10 patients in the United States generally at any time. In the FDA briefing document for the January 13, 2010 Advi-

sory Committee meeting, FDA explained that while Congress in 1962 added a new statutory standard requiring that a drug prove its effectiveness,

“FDA has been **FLEXIBLE** within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing . . . Thus, evidence obtained from retrospectively reviewed case series could be considered as substantial evidence of effectiveness . . . The fact that the case series presented in this application is retrospective, un-blinded, and uncontrolled precludes any meaningful formal statistical analyses of the data. Under these conditions, any statistical inference from confidence intervals and/or p-values is uninterpretable and, consequently, should not be utilized to inform clinical decisionmaking.” (See pages 9 & 10 of the briefing document attached to Dr. Griebel’s December 16, 2009 memo to the Advisory Committee, emphasis added.)

### 3. DR. GOODMAN’S JUNE 23, 2010 STATEMENT TO CONGRESS

Dr. Jesse Goodman, FDA Chief Scientist and Deputy Commissioner for Science and Public Health, testified last week before the Senate Appropriations Committee Agriculture Subcommittee on “FDA’s efforts on rare and neglected diseases.” In Dr. Goodman’s commendable testimony he cites to the Carbaglu example as well as several others to illustrate that:

“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” (emphasis added).

### 4. PERSONAL EXAMPLE FROM MEETING THIS MONTH WITH FDA

In a meeting I had this month the FDA told the sponsor at an End of Phase 2 meeting for a therapy to treat a very troublesome symptom of a very serious and common (that is, prevalent) disease that the sponsor had not only to prove the effectiveness of the drug to treat the symptom but also had to rule out that the drug did not increase unacceptably the risk of death in that patient population with this serious disease. FDA stated that the sponsor would have to show what increase in the risk of death could be excluded by reference to the upper 95 percent confidence interval. While we did not at that meeting arrive at an agreement on the size of the magnitude of risk that had to be excluded, even ruling out only a doubling of the risk of death would likely require a study of thousands of subjects for a long period of time. While I have been involved in scores, maybe hundreds, of therapies for rare disorders, I have never heard FDA express a similar requirement for a therapy for a rare disease. Why? This is likely because FDA is being flexible in interpreting and applying the statutory standards for safety and efficacy in that FDA knows that to require a similar type of showing for a therapy for a rare disorder would be impossible for almost all orphan drugs given the limited pool of potential subjects for clinical trials. The statutory standards are the same both for the prevalent disease and the orphan condition, but FDA rightly interprets and applies the standards in light of the disease and investigational therapy.

In other areas FDA can exercise similar flexibility. For instance, where the potential number of subjects is limited, the degree to which FDA demands dose selection be optimized in pre-approval studies may be reduced as can be FDA’s requirements for validation of a patient reported outcome instrument in a rare disorder population or proof of the sensitivity, specificity and clinical meaningfulness of a primary endpoint. Given that each investigational therapy for a rare disorder will present unique features, NORD understands that the granularity of the requested statement of policy on rare disorder therapies may necessarily be limited. However, even cataloging the nature and scope of the orphan product precedents that illustrate FDA’s flexibility may enable key stakeholders to better understand FDA’s position. That is, even while FDA states correctly that the statutory standards are the same for prevalent and rare conditions, FDA will have a formal companion statement of the equally important and consistent FDA historic position that FDA will exercise its scientific judgment to interpret and apply those statutory standards in a flexible manner, tailored to each rare disorder therapy.

NORD looks forward to the FDA issuance of an FDA Statement of Policy on FDA’s regulation of therapies for rare disorders and to the day when every FDA official who speaks to patients or to other stakeholders, including researchers and spon-

sors, about the FDA policies on regulating therapies for rare disorders does so in the complete and balanced way that Dr. Goodman did last week when he testified to both that as to the identical statutory standards that rare disorder therapies must meet as well as to the historic FDA flexibility in interpreting and applying those standards, exercising FDA's scientific judgment in light of the particular circumstances of that unique rare disorder and specific investigational therapy.

NORD RECOMMENDATION #II—REDUCING REGULATORY UNCERTAINTY IN THE DEVELOPMENT OF MEDICINES FOR RARE DISORDERS

In addition to the willingness of persons with rare, serious diseases to accept more safety risks and less rigorous evidence of effectiveness than for a prevalent disease or for a less serious disease or for one with some already approved therapy, and in addition to learning that some key stakeholders would benefit from a formal FDA statement of policy on FDA's exercise of its flexibility, the other consistent message we at NORD learned from our research and interactions since the NORD Summit in May 2009 is that the development of therapies for rare disorders could additionally benefit from a reduction in regulatory uncertainty.

It is axiomatic that the perfect is the enemy of the good. In the world of rare disorders, there is much that is often not known or not known well, starting with the etiology and pathophysiology of the condition, including its natural history, and ranging to a lack of agreement among even a small handful of world experts on the most common clinical manifestations of some conditions. Against this backdrop, it is entirely understandable that FDA on occasion will find it difficult to concur in advance with a development program, even the design of a registrational trial under a special protocol assessment. However, researchers, industry and FDA, as well as most importantly, persons with the condition, may find that sometimes a study needs to proceed because patients are suffering and can not wait for the perfect trial design with the ideal primary endpoint to be eventually determined or developed and consensually accepted.

Research resources in the universe of rare disorders are precious, with the most precious being the persons with the rare disorders who are heroically volunteering to participate in a trial, usually under conditions where there is less known than in trials of therapies for prevalent diseases about the safety and potential effectiveness of the investigational therapy from animal models, animal toxicology and early human trials. So, when these trials are conducted, sometimes with designs with which all parties may not be in full concurrence, including the FDA, great deference should be afforded the design of these trials and flexibility applied in the interpretation of their results. If such a principle were to be addressed and accepted by the FDA, much good would come of it.

CLOSING

On behalf of all those with rare disorders, NORD commends the FDA on its stellar, worldwide leadership role on orphan product issues for the past 27 years, and NORD exhorts FDA to continue to embrace even more fully the historic flexibility FDA has long noted and exercised in FDA's regulation of medicines for those Americans with rare disorders and to grapple with ways that can be managed by FDA to reduce the regulatory uncertainty in the development and review process.

NORD commits to do all it can to continue to provide input to FDA on matters related to FDA's vital responsibilities for the regulation of investigational therapies for each of the 30 million Americans with rare disorders, but especially for those more than 20 million who have the 5,800 rare disorders for which there are no current FDA-approved therapies.

Finally, NORD would like to publicly and formally express NORD's deep appreciation to the FDA for holding this hearing today on these critically important issues to so many Americans.

Thank you.

ATTACHMENT 2.—OFFICE OF RARE DISEASES RESEARCH NEWSLETTER

FOCUS ON RARE DISEASES—HIGHLIGHTS

RARE DISEASES CLINICAL RESEARCH NETWORK (RDCRN II) UPDATE

In the fall of 2009, the NIH Office of Rare Diseases Research (ORDR) in collaboration with seven NIH Institutes (NICHD, NHLBI, NIDDK, NIAMS, NINDS, NIDCR, and NIAID) renewed and expanded the RDCRN Program. The level of support received from the ICs (institutes and centers) has increased, and in the expanded RDCRN (called RDCRN II) ORDR was able to provide support for 19 consortia. The



Data and Technology Coordinating Center has been continued in RDCRN II as the Data Management Coordinating Center with a slightly different charge. In RDCRN II, 56 Patient Advocacy Groups (PAGs) are participating and collaborating in the clinical studies of more than 90 rare diseases at over 130 research sites. The first Steering Committee and Orientation Meeting for the Principal Investigators (PIs) was held on October 1–2, 2009. This meeting was also attended by PAGs, co-PIs, and relevant program staff from the ICs.

Below is a link to the NIH press release about the expansion of Rare Diseases Clinical Research Network. <http://www.nih.gov/news/health/oct2009/od-05.htm>.

#### COLLABORATION, EDUCATION, AND TEST TRANSLATION PROGRAM FOR RARE GENETIC DISEASES (CETT)

People affected by rare inherited diseases need the reliable information that comes through quality genetic testing. The goal of the CETT Pilot Program is to help facilitate the translation of new tests for rare genetic diseases. The program's objectives are to translate as many appropriate tests as possible, ensure that the best possible test is offered in light of current knowledge, and ensure that the test meets the needs of the community. All tests are important whether the specific condition affects 5 people or 50,000.

The CETT Pilot Program's objectives require a strong collaboration between researchers, clinicians, patient advocates and clinical laboratories. The program has several new enhancements to facilitate the development of collaborations, researcher consultation, and educational materials. The program also supports the electronic collection of genetic and clinical data in public databases to accelerate access to the information for new research and treatment possibilities.

Discussions are underway to determine the future function of this pilot program and how to move it to permanent status within the NIH to best serve the public. For more information, please visit: <http://rarediseases.info.nih.gov/cettprogram/about.aspx>.

#### NIH UNDIAGNOSED DISEASES PROGRAM

The National Institutes of Health (NIH) launched the Undiagnosed Disease Program (UDP) in May 2008 to evaluate patients with disorders that have evaded a diagnosis. Often such patients, seek help from multiple physicians and other health care providers over many years before a diagnosis is made. The UDP has been organized by the National Human Genome Research Institute (NHGRI), the Office of Rare Diseases Research (ORDR), and the NIH Clinical Center. The program's main goals are to provide answers to patients with mysterious conditions that have long eluded a diagnosis and to advance medical knowledge about rare and common diseases.

By all accounts, the program has been successful. More personnel have been hired and funding has been increased. Over the year and a half since its inception, there have been more than 3,000 inquiries, more than 1,200 medical records submitted, 300 patients accepted, and about 220 of these patients seen so far at the NIH Clinical Center in Bethesda, MD. It is interesting that over half of the applications fall into the realm of neurology. As an indication of the seriousness of the illnesses for which patients are applying, 13 who have applied have died, most before they could be seen at the Clinical Center. There have been 5 to 10 true diagnoses made. In one of these, a family with arterial calcifications of the lower extremities, a causative mutation was found in a gene not known to be involved in any other disease. The UDP provides both diagnostic support and new insights into rare diseases.

Additional information can be found at: <http://rarediseases.info.nih.gov/Resources.aspx?PageID=31>.

#### THERAPEUTICS FOR RARE AND NEGLECTED DISEASES (TRND) PROGRAM

Both the need and opportunity for Therapeutics for Rare and Neglected Diseases (TRND) are enormous. Of the 7,000 human diseases, fewer than 300 are of interest to the biopharmaceutical industry, due to limited prevalence and/or commercial potential. More than 6,000 of these diseases are rare (defined by the Orphan Drug Act as <200,000 U.S. prevalence), and the remainder are neglected because they affect impoverished or disenfranchised populations. 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 (RND).

TRND received \$24 million in the NIH budget for fiscal year 2009. TRND is a collaborative drug discovery and development program with governance and oversight provided by Office of Rare Diseases Research. Program operations will be

within the intramural research program administered by the *National Human Genome Research Institute*.

For more information, please see the Program to Advance Development of Drug Candidates for Rare and Neglected Diseases Request for Information (RFI) Web page: <https://www.fbo.gov/spg/HHS/NIH/NHLBI/NHLBI-NHGRI-2010-112/listing.html>.

#### CREATING A GLOBAL RARE DISEASE REGISTRY

In January 2010, the Office of Rare Diseases Research (ORDR) organized a workshop, *Advancing Rare Disease Research: The Intersection of Patient Registries, Biospecimen Repositories, and Clinical Data*, to discuss the development of an infrastructure for an internet-based rare disease patient registry, which would also include access to biospecimens. The workshop was sponsored by ORDR and the National Eye Institute (NEI), the National Center for Research Resources (NCRR), patient advocacy groups, and the private sector. Workshop attendees discussed approaches to creating a federated registry that would collect and aggregate patient data, serve as a core data repository and also link to other existing registries. This would allow expanded data access for patients, families, clinicians and researchers seeking accurate information. As an additional aid to research, the registry would also link to biorepositories of rare disease biospecimens.

During the presentations and breakout sessions, attendees representing advocacy groups, researchers, information technology experts, and government and private sector personnel dealt with issues related to this umbrella infrastructure. Workshop attendees expressed an enthusiasm and a commitment to getting involved and making it happen. Post workshop committees will guide the effort as it moves forward.

#### NIH ANNOUNCES GENETIC TESTING REGISTRY

The NIH announced on March 18 that it is creating a public database that researchers, consumers, health care providers, and others can search for information submitted voluntarily by genetic test providers. The Genetic Testing Registry aims to enhance access to information about the availability, validity, and usefulness of genetic tests. For more information please see: <http://www.nih.gov/news/health/mar2010/od-18.htm>.

#### NIH BIOSPECIMEN INTEREST GROUP

On Thursday, April 15, 2010, the NIH Biospecimen Interest Group (BIG) held a meeting that featured a series of presentations on biospecimen resources within and supported by the NIH. BIG is sponsored by the Office of Rare Diseases Research and the Office of Biorepositories and Biospecimen Research, National Cancer Institute (OBBR/NCI).

The event, which took place in the Masur Auditorium in the Clinical Center, was well attended, and the attendees found it very informative. The interest group offers a forum for trans-NIH interactions and enhanced information sharing. Members were asked to share ideas for future meetings. The meeting included the following presentations:

“The NIDDK Central Repositories”

“eyeGENE (NEI) Genotype/Phenotype Database, Repository and Registry”

“Tissue Biospecimens in Cancer Epidemiology Studies”

“The National Cancer Institute’s Cooperative Human Tissue Network”

“BioLINCC: Access to NHLBI Biospecimens and Data”

The event was videocast and is available for viewing. (<http://videocast.nih.gov/summary.asp?live=8662>)

#### VI INTERNATIONAL CONFERENCE ON RARE DISEASES AND ORPHAN DRUGS IN BUENOS AIRES (ICORD 2010)

A global meeting on international cooperation and policies for rare diseases and orphan products was held in Buenos Aires, Argentina on March 18–20, 2010. *The VI International Conference on Rare Diseases and Orphan Drugs (ICORD 2010)* convened for the first time in the southern hemisphere in agreement with its aim of globalization of rare diseases research and orphan products development activities.

Individuals and organizations from patient groups, academic research investigators, the pharmaceutical, biotechnology and medical device industries, and government policy and decisionmakers were invited to participate in this unique forum. Specialized courses, and open meetings with key people in the field were available for participation during the days previous to the conference (March 16 and 17), as

well as a pre-meeting about the Latin American and Caribbean initiatives (ER2010LA) in rare diseases and orphan products.

Because of its nature, rare diseases would be better researched and managed within an international landscape, and this conference offered the opportunity to join the discussion of the ideas and global needs of the rare diseases community. The economic impact of introducing new therapies and how cooperative strategies may influence the cost of these treatments was a special topic along with the special informational and individual needs of the patients and families across the lifespan. Also of interest were the particular needs of the developing world in the management of diseases that are rare in developed countries but neglected in the environments where the diseases occur more frequently.

GEISER Foundation, the first non-profit umbrella organization for rare diseases in Latin America and the Caribbean hosted the conference and the pre-activities. Information about the conference is found on the *ICORD 2010 conference Web site*. (Presentations will be available later on [www.icord.se](http://www.icord.se)). GEISER Foundation on the web: <http://www.fundaciongeiser.org>.

#### INTERNATIONAL COLLABORATIONS: JAPAN AND KOREA

The Office of Rare Diseases Research held two meetings in early 2010 with overseas visitors interested in rare diseases research and orphan products development. The first meeting took place in January with visiting scientists from the Japanese Ministry of Health, Labour and Welfare and the National Institute of Public Health. The second meeting was held in February with scientists from the Korean National Institute of Health, Sungkyunkwan University and Seoul National University.

The NIH agenda topics included:

- Genetic and Rare Diseases Information Center (ORDR)
- Undiagnosed Diseases Program (NIH: ORDR, Clinical Center, Institutes)
- Clinical Trials.gov (NIH)
- Therapeutics for Rare and Neglected Diseases Program (NHGRI)
- Rare Diseases Clinical Research Network (ORDR, Institutes)
- Genetic Test Translation Program (CETT/ORDR)
- Clinical Center programs and protocols
- Clinical and Translational Science Awards, Clinical Research Network Program (NCRR)
- Office of Orphan Product Development (FDA)

Presentations were also made by the Japanese and Korean visitors describing their health and research organizations, and their research and product development activities. The meeting agendas allowed ample opportunity for discussion following each talk. ORDR also included a presentation on an educational module on rare diseases designed for middle school students, which when completed, will be available at no expense not only in the United States but also to other countries for their use.

The NIH and other U.S. presenters and the Japanese and Korean presenters agreed that their meeting was successful in advancing communication, sharing knowledge, and stimulating potential research collaborations in rare diseases research and orphan products development.

#### SCIENCE OF SMALL CLINICAL TRIALS COURSE

“The Science of Small Clinical Trials,” a course created jointly by the FDA’s *Office of Orphan Products Development* (OOPD) and NIH’s *Office of Rare Diseases Research*, deals with issues concerning the design and analysis of clinical trials based on small study populations. While small clinical trials are a necessity in the context of rare diseases, being able to conduct small trials with scientific rigor is of increasing importance in other contexts, particularly as genomic science begins to provide opportunities for individualized pharmacology. Over 1,500 individuals requested for the course. <http://small-trials.keenminds.org>/<http://videocast.nih.gov/PastEvents.asp?c=88>.

#### RARE CANCERS WITH HIGH MORTALITY: CHALLENGES FOR CANCER PREVENTION AND TREATMENT

Recently a workshop, *Rare Cancers with High Mortality: Challenges for Cancer Prevention and Treatment*, was held to discuss the issues and challenges associated with rare cancers and to facilitate collaborations among the participants. Approximately 200 participants including scientists, clinicians, industry, government, and patient advocates met for the workshop.

The day and a half workshop was structured with plenary sessions for the first half-day followed by three Breakout Groups for facilitating discussions among the participants. The Breakout Groups were divided into the following areas: (A) Building a Knowledge Base—Biology, Epidemiology, and Etiology; (B) Facilitating Clinical Studies in Rare Cancers; and (C) Development of New Detection, Prevention Methods/Strategies, and Therapies. On the second day, the moderators of each Breakout Groups presented a summary for discussion to all participants.

All three Breakout Groups identified similar issues and challenges in the study of rare cancers and common themes for addressing these challenges. This report outlines the outcome of this workshop and the recommendations provided by the participants of this workshop: [http://rarediseases.info.nih.gov/RARE\\_CANCERS\\_WORKSHOP/](http://rarediseases.info.nih.gov/RARE_CANCERS_WORKSHOP/).

#### RESEARCH CHALLENGES IN CNS MANIFESTATIONS OF INBORN ERRORS OF METABOLISM WORKSHOP

On December 7 and 8, 2009, the Office of Rare Diseases Research, the National Institute of Neurological Disorders and Stroke and the Food and Drug Administration's Center for Drug Evaluation and Research, Division of Gastroenterology Products, hosted a workshop on the central nervous system (CNS) and inborn errors of metabolism, *Research Challenges in CNS Manifestations of Inborn Errors of Metabolism*. More than 150 participants attended the meeting to discuss the barriers to the development of therapies for central nervous system disease in inborn errors of metabolism (IEM). The conference focused on the challenges in clinical translation including the regulatory requirements to move from preclinical to the clinical stage of research and development, consideration of specific clinical trial design for rare diseases, the identification of appropriate outcome measures for evaluation of interventions, and ethical issues related to the investigation of products for these diseases.

Additional meeting information can be found at: [http://www.rarediseases.info.nih.gov/Inborn\\_Errors\\_Metabolism/AddContact.aspx](http://www.rarediseases.info.nih.gov/Inborn_Errors_Metabolism/AddContact.aspx).

#### OPSOCLONUS MYOCLONUS SYNDROME (OMS) WORKSHOP

The *Opsoclonus Myoclonus Syndrome (OMS) Workshop* was held on April 10, 2010 at the Westin Harbour Castle in Toronto, Canada. Approximately 35 researchers, patient advocates, and industry representatives from seven countries met along with several NIH representatives to discuss issues of importance to the OMS community, including the differences between pediatric OMS and adult onset OMS, therapeutic strategies in the United States and Europe, diagnostic criteria, current research activity and future directions. It was felt that there was enough agreement in several areas that consensus documents could be drafted. It is hoped that another OMS conference can be scheduled in approximately a year both to leverage the momentum from the first meeting into real collaborative progress in the OMS community and to fit better with the biennial meetings held in Europe. [http://rarediseases.info.nih.gov/oms\\_workshop/](http://rarediseases.info.nih.gov/oms_workshop/).

#### ORDR SCIENTIFIC CONFERENCE PROGRAM

ORDR collaborates with Institutes, Centers, and Offices at NIH to stimulate rare diseases research by cosponsoring scientific conferences where research is lagging or to take advantage of scientific opportunities. In 2009, ORDR co-supported over 90 conferences. This year, ORDR will co-support up to 50 conferences.

Since the program inception in 1995 ORDR has co-supported almost 1,100 conferences. For more information please visit [http://rarediseases.info.nih.gov/Scientific\\_Conferences.aspx](http://rarediseases.info.nih.gov/Scientific_Conferences.aspx).

#### ABOUT ORDR

The Office of Rare Diseases Research (ORDR) was established in 1993 within the Office of the Director of the NIH, the Nation's medical research Agency. Public Law 107-280, the *Rare Diseases Act of 2002*, established the office in statute. The goals of ORDR are to stimulate and coordinate research on rare diseases and to respond to the needs of patients who have any one of the almost 7,000 rare diseases known today.

Definition of rare diseases: (Orphan Drug Act as amended in 1984 by P.L. 98-551 to add a numeric prevalence threshold to the definition of rare diseases.)

“. . . the term, rare disease or condition means any disease or condition which (a) affects less than 200,000 persons in the U.S. or (b) affects more than 200,000 persons in the U.S. but for which there is no reasonable expectation that the cost of devel-

*oping and making available in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug.*

RESPONSE TO QUESTIONS OF SENATOR ENZI BY JOHN F. CROWLEY

*Question 1.* Your industry is among the most innovative there is. I think when it comes to incentives for innovation in the area of rare and neglected diseases, we should take an “all of the above” approach, and try a variety of different mechanisms to encourage innovation. Can you weigh for me the pros and cons of different types of incentives, including prize funds?

Answer 1. I agree completely regarding an “all of the above” approach relative to utilizing a variety of mechanisms to encourage continued innovation and entrepreneurship in the biotechnology and biopharmaceutical industries to develop medicines and devices to satisfy unmet medical need amongst those suffering from rare and neglected diseases.

One of the key intentions of the Orphan Drug Act of 1983 was to encourage innovation in our industry by providing extended patent exclusivity and tax incentives to foster a new market dynamic. At this point now 27 years later, we need to reassess existing mechanisms, and to put in place a new series of incentives that will foster the risk taking and capital investments from private industry to develop a whole new generation of medicines to treat a range of rare and neglected diseases. Some possible mechanisms to consider include:

- The Therapeutic Discovery Project Tax Credit of \$1 billion as provided in the Patient Protections and Affordable Care Act (PPACA) was a first step, utilizing tax credits intended to encourage investments in new therapies to prevent, diagnose and treat acute and chronic diseases by companies with 250 or fewer employees. The potential “con” to this is having the greatest number of potentially eligible applicants benefit from the funds rather than focusing on scientifically innovative projects. The final HHS/Treasury process may potentially dilute the funds allocated; reducing the likelihood of any particular project being awarded the resources it needs to have a significant impact. This tax grant program should be considered for extension and expansion beyond the current allotted 2009 and 2010 credits/grants to the extent that it can leverage private capital and provide meaningful capital through the tax credit mechanism.

- Investment tax credits for angel and venture capital investors can provide incentives for those whose participation early on in the drug development process is essential to getting start-ups off the ground and compound identification and similar early drug discovery projects initiated. Capital markets have dried up in recent years and IPOs are no longer options for most biotechs. Investment tax credits could facilitate risk and encourage these important investment dollars early in the process, rather than later where they now are.

- R&D tax credits for drug discovery companies should become permanent, as an ongoing incentive. The United States has fallen behind because of foreign tax havens that other nations offer to attract drug manufacturing.<sup>1</sup>

SBIR—Small Business Innovation Research (SBIR) program grant eligibility rulings need to be changed, reverting to pre-2001 definitions. Current requirements prevent small businesses that receive venture capital investment in excess of 50 percent from qualifying for these grants. SBIR eligibility should be restored to businesses reliant on VC financing. Both the House and Senate have passed a series of short-term extensions of SBIR in the past year, but no final reauthorization of the bill has been reached. It is again before the current Congress and should be passed this session.

*Question 2.* In the late 1980s and early 1990s, Europe was approving new medicines faster than the United States. The medical product user fee programs turned that around, but I am hearing that the pendulum is swinging back the other way. Now that we have a solid foundation, what can we learn from the incentives in place in Europe?

Answer 2. In the 1990s, national drug approvals, in general were taking variable lengths of time in Europe and there were rigid review clocks associated with these (perhaps the models for today’s PDUFA clocks). Sponsors could seek approval in the EU nationally, by using the mutual recognition (decentralized) procedure or by using the centralized procedure. While the national route is now obsolete and there is the common EU route, a unified approval is not synonymous with unified access. Market availability of a medical product, i.e., reimbursement, is still very much de-

<sup>1</sup> Gone Tomorrow? A Call to Promote Medical Innovation, Create Jobs, and Find Cures in America, Prepared for The Council for American Medical Innovation, June 10, 2010.

terminated on a country-by-country basis. Today, the rare disease community is advocating for “no borders” when it comes to accessing diagnoses and medical care at centers of excellence across countries. However, with diagnosis in one EU country, access to an approved drug is not guaranteed in another.

In terms of the pendulum swinging, PDUFA has been widely credited as an innovative program that has strengthened FDA’s capacity to evaluate expeditiously and efficiently the safety and effectiveness of new drugs and biologics, thereby making needed new safe and effective therapies available to patients in a timely and responsible fashion. However, recent FDA review data suggests that the Agency has been struggling to complete reviews in a timely manner. This drop in performance may be due in part to a lag in recruitment that coincided with additional workload from implementation of the FDA Amendments Act of 2007, but also calls for a thoughtful evaluation of the Agency’s human drug review processes. Patients deserve a clear and predictable drug review process that is science-based, judicious, timely and one in which they can have confidence. We look forward to working with FDA and Congress to continue to strengthen the new drug review process and refocus on the original intent of the program: to provide the FDA with adequate resources to fulfill its essential public health mission of assuring the safety and effectiveness of new medicines.

Lastly, the quality and completeness of sponsors’ marketing applications matters in both the United States and in Europe. Sponsors across the board would serve themselves well by submitting well-written, high quality applications. Seeking and applying guidance from the regulatory agencies throughout the process is important and can help with this.

*Question 3.* Some have proposed a new division within FDA to evaluate therapies for rare diseases. While I think this approach has merits, I wonder if one set group could ever have the necessary expertise to address the thousands of rare diseases we hope to treat. Would a “swat team” approach where experts from other parts of the Agency are brought together on an as-needed basis be more efficient?

*Answer 3.* A new division within the FDA dedicated to evaluating therapies for rare diseases is essential. One, discrete review division comprising expertise in rare diseases will enhance the Agency’s ability to follow an orphan drug product application from its earliest stages through clinical trial design and implementation, data evaluation and final review and approvals. Organizing the best and brightest from rare disease science and medicine will result in a concentrated think tank that can establish its own organizational alignment, but not function within a vacuum. It will have an assembly of those who best understand myriad scientific and clinical elements of disease, drug development, trial design and analysis. And with time and a multitude of reviews, that collective body of knowledge will enhance as it progresses. Should additional knowledge or perspectives be needed, those can be drawn upon from elsewhere within NIH or from outside academic or medical institutions to augment a particular review process on an ad hoc basis, as the exception, however, rather than the norm.

Currently, the Office of Orphan Product Development (OOPD) has limited long-term effect on any particular rare disease once an orphan designation is granted to a product. That product, and its potential, is handed back to the applicant; there is no direction or strategy beyond designation. OOPD staff become involved in the FDA review process only upon request and on a consultative basis. Presently, orphan product reviews are assigned across different review divisions at FDA. Expertise for particular rare diseases can build, during the course of a product’s clinical trials and review period, if that disease assignment has been with a particular division for a while, and if a disease has more than one product indication under review. However, division assignments change and a group that reviews programs for a particular disease may be moved off that disease within just a couple of years’ time. Staff turnover within these divisions also has been a significant hindrance. Expertise often leaves with those employees, necessitating training anew and impeding progress. Within the framework of one rare disease division, clear career development could be established, thereby attracting and retaining the talent that can both establish and evolve the evaluation process to most efficiently bring safe and effective treatments to satisfy unmet medical needs.

*Question 4.* You use the term venture philanthropy in your testimony. This is a new concept to me, and I’d like to learn more. How does venture philanthropy compare to venture capital endeavors?

*Answer 4.* Venture philanthropy initially applied to efforts that brought business or venture-oriented systems and processes to nonprofit organizations in the social service sector. Some examples of this concept include Venture Philanthropy Part-

ners in Washington, DC, Social Venture Partners, throughout the United States, and the Acumen Fund.<sup>2</sup> Now, more frequently, the term describes the efforts of patient advocacy and other nonprofit disease organizations to fund research and development in the commercial sector. It also refers to the activities by these advocacy groups who use business models to organize their activities.

They have taken more aggressive postures because they are frustrated with the typical pace of translational research in their respective disease areas. This is increasingly the case in the rare disease field, where the risk/reward profile for orphan product development is often viewed as a disincentive by the capital markets. In addition to their obvious passion for change, these venture philanthropists bring their financial resources, extensive disease knowledge, access to patient communities, and sometimes early registry data that emerging companies may not have. Venture philanthropists usually come in to the process at the second state of pre-clinical drug development: between drug discovery that often occurs at NIH and other academic institutions when a large number of candidates are identified, but before the clinical trial stage when the number of drug candidates has been narrowed to the select one or few and the capital markets and larger pharmaceutical companies are ready to become involved. This translational research stage of “valley of death” has experienced a dearth of momentum and health venture philanthropy fills some of the void. We need to find additional ways to fill that void.

The funding models used vary, and range from fairly straight forward grants or sponsored research agreements to convertible loans by private foundations, to equity arrangements that include company stock or royalties. Grants or research agreements can run from under \$100,000 to upwards of \$50 million, or in the case of the Cystic Fibrosis Society (CF) and Vertex Pharmaceuticals, more than \$100 million back in the middle of the last decade. Around that same time period, the Leukemia and Lymphoma Society allocated \$3.5 million to Aegera for drug development and the ALS Association committed the same amount to Cambria Biosciences. In 2008, CF Foundation Therapeutics, Inc., the nonprofit affiliate of the CF Foundation, expanded its collaboration with PTC Therapeutics by committing an additional \$25 million in support of the company’s Phase 2 trials.

RESPONSE TO QUESTIONS OF SENATOR ENZI AND SENATOR CASEY BY SUERIE MOON

SENATOR ENZI

*Question 1.* My colleague here on the committee, Senator Brown, was involved in the development of an innovative incentive for developing therapies for rare and neglected diseases. Do you feel this type of non-exclusivity incentive is sufficient to entice more and bigger industry players into developing treatments for rare and neglected diseases?

*Answer 1.* The Priority Review Voucher (PRV) is one mechanism to stimulate R&D for neglected diseases.<sup>1</sup> While the PRV has the potential to increase innovation for rare and neglected diseases, an array of complementary policies is necessary to ensure effective and affordable new product development for neglected diseases, and the PRV is unlikely to be sufficient on its own, as explained further below.

The PRV was introduced as part of the FDA Amendments Act of 2007 (FDAAA) which amended the FDC Act to add §524: “Priority Review to Encourage Treatments for Tropical Diseases.” FDC Act §524 established a transferable priority review mechanism for drugs and biologics for certain specified tropical diseases. Drugs for qualified diseases approved by the Food and Drug Administration (FDA) are entitled to a PRV that allows for expedited review—of 6 months instead of the typical 10 months or more—of a drug or vaccine. The voucher is transferable, including by sale, and does not need to be applied to drugs in specified disease areas.

As applied to neglected diseases, the PRV effectively provides an incentive estimated to be worth more than \$300 million for the development of drugs for par-

<sup>2</sup> Venture Philanthropy: An Emerging Source of Capital for Drug Discovery and Development, Timothy Coetzee, Ph.D., Executive Director, Fast Forward, LLC, December 2008.

<sup>1</sup> The PRV in the presently enacted form does not require non-exclusivity though its original proposal did outline a structure in which the neglected disease drug developed would not be patent-protected, and also in which manufacturing commitment was ensured. In the original conception of the PRV outlined in this article, a sponsor would need to meet the following conditions in order to receive a PRV: (1) treat designated neglected diseases; (2) receive approval from the United States or European drug regulatory authority; (3) be clinically superior to existing treatment options; (4) forgo patent rights; and (5) ensure at least one manufacturer. Ridley D, et al. Developing Drugs For Developing Countries. *Health Affairs* 25.2 (2006): 313–24, <http://content.healthaffairs.org/cgi/content/full/25/2/313>.

ticular diseases.<sup>2</sup> The transferability of the PRV to a producer of a blockbuster medicine makes this a potentially lucrative incentive for neglected disease development.

While the PRV can be a useful tool if structured appropriately, it is insufficient on its own to stimulate new product development for neglected diseases, and as currently enacted also has several important shortcomings.

First, PRVs leave to the company entirely the choice of diseases to prioritize for R&D. While current legislation identifies diseases for which the PRV may be applicable, it remains at the company's discretion whether to invest in drug development in these diseases. This means that priority diseases may be left unaddressed despite unmet needs.

Second, the ability of the PRV to incentivize innovation of new neglected diseases R&D remains untested. While it is important to explore new approaches to incentivizing needs-driven R&D, new mechanisms should be designed carefully to maximize the public interest; they should also be monitored closely so that we learn from the experience and make improvements to policies along the way.

In April 2009, the FDA granted the first PRV to Novartis for its combination antimalarial medicine of artemether and lumefantrine (Coartem) although this medicine had been on the market many years prior: Novartis developed Coartem in 1996 and the medicine has been used, including by MSF, for more than a decade in developing countries. It had not previously been submitted to the FDA, but it had been submitted to and approved by other drug regulatory authorities. Whether companies will actually be motivated for neglected disease drug development by a transferrable PRV is not yet known and should be monitored closely.

Third, the PRV in its current form does not ensure that products developed for neglected diseases are made available and affordable to patients in developing countries. The new incentive is not tied to agreements to license patents and other intellectual property rights in order to enable generic competition or more efficient procurement of products in developing countries.

Fourth, the PRV is not available for re-purposed drugs, a possibly important area for the development of new treatments for neglected diseases.

Proposed S. 3697<sup>3</sup> is legislation newly introduced by Senators Brownback, Brown, and Franken that responds to some of these problems. In particular, it would eliminate from eligibility for the PRV a drug approved more than 24 months prior outside of the United States for commercial marketing for tropical diseases. This would help to eliminate the possibility that a company would receive a windfall for a drug developed years earlier and it would reserve the PRV as an incentive for new drug development as intended. The act also expands the list of diseases eligible to benefit from the PRV to include Chagas disease. Chagas disease, the largest parasitic killer in the Americas, affects 300,000 in the United States and 15 million people around the world. The proposed amendment still would not require that a company ensure production, but it would expand the reporting requirements to include a good faith intent to make the drug available in developing countries.

A variety of push and pull mechanisms are necessary to respond to the current lack of incentives for drug and vaccine development for neglected diseases. One of the reasons MSF supports delinkage principles generally, and innovation prizes in particular, to complement other mechanisms is that they can incentivize R&D without the limitations described above. A prize would bring attention to priority areas and could be structured to ensure affordability and accessibility principles.

*Question 2.* Although rare and neglected diseases share some challenges, such as access issues, unlike rare diseases, neglected diseases have huge numbers of sufferers. Do the incentives for developing treatments for rare diseases carry over to neglected diseases? Which ones may not be applicable? Are there incentives for neglected diseases that may not be applicable to rare diseases?

The primary incentives in the United States for the development of drugs to respond to rare diseases, with relatively few domestic sufferers, are established within the Orphan Drug Act (ODA). The ODA provides exclusive marketing protection, substantial tax benefits, grant support for R&D, and FDA counseling related to conditions for approval to the sponsor of a drug for diseases with fewer than 200,000 domestic sufferers. The FDA reports that the ODA has incentivized the development and registration of more than 200 drugs and biological products to respond to rare

<sup>2</sup>Ridley D, et al. Developing Drugs For Developing Countries. *Health Affairs* 25.2 (2006): 313–24. <http://content.healthaffairs.org/cgi/content/full/25/2/313>.

<sup>3</sup>Creating Hope Act of 2010, or “A bill to amend the Federal Food, Drug, and Cosmetic Act to improve the priority review voucher incentive program relating to tropical and rare pediatric diseases.”



diseases since the introduction of the act in 1983, compared to 10 in the decade before the introduction of the act.<sup>4</sup>

The ODA incentive of exclusive marketing protection would be largely inapplicable to neglected diseases because exclusive marketing protection as an incentive relies on U.S. consumers being able to pay very high prices during a period of market exclusivity. It is debatable whether the exclusive marketing protection is even advisable for U.S. populations given the extraordinary prices charged due to the market exclusivity.

Forbes Magazine recently explored the most expensive drugs, and identified nine that are priced at more than \$200,000 per patient per year; most treat rare genetic diseases. "For these diseases, there are few if any other treatments. So biotech companies can charge pretty much whatever they want."<sup>5</sup>

The high prices of the treatments for these rare diseases create barriers and burdens for patients, employers, governments, or others who provide insurance or reimbursements for such treatments in the United States and abroad. But high prices are not the only problem of an incentive mechanism based on providing market exclusivity. Some companies use this exclusivity to delay the entry of competing products that may be better for some patients, or have superior delivery mechanisms.<sup>6</sup>

Those affected by neglected diseases will not be able to compensate manufacturers through high drug prices. Similarly, companies will not be able to recoup R&D costs for drugs for neglected diseases through exclusive marketing and resultant high prices to these resource-poor consumers.

Tax credits available through the ODA to incentivize drug development for rare diseases are equivalent to up to 50 percent of the cost of qualified investments in clinical testing of products. Insufficient information is available about how the tax credit is used in practice. Grant support to investigate treatments can be a useful push mechanism to subsidize R&D for both rare and neglected diseases.

Incentives for neglected diseases that are based on delinkage, such as prizes, should work as well for rare diseases. While compensating for R&D at the outset, when appropriately structured, these incentives have the added benefit of minimizing access barriers. The few patients suffering from a rare disease will not be doubly burdened with health costs of hundreds of thousands of dollars annually for their lifetimes. Patients suffering from neglected or rare diseases would benefit from price-lowering generic competition or other cost control mechanisms as soon as a product is developed.

*Question 3.* Innovation prize funds have been successful in aerospace and engineering fields. Are there any health-based funds that have awarded prizes for treatments?

*Answer 3.* Over time, there have been a number of prizes for health care related innovations. For a comprehensive review of existing innovation prize funds through 2008, including for medical innovations but also for innovations in other areas, please see *Selected Innovation Prizes and Reward Programs*, by Knowledge Ecology International (KEI).<sup>7</sup> Further information is available in the 2009 McKinsey Prize Report, "And the winner is . . .": *Capturing the Promise of Philanthropic Prizes*.<sup>8</sup>

Prizes for medical innovations have been used since the 1800s to incentivize and/or reward R&D. There is tremendous variation in the prize amount, the specificity of the requirements for the prize to be awarded, and the level of development and utility required for the prize to be awarded.

In the 19th century, a number of prizes were offered to advance medical science, including in particular prizes offered by various French academies, and British or U.S. scientific groups. Many among these focused on developments in tuberculosis treatment.

More recently, Eli Lilly developed a program of small prizes to address discrete challenges that were part of larger efforts on drug development. This was later spun off as InnoCentive, a for-profit entity that currently manages hundreds of prize competitions, many of which involve biomedical inventions.

<sup>4</sup>U.S. Food and Drug Administration. Developing products for rare diseases and conditions, <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>.

<sup>5</sup>Herper M. The World's Most Expensive Drugs. *Forbes*, Feb. 22, 2010, <http://www.forbes.com/2010/02/19/expensive-drugs-cost-business-healthcare-rare-diseases.html>.

<sup>6</sup>See, e.g., Pollack A. Genzyme Drug Shortage Leaves Users Feelings Betrayed. *New York Times*, 15 Apr. 2010.

<sup>7</sup>The information described below is largely drawn from this compendium. Knowledge Ecology International (KEI). *Selected Innovation Prizes and Reward Programs*, Research Note 2008:1, [http://keionline.org/misc-docs/research\\_notes/kei\\_rn\\_2008\\_1.pdf](http://keionline.org/misc-docs/research_notes/kei_rn_2008_1.pdf).

<sup>8</sup>McKinsey & Company, "And the winner . . .": *Capturing the Promise of Philanthropic Prizes*, 3 Mar. 2009, [www.xprize.org/about/the-mckinsey-report](http://www.xprize.org/about/the-mckinsey-report).

Through InnoCentive, the Rockefeller Foundation offered a prize related to developments in tuberculosis research. This prize, like a number of others, was successful in inducing the desired innovation. In 2007, for instance, the Gotham Prize was launched to reward the sharing of knowledge to accelerate progress in cancer research. The prize was used to reward a researcher \$1 million for a new approach to cancer treatment; and to reward another \$250,000 for developments in pediatric cancer.

The following prizes have been used since the 1980's in the medical field:

- The Armand Hammer Cancer Prize (1981), offering \$1 million for the scientist who found a cure for some form of cancer over the next decade;
- Rockefeller Prize (1994), offering a \$1 million prize for developing a low-cost and efficacious test for gonorrhea or chlamydia useful in developing country contexts;
- InnoCentive (2001), a company established by Eli Lilly, hosted several prize funds for companies in need of scientific research; and expanded in 2006 with support from the Rockefeller Foundation including into the public health arena; prizes included in at least one instance an obligation that the awardee not patent or otherwise prevent the use of the innovation;
- Methuselah Mouse Prize (2003), offering a \$4.5 million prize for research into aging;
- Project Bioshield (2004), a U.S. government-sponsored prize fund, provides for automatic payment for the development of bioterrorism countermeasures;
- Archon X-Prize for Genomics (2006), offering \$10 million for genome sequencing developments;
- Prize4Life (2006), offering prizes for developments related to ALS (Lou Gehrig's disease);
- Hideyo Noguchi Africa Prize (2006), offering a 100 million yen (then approximately \$860,000, now approximately \$1.2 million) every 5 years;
- Stop TB Partnership Kochan Prize (2006), offering a prize for achievements in combating tuberculosis;
- Gotham Prize for Cancer Research & Ira Sohn Conference Foundation (2007), offering annual rewards of \$1 million and \$250,000 respectively for cancer and pediatric oncology, and described further above;
- Piramal Prize for Innovations that Democratize Healthcare (2007) offering 10 lakh rupee (\$25,000) for health improvements benefiting the Indian poor; and
- InnoCentive Tuberculosis Prize for PA-824 (2007), offering a \$20,000 prize funded by the Rockefeller Foundation, for a "safe and economical synthetic route" for a candidate drug for tuberculosis, and InnoCentive described further above.

There have also been various unrealized proposals for medical innovation prizes in the United States and elsewhere. This includes the Medical Innovation Prize Act introduced in the U.S. Congress as H.R. 417, 109th Congress; and S. 2210, 110th Congress. This legislation would establish a U.S. government-sponsored prize fund for drug development based on the medical or public health benefit of new tools developed. According to the proposed legislation, the prize would compensate for R&D for pharmaceuticals in place of patent exclusivity and monopoly prices, thereby allowing for price-lowering generic competition upon FDA approval rather than after patent expiry.

From the historic experience of innovation prize funds, lessons have been learned about the importance of offering a sufficiently remunerative prize to compensate the R&D and appropriately value the objectives set out in the prize fund; permitting flexibility and the possibility of both interim "milestone" as well as end-stage rewards; and specifying with sufficient detail the desired end product, as well as including affordability and accessibility requirements.

One lesson learned from the experience thus far is that prizes can generate private investment even exceeding the prize amount. The X Prize Foundation reports that the 26 teams competing for the \$10 million Ansari X Prize in aviation combined spent more than \$100 million to win the prize.<sup>9</sup> As stated in the McKinsey Prize Report: "One of the prizes' great strengths is their ability to attract investments from competitors many times greater than the cost of delivering and awarding a prize."<sup>10</sup>

However, the funds dedicated to prizes have been quite limited. Whereas approximately \$1 million has been made available annually for prizes to incentivize medical R&D, approximately \$17–\$20 billion has been made available annually to fund R&D

<sup>9</sup> See <http://spaceprize.org/ansari-x-prize>.

<sup>10</sup> McKinsey & Company, "And the winner is . . .": Capturing the Promise of Philanthropic Prizes, 3 Mar. 2009, [www.xprize.org/about/the-mckinsey-report](http://www.xprize.org/about/the-mckinsey-report).

through NIH grants while private sector R&D has been facilitated with the promise of substantial rewards, estimated at approximately \$150 billion, earned through high prices paid by consumers.<sup>11</sup>

SENATOR CASEY

*Question 1.* Can you comment on the balance between public investment and private investment in finding cures for rare and neglected diseases?

Answer 1. According to recent estimates, international financing for health-related R&D exceeds \$160 billion and includes a diversity of sources: 51 percent private for-profit, 41 percent public, and 8 percent private not-for-profit.<sup>12</sup>

Drug development for diseases where a profitable market exists—i.e., because there are a significant quantity of people suffering from the diseases in upper income countries—generally relies on both public and private investment. Even highly profitable so-called “blockbuster” drugs often benefit from significant outlays of public funds in the early stages of development.

Typically, earlier stages of development, such as drug discovery and research, benefit from a high level of public funding, including both university research and research in government laboratories. Pharmaceutical companies generally focus private resources on the later stages of R&D.<sup>13</sup>

One of the primary differences between R&D for diseases which affect a significant number of people in high-income countries, and for rare and neglected diseases where the small number or great poverty of the afflicted does not suggest the likelihood of a profit, is whether private sector investment can be motivated by the promise of high profits from monopoly prices during the patent term.

One study found, for instance, that in a 25-year period (1975–99), there were 179 drugs developed for cardiovascular disease whereas only 16 drugs were developed for tropical diseases and tuberculosis (TB). At the time, both cardiovascular disease, and tropical diseases and TB represented a roughly equivalent global disease burden (11 percent and 12 percent respectively), but R&D for tropical diseases and TB is underfunded because it disproportionately affects poor populations in developing countries.<sup>14</sup> Few drugs used to respond to tropical diseases were even developed intentionally targeting these diseases or relying primarily on private funding.<sup>15</sup>

<sup>11</sup>Love J & Tim Hubbard. An Agenda for Research and Development. Lecture. Meeting on The Role of Generics and Local Industry in Attaining the Millennium Development Goals (MDGs) in Pharmaceuticals and Vaccines. The World Bank, Washington, 24–25 June 2003, [www.cptech.org/ip/health/rndtf/lovehubbard06242003.doc](http://www.cptech.org/ip/health/rndtf/lovehubbard06242003.doc).

<sup>12</sup>See Feletto M and Stephen Matlin. Global R&D financing for communicable and non-communicable diseases: a report to the WHO Expert Working Group on R&D Financing, Oct. 2009, <http://www.who.int/phi/ewg3rdmeet/en/index.html>. According to Feletto and Matlin's study: “The gap between LMIC [low- and middle-income country] relevant R&D and all health R&D is considerable.”

<sup>13</sup>Notably, this means that consumers typically pay twice. First, they pay through tax dollars for publicly funded early stage research. Then, where the research is transferred without obligations for affordability, the consumers pay through high prices during the patent term. In recent years, some universities and the National Institutes of Health (NIH) have begun to respond to concerns raised by various actors that the licensing agreements made to transfer university and public sector research to the private sector for subsequent development should include certain critical humanitarian terms.

See, e.g., Universities Allied for Essential Medicines. Universities Allied for Essential Medicines, BIG VICTORY: 6 Universities, AUTM and NIH Agree to Access Principles/Universities Allied for Essential Medicines, 11 Nov. 2009 (National Institutes of Health). Check E. Universities Urged to Do More for Poor Nations. *Nature* 444 (2006): 412–13. 22 Nov. 2006. (University of California at Berkeley). Kelbie P. Edinburgh University Forces Firms to Supply Cheap Medicines to Developing World. *The Guardian*, 26 Apr. 2009 (University of Edinburgh). Lin B. Rethinking Drug Development: A New Commitment to Global Access. *UBC Public Affairs*. University of British Columbia, 8 Feb. 2010 (University of British Columbia).

The transfer from the public sector to the private sector also comes without obligations for product development and accessibility.

<sup>14</sup>Trouiller P, et al. Drug Development for Neglected Diseases: a Deficient Market and a Public-health Policy Failure. *The Lancet*, 22 June 2002, [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(02\)09096-7/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(02)09096-7/fulltext).

<sup>15</sup>The two primary drugs for Chagas disease (benznidazole and nifurtimox), as well as the drugs for schistosomiasis (praziquantel and oxamniquine), and the drugs for helminth infections and onchocerciasis (albendazole and ivermectin respectively), were developed in the context of veterinary research. Maskalyk J. New Prescriptions for Neglected Diseases. *pen Med*. 1.2 (2007): 89–91, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2802011>; Trouiller P., et al. Is Orphan Drug Status Beneficial to Tropical Disease Control? Comparison of the American and Future European Orphan Drug Acts. *Tropical Medicine & International Health* 4.6 (2002): 412–20. Wiley Online Library. 5 Jan. 2002, <http://onlinelibrary.wiley.com/doi/10.1046/j.1365-3156.1999.00420.x/full>.

The requirement of public sector investment in neglected disease research is apparent through looking at current clinical trials. The four diseases considered to be most neglected, which MSF prioritizes in our programming and which the World Health Organization (WHO) identifies as in need of innovative and intensified disease management (IDM),<sup>16</sup> are Chagas disease, leishmaniasis, sleeping sickness (or human African trypanosomiasis), and Buruli ulcer. Each have a limited number of ongoing clinical trials, and all clinical trials are disproportionately funded by public funds, including the NIH, and/or universities or philanthropic organizations.

There are seven reported ongoing clinical trials related to sleeping sickness; public, university or organizational funds support all seven while three have some industry funding. There is one ongoing clinical trial related to Buruli ulcer; it is publicly funded. There are 38 clinical trials related to Chagas disease; 29 are funded by the public sector, university or organizations, and 9 funded by industry. Lastly, there are 76 ongoing clinical trials related to leishmaniasis, but virtually all (73) are funded by the public sector, university or organizations; 7 receive some industry funding. For perspective, there are 243 ongoing clinical trials related to erectile dysfunction; 172 receive industry funding.<sup>17</sup>

Neglected diseases for which there is no or limited anticipated profitability require a higher level of public investment because the private sector will not be motivated by the possibility of exclusive marketing. The populations affected are unable to compensate drug development through high prices during the patent term because, even where they are numerous, they are too poor.

Major benefits of public sector investment in health-related R&D are that (1) funds can be directed to identified public needs rather than areas of likely profit where the incremental health benefit is less substantial; (2) the cost of compensating R&D is not borne exclusively by the most vulnerable, i.e., afflicted patients, through out-of-pocket expenditures or insurance premiums, and the costs are dispersed rather than targeted at these patients alone; (3) public sector resources can be directed towards ensuring the accessibility of drug development even where the development is less profitable, i.e., ensure that R&D does not result in a product that does not reach the potential beneficiaries; (4) open source innovation models, in which new knowledge is shared, in real time to accelerate innovation and access, can be more easily implemented; and (5) public sector research may be more cost-effective and efficient than the patent system as an innovation tool as it has been estimated that U.S. taxpayers pay “at least \$150 billion per year in higher prices . . . to fund \$20 billion in private sector R&D.”<sup>18</sup>

Therefore MSF supports both public sector and private investment in both rare and neglected disease R&D, but recognizes the essential role that public sector funding plays in these areas. MSF also considers that a variety of push and pull incentive mechanisms are necessary to support R&D for these diseases. As explained, grants and NIH funding as push incentives are essential for the development of treatments, vaccines, and diagnostics for rare and neglected diseases. Pull incentive mechanisms are also necessary. MSF favors pull incentives, like prizes, that delink the cost of R&D from the price of the products and that do not rely on marketing exclusivities, for the reasons described above.

RESPONSE TO QUESTIONS OF SENATOR ENZI AND SENATOR FRANKEN  
BY DANIEL A.C. FRATTARELLI, M.D., FAAP

SENATOR ENZI

*Question 1.* Are existing incentives sufficient to support the development of therapies for rare diseases? How might these incentives be improved and increased?

*Answer 1.* The development of therapies to treat rare diseases is challenging, and it is especially so in pediatrics. We must be constantly thinking of new and creative ways to incentivize more and better therapies. One area that needs specific attention is older, off-patent drugs. Current incentives for pediatric and rare disease therapies can only offer added exclusivity to drugs that are still protected by patents and marketing exclusivity. Many off-patent drugs lack pediatric safety and efficacy data and the National Institutes of Health (NIH) has worked to identify many of

<sup>16</sup>World Health Organization, Neglected tropical diseases: innovative and intensified disease management (IDM), [http://www.who.int/neglected\\_diseases/disease\\_management/en/](http://www.who.int/neglected_diseases/disease_management/en/).

<sup>17</sup>This information was obtained through clinicaltrials.gov, a service of the NIH, on August 19, 2010, and may include some overlap in funding sources.

<sup>18</sup>Love J & Tim Hubbard. An Agenda for Research and Development. Lecture. Meeting on The Role of Generics and Local Industry in Attaining the Millennium Development Goals (MDGs) in Pharmaceuticals and Vaccines. The World Bank, Washington, 24–25 June 2003, [www.cptech.org/ip/health/rndtf/lovehubbard06242003.doc](http://www.cptech.org/ip/health/rndtf/lovehubbard06242003.doc).

these gaps in pediatric therapeutics. However, there are no existing incentives available to remedy this problem. We look forward to working with Congress to explore new policy solutions to increasing the number of these older drugs studied for the benefit of children.

*Question 2.* Some of the incentives available for pediatric and rare and neglected diseases are stackable—a business can get more than one for a given product. Do the different programs work well together? Could they be more coordinated?

Answer 2. The orphan drug exclusivity provided by the Orphan Drug Act and the pediatric exclusivity offered by the Best Pharmaceuticals for Children Act (BPCA) work well together to improve access to safe and effective drugs for children and patients with rare diseases. The Orphan Drug Act incentivizes the development of drugs for rare diseases and BPCA incentivizes the study of drugs in pediatric populations. Pediatric exclusivity under BPCA is only granted in response to fulfilling the requirements of a written request issued by FDA and is not given in conjunction with any other incentive program.

Both incentive programs are necessary and serve distinct purposes. Whereas BPCA may be used to add pediatric labeling information to a popular adult drug, the Orphan Drug Act may be used to incentivize the development of that same drug to treat an entirely different condition that classifies as a rare disease.

*Question 3.* You recommend a central repository for data on rare conditions so that fragments of data do not reside with different physicians. We have a database called ClinicalTrials.gov that could be used for such a purpose. Do you think this is a possible way to do what you suggest?

Answer 3. ClinicalTrials.gov is a useful tool now available to patients, providers, and researchers to share and disseminate information on ongoing clinical trials. This can be particularly helpful for families that cope with rare diseases and are desperately seeking treatment. The unique nature of rare and pediatric disease research, however, may require specially designed data sharing networks not currently in place.

*Question 4.* What more can be done to speed the diagnosis of rare disorders?

Answer 4. The National Organization for Rare Disorders (NORD) has been a leader for decades in the effort to increase information on the diagnosis and treatment of rare disorders. More investment into activities like these will be necessary to continue to improve the standard of care. There is much we do not yet know about rare disorders, but we must make sure that what we do know is readily available to patients, families, and providers. We need more outreach to primary and specialty care physicians, medical societies, and medical schools. Newborn screening also plays an important role in the early diagnosis of rare disorders and deserves our continued support.

SENATOR FRANKEN

*Question 1.* The FDA has recently appointed a point person for oversight of orphan drug development in FDA's Center for Drug Evaluation and Research's Office of New Drugs. This appointment seems like a positive step. Do you think establishing a similar ombudsman for Orphan and Pediatric Devices in the FDA's Center for Devices and Radiological Health would encourage innovations and development of medical devices for these populations?

Answer 1. The Center for Devices and Radiological Health (CDRH) is currently in the process of hiring a Chief Pediatric Medical Officer who will report directly to the CDRH Director. This Chief Pediatric Medical Officer will be tasked with coordinating and integrating pediatrics across the center. The American Academy of Pediatrics strongly supports this move.

Similar efforts to integrate pediatrics in the Center for Drug Evaluation and Research (CDER) have been successful. The Pediatric and Maternal Health Staff and the Pediatric Review Committee (PeRC) have helped standardize high quality pediatric research across the review divisions of CDER and Center for Biologics Evaluation and Research (CBER). The Office of Pediatric Therapeutics in the Office of the Commissioner continues to do excellent work coordinating pediatric efforts across the centers at FDA.

*Question 2.* You mention in your testimony that physicians often don't recognize many of these diseases because they are so rare. What can we do to help physicians to get the best information to diagnosis and care for these patients?

Answer 2. The National Organization for Rare Disorders (NORD) has been a leader for decades in the effort to increase information on the diagnosis and treatment

of rare disorders. More investment into activities like these will be necessary to continue to improve the standard of care. There is much we do not yet know about rare disorders, but we must make sure that what we do know is readily available to patients, families, and providers. We need more outreach to primary and specialty care physicians, medical societies, and medical schools. Newborn screening also plays an important role in the early diagnosis of rare disorders and deserves our continued support.

[Whereupon, at 12:19 p.m., the hearing was adjourned.]

