

**PARTNERS IN PROGRESS RARE DISEASE SUMMIT:  
MORNING PANEL**

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PETER SALTONSTALL: Good morning. I'm Peter Saltonstall, the CEO of NORD. I'd like to welcome you all to this milestone event for NORD...

The goal for today is to set the policy agenda for patients with rare diseases. We at NORD see ourselves as the driving force working to actively bring positive change for patients with rare diseases. Through our discussions today we hope to again be a catalyst for change.

We've invited the leading thought leaders in the country who are here today to help us better understand the strategies and programs that must be put in place to best represent the needs of the 30 million patients with rare diseases.

The policies that NORD advocates over the next few months and years must assure that patients with rare diseases have their interests at the policy table represented and are not left behind as changes occur with healthcare reform.

We're focusing today on innovation and access. We must make sure that innovation in developing new treatments is supported from the bench through the regulatory process at the FDA.

When a disease affects a few hundred or a few thousand people, it can easily be ignored, misunderstood, and we cannot permit that to happen. National policies including regulatory policies must take into account the special needs of patients with rare diseases and must be sufficient to protect the health and well-being of patients without being so burdensome that they limit the development of therapies.

Second, we must make sure that patients with rare diseases have full access to proper diagnosis and proper treatments. Many rare diseases are poorly understood, under diagnosed, and have no approved treatments. Most do not even have dedicated research funding from the government.

So what we hope will emerge from today's session is a clear and concrete policy agenda for patients with rare diseases. We hope to gain the understanding of what specific federal policies especially affect patients with rare diseases – what are the specific policies especially affecting the patients with rare diseases, and what changes do we need to advocate for to ensure innovation and access.

So, as we start today, I want to especially thank Dr. David Kessler, who took time out of his book tour to be here. We're going to also make sure that at lunch we get him no salt, no fat, and make sure that he is able to eat healthy. I would really like to thank David for being here today to help us run this meeting. David is going to introduce the panel members and the commission members.

Tommy Thompson was our first speaker but I don't believe the governor is here yet, so I think we ought to begin, and so I'm going to turn it over to David.

DAVID KESSLER: Thank you very much, Peter, and thanks for the plug on the book. (Laughter.) I very much appreciate the opportunity to be here with all of you.

There is a real commitment – you wouldn't be here unless you really cared, as I think we all do, about people who find themselves at a point in their lives where there are just challenges that seem overwhelming. And that's our focus and that has to be our focus.

I want to acknowledge the leadership both of Peter, the extraordinary opportunity that you give us this today to really help you, the board of NORD, the staff at NORD, to develop the policy agenda for the organization, to help you do that in a time of this very exciting national debate on healthcare reform.

NORD has always taken a central role in leadership. I remember I was a junior Hill staffer when the idea of the orphan drug legislation 25 years ago was raised. And I think, for all of you who've been involved over the last several decades, the progress is very, very real, and to the patient groups, to the agencies, to the Hill, to the industry, the progress is close to historic if you look at what's been accomplished. But we're living in a very different world.

My job is to listen and facilitate. Maybe herd cats is a better way to do it, because there are a host of different avenues we can go down, a host of different roads. Access, innovation, obviously key. How do we continue to push the pipeline? How do we design studies that make sure the outcomes are good for patients? How do we deal with drugs that are today viewed as too expensive both to develop and to pay for? The challenges, in some ways, with all the progress still remain very great.

Everyone should have in their packets is a formal agenda of speakers. We're going to try to keep those speakers on time about nine, 10 minutes, not more.

At the end of the formal speakers, I will ask the audience for a show of hands of how many would like to speak at the podium, and then we'll take about 20 minutes or so and divide that time to make sure that everybody has voice.

Immediately after we've heard from both the speakers and the audience, the members of the Blue Ribbon panel that, Peter, you have assembled, will start off by identifying the key one or two principles or policies that you think should guide NORD over the next period of time that really need to be addressed or that the agency needs to be able to stand for. And then we will work through what we hear and see if we can narrow them down into a couple of key principles, key policies at the end of the day. And there obviously will be work necessary to follow up after this meeting.

It's an extraordinary opportunity and I thank you for it. Governor Thompson is not here. I ask all the panel members to introduce yourself, and then if the Governor is not here, Dr. Woodcock is going to lead off.

BRUCE VLADECK: I'm Bruce Vladeck. I'm currently a senior health policy adviser at Ernst & Young. I spent about five years in Washington in the last decade as administrator of what was then the Health Care Financing Administration. And I'm also a proud trustee of the March of Dimes which has devoted an awful lot of effort the last decade to earlier identification of all kinds of rare diseases in newborns, so an issue close to my heart in a variety of ways.

STEPHEN GROFT: Good morning. I'm Steve Groft, the director of the Office of Rare Diseases Research at the National Institutes of Health.

TIMOTHY COTÉ: Good morning. I'm Tim Coté. I'm the director of the Office of Orphan Products at the Food and Drug Administration. And so, I'm responsible for implementing the Orphan Drug Act which is intertwined in the history of NORD and my office.

FRANK SASINOWSKI: I'm Frank Sasinowski. I'm vice chair of the board of NORD. Abbey Meyers started this organization because of her family involvement with Tourette's. Like the founder of NORD, I too have a son with Tourette's. When I was at FDA, I was the person who was assigned by the Commissioner to help figure out why, in January 1984, one year after enactment, nobody was coming to see Dr. Marion Finkel, the FDA's first director of the Office of Orphan Drugs. And it was my analysis that led to the 1984 and 1985 amendments that helped open up the law and make it the success it has been. Since leaving the agency 22 years ago, I've been helping develop new therapies for people with rare diseases.

WILLIAM SCHULTZ: My name is Bill Schultz. I'm an attorney at the law firm of Zuckerman Spaeder. In the '70s and '80s as a public interest lawyer, I was a little bit involved in the original Orphan Drugs Act. Then for five years I worked on Capitol Hill for Congressman Waxman and was very involved in amendments to the act which we passed unanimously through the House and the Senate only to get vetoed by the first President Bush – a great success. And then I was Dr. Kessler's deputy for policy for four years. And at the end of the Clinton Administration I was deputy assistant attorney general in the Justice Department. But I've been in one way or another involved in these issues throughout my career.

EILEEN OUELLETTE: I'm Eileen Ouellette. I'm a past president of the American Academy of Pediatrics. I'm a pediatric neurologist. I went through the database on Sunday morning because I knew I'd taken care of a number of children over the last 50 years with rare disorders and found that I had had some contact with children with 468 of the rare disorders in your database.

WILLIAM NOVELLI: Good morning. I'm Bill Novelli and up to a few weeks ago, I was the CEO of AARP. And now I'm at the Business School at Georgetown University, working on social enterprise and social responsibility. And I'm working also on healthcare reform, particularly wellness and end of life.

BRUCE DAN: I'm Bruce Dan. My interest has always been in communicating to the medical profession and the public about health conditions. I was a senior editor of the Journal of the American Medical Association, involved in American medical television, helped found WebMD. I now head up NBC's Digital Health Network, where we have both the Patient Channel and the Newborn Channel and about 2,500 hospitals in United States where 24/7 patients learn about the 50 most common diseases. We certainly have an interest of communicating to the public about all diseases and what can be done about them.

DR. KESSLER: Dr. Woodcock, would you be willing to lead off and then we'll break the order of speakers when the Governor arrives? And thank you, Janet. Everyone knows Dr. Woodcock is the director of CDER, has been deputy commissioner, a whole host of roles. How many commissioners have you served?

JANET WOODCOCK: More than my fingers.

DR. KESSLER: Thank you for being here, Janet.

DR. WOODCOCK: Certainly. We were asked to think out of the box here. And many of the thoughts about orphan drugs have to do with some of the difficulties navigating the regulatory pathway. Obviously for mainline drugs, it may cost up to \$1 billion to get a drug onto the market. And that's just not feasible for the kind of drugs that we're talking about here or even for diagnostics or preventives. We have to find different ways.

I was not going to talk about the regulatory hurdles today, because I think other people are going to discuss that. And I think that is a very reasonable policy option, a set of options that are going to have to be considered to see if there are additional things we can do beyond the current, say, subpart H regulations that we have for serious and life threatening diseases and approval on surrogates and so forth. Is there more that could be done there?

What I want to talk about is a proposal to accelerate development of treatments for rare diseases. And this could also apply, I think, to diagnostics and preventives. And I know Dr. Collins is talking this afternoon about how we can accelerate discovery, how we can fill the pipeline up better. But then – okay, we have this great pipeline of potential, wonderful treatments, what do we do? What else can be done to get these to patients?

The drug development model is really changing. And this community may not be aware of this, but there's big change afoot in how drugs are being developed today because the drug blockbuster model that held in the '80s and '90s is really no longer a viable model for a variety of reasons.

And success rate is plummeting for the pharmaceutical industry. They have a productivity crisis where they have much more investment that they're putting in and yet they're failing to get viable treatments out the other end. And nothing like a crisis in a business to focus the mind and to make people more open to alternatives.

There's need for new development models with better predictive capacity. In other words – and I think maybe Rachel will be talking about that -- that's the critical path: how do we actually figure out the winners quicker that yield high-value drugs?

One of the changes that we're seeing – this is what I want to talk about – is that we have an increasing involvement of nonprofit and disease advocacy groups in not just funding basic biomedical research, which they've been doing for four decades at least, but in actually getting involved in the development of drugs for their disease that they're interested in.

So, that is a big change that we're seeing. And we don't know at the moment how successful this is going to be. But early indications seem to show that this focus by the disease advocacy groups and some funding are making a difference in pushing drug development in certain areas toward those desired diseases.

So my thesis that I want to talk about is that the orphan drug community can take advantage of the changes. If you understand the changes that are occurring in the industry, the changes that are occurring in academia, the new opportunities that are being posed, then NORD could potentially take advantage of these changes to really help advance the development of rare diseases.

So what other changes are happening that really make this possible, because this wasn't possible really even a decade or so ago? One of the main ones is the availability of new scientific tools, and I think Dr. Collins will probably talk about this a little, in making drug discovery and drug development more accessible for the academic community.

So, in the last 30 years, it's taken an army, it's taken a huge pharmaceutical company, a biotech company backed by a lot of venture capital to do what needs to get done.

But this is changing somewhat because the scientific tools that we have, the genomics, many other kinds of tools, are making the science more accessible.

And frankly, the recent NIH focus on translational research, I think, is going to be very helpful. The NIH roadmap initiatives and the money they're putting in there as well as the CTSA's, the translational research centers that are being set up around the country, to specifically focus the academic community, and the academic community responds to money because they don't have money of their own, so they respond to money, and they will put their intellectual capital against where they're able to get money. So, these CTSA's are going to provide more infrastructure in academia to do this kind of work because NIH is specifically saying, academia, we reward you for being involved in translational research. And that's a big change.

The difficulties with the current drug development model which I already described make the pharmaceutical firms more willing to consider new development options. And right now, what many of the firms are doing is buying those options in; they might buy a whole small company, purchase its portfolio, but also partnerships and different modified roles.

The pharmaceutical sector has certain competencies that we shouldn't lose in this. They're good at activities such as medicinal chemistry, high-throughput screening, something

called lead optimization, which has to do with the molecule, manufacturing a scale up of drugs, late phase development, and then, of course, marketing and distributing a product.

Academics understand the molecular biology of the target and the pathogenesis of a disease. In other words, for rare diseases somewhere in the United States, for most rare diseases, you have a group of academics who are intensely interested and have devoted their entire life to studying the disease or pathway that's implicated in that disease. And that type of knowledge is priceless.

And academics intend to develop animal and in vitro models to mimic the disease so they can study it in the lab. And they also have relationships with relevant parties, patients, because they're interested in the disease because they have patients with this disease. And also, they have patients in proximity to their laboratories. So the academic communities are a priceless resource, especially for these rare diseases.

There are a lot of other people who can help in this, such as contract research organizations, laboratories, specialty services. And then us regulators, although we're much maligned, actually have developed a greater role in post market safety, and we have a tremendous understanding of how drugs are developed because we look across all drugs.

In Europe, the Europeans have actually put 5 billion euros against something called the Innovative Medicines Initiative where they're tackling very specific problems in drug development, with matching grants between the government and industry and having academic centers perform research projects. They have a Web site for IMI, the Innovative Medicines Initiative, and I think that's a nice example.

The regulators can do things to make development easier. A number of years ago, for example, we put out these two guidances, and actually a regulation, something called "Exploratory IND" guidance. And this allows developers to get into patients quicker with less testing for lower doses, to enable, say, academics in particular to do proof of concept studies in people without having to do this gigantic preclinical workup. And this has been utilized by the academic community.

So, how would you develop therapies better, perhaps more rapidly, for diseases with little commercial interest? How do the nonprofits have a role? Well, we have some examples. And these examples involve, usually, uncommon diseases or the neglected, say tropical diseases—maybe millions of people have these diseases but there's very little commercial return on investment, so it has similar to an orphan status.

And the emerging model is that nonprofit or disease advocacy groups assist in development via partnerships. So they set up partnerships, they assist at various stages in development, and they may be involved in the decision-making or project management of the specific projects, but they don't retain intellectual property. In other words, they're not trying to make a profit out of this. They're trying to get products developed for the disease they're advocating for.

An example is the cancer research at the U.K. Center for Cancer Therapeutics in the Royal Marsden. They have academics there who have developed expertise on specific pathways, and then they bring other expertise to bear on this, and they're actually developing these therapies through early human trials, and then they'll out license them.

These are cancer treatments; however, as we get into the genomic era, and I think they're going to talk about this later today, these cancer treatments may be sub-grouped to the extent that they would actually be eligible as orphan diseases because the pathways identify such small groups of people.

Another example is the Global Alliance for TB Drug Development where academia, industry and advocacy groups got together and are trying to develop TB drugs. And there are additional examples: Harvard is doing a development program and so forth. I'm not going to go into them in great detail, just to say this is a viable model. Its productivity, as far as products on the market, remains to be seen. But certain groups such as the Multiple Myeloma Research Foundation, I think, have seen products they have assisted in moving along all the way through to the market.

So the Orphan Drug Act shows that a relatively modest incentive can have a very large effect on development. We probably wouldn't have had many of these orphan drugs that we have if we hadn't had the Orphan Drug Act and that focus and incentive.

And I think NORD and constituent organizations of NORD could focus more on translational research – that is one option – and create and support industry academia advocacy partnerships around translation of specific therapies or preventives for rare diseases. Or, diagnostics and devices as well, obviously.

What would this look like? Well, you could do fundraising for translation, not just research. That's sort of a no-brainer. That wouldn't require a lot more change in the focus except for what types of investments were done with the money.

Expertise in partnerships: simply brokering these partnerships for the rare diseases.

Locating academic interests and expertise: Where are the sites? Who are the people? I know NORD does some of this now, identify the expertise that is available.

Developing patient registries or networks so that trial subjects are available, this is something the Multiple Myeloma Research Foundation has done, so that there's a ready network of clinical trials that a therapy can be plugged into and rapidly evaluated.

Focus on deliverable translational activities. In other words, not just sort of kumbaya, we're giving money to medical research, but what are the deliverables that we expect? And in some, provide infrastructure for innovations for rare diseases to be translated and tested.

I think that's all. Thank you very much.

(Applause.)

DR. KESSLER: Absolutely brilliant. A speaker who actually listens to the agenda and thinks outside of the box and gives us just a lot to think about. If we can carry forward on that example, it will be a great day. Dr. Woodcock, I'm most appreciative.

We're very honored that Governor – Secretary Tommy Thompson is here. You all in this room know him well, the governor of the state of Wisconsin, secretary (of HHS) from 2001 to 2005, a partner at Akin Gump, a chairman of the AGA Medical Corporation. Governor, we are most appreciative for you being here today. Help us think through these great questions.

TOMMY THOMPSON: Well, David, there couldn't be a better spokesperson and a better convener than you yourself. And I thank you for your introduction but more importantly I thank you for your continued dedication and being involved.

What a fantastic group of individuals you have here on the dais, an absolutely star-studded cast that all you have to do is convince these individuals and have them carry your water up on Capitol Hill and you'll do very well. I thank all of them for what they do and what they stand for.

Janet, it's great to see you again and congratulations for what you do.

Francis Collins, who was a very good friend of mine who has probably done more for personalized medicine than anybody else in the world. And I'm absolutely in your debt, Francis, when I was secretary, for what you did for the Human Genome Project.

Ladies and gentlemen, first off let me say thank you. Thank you for giving me this opportunity to speak to you but more importantly let me say thank you to you for what you stand for.

Winston Churchill said: "We make a living by what we receive. We make a life by what we give."

When I look at this audience and look at the speakers and the dais and the absolute outstanding motivated individuals, I would have to say thank you. You are absolutely what this country needs at this particular time. And NORD is very well represented because of your capabilities, your desire to do what Winston Churchill was talking about and making a life for people that really need your particular help.

And then Margaret Mead said: "Never doubt that a small group of thoughtful, committed citizens can change the world." Indeed, it's the only thing that ever has.

And when I look at this group, the daunting tasks that face you and the patient groups that you are involved with, and the patients you're involved with, I think Margaret Mead said it best: "A small group of individuals very committed can change the way we do things in this country and for patients that need our help a great deal."

I wanted to talk to you today about the best of times and the worst of times for health care. The worst of times is that Medicare, which we heard yesterday makes up 18 percent of the cost of health care and just about 42 percent of the decisions made by insurance company and private insurers all over this country, is on its way to being bankrupt. And we have no individuals really willing to talk about it, willing to change it, willing to make it better, fix it, and it's going to have tremendous problems.

To give you some idea, Medicare right now takes up about 3 percent of the total cost of all of the expenditures in America. In a few years, in the next 50 or 60 years, it will take up 15 percent. And that is almost impossible to maintain.

The unfunded liabilities of Medicare right now today, over the next 75 years is somewhere between \$40 and \$60 trillion. And when you compare that to the gross national product of America which is \$14 trillion and is going broke and nobody in Congress is willing to take on and make the tough decisions, you've got to realize that Medicare has got a very rocky future, and it could affect every single thing that you do and everything we do in health care.

And the problem is that you're going to have to look at how you're going to restructure Medicare in order for it to survive. And nobody wants to do that. And I think the only way that that's going to happen is to have an equal number of Republicans, an equal number of Democrats, scientifically based, hopefully, and medically based to make the tough decisions like we do in closing bases and allowing Congress to vote it up or down. That's the worst of times for Medicare.

The best of times is that a group of individuals decided that they were going to come together and do things necessary to restructure and bring the resources necessary for FDA. And that coalition, which your organizations are prominent members of, have done a fantastic job of being able to come together and convince America and Congress and the President about additional resources for FDA. That's the best of times.

And along with the best of times is that I've never in my life seen the opportunities for changing health care, health care for the better, hopefully, than we have right now.

When you take a look what's taking place right now,— the Senate Finance Committee has been holding hearing with (Sen. Charles) Grassley and (Sen. Max) Baucus for the last 24 months, and they've already submitted a thesis to Congress and to the President of over 100 pages of what they want to accomplish. And you have a bipartisan group meeting every single week in order to change health care.

And then you have Senators Wyden and Bennett, seven Democrats and six Republicans that have been holding hearings. How do we cover every American? How do we do it? That's the best of times, coming together.

And then, the 800-pound gorilla is the fact that Ted Kennedy, who was universally loved by both Republicans and Democrats, wants to accomplish something before he leaves the United

States Senate, and that's a comprehensive healthcare system in which every man, woman and child is covered.

And when you look at the presidential election this past time, when President Barack Obama was in trouble, it was Ted Kennedy that announced his support of all the Kennedys that came out in favor of Barack Obama. For Barack Obama, the change was dramatic. And the support for Barack went up and the Kennedys went all over this country campaigning for Barack Obama to become president of the United States, and he was successful. Barack owes a big debt of gratitude to Ted Kennedy and he wants to make sure that Ted Kennedy gets a healthcare reform package covering every man, woman and child before he leaves the Senate.

And then, on top of that, you have \$634 billion that the president has set aside. And one thing we know for sure is that Congress has never left \$634 billion without spending it. (Laughter.) It's an impossibility. And so, you can absolutely be certain that we're going to have a healthcare system completely transformed over the next 12 months.

I have been saying that for 18 months now that this year, 2009, is going to be the biggest year of transformation of health care. And that's the best of times and that's also the worst of times.

The best of times is that it gives you an opportunity to be very much informed, and advised, and persistent, and adamant about your causes. And the time is now. The Senate and the House will be marking up this bill in June. And we need some champions.

The best of time is if we can find some champions on the Senate Finance Committee and the House to carry on and do what is necessary to rejuvenate, innovate and change the Orphan Drug Act of 1983 and make the necessary changes. This is the time.

And we've already seen massive changes in the healthcare system which is already law. We saw S-CHIP which expanded the healthcare coverage for children by an additional 4 to 11 million children. We've seen the uninsured that have been laid off be covered by an additional 30 some weeks. And we've seen a law passed and funded, called comparative effectiveness.

Comparative effectiveness, ladies and gentlemen, has got the best and also the worst opportunity to change health care in America. And I started out with Medicare and I'm now at comparative effectiveness. And I want to join those lines and have you really understand what can take place.

Medicare, in order to survive, is going to have to have a readjustment or an expansion of taxes or both, big time. Comparative effectiveness is going to determine the kind of treatments. And the people that are going to be making those decisions are the ones that are going to affect your organizations and your patient groups.

The best of times of comparative effectiveness is based not on rationing care but on providing services, medicines and treatments for the individuals that you represent. But when you compare the tremendous cost of Medicare and the fact that it's deeply in debt and you look

at what OMB (Office of Management and Budget), the super god of our society, is going to be talking about, you have to be concerned, like I am, and worried about comparative effectiveness.

Comparative effectiveness can have the biggest change in health care that any of us could ever imagine. It can be good, it can be mediocre, or it could be bad.

And what I'm telling you today is that right now is the most important time for you to be in Washington. And right now is the most important time for your organizations to be involved: first, for the rejuvenation of FDA; secondly, to be involved in Medicare; third, to be involved in comparative effectiveness; and fourth, and most importantly, the transformation of health care that's going to be marked up in June and July that's going to pass and is it going to be passed with provisions that NORD finds acceptable or we're going to be left out.

And that's the best of times and worst of times of health care today. We know it's going to be transformed completely. Now it's up to us, through the FDA coalition, through NORD, to make sure that the Orphan Drug Act and FDA get the necessary help and assistance in order to accomplish their objectives. And hopefully their objectives are going to be our objectives, your objectives, and my objectives to make NORD as strong and as effective as it possibly can be.

Now, we can do this through many different ways but the most important way is to find somebody on Capitol Hill right now, our friends that understand us, and convince them to carry our message to the committees, to the markup, to the conference committee and get it signed into law.

The most effective, most important thing that all of you can do right now is to convince your friends in Congress, your own representatives, of the importance of your cause and have it written into law.

Now we all know that the Orphan Drug Act was a tremendous emancipation for orphan drugs and the opportunity for your patients. And we also saw that after Vioxx, that Congress has taken really a supervisory role over FDA.

And I happen to be a tremendous fan of Janet Woodcock and the people at FDA and what they do, as I'm sure you are too. It's a tough job. But we also know that that agency has been rocked with some real serious problems resource wise, employment wise, and the fact that some members of the United States Senate especially feel that they can do a better job of regulating, and supervising, and approving drugs as some of the experts and scientists in FDA. I know some of you probably don't want to hear this, but the truth of the matter is FDA has got to keep their eyes looking at Capitol Hill and watching what's going on, on a regular basis.

And there is a tremendous temptation to hunker down because you don't want to look up and make a decision on an orphan drug or on any drug that may come back and have Congress say you made a mistake. And we're all humans; we're going to make mistakes, but the truth of the matter is that's the lay of the land today. And we have got to convince Congress that FDA is the gold standard and they should be making these decisions, and we've got to convince FDA – and I think Janet Woodcock understands this better than any of us can – of the importance of

making the right decision but also of taking a look at the statistical significance of a small group, a small cohort, of being able to make a determination on what orphan drugs can be approved, because we know that about 75 to 80 percent of the drugs being given to some of our patients are off label. And we have to make sure that those individuals continue to get those drugs.

We've got to make sure that we can convince pharma and bio to be able to continue to put the research into orphan drugs so that we can accomplish the breakthroughs for our patients that all of us want. That's why we're here. That's why you're here.

And so, ladies and gentlemen, my message is that it is the best of times and worst of times right now for health care in America, and for NORD, and for FDA. And the nice thing about it is that we can change and improve over the course of the next several months. And it's not going to wait until next year when you have your annual conference again. Right now things are moving very rapidly. And they're going to move a lot faster than most people expect. And the healthcare system that we know today is going to be completely transformed over the next 12 months. Now that transformation can be the best of times or can be the worst of times for our group.

The best of times would be to expand the Orphan Drug Act, give FDA the resources it needs and allow FDA to make those correct decisions and encourage FDA to be involved with the orphan drug movement as much as they possibly can be to understand our concerns and approve the drugs, and to be able to expand the tax credits for pharma and bio to be able to do the research necessary for the drugs that we know are out there waiting to happen.

And with Francis Collins and the human genome being able to put the necessary resources in there to expand our personalized medicine, because one thing we've learned from the Human Genome Project is drugs affect people differently. And the more we can personalize medicine, the better off we're going to be to treat our patients and give them the kind of treatment they deserve and need.

So let me finish by encouraging you to be very much involved and to listen to what Teddy Roosevelt said about your group. And I changed this, my favorite quote, to really embody the movement in this room. "It is not the critic who counts, not that man or woman who points out how that strong man or woman might stumble or make a mistake or where the doer of the deeds could have done them better."

We're human, ladies and gentlemen. FDA is human. They have some great scientists, but they need our support. And they're going to make some mistakes, but we need to be involved with them and encourage them that orphan drugs for a small cohort of people is absolutely important to be tried and that we have to also look at approving some drugs and have post surveillance sooner and allow that so the orphan drugs can get to the market faster than they had before. That's a big change but a change that is absolutely needed in FDA.

The credit, ladies and gentlemen, belongs to you, the man or woman who's actually in the arena. You're in that arena. You're here. You're what Teddy Roosevelt called the good citizen. You're involved because you love and revere your patients and want the best for them. You

want to make sure that they get the treatments necessary. Your face is marked by dust, and sweat, and blood. You strive valiantly. Every adversity you're there to try and change it and improve it for the better.

You err. Who doesn't? We're human. We make mistakes day in and day out. We come up short again and again because, ladies and gentlemen, there is no effort without that err and shortcoming. And every drug that FDA approves has the possibility that it won't work and make a mistake. But we also have to realize that without that decision we will not make progress. And we can't be so quick to criticize and support Congress belittling FDA when they do make a decision and it turns out maybe it was not completely 100-percent correct.

But who has actually strived to do the deeds? You're the ones that strive to do those deeds every single day. You know the great enthusiasm when the breakthrough drug comes, you know the great enthusiasm when a new medicine comes out for one of your groups that solves that particular patient's problems, the great devotions that you have to your patients and to your organizations. You spend yourself in that worthy cause to make sure that what you believe in is going to be carried through in Congress.

And who, at the best, knows in the end the triumph of high achievement, and who at the worst, if you do fail, and we will fail occasionally, at least failing while daring that you're going to change the system for the better for NORD and all your 140 organizations, so that your place shall never be with those cold and timid souls who neither know victory nor defeat, those individuals who sit in the backside, the sidelines and criticize you eat grapefruit and suck lemons all day.

I like people like you that believe in yourself, have a smile on your face, are dedicated and passionate about your causes and believe that you can make things better for yourself, your organization, your patients, your community, your state and your country.

So, ladies and gentlemen, may the road always rise to meet you, may the wind be always at your back and may the sun shine warm upon your forehead and the rains fall soft upon your fields. And until we meet again, may God hold you in the palm of His hand.

Thank you very much.

(Applause.)

DR. KESSLER: Governor, thank you very, very much for the charge to all of us and for the dose of reality for the times that we are facing.

Dr. Behrman, who is associate commissioner and director of the Office of Critical Path Programs, if you can follow the Governor and Dr. Woodcock. Thank you, Governor.

RACHEL BEHRMAN: Thank you, David.

The power of collaboration, the power of advocacy, and within the context that every day at the FDA we think about balancing the needs of an individual with the needs of a society, but we can't lose sight of the fact that in the middle there's a small population, and we don't talk about that often. And in a sense, the Orphan Drug Act does talk about that. We discuss that in the proposed expanded access rule which – it's no secret – we hope to finalize very soon. But really we're talking about, where does that small population fit in the niche?

So, first, just a couple of words about the Critical Path Initiative. This initiative was launched, it was conceived of and launched in 2004 by (former FDA Commissioner) Mark McClellan and Janet Woodcock and has made significant progress in that short period of time.

But functionally what it really is the notion, as Janet alluded to, of driving innovation, of transforming the sciences. The question in 2004 that was batted around was why are we spending all this money and not seeing, if you will, product. And I think Janet articulated in a sense the answer is a pipeline problem that we're all talking about, and the hypothesis was that we're working with antiquated science.

So the initiative is all about developing the sciences, as Janet mentioned, the toolkit. It's not about a particular product. And very much what we've learned in the last five years, as we've evolved in this initiative and learned the power of it, is that it's really very much about the collaborative efforts. If one gets everyone in the room – and I'm going to frame this with two examples, one from about 20 years ago and one current – if we get everyone in the room sharing thoughts, and information, and data, we go a lot further than we ever would have at home or alone in our silos. And, of course, that can't be done though without a similar effort in terms of regulatory modernization, and obviously, bioinformatics. If we can't access the data, we cannot use it. And that is a terrible shame.

We have a huge breadth of collaborations and a common theme is we seek a nonprofit neutral host to help us. There are many things that we, as a regulatory agency, can't do but others can, and can help us do it and then we can collaborate. And so, we very much look forward to having the Reagan-Udall (Foundation) built this year, having Reagan-Udall up and running and able to partner with us in some of the things that are very difficult for us to do alone.

Just to mention a couple, obviously there's the standards efforts, our effort to modernize adverse event reporting, and Sentinel. The mandated effort is very welcome to better utilize the data that are already out there on what's going on with these products in the marketplace and assuring that we know as much as we can as quickly as we can. And we know that when a product is released in the market we don't know everything and we have to be able to pick up information and utilize information that's already out there.

The first Critical Path initiative in my opinion was the development of antiretroviral drugs. This was in the late '80s. Obviously there was no Critical Path initiative but there was a clear public health emergency and to some it was very frightening. Business as usual was clearly not an option, and this is something David (Kessler) knows very well since he was leading the charge of the agency for much of this.

And by getting everyone in the room, by hearing all sectors, by understanding the limitations and the strengths, we were able to not just dramatically accelerate the pace but probably get to better places, more effective therapies and certainly meet the need of the patients much better than we would have alone.

And so this is when it works. And this is when we have strong advocates by our side, well-educated, well-versed in the science, and helping figure out what it is exactly that the patients need out there.

We also having, quite frankly, the drug developers. Janet presents an interesting hypothesis about where drug development can and should occur in this time in our history – but whoever is developing the drug – or the private medical products, they have to be in the room as well because they have certain constraints.

And in addition, it's collaboration that allow that discussion to occur. The way we were able to approve the second antiretroviral, DDI, on the basis of 91 patients was that we were able to, for the first and I think only time in history, look into three ongoing collaborative trials sponsored by the NIH, and we were able to do that because very early on, we were in the room with the NIH when we realized that, in fact, this could be made to happen.

Similarly, when it became clear we could not do large outcome trials waiting for patients to die or develop pneumocystis pneumonia, very much it was the collaborative forums that this time was hosted in part by then Vice President Gore's reinventing sort of initiatives, getting everyone in the room and us realizing that, in fact, even if patients said they would enter these trials, they weren't going to stay on these trials, or if they stayed on the trials, they were going to be getting other drugs from elsewhere as they watched the load of the virus in their blood go up. So then we were aware what changes had to be made.

The final point I'd like to make on this is that we did that within the existing regulatory framework. DDI, which was truly the first accelerated approval, was approved before there was an accelerated approval regulation. The first treatment IND, at least for HIV, for AZT was before there was a treatment IND regulation. So we make the regulations work. Sometimes we then go back and tinker, but we make the regulations work.

I put the anti-CMV drug example up just as a word of caution because of the need to balance the needs of the individual, the needs of the society and those in the middle. As one who was in (medical) practice at that time, people were losing their sight and the companies were helping us, the FDA was helping us. We were using a lot of acyclovir to prevent that, but when it came time to try to improve the drug, it was very, very difficult. We had very little evidence that it in fact worked, what the dose should be, what the schedule should be. That reverberated a number of years later when we wanted to go to an oral formulation. So we have to do this cautiously. We have to do it with our eyes open, and we have to do it knowing that ultimately, the safest, most effective mode of access is in fact marketing.

I want to contrast that with something we're working on right now which is the DAPT trial, dual anti-platelet therapy trial. There's a real serious question facing cardiologists in this

country: what to do with patients who've had a drug-eluting stent, that's a stent that's coated with an anti-platelet agent, one year following implantation. Do they take them off dual anti-platelet therapy, clopidogrel? What do they do if the patient needs a colonoscopy? What do they do if the patient needs emergency surgery? It's simply not known. And it's a huge problem. Although it's not as dramatic perhaps as a new virus, it's threatening millions of lives potentially in this country, and we don't want a couple of years from now to find out that by guessing we were doing the wrong thing.

Now, in the past, what we might have done is go to each device company and say you've got to figure this out. Your product is going to be misbranded if we don't know. But instead we got all involved device companies and drug companies in the room and painstakingly have been forging a collaboration.

And the trial is going to go forward, and the first patient is going to be entered on October 1. This will happen, but this has been really hard because what was missing? Advocacy.

Amazingly, given the prevalence of heart disease in this country there really isn't an advocacy community. Now, again, this is not a small population but there's a point here. In this instance, FDA has had to function as the advocate and that is a very uncomfortable role for us. We are used to being scientific advocates, public health advocates, regulatory advocates, but it's a fine line when we're working with the regulated industry and we're functioning as the advocates.

So, again, we look forward to other options in the future because we feel that we are setting precedent here. We're making history in terms of how to get things done. We want to do this again and again and again. It is more efficient. We get a better answer, we get it faster, and we save a lot of money in doing it. Instead of running six separate trials, we run one large trial. So, again, the power of advocacy.

So, what's new, what's different, what can be done? Well, Critical Path is going to help, is helping, and is going to help medical product development, drug development in all arenas, in all sectors. It will give us new tools. We're concentrating on clinical trial modernization. We're developing biomarkers looking at new science. We're incubating. It's cutting edge.

But what might that look like for NORD? I'd like to leave you with a challenge not so dissimilar to what you just heard. We stand ready to partner. We stand ready to work. But help us prioritize. It's true that we have not only many critics but we have many, many forces acting upon us, pushing us in a variety of different directions, advocating very strongly for their programs, their populations, their agenda. Help us to figure out how we can best serve the community that you represent because that is what we're here to do. We're eager to do it. We just need you to help us. Thank you.

(Applause.)

DR. KESSLER: Thanks very much, Dr. Behrman. That was terrific following on Dr. Woodcock and the Governor's remarks.

Dr. Jenkins, could we kindly ask you to take the podium? Everyone knows that John Jenkins is director of the Office of New Drugs at CDER.

JOHN JENKINS: Thank you, Dr. Kessler. And good morning, everyone. Just so everyone understands, the Office of New Drugs is in CDER. I oversee the 17 new drug reviewing divisions that are in therapeutic areas, so they oversee drugs in the various therapeutic areas be it pulmonary disease, cancer, heart disease, et cetera. We're the final common pathway for drugs and therapeutically biologics to come through the approval process.

I want to talk a bit today about the drug approval standards so you can understand what the standards are and also explain some of the flexibilities that we've been able to utilize to bring rare disease drugs to the marketplace over the past 20 years or so.

Janet started us out by talking about thinking out of the box. And I think you can think about the drug approval standards to some degree as being the box. That's what we have to fit things through to get them through the regulatory process. But I think and hope that you will see that we've used a lot of innovative thinking over the years to think a bit out of the box as we bring things through that box.

I wanted to just start out with a bit of a rhetorical question: What is the best means of access to safe and effective drugs for patients with rare diseases? And the answer is FDA approval of an NDA or a BLA for that drug. It may seem self-evident, but I think it helps to focus all of our thinking that we can have innovation, we can have advocacy, we can have great strides in research, but the bottom line is what our patients need is to have those drugs approved so they can go to their doctor and have ready access to them. Expanded access is great but approval is the best access we can offer to patients with rare diseases.

Let's talk a bit about the approval standard in drugs. I put on the top of the slide that the approval standard is the same for all drugs. So the statutory standard doesn't differentiate between drugs for rare diseases, or drugs from small companies, or drugs from big companies. The statutory standard is the same.

I want to walk you through exactly what the standard is so you'll have that as a baseline.

The first part of the standard is substantial evidence of effectiveness. This is an area where we've been able to exercise a great deal of flexibility. In 1998, we issued a guidance called "Providing Clinical Evidence for Effectiveness for Human Drug and Biological Products." It's available on our Web site. We lay out in that guidance ways that we can be flexible in getting to a demonstration of substantial evidence of effectiveness that may not be the traditional large, randomized multi-center control clinic trials that we usually think of when we're thinking about the blockbuster model that Janet talked about earlier.

The second component under the statutory standard is demonstration of safety. And this is a bit of a misnomer in some ways because there is no such thing as a safe drug, or if your drug

is totally safe, it probably doesn't work, is what I learned in medical school. But again, an area where we can apply flexibility, and I'll talk about this more in a second.

And then, finally, an area that a lot of people don't pay much attention to outside of the FDA but it's critically important because it's one that we all take for granted, and that's that the products that we're taking are of high quality.

So demonstration of effectiveness, safety and quality are the real three-legged stool of the drug approval standard for all drugs.

When you put all that into the mixture, though, what we do at FDA every day all the way through the drug development process and during the approval process is we have to make decisions and judgments based on a balance of the benefits of the drug and the risk of the drug.

When we make those decisions for approval, we're making the decisions on a population basis, so a population of patients for a given indication. The decisions that have to be made at the bedside or in the office are individual patient decisions.

So keep in mind, FDA makes population level risk-benefit decisions; doctors then need to take that information that we've generated through the approval process and through the labeling to make individualized decisions for their patients.

These benefit-risk findings occur on what I call a sliding scale. I may be dating myself a bit here as a physician. I don't know how many people remember sliding scale insulin. But sliding scale to me means that you can apply different relationships for benefit and risk and what's acceptable depending upon certain characteristics of the disease, the patient population, the available therapies, and the nature and the frequency of the adverse events.

Governor Thompson talked earlier about criticism of the FDA. When you talk about diseases that have no available therapy or are serious or life threatening and people are looking for new therapeutic options, the criticism we receive is not that we're too fast, it's that we're too slow.

So that helps to illustrate the spectrum of benefit-risk. For serious diseases life threatening diseases with no available therapy, patients, doctors and society are very willing to take significant risk for the possibility of benefit. That's very different than the other end of the scale of, say, a drug to treat allergic rhinitis. There are a lot of drugs available. It's not a serious or life threatening condition. The standard for a benefit-risk balance there is very different.

Now, we're from the government and we're here to help. And I mean that seriously because we have shown a lot of flexibility in rare diseases over the last 25 years under the Orphan Drug Act to get drugs approved.

We provide a lot of advice. Dr. Woodcock mentioned we have the luxury of seeing everyone's drug development program. So, you as an advocate or a company may see only one

or two; we see everyone's drug development program, and we translate that into advice that we can offer about how to most effectively and efficiently develop the drug.

We do that through formal guidance documents. We do it through meetings. We have over 2,000 meetings a year with industry to discuss drug development programs. We do special protocol assessments, et cetera. We have streamlined procedures that have been put in place over the years such as Subpart E, the fast track program, rolling review and priority review to try to speed up the process for truly innovative drugs.

We have flexible approval pathways. Dr. Kessler was at the agency when the accelerated approval regulations were put into place. This allows us to approve a drug based on a surrogate end point that's reasonably likely to predict clinical benefit and then allow us for the actual demonstration and verification of that clinical benefit to occur later after approval. It's been a very successful program.

And then finally, we do have access programs. While I started it out by saying the best access is approval, we recognize that sometimes while the approval process is going forward, we need to have access so patients can get those investigational drugs. We can do that through emergency INDs; we can do that for treatment INDs.

So, in closing, I just want to emphasize that we at CDER are committed to working with you as partners to facilitate development and approval of new drugs for the treatment of rare diseases. And I think as we work together, we can leverage the emerging science that Dr. Woodcock and Dr. Behrman talked about to build on their track record of success over the last 25 years. So I'll stop there. Thank you.

(Applause.)

DR. KESSLER: Thanks so much, Dr. Jenkins.

Dr. Schultz, can I ask you if you'd be so kind to talk from CDRH's medical device perspective? Thank you, sir.

DANIEL SCHULTZ: Good morning. My name is Dan Schultz. I run the Center for Devices and Radiological Health at FDA. And I know a lot of the focus here has been on drugs, but we're trying to sort of shift that nomenclature and start talking about medical products. And I think Janet has been a champion of that.

I'm going to talk to you a little bit about how we might work together, and I think there's an understanding that there has been an increasing importance in the area of medical devices. There's a lot of new technologies to serve large populations and small populations. And clearly, when we talk about personalized medicine, a big part of personalized medicine is having good diagnostics. So I think that this is an area that perhaps you don't know as much about but perhaps you should. And I'll hopefully try to provide some of that information for you.

But the first question I want to ask is: did everybody eat their Cheerios this morning? (Laughter.) Because if you had, you can go out and eat whatever you want because your heart will be protected. Okay.

It's really nothing new to us in devices to look at the dilemma that we face between trying to make sure that products are available for individual patients and wanting to be sure that in fact we're doing a good job protecting public health and making sure that there is adequate data on both safety and effectiveness.

This is the push and pull and it's what we do when we go to work in the morning, these are the kinds of decisions that we have to make every single day.

The device regulation scheme is a little bit different from drugs, recognizing the fact that we deal with a group of products that have very, very, very different risk profiles, starting with things like gloves and tongue depressors and going all the way up to artificial hearts. So, we're used to this idea of looking at risk and trying to adjust the regulatory paradigm to meet that risk.

I'm not going to bore you with all the different classifications, but we have class one, class two, class three, and you can see the different products that tend to fall into those different levels.

Congress has also provided us over the course of the last few years with some additional tools. And one of those tools is what's called the de novo process whereby even newer technologies can go to market through a less stringent pathway if they don't pose a significantly high risk. That's the so-called de novo process.

And then finally, one of the things that I know is of interest to this group is Humanitarian Device Exemption or so-called HDE, for which we partner very closely with the Office of Orphan Products.

Working together, the Office of Orphan Products and CDRH, when a company wants to go through the HDE process, it's basically a two-pronged approach. One, going to the Office of Orphan Products for their evaluation in terms of the population being served, the size of the population; and the second, coming to us for the scientific review of the product with respect to safety. And in this case, we're talking not safety and effectiveness but safety and probable benefit recognizing that there is a different standard.

There's an acknowledgement that for rare diseases, there may not be enough patients to generate the same amount of clinical data as for more common condition. And I mentioned earlier that this is very much a collaborative program and that a big part of the program is actually outreach and educating people, working with other government agencies to try to identify these products and make sure that we communicate that this pathway does in fact exist.

So here are the two parts of the program: humanitarian use designation to encourage development of medical devices for rare diseases. FDA will approve such devices if manufacturers demonstrate safety and probable benefit. A medical device intended to benefit

patients in the diagnostics, treatment of a disease that affects or is manifests in fewer than 4,000 patients per year in the United States.

So how does this work? Well, since October 1996, 49 devices have been approved as HDEs. In calendar year 2008, the Office of Orphan Products granted eight new humanitarian use designations. In fiscal year 2008, CDRH approved two HDEs, and I'm going to come back to that, and 32 HDE supplements. So this is where, the supplement is where changes have been made to the product and these are sort of expansions or extensions of what was originally approved.

So far in fiscal year 2009, actually things are looking up a little bit, we've approved four more humanitarian device exemptions. They span a wide variety of areas: One is for obsessive-compulsive disorder; one is an IBV valve that's used in patients with severe emphysema; the third is an orthopedic device and a right ventricular assist device to be used in cardiology.

There's also a grant system, and I suspect that that's going to be discussed later so I'm not going to go into that, but there is a way to go through the Office of Orphan Products to get grants to do research on a number of device related topics related to small populations. And again, here are some examples of research funding that has been put out in order to allow some of this research to go forward.

And in PDUFA, the most recent legislation, there was actually a specific piece of legislation authorizing FDA to spend \$2 million looking at ways to enhance the development of devices related to pediatrics. In figuring out how to actually implement this, it was decided that that program would be actually implemented and run by the Office of Orphan Products, I think for good reason. Since we actually end up reviewing a lot of products, it seemed that there needed to be some separation there. So we're very happy to have the program run out of the Office of Orphan Products, and we will collaborate with them, have already started collaborating with them to make sure that we can help review some of these submissions.

But the idea being very clearly, pediatrics, at least in our world, in medical devices, is very clearly an underserved population. I speak to pediatricians. I actually have a background in pediatric surgery so I can tell you first hand many times we end up jerry-rigging devices that were really designed for adults to try to make them useful for pediatric population. And this is an area that really needs some additional focus, and fortunately, I think that was recognized in the most recent legislation. So as people have said before, there is hope when there's a focused effort. And the pediatric groups have actually been very, very active in lobbying to place more attention on pediatric devices.

Section 305 enables us to facilitate the development, production, and distribution of medical devices by encouraging innovation and connecting qualified individuals with pediatric device ideas with potential manufacturers; mentoring and managing device projects through the development process; connecting innovators and physicians to existing federal, non-federal resources; assessing the scientific and medical merit of proposed pediatric device projects; providing assistance, as needed, on business development, personnel training and prototype development, post-market needs, and other activities. So that's all good.

Let me provide a little cautionary note of something that I think is important and it's something that I think this audience needs to be paying attention to.

I mentioned earlier that diagnostics are increasingly being recognized as an important part of the medical system. And if you talk about personalized care, really it all starts with knowing what you're treating and knowing who the patient is and what their disease is, and now we have some really good tools to be able to get us there.

We put out a draft guidance some time ago on a topic called IVDMA. And this is a little cartoon showing what that means. Basically, you look at an individual patient, you take a number of samples, multiple tests are run, and then those samples go through some type of proprietary algorithm which then leads to a score that may tell you that you have cancer or don't have cancer, that you have Alzheimer's or don't have Alzheimer's, that a certain drug or a certain therapeutic regimen may or may not be appropriate for you as an individual patient. And that's a good thing.

This kind of new diagnostic test actually offers a great deal of promise in leading to better healthcare choices, better drug discovery and a whole variety of things.

We've gotten a lot of pushback on this particular guidance because many of these tests are developed in laboratories, and they're developed without having to go through a formal review process at FDA. And there are a lot of people that would like to see it stay that way.

We don't think that that's a particularly good idea, quite frankly. These tests are very difficult to develop. And we have many examples of where that hasn't happened.

One of the reasons for opposing this type of regulation is that it would slow down the development of these tests specifically for rare diseases. And if you're interested in this, I'd like you to go back and look at the draft guidance that's out there and look for the section that specifically talks about rare diseases which says FDA will continue enforcement discretion for laboratory-developed IVDMA's intended for rare disease testing.

So we have made it very, very clear, we're not talking about rare diseases. We're talking about exercising enforcement over tests for things like breast cancer, ovarian cancer and Alzheimer's disease. Rare diseases are not part of this regulatory process. So, "don't be used" is, I guess, the message there.

Final thoughts. We are certainly committed to providing all patient populations with access to safe and effective devices. As I've tried to show you in a very short period of time, we have a lot of mechanisms and a lot of flexibility. Sometimes our box has actually been called either a balloon or a sieve depending on who the commenter is. So we're very able to sort of modify our approach in different ways in order to treat different risk profiles.

We would like to see sponsors take full advantage of all existing mechanisms. I presented you with some numbers in terms of the number of HDEs that we've seen, and I don't think, quite

frankly, that we're there yet in terms of people knowing that this process exists and that we are anxious and willing to work with manufacturers and with sponsors of various types and interest groups to try to see if this mechanism could be used more fully.

We're certainly open to new ideas in terms of science policy and regulatory programs. We are now, we always have been and we will be in the future. And we are very, very interested in improved collaboration with NORD and other interested parties and ways to achieve our mutual goals. We've already talked a little bit about the need for some specific follow up when it comes to what's going on in the Center for Devices and I'm hopeful that that will happen.

An example of how this can work: I have to leave here this afternoon because we have a meeting with the Juvenile Diabetes Foundation on one of the Critical Path projects that Rachel was talking about, the idea to be able to develop an artificial pancreas for people with type one diabetes.

And that organization, as you probably are aware, has been very, very focused on this effort and we, in turn, have responded by setting up quarterly meetings – and I can't promise everybody quarterly meetings – but we've basically set our quarterly meetings with the organization. They have a number of early feasibility studies that they're running and that they're supporting to try to sort of push this process ahead. And we've set up time to work with them individually to try to make sure that there are no unnecessary regulatory roadblocks. So that type of thing is available and something that we like to do.

We tend to take some ownership and pride when these new technologies make it to market and actually start helping patients, so please take advantage of that. Thank you very much.

(Applause.)

DR. KESSLER: Sure. Dr. Woodcock.

DR. WOODCOCK: Just one comment. The juvenile diabetes example that Dan just mentioned is another example, I think, of where a disease-focused group has really concentrated on the translational research necessary and brought together all the partners. And, of course, again, we don't know if this would be successful or not, but it's certainly moving the ball down the field.

DR. KESSLER: I'm struck by the thread that's running thorough all of your presentations because you really are looking for the entities to collaborate with you, disease focused, and thinking through that is a very important challenge.

Dr. Yetter, associate director of review management from CBER. Thank you, sir, for being here.

ROBERT YETTER: I'm happy to be here this morning and it's an honor to participate in this forum.

You've already heard from Dr. Jenkins, from Dr. Woodcock, from Dr. Behrman about some of the things. I'm not going to stress too much some of the procedures that we go through. But I do want to make it clear to everyone that in CBER, as in the rest of the FDA, we are interested in fostering the development of products for rare diseases. We will do everything in our power to do so.

Some of the things that we do include public discussions of evidence that can support licensure of orphan products in order to foster their development. We advocate strongly the early involvement of the Office of Orphan Products development during the IND process, in some cases even before the IND process begins.

We are very interested in working with those people who are coming forward with these innovative things to deal with rare diseases. For instance, our Office of Cellular Tissue and Gene Therapies has a process for not just pre-IND meetings, but what they call pre-pre-IND meetings in order to be able to start at the very earliest stages to facilitate the process.

We will and we have approved treatment INDs to run concurrent with IND studies because, as has been said, while the best thing is an approval, you still want to make these technologies available. We use all of the available tools that we have for streamlining review processes, accelerated approval with surrogates, priority reviews and particularly use of post-market surveillance to further study safety and efficacy when we're dealing with small populations.

We also participate in international collaborations to foster these developments. We're an active participant with the FDA/EMA advanced medicinal therapy cluster. It used to work. It still does.

Now, I myself come from the vaccines field. When people look at biologics, they think of perhaps a vaccines trial, where the randomized, blinded study with multiple thousands in each arm is not uncommon.

However, we understand that for these types of studies, for these kinds of products, we have to have flexibility. As John told you, the standard itself does not change, but how we interpret that standard has to be tailored to the product and the population in which it is being used.

We do use historical controls when that's possible and prudent. Sequential trials are not uncommon. This usually involves early stopping rules in case of strong negative or positive information. We use adaptive trials in which during the course of the study, treatment regimens, dosing schedules, and so on can be varied. And also crossover trials in which the subject himself can serve as his own control.

We also deal with study designs for very rare diseases – what we tend to call ultra-orphans. In fact, there are cases where it really is not feasible to consider a normal Phase II or III clinical efficacy study. An example of this would be anti-venom for coral snake bite. Coral

snake bite is fatal. You really can't do a clinical trial the way you normally would think of one. (Laughter.)

Fortunately, through the good offices of the National Institutes of Health's Office of Rare Diseases, a public workshop was held in which we could discuss the state of the data, the data that might be needed, economic aspects of the development of a product, and regulatory challenges.

We considered the animal rule. For those of you who are not familiar with this, the animal rule allows us to base an approval on data not generated in humans, but in animals when it is not ethical to generate data in humans. This laid the foundation, the groundwork if you will, for continuing discussions to identify potential pathways to an approved product and the sponsor to develop that product.

Another example would be the problem surrounding designing a pivotal trial when blinding is not feasible. The very fact of treatment is obvious. And in fact, in many cases, patients are not willing to enter a randomized trial because they are not willing to take the risk of being assigned to a control group.

Fortunately, in a case such as we have with transplantation of cells, there is potentially a large treatment effect and that allows you to use a smaller population of subjects with dual primary endpoints to reach a significant conclusion – to allow us to balance risk and benefit.

We've been talking about what you can do. I'd like to talk a little bit about what we are doing, have been doing. Some of the rare disorders that we deal with are clotting disorders. They're handled in our Office of Blood. An example would be protein C concentrate, which was approved a couple of years ago. It was approved under a priority review. The approval was actually based on data from an open label, nonrandomized, historically controlled study in 18 subjects. This allowed us to develop what we believed to be sufficient efficacy data. We are extending the safety data which is being collected post-marketing by a registry, one of the tools that we can use to assure that the decisions that we make are valid and can stand the test of time.

Another example would be an approval that happened just a few months ago for fibrinogen concentrate. This was accelerated approval and it was based on data from pharmacokinetics and the surrogate efficacy endpoint in 15 subjects with afibrinogenemia. A Phase IV study is ongoing to evaluate the clinical efficacy and also to extend safety data.

Recombinant antithrombin III, also recently approved under a priority review. This is a product that's actually made in genetically engineered goats. Again, approval on data from two efficacy studies, total N of 35 compared to historical data for patients treated with plasma derived antithrombin III. Additional safety data, again, is being obtained by a post-marketing registry.

Again, I want to stress our willingness – and this is not just CBER's willingness. This is the agency's willingness to work with advocacy communities, to work with sponsors to develop these products which are necessary to treat rare diseases. We are more than willing to look at

innovative ways to demonstrate the safety and efficacy of these products. We encourage international cooperation in product development. We stand ready to do what it takes to get this job done.

This is what we're doing now. What else might we do? We heard some very interesting proposals from Dr. Woodcock this morning and I would say that these are the sorts of things that we really need to be considering.

One last point. As we move further and further towards personalized medicine, which is something that we look at particularly in gene therapies, we need to be cognizant that not only are we going to have to be flexible in how we look at demonstrations of safety and efficacy, we're also going to have to be flexible about how we look at production and ongoing safety so that we can assure access to the product once it's approved.

Thank you.

(Applause.)

DR. KESSLER: Thank you very much, Dr. Yetter.

No individual has more led the current era of modern medicine than Francis Collins. First, let's see if I can get the genes that you've been instrumental in the list. If I'm right, it's cystic fibrosis, neurofibromatosis, Huntington's, diabetes, and a form of progeria is on my list.

FRANCIS COLLINS: That's good enough.

DR. KESSLER: And, in full disclosure for the plug, a New York Times best selling author, also presidential Medal of Freedom. Francis, I know you have thought mightily about this. You led the modern era in the Human Genome Institute for 15 years. Help us think this through.

DR. COLLINS: Well, thanks, David, for such kind introduction. It is really a treat to be here at this meeting. And I want to thank NORD for organizing such a thoughtful gathering – summit. And Peter Saltonstall's especially for the leadership of NORD and for bringing us all here together to talk about these critically important issues.

I'm going to focus particularly on areas that Janet Woodcock introduced in her wonderful presentation this morning, less so, therefore, on the FDA issues which we've heard outlined quite nicely by leaders from FDA. And I must say their enthusiasm for thinking boldly about how to handle applications for therapeutics for rare disease were welcome words indeed, and I think we all look forward to seeing how that plays out as we have hopefully a larger and larger number of opportunities for new therapeutics to come forward and to be looked at by FDA.

So my focus is really going to be, how do we feed that pipeline. I think Janet pointed out that there's a real crisis at the present time in terms of the development of new therapeutics.

But there's also an opportunity and a particularly strong opportunity now scientifically because of what we're learning about the causes of rare disease, and also what we're learning about the pipeline for developing therapeutics and ways to engage the academic community in a fashion that hasn't really been the case before, in which I think the academic community is hungry to begin to be a broader participant in this but needs some tools, some support.

And clearly, there's also an opportunity here for partnering with foundations, with patient advocacy groups, especially for rare diseases where it may not be so easy to line up thousands of patients for a clinical trial. How do we make sure that we're paying attention to that part?

So what I want to talk about is a potential novel partnership model between public and private, and by that, I mean the government-supported academic research through NIH, as well as private foundations that are interested in specific diseases, as well as FDA oversight, and as well as bio and pharma who are going to play a critical role here.

My bottom line is going to be perhaps we can come up with a model which de-risks these kinds of projects in a way that makes them more attractive for commercial development, not in any way superseding what the private sector does so well, which is to get drugs into patients effectively, but actually makes a project which may otherwise seem commercially not viable because of the limited market size begun to be more appealing. And that's what I want to talk about.

To get there, we have to go through the steps involved in drug development, and I will talk specifically about small molecules, but some of the same arguments can apply to biologics, and to see where the pieces are that already in place to stimulate a more effective pipeline, but also to point out where they're not in place – a series of three brick walls that I want to highlight that, I think, we could actually knock down.

I come before you this morning as an unemployed geneticist – (laughter) – but as someone who's had a great time over the last few months talking with other leaders about this new model, and many other people involved in this, including Peter, can no doubt share more about it in the course of today if there is interest.

I think the statistics here are familiar to this group, something like 7,000 diseases affecting humankind, only a very small fraction of those common enough to support commercial development.

And while we're here particularly to talk about rare diseases, I would say that there are also other diseases that are not so rare that are neglected. The rare disease, also known as orphan diseases, something like 6,000 of them, fewer than 200 having any therapy currently available, cumulated prevalence – I heard 30 million today. I thought it was 25. It's going up and we need to do something about that. Most of these are single gene disorders. And with recent discoveries, of course much of this coming from the genome project identifying the specific molecular basis of these conditions, and therefore, opening an opportunity for therapeutics which just wasn't there before because we now have a target to go after. Many examples could be cited.

I'm not going to say much about it this morning, but I do think we should all notice that there's a possible collaborative opportunity here between rare diseases and neglected diseases of the developing world which are not so rare, but that also present serious barriers as far as commercial opportunity, and where it is also scientifically something that could be done because of the advances in genomics with many of these infectious conditions being understood now much more in detail because of the ability to sequence the genomes of the host and the particular pathogen.

So let's go through the current drug development paradigm and see whether it fits in this situation. You start with the ability to identify a target, which depends of course upon understanding the disease well enough to know what the Achilles' heel might be. So that's basic science.

Then if you are planning to move this in the direction of therapeutics, you would want to develop an assay so that you could screen a very large library of potential therapeutic compounds and identify those that might have some promise, which means you've got to take what you've learned about that disease and move it into something that can be screened at high throughput, preferably in a 1536-well plate so that you could look at hundreds of thousands of compounds and figure out where in this mix of shapes is something that might have positive benefit for the disease. That means you need a high-throughput facility to do that kind of screening that could handle that kind of throughput at very high quality.

If you are fortunate, after going through that, to get some compounds that look promising, many people naively think you're done when in fact that's really where the hard part starts because those compounds, in general, do not have the appropriate properties of sensitivity, or specificity, or non-toxicity, and so, a long and involved and very expensive and failure prone step occurs here, this so-called preclinical step where you're trying to iterate your original findings to identify a compound that has the right properties, rather like a Rubik's cube where every time you make one change, you realize you've screwed up something else. And so there's a lot of medicinal chemistry necessary. And a lot of biology here. And this is often where for rare diseases things get hung up because this is risky and expensive.

If you managed to get that part done, and I'm just going to briefly touch on the regulatory part here, then you're ready for your IND and if all goes well, you go into your Phase I, II or III trials. But of course, you can't do those and get FDA approval unless you have patients.

And I want to particularly mention that, because for rare diseases, all too often, maybe that part wasn't prepared for. So you get to the point where you have a promising compound and then realize, oh, my gosh, where's the cohort of patients that we would like to study? What's the natural history of this disease anyway? And what kind of biomarkers are available to be able to use these clinical endpoints?

So that's the paradigm, a familiar one. And who does these paths work for rare diseases and what parts of it are already in place?

Well, I want to tell you that, in fact, one part of this, which was not there four or five years ago, is, thanks to the NIH Roadmap and to a very bold set of investments that have been made, and that is the high-throughput screening capabilities – as one example up here in Rockville (Maryland), the NIH Chemical Genomics Center, founded 2004, now has 65 scientists there who come from a variety of different companies.

As you can see here (on the slide), this is basically a list of the companies from which those scientists have been recruited, mostly experienced in the private sector, lots of collaborations, and focused specifically on rare and neglected diseases. And in their screening capabilities, they screen all known compounds that are approved in case you get lucky and find something that has activity against your rare disease that allows you to basically leapfrog over many other steps in order to try to get something that could go into a clinical trial.

This is one of four such large scale screening centers. The NCGC can screen 300,000 compounds in the space of about 48 hours, with each compound being tested at seven different concentrations so that you have a very good sense of what is a true positive and what's a false positive. And in fact, with a well-designed assay, it is usual that you get several hits from this that are promising start points toward therapeutics.

This is available to academic investigators who wish to take advantage of it. This and the other three such centers receive applications from investigators who designed an assay which then goes to peer review, and if it passes that as having appropriate properties, it gets run through the center, and candidate probes are developed. There is some optimization capabilities here using medicinal chemistry to get a compound that is perhaps more potent and certainly soluble.

And so, you can circle through this a couple of times. And then, ultimately, the compound goes back to the investigator and all the information goes in a public database called PubChem, which has been another revolution in this business as having gthis a public database that anybody can go and look at and actually compute on.

This particular network has now run through more than 100 projects. There are more than 30 publications that have come out of this of new discoveries of compounds that show promise. Just as an example, of some of the diseases that one in Rockville has been studying, the NCGC has made early strides on the disease you see here (on the slide), quite a number of them of interest to this audience including rare and neglected diseases.

As just one example, for Gaucher Disease which, of course, does have a biologic therapy but the idea of having a small molecule would appeal to a lot of people because of the convenience and perhaps the reduced expense.

And so, this publication, PNAS, revealed doing a careful assay in the collaboration with an experienced investigator, Ellen Sidransky, who knows a lot about the disease, and coming up with a compound that appears to stabilize the protein in the most common mutation seen in 370S (sp), and therefore, has some promise as an oral therapeutic for this disease.

But again, let me emphasize this is a long way from being ready for a clinical trial because you have that preclinical stage that then comes ahead.

So looking at this diagram again, I think it's fair to say we have some capabilities. The target discovery is basically what academia is doing anyway, although I think many academic investigators don't necessarily think of their research as target discovery. It is. When you're finding the genetic basis of a rare disease, you are identifying a target.

We have this screening capability now present already paid for as part of the NIH Roadmap, already being used for rare diseases to some extent, but could be used much more if there was a groundswell of opportunity to provide assays to those screening centers by investigators who understand the diseases.

And I think it's fair to say that when it comes to the Phase I, II and III trials, if you've reached the point at that juncture where you have a compound that's promising and you could hand it off to the private sector, having de-risked it substantially so that pharma and biotech would be pretty interested even for a condition that's relatively uncommon.

I should also, though, point out that NIH through the Clinical Center and the CTSA's has more capabilities in this regard than many people realize and maybe capabilities that haven't been fully utilized.

And so here we have the parts that maybe seem to work. But let me say that's unfortunately not sufficient. And I want to now briefly talk about the three brick walls that we need to knock down if we're going to see this fully empowered for rare diseases.

First of all, and maybe it shouldn't be a barrier but it is, is the assay development. Most basic science investigators who possess the expertise about the molecular basis of the disease have not been trained in this particular kind of science. It is not particularly difficult or expensive to imagine doing something about this, but there it is.

Certainly, the preclinical phase, as I already mentioned, is complicated and expensive, and that's a very substantial barrier where many projects got hung-up.

And I think it's fair to say the clinical capabilities, as just mentioned, where you don't necessarily have the cohorts ready to go just because you're ready for them, could also be a brick wall.

So what are we going to do about this? Well, what's needed is an innovative, integrated, and generalized drug development process. We could support assay development and this is already coming to pass through efforts that NIH has been encouraging where investigators can apply for support for this, but it would be the feeling of many of us that that needs to be ramped up so that projects that could get started get into this, perhaps by running boot camps, if you will, for basic science investigators to come to a boot camp for a couple of weeks and go away with an assay that will work for their favorite disease.

Assay developments come in various types. There you need obviously some kind of starting point and your endpoint needs to be an assay that works in high-throughput screening. This is not something that happens overnight, but it's certainly achievable, especially with advice from experts. Some assays are based on phenotypes of cells, some on pathways, some on proteins, but all of this is fairly well traveled science. It's just not familiar to many people who know about the molecular basis of a disease.

So that could be accomplished, I think, with modest investments, and probably this is something that NIH could do a lot more about.

Probably the most expensive and challenging part of brick wall knocking down here is going to be in this area of preclinical development, just because this is so failure prone and so many steps involved in taking a promising initial compound and bringing it to the point of having something that you could go into an IND.

And I won't go through all the details here because of time, but clearly there's many things you need to do in-house and you could probably contract out some of this. I'm happy to say that the Congress, in their wisdom, seeing the opportunity here have allocated in FY '09, the current year, \$24 million to stimulate this kind of activity for rare and neglected diseases.

So, in the FY09 appropriations bill there's a \$24 million allocation, the RNDI, Rare and Neglected Disease Initiative, which is already being rapidly figured out in terms of how to apply that and put together capabilities in this regard. And I would say that's a good start. But considering the cost of doing this and the fact that if you are going to begin to initiate a pipeline of this sort for rare diseases, you wouldn't want to do one disease every two years. You'd want to have a capacity to handle five or 10 diseases at one time. And frankly, that means an effort of this sort would probably need between \$100 and \$200 million a year, not just 24. Maybe all of that doesn't have to come from the government. Some of that could very well come from partnerships with foundations.

And I should also say that one of the things we could learn from this, which doesn't currently happen, is by doing this in a publicly funded enterprise with scientists who learned from each other and the ability to compare across projects, what worked and what didn't. Perhaps we could improve upon the current failure rate, which is about 95 percent of these enterprises, by learning how to improve the technology, how to assess when a project is in trouble as early as possible.

So those things need attention. And then the clinical effort needs attention as well, and I think the bottom line is here this has to be thought about at the beginning. Why don't we now empower all of those advocacy groups and foundations that have access to patients with rare diseases to start today to begin to plan for the time where there is a possible clinical trial instead of waiting until that point?

We have already some parts of this in place, characterizing disease, doing the testing to be sure you've got the diagnosis right, and registries and biobanks which many such foundations are already doing. But what is often not in place is really adequate detailed natural history

studies and the identification of clinical endpoints that you could then use in a clinical trial to decide if the drug is working.

So this is basically the image that I hope we could talk about as a possibility: a new public-private partnership, putting all of these pieces together in a thoughtful way so that they're timed, so that nothing ends up being rate limiting unless it has to be, and in the process also developing a paradigm to approach this problem short in timelines and decrease cost and increase success rates.

This is a bold effort, but I think the pieces are beginning to fall together. It won't happen, though, without a partnership between all the necessary parties.

And again, the idea here is not to supplant what bio and pharma would be doing in any way. It is to de-risk project so that as they come through this pipeline they reach the point of economic attractiveness and they are quickly picked up with very favorable licensing by NIH to the company that wants to take the ball and run with it. That would be the model.

If you think this sounds like pie in the sky, I'd point to what's happened with cystic fibrosis. Melissa Ashlock is here and could tell you more about that. Here's a disease caused by a single gene disorder, with many people thinking it as a very difficult target for a small molecule therapy, now with two very promising compounds for different mutations in clinical trials showing a great deal of promise.

Now, the CF Foundation took a great risk by investing in that and many diseases don't have the resources that the CF Foundation has had to do so. But I think that is a proof of principle that ought to be looked at very carefully and is one of the motivations for putting this forward as a more general paradigm instead of series of one-offs, because we shouldn't really think about this as, okay, we're going to tackle this disease, we're going to tackle that disease and we'll think of them all going on parallel tracks. If there ever was an opportunity to put together a system that could be applied to lots of diseases, this seems to me like it should be that.

So in conclusion, I think we have made rapid progress in biology and chemistry so that it's more feasible now to imagine this kind of novel therapeutics being put together. Some of the pieces are already in place, particularly the high-throughput screening, so that we don't have to start that from scratch. The limited commercial potential, though, makes it unlikely that this will be taken fully advantage unless a partnership is established. I think we could knock down those brick walls with major investments of ingenuity, dedication, collaboration and financial support and certainly this seems like a great meeting to talk about.

And so just – even though that's a bit bold and ambitious, that is after all I think what we're all about, that's what NORD is all about, so maybe just like James Russell Lowell suggests here, we shouldn't worry too much about failure, but we certainly should not make the mistake of aiming too low.

Thank you very much.

(Applause.)

DR. KESSLER: Francis, I think that was just so great. Dr. Kakkis, if you could take us through some of the challenges to the status quo, and then maybe we can all begin discussion.

EMIL KAKKIS: Thank you, Dr. Kessler. I'm very happy to be here today to talk a little about my personal experiences with drug development, and what I think could be changed to make things better. The projects that I'm going to talk about are not quite as grand as the project that Dr. Collins is talking about, but I think the changes I'm going to be talking about are at the core of what might help get more rare diseases treated.

Now, there have been a number of successes in drug development, so we have to recognize that companies working with FDA have had a number of diseases treated that have been treated before in the last few years, so it's been quite successful.

But we also have to recognize that there are a number of challenges, and those diseases – just a few of them listed here – some of them could be treated but because they're either more rare or they don't have appropriate surrogate endpoints or are very difficult or have what I call, inconvenient biology – they affect the connective tissues like bone and things that are very hard to treat – some of these won't get treatments, even though some of them have technology that exists that's NIH funding could be put into use, but they won't make it.

And so, I want to highlight what I think are the three areas of most concern, and I will take you through our own Aldurazyme experiences -- jumping off points to why I think these are the areas that we could improve things.

You've heard a little bit earlier about the accelerated approval regulations. This is where use of a blood or urine test, for example, is one possible way of testing whether a drug is working. And those regulations, I think, are extremely important in getting HIV drugs through the process and have been very successful, although for a rare disease, it's very difficult to use these regulations because there's not a lot of clinical experience which is usually needed to validate or at least support the use of a surrogate. I'll talk more about that example later.

The traditional study designs and analyses that are used, the double-blind controlled studies traditionally are the gold standard. But gold turns to lead sometimes for rare diseases because there's so much baseline heterogeneity that the disease treatment effects are very hard to discern and very difficult to manage. And I think we need to look at that issue as well, how to design studies for very heterogeneous complex multisystem diseases.

I think there's also insufficient expertise both in FDA and industry. I think there is certainly a group at FDA that's been working the last few years in gaining experience and working very hard and with some success. But I think, in fact, there is substantially more expertise that could be brought to bear, an organizational change that might be an improvement. I'll talk about these in a little bit more detail.

Aldurazyme is a project I started in academia. It's an enzyme replacement therapy for a disease called MPS I or mucopolysaccharidosis. (

We developed an enzyme therapy in dogs. We were able to show that we can treat the dogs effectively. And we began with a small startup company. I was able to get the project to enter the clinic. And we visited FDA and CBER and, working together, came up with an open label study in 10 patients to get approval. And we were going to use surrogate measures of storage. These patients build up material in their body and we're going to measure whether that buildup goes down. It was very similar to what was done for Ceredase with Gaucher, another lysosomal storage disorder.

We did the study that we planned and we showed storage in the liver went down and the storage in the urine decreased. And we even had some successful clinical endpoints. These were very statistically persuasive results, both surrogate and clinical endpoints improved. I certainly was extremely excited because I set my whole career to treat one disease and we seem to have gotten there very quickly. We published this work in the *New England Journal of Medicine* which, of course, is a great thrill for any academic investigator.

We were very happy with what happened. And at this point, the FDA asked us a question, which is: What does the liver size and urine test really mean? That is, does it predict clinical benefit? And can you show us that it predicts clinical benefit? This is a normal question, and I think it's normal because when you're using surrogates, you need to be able to show that they relate to something clinically important.

So it is a normal question, although it did come after the positive study that we had designed and it did involve different reviewers at FDA. What we could show them is we had excellent canine data. We could show them the science behind this, the fact that these patients are missing an enzyme, the material accumulated. We reduced that material and we showed how that worked in the dogs.

But we were lacking independent human data, and without that data the surrogates were discarded. And, as you can imagine, how many rare diseases actually have previous human clinical data from trials? Well, none, very commonly. And so you end up basically unable to meet that standard.

So once that was gone, then the study was open label because it was based on using objective primary endpoints, and therefore, the clinical data couldn't be relied upon in their view, which is understandable, although I think things like sleep apnea and growth rate were objective enough.

But in any case, we were basically delayed at that point. We needed to design a Phase III study, so we designed a randomized control trial, a double-blind trial actually. David Meeker, who is sitting in front here, was with me in the room as we were trying to design the study. And what we ended up doing was picking two endpoints which had never been studied in MPS patients before. But there were ones that were relevant for other drug approvals. And we conducted a Phase III study having no idea what the treatment in fact was going to be.

And we selected endpoints on how well the patients breathed and how well they walked, the six-minute walk test. And we selected four patients who had abnormal breathing, but we

couldn't select for both things because we didn't have any patients that had everything. And so, we selected only for the breathing problem, not the walk problem.

And we did the study. We had a very good result with the statistical significance with the breathing problem, which was improved. The walking, though, we just missed, but the problem here was that we had, in this study, patients walking from 10 meters to 500 meters in the same study, which is 10 times the size of what is considered a clinical and meaningful change of 50 meters. That's the baseline variation. It's 10 times what is a reasonable effect. So that is extremely hard to manage.

Now, if you used alternative analyses using co-variables or repeated measures, other types of statistical tests, you could get significance, but that wasn't allowed and so we were stuck at that point.

So what we ended up having to do was additional work on extension data and we ended up, of course, delayed again. Now, so what ended up happening in the program was the surrogates got rejected and we had to do the study and then we needed extension data after the Phase III study. Eventually, it reached an advisory committee and then approval in 2003, but the total path here took a three-year delay from what we were intending.

The real impact, of course, was patients who with MPS I during this process that did die waiting for approval, and it was very difficult for me because I get the calls and the urgent crises that occur and certainly it is a burden I still carry because it's not a simple process when you're dying from MPS I.

The MPS VII program, which I'd gotten the company to consider as a sort of charitable venture, was eliminated because we couldn't predict that we were going to be able to do one study as with the MPS I program.

And the 4A program which is another bone type – bone cartilage type MPS disease -- fell off the radar and then got canceled because we couldn't predict whether we would be able to use a surrogate.

And Vyormin (?), of course, nearly failed. We nearly ran out of cash at least a couple of times during this period. Now, we did survive and eventually developed three approved products. But these are the real costs of what happens when you get hung up in this situation.

So I want to talk a little about MPS VII, the study that we weren't able to do. This is a very rare disease and this (slide) is a child, Matthew, who's now seven years old, but he was born 10 years after the disease itself, MPS VII, was successfully treated. And this kid still lives in a hospital in Queens and hasn't been treated.

And I will tell you very honestly this disease will never be treated in the current situation. And so if we want to treat these really rare diseases where we have the technology, we need to do something different.

This is a photo of Ian Michael Smith, another child who I think you should be familiar with; Ian is a young man with Morquio syndrome and he was famous for his portrayal of Simon Birch in the movie “Simon Birch.” In that movie, his defects were part of why he was searching for his purpose in life, which a lot of genetic patients do. Here he is now (slide photo). He’s graduating from MIT with a degree in computer science. And he’s using a scooter and he has the physical problems that relate to Morquio syndrome.

But what you didn’t know is that, see, at that time, as I just told you, we had a program and he visited us as we were trying to work on Morquio syndrome, but this got cancelled and now, many years later, of course, no treatment. And I struggled over a few years to try to figure out a way through forward. I was able to get the program reinitiated at Biomarin, and in April we just treated the first patient in the study coming back again.

But it’s only because we think now that we can get some treatment that will be measured clinically using the walk test or the breathing. But if that doesn’t happen, then we will have a problem that may put this program more at risk. But we think, right now, that there will be substantial benefit in these other areas. But this is obviously another case that it’s very difficult.

So what I want to very quickly go through is the fact that surrogates are very hard to use. You have a defect. We know what accumulates. We treat the model, but we can’t get to here because in order to do the clinical study and get validation, you have to do many clinical studies – a very difficult, process to get to something that’s validated in approval, approval based on the surrogate. Now, so that process is never going to happen with some of the rare diseases.

But what does happen is another process, which is somewhat unpredictable and which we can negotiate and use data and get through. But the truth is that this is a very difficult path. Fabrazyme got approved in this, but it was very difficult, coming down to an advisory committee meeting. Kuvan, which I was involved with, got approved but there was a lot of data on PKU. But for a lot of diseases, that data doesn’t exist and this path doesn’t happen.

And what really happens is it stops right here because this projects never gets into the company because the company thinks you’re never going to get through, and I’m not going to negotiate through whether that rare disease might actually make it and so it gets stopped right there.

So we need a practical way forward for accelerated approvals, on qualified surrogates. I don’t want bad science. I want good science. We need to figure out how to do it without having to have clinical proof ahead of time.

And I think there’s a good way to figure that through. I think we can work on that. Good science needs to count. We need to figure out how to get qualified surrogate endpoints, and these qualified – not validated, qualified – are reasonably likely to predict clinical benefit we think if we can accept those criteria what those would be.

With clarity in regulations or guidances, at venture capitalists’ offices where someone is trying to pitch a project, it could get started again. We’ll start getting investment to occur.

I think we need to look at study designs and really figure out how to deal with the heterogeneity and deal with a variety of patients. And I think we should look at some kind of all-comer designs and there some other discussions of alternative study designs. I think we need to either create the guidance or other things that are set not as a negotiation, one by one, but rather something we agree up front is a reasonable thing for some of these rare diseases. And this is not to create the appearance of efficacy where there is none. This is to capture that to see that really is there.

We need to be able to evaluate multiple endpoints, which is not done today. We need to analyze endpoints in patients who have the problem at baseline, be able to exclude patients who don't have the problem as we had with our six-minute walk test result, where if we had just gotten rid of some of the patients who walked normally at baseline, we had an excellent result.

We need more sophistication also in how we analyze these data. We need to look at that and figure out how to create a guidance that would improve study design statistics.

When I left Biomarin, I set up a foundation. We're setting these "cure the process" campaigns to try to fix these areas and we want to work with all of you, with FDA, everyone, to figure out how to make improvements in the process that will allow us to move forward.

I want to point out to you that while there's a lot of success and we could be complacent, I look back at the story in the Titanic when people were sitting in their boats and they were singing so they didn't have to hear the people who were drowning. Well, there are patients out there with genetic diseases who are the same as drowning in the cold, dark Atlantic.

And we could say, well, we want everything to be the same. But I think what we need is to be smart. We need regulations to be smart and do the right thing for patients, and not be worried about the risk to us and our situation, status quo. We need to go back and start figuring out ways to catch some more of these patients, and take a certain amount of risk that's smart risk and to move it forward.

So I am pleased that you're working on this, assembling a scientific committee that's focusing on creating the right kind of scientifically sound changes and proposing those for improving the process and getting more rare diseases treated.

Thank you.

(Applause.)

DR. KESSLER: Thanks so much, Dr. Kakkis. Very insightful.

I do want to give the audience a chance to come to the podium.

Q: My name is Desiree Lyon. I'm with the American Porphyria Foundation. And one of my concerns over the last number of years is, if I were either with a drug company or a

stockholder in a drug company, would I even want to invest the money for a rare disease drug in this climate, where you're attacked by the newspapers and the media, and where you have certain members of Congress who grandstand on this issue? Would I really want to do this?

And how can we, as patient organizations, or just a person with a rare disease, how can we help change that climate, because you're not going to get any innovation if you don't have any money to innovate.

DR. KESSLER: Thanks very much for those comments. We'll certainly take that one up in the discussion.

I think there was one other individual. Please.

Q: My name is Kaitlin Thaney. I work for the organization Creative Commons, specifically for the project Science Commons. We work to help alleviate some of the barriers to scientific research to help accelerate discovery and leverage the power of the network and access to information to really start seeing these exponential results. The concepts of innovation and access are near and dear to my heart and something I deal with on a daily basis.

I'd like to pose to not only the people that are sitting on stage, but also to the entire group as we craft this discussion today to possibly think of innovation and access on a broader level. The actual problems with scientific research are almost precursors, actually definitively precursors to getting things even into the pipeline and without sharing the scientific knowledge specifically with rare diseases where the resources are so limited. It really can be a blocking factor to even getting more information out about certain gene therapies and being able to evaluate information.

So I'd like to encourage the group, when we talk about innovation and access, to start thinking about better ways to share the knowledge. I know it's been touched on in a number of presentations today, but I'm interested in finding out more about whether that sort of pushing forth the idea – the somewhat arcane idea of a walled garden approach and are we really breaking down the silos of research to really start maximizing the investments that are being poured into all this research.

I'll close with a comment. I was at a working luncheon last week with the same sort of crowd. It was venture philanthropy and different organizations involved in rare and neglected disease research. There was a gentleman who worked in cancer research who said to me, when you think about it, there are certain cancers that are seen as common cancers in comparison to the way that rare cancers may be funded. He said, all cancers are rare. No two people that have pancreatic cancer have the exact same disease. So even the funding model for how these diseases get allocated is broken, let alone the actual pipeline of 17 years for a drug to market.

Thank you.

DR. KESSLER: Very important points. And thank you.

. Thank you.

Q: I'm Randy Eady with the Quest Educational Foundation. We're part of a patient advocacy group that works with Governor Crist's new taskforce down in Florida that's focusing on integrative health and preventative medicine.

And one of the areas that I'd really like to direct to the panel for discussion is thinking about complementary and alternative methods that integrate particularly what we've been doing down in Florida where our patient advocacy is looking at rare diseases that we can offer homeopathic symptom relief towards, such as restless leg syndrome.

And so that's a question I'd like to address to the panelists: how have you been looking at configuring in these non-physician care system and patient advocate kinds of things?

DR. KESSLER: Thanks. Again, a very important point.

Let me turn to my colleagues that you've asked to serve on the Blue Ribbon panel. And give you an opportunity to do one of two things.

One, I have a whole list. I find the morning session just very stimulating of things that really should be priorities for NORD as far as agenda in both principles and policies and things to do. So talk what you've heard this morning but also feel free to take the opportunity, if you any questions for this side of the room, any of the speakers to draw them out further and pull ideas together. Who would like to start?

DR. COTÉ: I'd be happy to. Tim Coté. I'm the director of the Office of Orphan Products. I've been collecting ideas and comments throughout the morning. Thank you so much for all the speakers because it's been a lot of very interesting things that have been said about innovation and how we can move that forward.

Governor Thompson talked a little bit about the Orphan Drug Act earlier today and he mentioned the possibility of opening it back up and reconsidering what kinds of provisions might be in it.

I'd just like to make the comment that the 25 years of the Orphan Drug Act have been radically successful – uncharacteristically successful of a legislative initiative actually, and what has produced in terms of 339 approved products.

The HDE program that was mentioned by Dr. Schultz has likewise been successful, but a full order of magnitude less so, in part because I think that the incentives of the HDE program are considerably less valuable to industry than that of the Orphan Drug Act.

And the final comment that I'd like to share in this opening volley that is Dr. Yetter's comments from CBER understate in many ways the great promise that CBER products have for the future. I see things at the designation side, the very earliest phase of drug development and

we have a number of stem cell therapies that I'm sure he would have mentioned if he had more time, that show incredible promise for being developed.

And in fact, we just celebrated the 2,000<sup>th</sup> designation that was awarded last month. H1N1 sort of took the media limelight away from it, but we're very excited about the fact that 2,000<sup>th</sup> milestone really shows how well the Orphan Drug Act has been working.

Thank you.

MR. SASINOWSKI: In listening to the various speakers, I picked up a common thread that was reinforced by my experience in which almost every day I'm involved helping sponsors develop new therapies. One thing I heard was Francis Collins talk about the three barriers to innovation with the third barrier being clinical. Within that third barrier, the clinical barrier, there's natural history and clinical or surrogate or other endpoints.

Natural histories are something that we – now I'm speaking as vice chair of the board of NORD – we in the patient or advocacy community can help develop, together with the academics and the physicians dedicated to treating those patients with rare disorders, to address that third barrier.

But I also want to address even more the clinical endpoint side of what Francis raised. That is defining the endpoint for a pivotal registration trial for an orphan disorder is a major stumbling block to developing new medicines for those with rare disorders. We get to this point often in drug development. We get to that last stage, the pivotal trial, and everybody thinks – and what I mean by everybody, all the top medical experts in the world, the FDA experts who are looking at it, and the patient community -- we think we have an idea as to what might be the best trial, but because we have so little experience with pharmacotherapeutic interventions in that disease, we don't know how the disease will respond, which symptoms will respond to the therapy, and which kind of surrogate might respond to the therapy. And we don't have the numbers of patients to be able to do the type of robust Phase 2 trial to be able to tell which endpoint will be most sensitive to that drug.

We've been fairly passive in the patient community on this, and I'll challenge others as well. We've waited for industry to drive this, waiting for the industry to take the lead. That's what Emil Kakkis was talking about with his work at Biomarin. Companies like Biomarin have been the ones who have been the ones going forward and being the advocates for developing the right endpoints for pivotal trials.

Maybe we ought to rethink that model and go back to the "Field of Dreams" idea, that is: if we build it, they will come. Desiree Lyon asked why would any company invest in developing an orphan drug? Maybe if what we did is to assemble the medical experts who are committed to this disease, understand the pathogenesis of the disease, understand the symptoms, and together with the people at FDA and NIH along with the patient advocacy groups, we tried to develop a consensus statement on the endpoints for particular rare diseases, then maybe like in "Field of Dreams," the corporations would come and invest because there would be less regulatory uncertainty.

Maybe if we had that kind of statement, for instance, on Morquio syndrome when Biomarin came around in 2000, they wouldn't have had to cancel that development program because they would have had more confidence that they could proceed with endpoints that they could pursue. I have a friend who has a son with Kabuki syndrome. If we had a consensus statement that declared the endpoints in a pivotal trial for Kabuki syndrome, then maybe a company would come and begin to develop a drug for that condition. And we could go on and on for each of those 6,800 diseases..

The point is that we who are patient advocates can pull together with those in FDA and NIH and in the medical and academic communities and develop consensus statements. Let's take industry almost out of this process so that no one thinks the consensus building process is in any way motivated by anything but the interests of patients. Today, here we have FDA, NIH, the scientists who understand rare diseases like Sami Said, the head of the NORD Scientific Advisory Board, and I see lots of other notable experts but I won't go through and embarrass you all – I see a lot of world experts in rare diseases here. Can we pull them together with patient organizations and try to develop consensus statements? Maybe that would provide a beginning of an answer to Desiree Lyon's question of why would any company want to invest in developing an orphan drug. If companies knew that there was a way forward to test it, maybe then we would get that investment. Maybe then, as in "Field of Dreams," they would come to the other 6,800 rare diseases because we had reduced the regulatory uncertainty.

DR. KESSLER: Why don't we ask both Dr. Woodcock and Dr. Collins and our other colleagues to comment?

DR. WOODCOCK: Yes. I think, Frank, that's one of the things I was suggesting is that the public-private collaborative partnerships not only to look at natural history, but where we're going is to construct to the best of our ability a quantitative disease model where we actually quantify all the different endpoints. The things that are happening to the people as you build a registry; you can follow them, you can quantify what's the variability in a rate of decrease of walking time, or the people who have been pulmonary compromised, what is the rate of loss of pulmonary function so that when a treatment finally comes along, you have something to work with other than just kind of expert opinion on, in my experience, this is what has happened.

So I think that's something that could be done now and it could be done not that expensively. We're doing major collaborations on disease models, say, in Alzheimer's and so on, but there's no reason why it can't be done here. And then you can construct composite endpoints formally and use those in your trials. We do that for other diseases, based on what you learned in the disease model.

DR. COLLINS: I certainly agree there's a great opportunity here. Again, look at what CF (cystic fibrosis) did to prepare themselves for this opportunity to run these trials by having a registry, having a biobank, having lots of natural history information, knowing therefore what kind of endpoints they wanted to track. And I think that is beginning to be possible for lots of rare diseases.

I saw Sharon Terry here earlier from the Genetic Alliance. They're certainly also engaged very much in the effort to try to empower groups that have interest in rare disease to develop biobanks and to have registries and therefore to begin to have some of the raw materials necessary for identifying such endpoints, and NORD very much in doing the same sorts of things. But I don't think we quite pulled it all together and we could.

DR. KESSLER: Francis, you laid out three walls to knock down. Is there a fourth one, the validation of endpoints? Is that also one or is that different?

DR. COLLINS: That's a subset of the clinical wall. I went through it rather quickly, but I think the natural history studies which in many diseases aren't yet being supported, and need to be, relate to identification and validation of clinical endpoints. That's a big part of that clinical wall, but it's certainly something that shouldn't wait until the day where you have a promising compound and you're ready to start a phase one trial because it might take you years.

And, with rare diseases, you can't afford to get it wrong. If you do the study with the wrong endpoint, it's not like you have a bunch of other patients waiting to do the next study or a bunch of other money waiting to spend on the next study. You've got to do it right the very first time.

DR. KESSLER: Bill. Mr. Schultz.

DR. SCHULTZ: Of course, when the Orphan Drug Act was passed, the whole focus was creating a sufficient incentive for industry to invest in research on drugs for rare diseases. And I guess what we've heard today is we really have two tracks. One is NIH, which is public money, and the other is industry. And the NIH track is, I think, very, very vibrant.

So I have two questions. One is for the FDA officials and the people who watched the incentive for industry. As you look back at drugs where industry has put money in and they have gotten approvals, and some of them, as we saw this morning, have been for very, very small disease populations, what is it about those drugs do you think that got industry interested? Why did it get interested in those drugs and not the many other diseases where there really hasn't been research?

I have a separate question on NIH, which is that the incentives in the statute were really set up to incentivize private industry. And you've got a very different situation when government money is being put into these products, and there have been some famous examples where the prices have been very, very high for products where NIH has done a lot of the research. And do you think that that needs to be looked at – the issue of whether the incentive needs to be adjusted in any way at NIH research or whether in some way there needs to be more attention paid to the NIH's role in the pricing?

DR. KESSLER: Bill, we have some real experts from industry, David Meeker, others. Would you care to share your insights?

DR. DAVID MEEKER: We often get asked what is too small. And for me, too small is a proof of approvability. I think this morning's conversation is its answer. There's nothing that's too small if there's a way forward.

The other part of that is sustainability -- is there a sustainable business model? And I will argue that the Orphan Drug Act was incredibly instrumental in terms of creating the appropriate incentives for industry to come in, but equally important -- Gaucher disease being one of the earlier ones -- was when that drug was priced at a point that allowed it to create a sustainable business model.

But unless there is a market, which means a market that's willing to reimburse, and a recognition that pricing is inversely related to the size of the disease -- this is an area that's all about rarity and we often don't understand rarity in the sense that we think of orphan drugs as being 200,000 patients or less, but of course 200,000 patient is an enormous number of patients, if you have that number to work with, and the numbers that many of the diseases that have most referencing and that we work on are in the hundreds. And when you start out, you can't find those hundreds.

So, all those things, both the approvability and the sustainability of it are directly tied to this issue of rarity and those are the issues that drive whether or not a biotechnology company will pick it up and invest some money.

DR. KESSLER: Dr. Groft?

MR. GROFT: Thank you very much, Dr. Kessler. I'm very appreciative of the FDA folks being here because it really does lend itself to what they do and what has been done in the past, and this relates to repurposing of drugs that was mentioned earlier.

And perhaps we need to go back a little bit in history, back to the '60s. Those who were around working at that time can remember the DESI project that we went through and classified. It has a tortuous history, very difficult. Should we get into this now?

At any rate, we have a tremendous amount of information about a lot of rare diseases, as we heard. Yes, there's a lot of research ongoing, information is available, bioinformatic sources and processes are available. Could we resurrect a DESI-like approach to all these rare diseases? And I realize now FDA is burdened with user fees. But this is something that we're never going to get around to evaluating all of these diseases, but what we're missing is information. The information is there. How do we utilize that the physicians out there in practice and the other healthcare providers really know how to dose, what to use.

And so what I'd like to propose is thinking about something like that. It would require, of course, additional funds -- and I can't really talk about funds for a project like this because it would be a large project.

But, as Francis mentioned, there are many, many mechanisms to fund research with rare disease and parts of it, but we don't know what all those parts are for every individual disease

and every product that has been used. We're using many cocktails for inborn errors in metabolism, but we don't know about the proper doses, the appropriate doses, how frequently, how much.

And so, I think what would be useful is to think about a process like this that we can really begin to address all of the rare diseases in a way that would make sense. We have some very active patient advocacy groups – maybe 1,000, 1,100 – throughout the world who are willing partners with very sophisticated scientific and medical advisory boards. But we are missing a large population of patients without advocacy groups. How do we address their needs?

And so at some point I would like to see us figure out how we're going to address all of these diseases. We can go individually – and we will – drug by drug, disease by disease, but it's really not going to take care of the major problem that we're confronted with: all of these diseases, all of the patients without any hope, without any treatment. And we've got to do a better job, frankly, than what we have been doing. And I think we can. I think we have the resources to do this but we really have to dedicate ourselves.

We have to get all segments of the population, all the partners who we've talked about here today, the industry, the academic researchers, the NIH, the FDA, CDC, HRSA, Congress to really come up with a program that we can get the information that we then can take the weaknesses and the missing parts, plug them into the existing resources and get moving on as many fronts as possible at one time.

And we don't have to go at this alone. We're seeing that global partnerships are developing and they're accessible to us, but we have to become smarter, how we're going to make this work.

DR. KESSLER: Are you suggesting using the metaphor of the DESI as the roadmap?

MR. GROFT: As a roadmap for the repurposing of existing drugs, taking the literature that exists to find out what are potential needs, plugging them into the system and the mechanisms that currently exist and then pushing it in, forcing it into the pipeline, so to speak, and getting more information that can be used as a basis of approval for that product.

I think we can adequately fund the studies that will meet the FDA regulatory requirements. And again, that's another problem. And there are so many things to talk about to get into regulatory rigor and meeting those requirements. But I think with guidance and direction, I think we have to sort of think about these things.

DR. KESSLER: So maybe it would be helpful if we try to bring some of these ideas together. So if you take what Janet and Francis and Steve, what each of you were saying, as you hear each other, put it together.

What I heard this morning is FDA wants to be flexible. It needs real partners. It doesn't have all the answers up front. It needs collaborators. If we're going to push the FDA to work to

get answers together, flexibility is key, and those areas include assay, preclinical, clinical validation. They're all roadmap issues and there need to be entities that are taking responsibility for driving this. Talk about what you're hearing – are you saying the same thing? Are there differences? Put it together for us.

DR. WOODCOCK: I think what we heard today, starting from Governor Thompson, was there are some opportunities on the legislative incentive front. That's number one. So you need to think those through.

I think what I said and what Francis said is matching -- that the NIH and the biomedical research community can get more involved in discovery and early development, especially with some assistance, with additional funding, but that the opportunities are there. I said that the scientific tools are available for people other than simply large drug companies to be involved in these activities, although the partnership, I think, needs to be long.

What I heard Francis saying, and others also, is that the later barriers to preclinical and clinical development also need to be addressed, and I agree with that. Some of that is regulatory and some of that could be strictly done in the public-private partnership by NORD or others in putting together the natural history, the disease models, the research networks, the availability of patients; in other words, the tools so that when these discoveries come forward they can be rapidly and effectively evaluated.

From the FDA standpoint, people can push us. They can submit draft guidance to us. They can work with us – perhaps we need to take a more realistic view of diseases that have 10 patients or fewer, or 100 patients or fewer as far as what could realistically be fit in within our current statutory requirements that drugs and devices be safe and effective.

So what I heard is a whole incremental series, all along the development and access pipeline of interventions that could be done that could make a major difference in development over the next five years. That's what I heard.

DR. COLLINS: Yes, that's very well said, Janet. I think what we're talking about then is a systemic solution, not a series of one-offs, identifying the way to put a process in place that provides the tools that all the partners need.

For NIH, that means providing tools to investigators who really are interested in getting into more translational applications of some area that they happen to be the world's expert but don't quite know how, have never really learned about how you make an assay work in a high-throughput setting.

For the private sector, I think that means coming up with a paradigm that really does de-risk projects, protects the IP (intellectual property) in a way that it makes it still attractive for licensing but provides them with an opportunity to go after a rare disease without having to assume a huge financial risk right up front.

For the patient groups, I think it means providing them with tools that enable this ability to do natural history studies and begin to identify clinical endpoints without having to figure out how to do that from scratch if you don't happen to be a large organization with a lot of resources.

I think those systematic solutions are potentially achievable, but it doesn't happen by chance. I think it really is the kind of conversation we're having right now, to try to bring all of those stakeholders together and to see how each one of these pieces is essential or the whole thing doesn't work.

And I want to just echo what was said by one of the commentators – that to the degree that you can do this in an open environment with complete access to the information by everybody and you still have to worry about protecting IP when the time comes, but a lot of this is appropriate for open access.

And surely, the process will both empower scientists to get more excited about things because they'll have a better sense of what's going on, but also will learn a lot from both the successes and the failures and perhaps develop a system that has a higher success rate than the current one, which is one of the big reasons why people are so reluctant to invest in it just because of the low chance of success.

And certainly along the way, picking up on what Steve Groft said, the ability to repurpose compounds that have already been through an awful lot of this evaluation should be high on the list. I mean, suppose we just took, for instance, all the FDA approved drugs and did a matrix comparison of what we think their activities are against all of the proteins in the genome with what we think actually all the diseases we're trying to treat actually affect as far as pathways. Who knows? There might be some interesting ideas out there right now that haven't been explored. That kind of systematic approach to think of this as a big, integrated problem instead of a series of rare diseases could help us a lot.

MR. VLADECK: I'm sort of the token outsider to this entire process, but as I listened to the comments this morning and the questions and the proposals for change, I cannot understand how in a rational world one would apply the division of labor that we have in most of the industrialized world for the development and bringing to market of new drugs where there are large populations likely to benefit from them – why one would apply that model at all to rare diseases, just as it doesn't work for diseases that primarily affect poor people in the third world and we sort of acknowledge that.

If you're talking about a market of several thousand people a year, even if you hit the jackpot in terms of the basic model of financing drug development in this country, the only way you can recoup your investment is by charging an amount nobody can afford to pay – I know that's the afternoon session, not the morning – and creating another public policy crisis on the backend.

And so, if we're serious about talking about getting the academic community involved more up front about greater openness in terms of information and so on and so forth, it seems to me that to carry that logic just one step further is to say that the model of division of labor

between sort of the basic scientists and pharmaceutical biotech industry that applies in more common illnesses just can't work below some threshold of prevalence of a disease.

And we ought to stop kidding ourselves about it or tying ourselves in knots about it and recognize that we need a new financing model for getting adequate investment and development. And once you do that, I think you also begin to short-circuit some of what everybody sees as the regulatory and other barriers because you've got a different process on the front end that's going to fit in with some of the kinds of reforms on the back end that the FDA folks are talking about.

DR. KESSLER: So give me an idea what's that drug development model you're talking about?

MR. VLADDECK: Let's talk about a desired end state. Let's talk about 100 of these diseases having drugs that are efficacious. And figure out what it's going to cost to have them. It makes much more sense to pay some of those costs up front by financing on the academic side, by financing on a contract basis drug manufacturers and others who know how to do those sort of intermediate stages as though you were developing a new product in the aerospace industry, for example, or new products in the cyber security industry, where the government is paying for halfway through the commercialization because no one else can have access to the intellectual property of the risk or whatever.

And having some kind of coalition or group with access to both public and philanthropic funds, managing the process much further down the developmental road, which is what I thought Dr. Collins was saying. He just wasn't, I think, quite as explicitly connecting it up to the back end of the financial part of all of this.

DR. COLLINS: Well-said. I like your financial implications for the model and I think you're right on. I do think we could be somewhat optimistic that because the science is advancing rather rapidly in our understanding of rare diseases that we could expect that the cost of bringing a drug to market might not actually stay quite as awfully high as it is right now, and particularly with the investment of ingenuity and creativity from a whole cohort of scientists who haven't been that involved in the process and in an open access atmosphere where people are learning from each other that we could improve success rates and drop cost quite substantially.

That may sound naïve by somebody who's not been involved in this process to the degree that many people in the room are. But I think it's a fair prediction. I can't tell you how much and over what period of time.

I mean, basically, if this is like a sports model while you're trying to cross the finish line and make a touchdown. And at the moment we ask pharmaceutical companies to receive the kickoff and run all the way down the field – and that's expensive and failure prone. And, if we could, in fact, have the academic sector, with appropriate support financially and intellectually, carry the ball down the field to the 50-yard line, or the 30-yard line, or maybe the five yard line and then hand it off, you might therefore have a lot more attractiveness for that handoff to happen.

So the idea for every project would simply to be to have some public support, carry it as far as it needs to go until it becomes economically attractive and then hand it off and let the private sector run with it, but recognize, for rare diseases, that means you're going to have to carry it quite a way down the field. I think we could do that.

DR. KESSLER: Dr. Woodcock and then Dr. Dan.

DR. WOODCOCK: I want to comment on what some of the last three speakers said, including Bill Schultz. I don't agree that the government is a good model to develop anything. (Laughter.) Nor is academia. So what I'm suggesting is that there's more involvement and specific bringing in academia and others into this in the way we've been talking about perhaps through partnerships and so forth.

I think the successful disease advocacy organizations that have been doing this have been project managing this with deadlines and deliverables and expectations. If we get into the model of grants and pursuing your own interest, we're not going to have 100 new treatments for orphan diseases.

And, therefore, maybe some of the costs might be mitigated. The competency of the private sector is in rigor of process and also in product development, the physical product itself it's scaling up, its manufacture, its distribution, and all these things. Neither the academic sector nor the government has competency in those areas, so there could be some tradeoffs on that because of increased government contribution, but I think you'll go down the wrong path if you imagine that this could be strictly sort of an academic kind of development program.

DR. DAN: I want to go back to, Bruce (Vladeck), what you said, and it helped me to realize that when the Orphan Drug Act was passed, that was the same year that Leonid Brezhnev had died and that the United Kingdom was fighting Argentina the Falklands War, that's how long ago it was. And I think in the quarter of century it seems we need to get to rethink this. I think it does have to appear a time shift.

One of the myths about the sliding scale is that you can do the same thing, but just a little less and then certainly it worked. Eileen, as a pediatrician one of the things I learned is that kids are not small adults. They're totally different species and have to be treated differently. I don't think rare diseases are just diseases with a smaller number of people and I don't think you can treat them with the same rubric you treat others. We've already found out the obstacles to the law of small numbers. You can't run clinical trials in science the way you do with large groups. You can't get the return on investment you can with large groups. So I think we need to totally rethink more than just systemic, we need to rethink how we approach that and say it's a different class of an animal. We have to approach it differently than we do with other diseases.

DR. KESSLER: Bill.

DR. SCHULTZ: I think Bruce Vladeck makes a very powerful and attractive point, which why would industry invest in these rare diseases. But before we let that go and just assume that this is all going to be done with public money, I really do think it's worth looking

back – and I think people at FDA are the best ones here to do this – and say look at the situations where industry has developed these products and say why did that happen. When the Orphan Drug Act was passed, it was believed that there were a lot of products on the shelf that could treat these diseases, but that industry wasn't doing the research because the patents had already expired. And so that's why the Orphan Drug Act has the seven years of exclusivity. I don't know whether that ever came to pass, whether there really were such products.

I've also heard that there are some cases where new companies just wanted to get an approval, and so it may not have made economic sense to do this kind of study, but they wanted to get one drug through FDA because they thought it was a good investment strategy. I don't know what the other reasons are either, but I just wonder whether the people at FDA can shed any light on this.

DR. WOODCOCK: I think our representative here on the panel could say something about this. Often it's been the passion of somebody who's been studying the disease and then decides to do a company to get their discovery to their patients. So a passion has been a great deal of this I think over the years. I don't know.

DR. COTÉ: I think that usually transformative ideas speak clearly and tell people that they just need to move forward on things. I wanted to make one comment in full agreement with Dr. Woodcock, that the government is not a great model of efficiency for propelling things forward, but our grants program in the Orphan product world has been incredibly successful. We have had 41 products move forward to full approval. Actually it's 43 now – 43 products move through to full approval based on a measly budget of \$14 million per year, which it is right now, and that buying power has been eroded for the last 15 years. You talk to pharma, they'll tell you it costs \$802 million to make a drug and we've been pretty darn successful in the orphan model, so I agree that they're not just like diseases that are more common.

I'd like to offer a practical starting point as we start to think about which kinds of models we might want to move and change things through. I mentioned that we've had 2000<sup>th</sup> designation. This means that these are products that we found that there is promise for, that there is scientific data that there is promise and have certified that they're for a rare disease. I've also mentioned that we have 339 approvals. You can do the math and figure out that there are somehow 1,700 things that have promise that somehow didn't go anywhere. A lot of them are going to be junk and Dr. Collins and I have talked about this a little bit. But there are going to be some diamonds in there and we're engaged in looking at it and as these models develop forward, I think that's a great place to start to look.

DR. KESSLER: Tim, let me just push you for one second. Fixes to the Orphan Drug Act – are there any?

DR. COTÉ: If there are some – there're little things that could always be improved. The Europeans have 10 years of exclusivity. We have seven. Wouldn't that be nice if we could do it their way? I think it might be. There're other little things that could be fixed. They have a ratio for their determination of five per 10,000 and we say it's a fixed number of 200,000. It never

changes. That might be nice to change. But would the cost of diving into open up – opening up that can of worms be worth it or not? I think that people are suspicious that it might not be.

DR. KESSLER: Bill Novelli.

MR. NOVELLI: David, like Bruce Vladeck, I consider myself an outsider to this domain of rare diseases. I thought this was an incredible morning. Listening to all the FDA presentations on what they're doing and how they're ready, willing, and able to do more, I thought Tommy Thompson was on target. We have a tremendous opportunity now with health care reform to really tackle some of the things we're talking about here.

Dr. Collins kept talking about partnerships and then he, just a few minutes ago, and everybody jumped on this, and said, we need some systemic change. We need some new paradigm. The one angle I would bring from my thinking this morning is I haven't heard anything about public engagement. It seems to me, as an outsider looking in, that I so often see competition disease by disease, competition for progress and for funding and for public attention. I wonder if there's some way – and I go back Dr. Collins' comment about not just rare diseases, but neglected diseases – is there some way that we can generate public engagement and support and demand for change, to use Janet's scientific term "passion," I'm talking about public passion. Can we have some global public strategies that can help us move this thing forward?

DR. OUELLETTE: Yes, this is an area that I came to this morning without a lot of knowledge and I am really very pleased to have been invited to be here. One of the things that I was struck by this morning – children have only been mentioned twice. Dr. Schultz mentioned them and Dr. Dan mentioned them. I think most of the time when these disorders are diagnosed, it's in children. And I think that generally it's a pediatrician who gets a lab result back or something happens and they frequently don't have the scientific background to deal with the disease, but then learns something more about it. And certainly in my lifetime a number of people, whom I know, ended up going into fields of studying these patients because of their passion, as someone said.

Now, people are talking about the fact that these fields are really opening up. We're going to need a lot more scientists in the future to carry out the studies and find the medications and products and so forth for these diseases. What are we doing, or is anyone doing anything, to encourage young people, young physician-scientists to go into this field? I'm concerned and I'm not the only one in pediatrics. We're very concerned that about two thirds of the pediatricians under 40 are women, and many of them are working part time. Yet my understanding is that the NIH won't fund people unless they're working full time. So there's this large group of young women who take some time off for childbearing, reenter the field in their late 30s or early 40s, but they've missed out on the opportunity to become physician-scientists because the funding opportunities aren't there. Now, I know this is off the subject of what we've been talking about, but just looking to the future, it seems to me we're wasting a lot of our potential person power and future physician scientists at this point. And I would wonder if someone could speak to this.

DR. KESSLER: I assume, Francis, in your model of a systemic approach this is a key element.

DR. COLLINS: Sure, and I think the fact that we don't have the person power we need, both in terms of numbers and backgrounds, and we don't have the training programs in place to empower people who might be interested in playing these roles, but don't know the particular kind of sciences necessary to do this. Those are both serious issues.

DR. KESSLER: I'm going to open it up to the audience in a minute for questions and comments for the panelists. But let me raise two issues and see if you can help put to rest or answer them. The first one is the issue that has been in the news of late that we need to be sensitive to, and that is the issue of conflicts. There is concern on the Hill, very thoughtful concern about the line between academia and industry. And that's still on a lot of people's mind. How do we approach this – this kind of systemic solutions and the systemic approaches, these kind of partnerships, not only between academia and industry, but between not-for-profits and industry? And do we have a sense of what the boundaries are, or are those issues irrelevant and we just need to forge ahead?

DR. WOODCOCK: I think they're relevant, but I believe they should be managed. I think we should all push back against the idea that we can't work together because that isn't in the best interest of patients. I think that a conflict of interest can be managed if it's fully disclosed and much of the furor about this has been about hidden conflicts or conflicts that people were not aware of. So we've been working under Critical Path to set a whole bunch of public-private partnerships and it's taken us a year or so, and I know there's an urgency, but a year or so to work through all the different issues, including conflict of interest, IP. Every time we do one of this, there's this long period of adjustment to one another. But I think the alternative is not doing this and I think we have to ask what is in the best interest of our patient populations and we just have to take it on and deal with it.

DR. COLLINS: NIH has just issued last week this advanced notice of proposed rulemaking about conflict of interest for academic investigators funded by NIH, which everybody should look at carefully. Clearly, David, you raise a very important issue in terms of public confidence in the whole process and that has been shaken by some examples. Clearly relationships between academic investigators and private companies were not disclosed and involved large sums of money, which at the very least doesn't look good, when that leads to some published manuscript that suggests that a particular drug ought to be prescribed even more than it has been. And that's the kind of thing that I think has caused a great deal of concern.

I do think, based on what's been done with the intramural program at NIH, which went through this scrutiny four years ago and therefore put into very stringent guidelines about conflict of interest that have been implemented and sustained since that time, that this does not mean you can't have productive working relationships between academic investigators in the private sector. In that circumstance you have to be sure that this is very much disclosed and that any kind of financial exchange, in particular, is very closely looked at to be sure there's neither the reality nor the appearance of a conflict. But the idea that this somehow puts up a firewall between the private and the public sector is not a necessary outcome, although many people have worried that it might be.

DR. COTÉ: As the voice of rare diseases in FDA I have to say that it's an especially exacerbated problem with rare diseases because you might have one or two experts in a particular rare disease and that they worked with a certain company makes it especially difficult. So I think, as we move forward on this topic of conflict of interest with rare diseases and therapies for rare diseases, we might want to think about how, as an agency, we can be more sensitive to this. This is another area in which rare diseases are special. They are different. It's just the reality of the facts on the ground are different than they are for the common diseases. And we need to grapple with those realities.

DR. KESSLER: Second issue. We've heard our friend Harold Varmus talk. You have so many different diseases. And here is the rare disease community. They're coming together and they're pushing for their causes. How do we avoid the perception that we're just all out for ourselves here and is there a way to broaden it so that we're not just silos?

DR. WOODCOCK: I think that what Francis has proposed, which I agree with, is a broader initiative, which isn't just disease by disease. We also have the idea that we are here talking about biology, we're studying biology, and when we put the pieces together – this is, I think, what Steve was talking about -- there are going to be networks and pathways that may end up being important in prostate cancer, or something else. We don't really know.

So what we're talking about is a broad agenda of studying certain pathways that are implicated in rare diseases, but putting that knowledge into the public domain so that everyone can benefit from it. And we may actually have spinoffs that would be incredible from this type of effort. So I believe that a disease-by-disease focus would probably be very unfortunate and actually has characterized a lot of the lobbying. And what we ought to talk about is new development pathways, new partnerships, new initiatives. And I think based on what Steve said, I would suggest to NORD that one of the things you ought to put together as a part of this is a research agenda that looks across rare diseases. And people have referred to this already.

Look at what about existing drugs, – could any of these factors apply to rare diseases? What pathways or what are the diseases? You're not saying this disease needs a treatment. Rather, here's the research agenda in this area and this will benefit our understanding of biology and pathogenesis, not just these specific diseases.

DR. COLLINS: So, David, I think you are asking all the right questions here and I think perhaps the rare disease community has not always been well served by the silo kind of approach. Understandably, if you're involved in a condition that affects some member of your family or yourself and you want to get attention to that disease because it's been neglected, it's a natural tendency to think, well, the first thing I should do is to go and find somebody who'll put an earmark and a bill for that disease.

I think at this point that's the wrong solution. I think that it ends up resulting in a competition that sometimes is counterproductive or even unpleasant between diseases, when what we really needed to see is a system put in place. And as Janet says, you never know when work on this disease might turn out to be just the thing you need for that other disease. And the system is going to be only effective really if it can be put in the place that it can absorb inputs

from lots and lots of conditions. So if as a community of people who really care about this field we could collectively agree that the problem is rare diseases and those 30 people who are affected and countless others who are family members and loved ones and we advocate for rare diseases as opposed to a long list of individual diseases that each have to be specifically getting attention, I think we'd get much further, both in terms of public support and in terms of the science that we could do.

Now, Janet said, and appropriately, we need to be careful about not assuming that the government will take care of all this. But remember, the government did the Human Genome Project and the government, if appropriately inspired, could, I think, put together some of the core facilities. I'm thinking in particular at that preclinical phase, where you take promising compounds and bring them through to an IND, not as a bunch of ones, mind you, but as an organized highly efficient, highly managed enterprise to try to push that envelope.

DR. SCHULTZ: Francis, assuming there were a lot of money to do this, how do you decide the priorities and what's the process?

DR. COLLINS: That's a great question and Peter and I have talked about this over the course of the past several months in terms of what that would look like. That would be a critical issue. You'd have to have a rigorous, highly-informed and non-conflicted body of experts to look at potential inputs to this pathway. Some of them might come in at an early stage. Some of them might be at a compound that's already quite far along and you'd want to have a capacity to take things in at whatever point they're ready. But you'd have to have an absolutely rigorous process of assessing what the likelihood of success is. And of course that's going to factor in at some level what's the frequency of a disease, how severe is it, whether there's any kind of treatment.

All those are things on your list as well, but you sure don't want to make decisions on those bases solely. You also have to be able to assess what's going to work. What is likely to result in an approvable compound and focus your efforts on that and try to achieve the success rates which have all too often been dismal.

DR. KESSLER: Steve?

MR. GROFT: Thank you. I talked a little bit about a more systematic approach to product development, but getting back to the patient groups a little bit more – in Tim's office and our office, as truly the primary government offices responsible for the rare diseases and orphan products; we've tried to make ourselves available to patient groups. And what we've noticed is the leadership factor that comes into play with individual diseases. Why did some diseases make such a tremendous and advancing research – and yes, they do get some appropriations language in the House and Senate bill.

That's definitely the case. But it's more than that. I think if you look around the room and you see some of the progress – John Walsh is here from Alpha-1, Ron Bartek, Pat Furlong, some familiar names to the rare diseases community. And they've taken the bits of information that have been provided by our offices and they've moved it forward. And we've tried to hold

weekend seminars for patient advocacy groups. And as frustrating as it is for the patients, it's equally frustrating for us to see many of the patient groups who we've known for 20 or 25 years and they still aren't making progress. So what causes that lack of progress? I would like at some point to address this a little bit more. How we can address the larger groups of patient organization and give models of success that they can actually believe in and move forward in their own determinations as far as products and research? And I think they can do it.

DR. KESSLER: Let's open it up to the audience.

Q: Hi. My name is Arlene Stanton. I'm here partly interested because in my work life I'm an evaluation person for the government, but today I'm here on leave in personal capacity as a patient with a rare disease. And there's a lot of rich discussion. I'm taking on one thing that was of particular interest. The second speaker that we had in the audience segment last time talked about perhaps getting more information into the pipeline and a few of you have picked up on that.

And I wanted to say I think one of the things that I've found out early on, because I was just diagnosed 18 months ago, was that the best source I've found, sadly, has been my online discussion forum with other patients and I have been kind of impressed at the range of information that we get. We get not only the anecdotal or the heartrending or whatever, but just as importantly, we have people who represent all sorts of professions. And so a lot of times we're also sharing information. I have access to PubMed, so I can pull journal articles, et cetera. Other people do too.

And why I'm bringing this up is to underline that not only can patients benefit from the information, especially if we're going in to physicians, who sometimes have less background in the whole area of rare diseases, let alone particular diseases which we understand, sometimes it's not a matter of something nice to do for the patients. It's something critical for the patients because sometimes we go in and we really need to know our stuff to be able to work with a physician in the best possible manner for our personal outcome and hopefully to build up their knowledge base and work with them if they're open to that. But at the same time, because of the range of people that I've been seeing, let's say on my particular forum – and I know there are others out there – it also strikes me that yes, we could potentially help inform research and I hope that there will be some kind of development of a better structure for that.

But the other thing that I'll take on is I used to be a reporter a long time ago and yes, when you're selling rare diseases, I think most people will respond more to the idea that whatever it is one out of 10 people are affected by rare disease and certainly a lot more if you include family members and those that they touch otherwise, probably going to be more likely to get that than they are if they hear that 400 people out the world unfortunately suffer from something. Thanks.

DR. KESSLER: Thank you.

Q: Hi, I'm Marlene Haffner and I spent 20 years directing the Office of Rare Diseases – Office of Orphan Products, sorry about that, Steve.

(Laughter.)

DR. COTÉ: Wonderfully directed.

(Laughter.)

Q: Thank you. And I've sat here – I have been sitting here very excited about what I've been hearing. A couple of things. Bill Schultz, I think you asked why do some products go forward and other products do not. Passion has a lot to do with it. The disease itself has a lot to do with it. Homogeneous diseases are easier to approach than heterogeneous diseases. PEG-ADA was approved for a certain kind of combined immune deficiency on a clinical trial of six or eight. And while we didn't have huge natural history, we knew that these children died before the age of six prior to this product. So we need to know more about these diseases. And I don't know whether the Office of Rare Diseases would, with their dollars, be in any way able to look at mechanisms and paradigms for doing natural histories of diseases. There are a huge number of rare diseases and there are more being discovered every day and as we learn more about the human genome, we'll see more and more, although hopefully we'll know more about some of those newer diseases than we know about some of the older ones.

Tim Cote mentioned the office is beginning to look at those 1,700 old designations to see what's sitting there. Are there promising products there and a company could not raise money because venture capital is hard to come by? Or is it just things that didn't work? Emil talked about every disease is worth treating. That's absolutely correct, but the scientists need to be there to treat it and that's where the background of some of this goes.

DR. KESSLER: Please.

Q: My name is Heather Early . I'm a parent and founder of Russell-Silver Support. My child has Russell-Silver Syndrome and I'm not going to tell you what it is because there's too many genetic people out there and they'll tell me I got it wrong. Anyway, something to think about: how do we tackle the challenge of clinicians who maintain a clinical base of raw materials for which data needs to be translated into quantitative clinical end points, when in fact these clinicians do not share their information or have not published their findings? How do we help them get through the process of the approval itself and when would we provide or create a common database through which to access all of that information. Oh, I got one clap.

(Laughter.)

DR. KESSLER: I get a lot of head nodding up here. Who's next?

Q: I'm Sharon Terry, president and CEO of Genetic Alliance, which I think most of you know, is a network of about 1,000 disease organizations. And we're very interested, obviously, in the issues that have been discussed this morning and really are heartened to see a coalescing around these issues. We've been working for some time on open access kinds of solutions. We

have a registry that's cross-disease and then BioBank and Wiki Advocacy, which is the textbook for all of us to not keep reinventing the wheel. This year, when we were asked to appear before the Appropriations Committee, we decided we really do need to put our money where our mouth is, so to speak, and we asked and proposed that we, rare disease organizations, no longer earmark for our diseases and that the Congress no longer accept earmarks or put forward earmarks.

This will, I think, really tear down the boundaries that we've all created in fact and that while we look to industry and academia and NIH and FDA for solutions, they have to start with us. And this is not just an ivory tower exercise for me. I have two kids with pseudoxanthoma elasticum who are destined to lose their vision in about 10 years and so it's very real for me. And I put on the table not receiving any earmarks for my disease because I think we do need to think about pathways like Janet was talking about. We do need to think about systems like Francis was talking about and we really do need to figure out how do we stop being us and them and start being us.

Q: Thank you. Kim Bernstein. I am the director of Patient Advocacy and Empowerment for Hemophilia Health Services, but for 15 years I ran an advocacy program that did Social Security and SSI. I'm very concerned about coordination. I think if you look at the schedule that we have today, we have in the morning research, at lunch Social Security, and after lunch reimbursement. What I'm concerned about is if we look at what's going on with research as sustainability being one of the greatest barriers to access, I think we need to look at the entire mix on the front end and understand there'll be a portion that would be Medicare. There's a portion that would be Medicaid.

If we look at this on the front end, rather than on the back end, and start making sure that we have appropriate listings for Social Security, which we can discuss at lunch, I hope, that through the compassionate listings programs, through other things, while the manufacturers set out to make a drug to treat a group that perhaps has no representation because it has no advocacy and is very small, that they know that at least on the back end there will be a place for their patients to go if they're on Medicaid and Medicare, where there is a reimbursement. If we can look at how we get the approval for the drugs through Social Security, through CMS on the front end, so we don't have to worry about the process on the backhand, I think we accomplish a lot.

I think that we also need to look at CMS taking a look at this, since when we deal with SSI, as I've been doing for the last 10 years, it's so hodgepodge that it takes so long that a manufacturer could decide not to do the drug if they're afraid that they'll have to do all of that in compassion listings and compassionate products. So if we can look at the Social Security and the public payer reimbursement, when we look at the front end, I think we'll have it.

I think we should also be looking at things such as the bill that would allow for people to buy into Medicaid if they have \$200,000 and health care costs so that we know that we won't have the problem again with the uninsured that end up being compassionate product that again put a damper on the research. So if we look at it by setting up the networks in advance, I think it would help, but I think it's going to take a coordinated government effort in order to do this. Thank you.

DR. KESSLER: Thanks. Please understand that the breakdown between innovation and reimbursement – those are artificial. But we will bring it together. We promise. There're a couple of other hands and then if any of you are from a not for profit organization, but you're really in a product development mode. I think we'd love to hear from you, what you think would be a relevant agenda.

Q: My name is Melissa Ashlock. I'm a physician scientist and I've been lucky enough to direct the Drug Discovery Program at the Cystic Fibrosis Foundation.

DR. KESSLER: Perfect timing.

(Laughter.)

Q: So I'm excited to be able to comment because before you said that there were a couple of things that I think are relevant here. The Cystic Fibrosis Foundation is a large organization with a lot of funding, and so it may not be completely applicable, but some of the lessons that we've learned in the past 10 years I think are truly instructive. And to take on what Janet has said about passion, I think that one of the reasons that the Cystic Fibrosis Foundation has been successful is besides passion there has been vision and risk taking, which was initiated primarily by our President and CEO Bob Beall. And this follows up on Steve Groft's comment about what is it that makes things happen. And I think one could talk for a long time about what vision and what risk are in this context, but just a couple of specific things about vision for this group.

One is that vision here could be seen a path to explore something that's never been explored before. And going back to something that Emil said earlier about his program at his company, there was a program that was cancelled and in contrast to the drugs that are perhaps known by Tim Cote and his group, there probably are a number of pharmaceutical companies that have cancelled programs that no one ever knew about. So one thing I thought would be a call to arms to get these companies to say what these projects are that had been cancelled that could be helpful to this group.

A second thing is with respect to risk. I think one risk-taking maneuver that we view at the CF Foundation is to try to educate people that you might not have thought needed to be educated before. And those include the people who do the regulatory evaluations so that they understand what it is that the outcomes are and what contributes to the disease spectrum and also to educate the academic groups so that when they're developing their assays, that the assays that they develop inform the clinical outcomes. And when that actually happens, it's much easier to have those things move through the regulatory pathway and not bring surprises at the end.

We've been spending a lot of time trying to explain to the academic groups that working together with us to divide the outcomes and the assays will make the whole team be successful and that helps to break down barriers when the academicians feel that they might own the disease. And I think that gets to someone else's point earlier that the academic groups need to be part of the team that's successful. I know that's quite a bit of things to cover in one small swoop,

but there're a lot of lessons that we've learned at the CF Foundation that I think are applicable and I'm happy to share.

DR. KESSLER: Okay, David, we have a couple of people over here.

Q: Hi, I'm Jennifer Mandell. The group I'm here for is really just me. It's about Madelung's. It's a disease that's extremely rare and fortunately now has an effective treatment that I actually figured out myself a few years ago. But I also have multiple other genetic rare diseases. I have cone dystrophy. I have several blood disorders, including the prothrombin gene mutation and Coumadin resistance, which is a real problem as far as treatment. But I'll just go on from there. There're several others to it.

I just have comments on a number of the things that you brought up today. For one thing, I don't think there's one message to deal with rare diseases. I don't know if any of you are familiar with the Web site [www.whonamedit.org](http://www.whonamedit.org) but there're a lot of these rare diseases that actually have lots of names and lots of people who have built up little empires sometimes over decades or even hundreds of years. Dercum's Disease is one of the diseases I have and it has about eight or nine names and Madelung's actually has a few other names as well.

Madelung's is a genetic disease where you have to be predisposed genetically first and then you have to have some trigger. There're a lot of other people who really have what seems to be a form of Madelung's disease and those are people with HIV who were on protease inhibitors that developed the same symptoms, but unfortunately the treatment that works for us with regular Madelung's – I guess you can call it – doesn't work for them. And that's simply to take pancreatic enzymes.

People who have multiple rare disease like I do – a lot of times it's very hard to get treatment and even good management because you don't know what the kind of cascading effect for treating one disease might be with some of the others.

I think HIPAA is a bad thing for rare diseases. It needs to be kind of reworked for us. HIPAA is the privacy aspect of diseases for – kind of regulation that's about privacy.

I myself went to a public health school at Ph.D. level and tried to specialize in small population rare diseases in school. And I won't embarrass the institution that I was going to, that let me finish all of my classes very successfully and then wouldn't fund a dissertation project related to rare diseases. And I think that's an important area that doesn't need to be more help to get into this field.

DR. KESSLER: Thanks so much. I want you to hand the microphone. to the chairman of the board at NORD, Carolyn Asbury. Why don't we let you have the final word from the floor and then let's come back to operationalize. Dr. Asbury.

CAROLYN ASBURY: Thank you. And on behalf of NORD and everyone here, I want to thank all of the presenters for this excellent presentation this morning. I have two questions.

Back when the Orphan Drug Act was being enacted, we did a survey and we found that one in every four drugs that was available for a common disease had been found to be effective for an orphan disease from among the drugs that industry had developed for orphan diseases. We also have heard that up to 70 percent of patients with rare diseases currently are being treated with off label drugs. So my question is to Dr. Collins and to Steve Groft. Would it be possible, for instance, to look at the drugs that are out there and have those drugs go through the process that Steve Groft was talking about, look at the resources that are available and then begin to look at any further work in terms of their orphan disease efficacy. That's question number one.

The other question is that back when the Orphan Drug Act was being designed, there was a provision initially in there that talked about only one clinical trial being required. That was because we found a major difference between drugs that had been on the market for rare diseases and those that were kept in Compassionate IND status for generally smaller patient populations and there was tremendous uncertainty on the part of the manufacture about what FDA would require in terms of clinical testing. And so my question to Dr. Woodcock is, is there any likelihood that there might be more opportunity to work now across the agency with manufacturers and with patient groups in terms of greater upfront consistency. Dr. Kakki was talking about not only do you have changes in who's reviewing it, but you sometimes even have changes in what division might be reviewing it. So those two questions for the panelists.

DR. COLLINS: Certainly the ability to try to repurpose existing drugs is very attractive and we've touched on it a few times. And I agree with Melissa Ashlock's call to arms here, if it's possible to also liberate compounds that have been already investigated in the private sector and perhaps already passed ADME-tox with flying colors, but failed somehow in the efficacy arena or were simply abandoned because the economics didn't make it look very attractive. It would be a terrible shame not to see that taken advantage of.

I think, though, it's true that there are certainly lots of off label uses already for rare diseases. I think when you look at those, a lot of them are certainly not what you would hope for in terms of efficacy. So simply because there are some out there that are being used, we could do better if we had an appropriate approach to really try to target things in a more specific way.

The NCGC that I mentioned has made considerable efforts to collect – and it's not as trivial as you might think – all FDA approved drugs. And that's in their library of compounds. So every time an assay gets run now through that library, you find out whether there's already an approved drug that shows activity against that particular target, in which case you may have just suddenly skipped over several years and hundreds of millions of dollars. So it's a very good thing to know that if you're lucky enough. But frankly, for most rare diseases, I don't think that's likely to be the answer. We shouldn't pass up the chance, but we should also expect that this is going to be hard in lots of instances and you would have to go the whole way, the ways that CEF has done, but that can work.

DR. JENKINS: The second question, I think, deals with not only the efficacy standard. Dr. Yetter talked about a lot of places where we have very few patients in a single study. The effectiveness document that I described, the guidance from 1998, was an attempt to standardize across the agency our understanding and our policies on standards of evidence. And it goes into

situations where a single trial can be adequate and there are multiple examples of where single trials have been adequate.

I think you asked at the end how can we make certain that they have consistency across the organization, but also consistency across time so that the advice that's given to a sponsor or an investigator early holds over time. And we make a lot of attempts to do that, importantly by putting our advice in writing. So a lot of the times, when we meet with people, our advice goes into meeting minutes. We have special protocol assessments where we can put that advice in writing. And we take great effort to ensure that even with changes in personnel, which are inevitable or even changes in the divisions that are responsible that we try to honor that advice. There may be situations where we feel that the science is changed and the advice needs to be rethought, but we don't do that lightly. And there're a lot of places where the advice changes over time, but it's actually changes that are favorable, becoming less conservative, so to speak, towards the pathway that's been proposed.

I think if there are situations where people feel like they're being given different advice, they should feel comfortable talking to the staff at the agency and if necessary escalating those disagreements to higher levels so that they can be carefully adjudicated.

MR. GROFT: Thank you, Carolyn, and I just want to mention that there's so much variability in information that is available on the individual products and the different diseases. I think we do have the capability of doing a tremendous literature research to look at all the pieces that are available. So I think we'd first had to do that and we've talked about attempting something like this in our office, but it does require tremendous effort to do so. But one of the first stages and first steps that we've taken is to take all of the terms that we've got, the 7,000 or so, that are related to rare diseases and forcing them to the MASH system so that we can now begin to get a better feel for the proper terminology and really will ease the searching for information for particular diseases. And so that's one thing that's ongoing.

Another project that we're involved with is International Classification of Diseases. That has started with major focus on rare disease and it is ongoing. It's just in very early stages, but coming up with procedures how to address the rare disease issue.

DR. KESSLER: How do we operationalize, for the lack of a better word, what we've been talking about? Let me see if I have the pieces and then let's talk about how do we move forward and what's useful to NORD. Lets stipulate upfront that the Orphan Drug Act, safe for maybe some tweaks, that remains good law, good policy, needs to be continued and we're not reopening that. .

There are, as I listened to this morning, a number of pieces that whether you call it a systemic approach, a new public-private partnership, new partnerships that collaborate with both the NIH industry and FDA, that there is a need to strengthen those entities and that needs to be strengthening in a whole number of different quarters, from assay development to preclinical development, to advocacy for patients for clinical development, for validating as surrogate end points, to liberating compounds, to training people. It's going to take the sum total of all that to advance the general field and if in essence we could do this with rare diseases, we can move

forward modern medicine significantly. The cancer community spent the last several years very thoughtfully thinking through what is now part of the Kennedy-Feinstein bill. If you look at it, it too has a lot of different pieces that only when you add them up make sense. So I guess the question is how do we implement, how do we take these ideas – some of them are going to require funding. Some of them are going to take place in different quarters. All are against the backdrop of a desired part of the FDA for flexibility in dealing with these issues. What's the right way we put these things together? How does NORD carry this agenda forward? Thoughts.

MR. SALTONSTALL: Thank you, David. I think you articulated it well and I think NORD's ready from the patient perspective. We understand that when a patient showed up on the Hill, especially if it's a regulatory or a legislative issue, that they seem to listen when you have a lot of people that are concerned about this or a lot of names on the left hand side of your stationery with you. Francis and I talked about the model. He articulated it and I agree. I think it's a model for the future. But we've discussed a number of different steps here and I'm trying to sequence it in some way so that we can take the shape of the baton and understand what are the next steps and then how do we start to initiate it and drive it forward.

DR. KESSLER: We have some people on this side of the table who spent their lives taking on big agendas and moving forward issues. What's the advice for NORD? Is this legislation? Is this their agenda? Is this – some of this can be done just by sheer perseverance. What's the way to bring this together? Bill, you've taken on big issues.

MR. NOVELLI: I've got the scar tissue to show, to prove it. (Laughter.) To paraphrase you, David, what I heard people saying is we need a global overview, comprehensive set of strategies, not specific diseases in silos and that this calls out for public-private partnership. And what I thought I heard is that there're three aspects to the agenda. One is research and science. One is advocacy. And one is public outreach. And that's how I would think about it and dissect it. I think if NORD is the architect or to be the architect of this with others, what you might consider doing is to try to put together each of those agenda separately and then comprehensively pull it all together.

DR. KESSLER: Other thoughts?

DR. COTÉ: Just one other quick thought that has been rumbling with me for some time is that earlier in the discussion we asked the question about how to make the case. How do you march up the Hill and how do you make the case to the world that this is important – the rare diseases? And it struck me over the past year-and-a-half that most of our medical science comes from people with rare diseases. We learn what aging is through Progeria. We learn that the DNA can repair itself through xeroderma pigmentosa. We learn what normal hemoglobin that we all have is through people with hemoglobinopathies. The urea cycle disorders are what taught us about our own urea cycle disorders. This is normal. All the clotting disorders are really what taught us how our blood clots. These people with rare disorders form the very fundamental basis of our materia medica. They're what we studied in school. They're what we understand in treating all disease that we ever reach. So somehow we need to communicate that – that these are not just odd things that happened to some people, but this collection of rare

disorders really are the essence of what medicine is for all people and somehow we need to communicate that to policy-makers.

DR. KESSLER: Bruce?

MR. VLADECK: Again, from a very different perspective, but it seems to me that the logic of the Orphan Drug Act is – and somebody said earlier – is basically, build it and they will come. But if you can just sort of shift the terms of the rules for the game that have applied successfully to development of drugs for large populations to drugs that benefit smaller populations, that'll be enough to tilt the playing field enough. And it doesn't seem to have been the case or not the case to a sufficient degree.

And I get back to, again, both what we've learned from places like the Fibrosis Foundation and to some of what Dr. Collins was saying to say we can no longer have a passive/reactive strategy relative to this. There needs to be somebody saying, okay, we need to be proactive and systematic in doing this. And I think if you do that, making the case for a public-private investment is also not that difficult to do, given both the amount of public money that's being expended on a continuing basis for inadequate palette of basically services to people with untreatable diseases.

And second, again the longer term economics of what the public sector would end up paying if the drugs do in fact get developed and come on the market and so forth, you might as well take a discount up front. So – but it seems to me it's really – it's again, in terms used earlier, a paradigm shift in terms of coming to accept the notion that the normal way in which drug development has occurred, although I'm not even sure it really has occurred that way, but the normal mythology about how drug development occurs for treatment of much more common sorts of ailments doesn't work for a whole bunch of relatively easily understandable reasons when talking about diseases with an incidence below X. And therefore you have to have a proactive strategy, both to organize the science and to rethink how you finance the drug development.

DR. KESSLER: In the three minutes remaining, why don't we do Frank and then Bill Schultz and then we'll break for lunch?

MR. SASINOWSKI: Bruce, you're right in terms of not being reactive. I had said build and they will come. And Janet's reaction was, yes, we can have the public-private partnership. We can go ahead and we can assemble the natural histories and gather the information for developing pivotal study end points. I know we can do this because of the passion that drives people in this area of rare disorders.

I know of many illustrations but let me share two.. When Martine Rothblatt had her daughter come down with pulmonary hypertension, she decided to give up her position at Sirius. She had started Sirius satellite radio and had been a pioneer in satellite communications generally but she gave that up, but started a drug company, United Therapeutics, to develop a drug for pulmonary hypertension. That's passion. There was no other drug then available for pulmonary hypertension except for Flolan. Dr. Rothblatt's company developed Remodulin and

today that drug is helping tens of thousands. What else does this illustrate in addition to the power of the passion of a single person to make a difference? Remodulin was the first of what today are many other drugs out there for pulmonary hypertension. Why? Well, one, we learned that drugs could have an effect on this disease. That's one thing. But the second thing we learned is that we had then a pathway. Because the drug Remodulin was approved, we knew what the endpoints were. So this reduced regulatory uncertainty and that attracted other people to develop more drugs for this disease.

My second illustration comes from John Crowley and his passion for his two children with Pompe Disease. His company, Amicus, is pursuing new medicines for Pompe, Gaucher, and Fabry diseases. Along with John Crowley's Amicus, we see other people also trying to develop second generation drugs for these conditions. Why? Same two reasons. One, because drugs have already proven that they can affect these three diseases. And two, we have the endpoints established, that is, the trail has been blazed.

And so I think getting to the endpoints is critical. Janet was talking about public-private partnership. We can form these in order to collect the natural histories and develop the pivotal study endpoints. We can have a consensus statement on these pivotal study endpoints, I think that would be proactive. This is what, Bruce, you're talking about, that is, urging us to be proactive rather than reactive.

DR. KESSLER: Bill Schultz and then Dr. Woodcock and then we're going to break.

DR. SCHULTZ: Just the only thing I would say. It seems like what was on the table here was what useful role can NORD play in health reform. And I think we've made a lot of progress here. There've been some just terrific ideas. Obviously one congressional action that would help is funding. But aside from funding, I haven't really heard anything else. And I think maybe as we have lunch we ought to think about whether there's any other sort of legislative action that we're really suggesting here.

DR. KESSLER: If you look at the cancer bill, some of that doesn't require legislative action. It could be done administratively, but there's something about putting it all together that provides the road map. And I'm not suggesting that that's the vehicle or not.

DR. WOODCOCK: I'll be brief. For this part of the agenda, I suggest that NORD should develop the vision for the new paradigm of drug development. And I agree with Francis. This may be the new paradigm of drug development writ large, but we could start with orphans. We've had a reasonably successful drug development paradigm for orphan drugs because we've gotten some orphan drug treatments. So that's really good because otherwise there was despair before that. But now, with the new science, there's an opportunity to go much further and develop many more. And so articulating that vision to everyone – to patient groups, to the Hill, to everyone – I think it goes a long way because I'm not sure that people share this common vision of this tremendous opportunity that's now opening up for a new kind of drug development. And I think that would be in and of itself – that's not a specific action, but it would go a long way to say where should we go in the future.

DR. KESSLER: Thank you all, a wonderful morning. Thank you very much.

(END)