

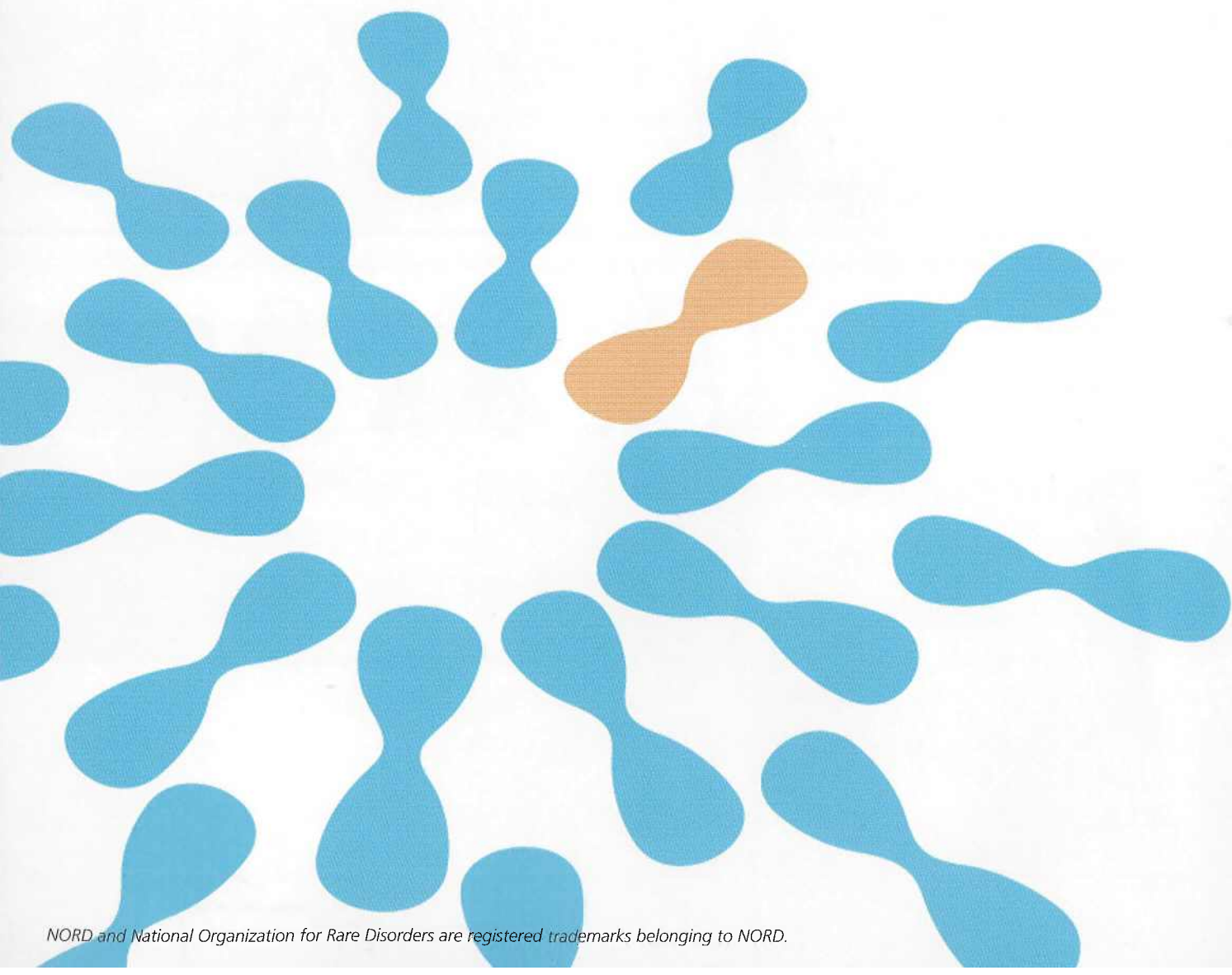
National Organization for Rare Disorders

Partners
IN
PROGRESS
2009

A Summary of the Partners in Progress Summit

May 14, 2009 • Washington, D.C.







The healthcare system we know today is going to be completely transformed over the next 12 months. Now is the time for action.



— Tommy Thompson, J.D.

Background

The National Organization for Rare Disorders (NORD), which advocates policies in support of the nearly 30 million Americans with rare diseases, sponsored the, "NORD Partners in Progress Summit," on May 14, 2009, in Washington, D.C. to establish its policy agenda.

NORD gathered together 21 national thought leaders on a Blue Ribbon Commission to discuss how to address the dual challenges of 1) stimulating innovation in the development of new therapies from their discovery through the regulatory review process at FDA, and 2) ensuring that those patients have full access to proper diagnosis and treatments.

Innovation

Because a rare disease might affect only a few hundred or a few thousand people, and can therefore easily be ignored or misunderstood, innovation in developing new treatments must be supported from discovery through the Food and Drug Administration (FDA) approval process. NORD's traditional position has been that national policies, including regulatory and reimbursement policies, must take into account the special needs of patients with rare diseases and must be sufficient to protect their health and well-being without being so burdensome that they limit the development of therapies.

The importance of an environment that encourages and supports the study and research of rare disorders and the therapies used to treat rare diseases cannot be overstated. Indeed, it is through the study of rare diseases that the scientific and medical communities come to better understand and define how physiological processes operate in the vast majority of persons. Moreover, there is a dearth of dedicated government research funding for most rare diseases.

Access

Patients with rare diseases must have full access to proper diagnosis and affordable treatments. Many rare diseases are poorly understood, under-diagnosed, and/or have no approved treatments. Indeed, of the approximately 7,000 rare diseases that have been identified thus far, fewer than 200 have an FDA-approved treatment. The objective of the Summit was to elucidate policies that would improve the timely diagnosis of individuals with a rare disorder, as well as policies to ensure full and timely access to therapies that are available.

Given this backdrop, the Summit aimed to achieve a clear and concrete policy agenda for patients with rare diseases, and in particular, to gain an understanding of:

- Federal policies that especially affect patients with rare diseases – the opportunities they offer, the obstacles they create; and ways to improve these policies; and
- Policy changes that NORD should advocate to assure innovation and access to therapies for rare diseases.

The NORD Agenda that Emerged

Based on the presentations and discussion at the day-long Summit, the following ten goals emerged as being key elements in NORD's policy agenda:

GOAL #1 – NORD should expand its current role to serve as a catalyst for public-private collaboration (government, industry, academia, and patient groups) to create an environment for the development of new treatments for rare diseases. In this effort, NORD should serve as the non-profit, neutral body representing the patient community in FDA's Critical Path Initiative.

GOAL #2 – NORD should work with FDA to establish greater certainty in the orphan product approval process, in particular with respect to clinical trial design and endpoints. For example, NORD should seek to develop valid natural histories for rare diseases that can be used to define clinical endpoints. What is needed is a new paradigm for orphan drug development. Greater certainty would encourage investment in, and the development of, products for rare diseases.

GOAL #3 – NORD should identify needed changes in the FDA law, regulations, and policies to encourage and facilitate product approvals. FDA is the gatekeeper for new products, but beyond that also sets the standard for clinical trials and product development. NORD should advocate for FDA to have the tools and policies needed to support orphan product development.

GOAL #4 – NORD should seek to obtain greater funding for FDA and the National Institutes of Health (NIH), and should continue to urge the Social Security Administration (SSA) to expand its Compassionate Allowance program. These agencies serve central roles in supporting innovation and access for patients with rare diseases. Their ability to continue to foster programs to benefit patients with rare diseases largely is a function of their budgets and the support they receive from the rare disease community.

GOAL #5 – NORD should develop systems that will enable greater patient access and participation in clinical trials of rare diseases. Recruitment to clinical trials for orphan drugs and medical devices often is an obstacle to timely clinical development.

GOAL #6 – NORD should seek to assure that there are no lifetime limits on medical care. Most rare diseases are chronic and, therefore, lifetime limits on expenditures for ongoing treatment affect patients with rare diseases. As the government and private insurance companies become even more focused on cost savings, the special needs of patients with rare diseases must not be ignored.

GOAL #7 – NORD should seek to assure reimbursement for off-label uses of drugs used to treat patients with rare diseases. The vast majority of patients with rare diseases have no FDA-approved medicines. When treatments are used, they often are medicines that are approved to treat common diseases but not rare diseases. Physicians are legally able to prescribe drugs for any patient who may, in their professional judgment, benefit from them, but reimbursement policies increasingly are denying payment for uses not specifically approved by the FDA. This means that patients with rare diseases may be denied reimbursement even when the accepted standard of care is to use a product that is not approved by the FDA for that specific use.

GOAL #8 – NORD should seek to assure that comparative effectiveness is not used to limit patient access to therapies for rare diseases. The Congress has appropriated more than \$1 billion to create systems to conduct studies that compare various treatments, with the goal to be sure that the safest and most effective treatment be the treatment of choice. The concerns are that such studies are not likely to be conducted in rare diseases, and that some drugs used to treat rare diseases may be denied to patients with rare diseases if they are not found to be superior to other treatments when used in patients with common diseases.

GOAL #9 – NORD should seek to define and communicate with more precision the differences between the needs of patients with rare diseases and those of patients with more common diseases, and advocate policies and processes that are different when needed. Orphan diseases and the products used to treat them require different policies and processes; the current product approval paradigm does not adequately address rare diseases and the unique obstacles in product development.

GOAL #10 – NORD should provide policy leadership as more personalized medicines are developed. Medical advances increasingly are focused on medicines and treatments that will be designed for individual patients based on their genetic makeup. New policies will be established by the FDA and other health agencies that must take into account the special needs of patients with rare diseases.

“ 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. ”

— Janet Woodcock, M.D.

The Participants and Agenda

The May 14 day-long Summit took place at the Willard Hotel in Washington, D.C. NORD convened a Blue Ribbon Commission of national thought leaders and invited speakers from the government and private sector to share their perspectives on innovation and access. NORD is especially grateful to David A. Kessler, M.D., J.D., former Commissioner of the FDA, for chairing the meeting; former HHS Secretary Tommy Thompson, J.D., for delivering the keynote address; and Social Security Commissioner Michael Astrue, J.D., for his luncheon address. Following is the agenda:

8:30-9:00 a.m. Introductions and Statement of Purpose

- Peter L. Saltonstall, President and CEO, NORD
- David Kessler, M.D., J.D., Professor of Pediatrics, University of California, San Francisco School of Medicine; former Commissioner, U.S. Food and Drug Administration
- Introduction of Blue Ribbon Panel Members;
 - > Bruce B. Dan, M.D., Executive Medical Editor, the Patient Channel, NBC Digital Health Network
 - > William Novelli, Distinguished Professor of the Practice, Georgetown University McDonough School of Business; former CEO, AARP
 - > Eileen M. Ouellette, M.D., J.D, FAAP, Past President, American Academy of Pediatrics
 - > William Schultz, J.D., Zuckerman Spaeder LLP
 - > Bruce C. Vladeck, Ph.D., Principal, Health Sciences Advisory Services, Ernst & Young LLP; former Administrator, Health Care Financing Administration
- Introduction of Ex-Officio Blue Ribbon Panel Members;
 - > Timothy R. Coté, M.D., M.P.H., Director, Office of Orphan Products Development, U.S. Food and Drug Administration
 - > Stephen C. Groft, Pharm.D., Director, Office of Rare Diseases Research, National Institutes of Health
 - > Frank Sasinowski, M.S., M.P.H., J.D., Hyman, Phelps & McNamara

9:00-9:30 a.m. Keynote Address

- > Tommy Thompson, J.D., Former Health and Human Services Secretary and four-term Governor of Wisconsin, Partner, Akin Gump Strauss Hauer & Feld, Chairman AGA Medical Corporation

9:30-11:30 a.m. Innovation of Therapies for Rare Diseases

FDA's View of Orphan Product Approvals

- Rachel Behrman, M.D., Associate Commissioner for Clinical Programs, Director, Office of Critical Path Programs, U.S. Food and Drug Administration
- John Jenkins, M.D., Director, Office of New Drugs Center for Evaluation and Research, U.S. Food and Drug Administration
- Daniel Schultz, M.D., Director, Center for Devices and Radiological Health, U.S. Food and Drug Administration
- Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- Robert A. Yetter, Ph.D., Director, Associate Director for Review Management, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration

Challenges and Opportunities in Researching Rare Diseases and Orphan Products

- Francis Collins, M.D., Ph.D., Special Volunteer and Former Director, National Human Genome Research Institute, NIH

11:30-12:30 p.m. Panel Discussion with Audience Participation

Recommendations for Enhancing Innovation in Product Development for Rare Diseases

12:30-2:00 p.m. Lunch

- Michael Astrue, J.D., Commissioner, U.S. Social Security Administration

2:00-3:30 p.m. Assuring Access to Therapies for Rare Diseases

Issues Arising From Genetic Advances

- Gail Javitt, J.D., M.P.H., Law and Policy Director, Genetics and Public Policy Center, Johns Hopkins University

Health Care Reform and its Impact on Development and Access for Rare Diseases

- Chris Jennings, President, Jennings Policy Strategies, Inc.

Assuring Access to Orphan Products

- Sol Barer, Ph.D., Chairman and CEO, Celgene
- Emil Kakkis, M.D., Ph.D., Founder, Kakkis EveryLife Foundation
- David Meeker, M.D., Executive Vice President, Therapeutics, Biosurgery and Transplant, Genzyme

3:30-4:30 p.m. Panel Discussion with Audience Participation

Recommendations for Assuring Access to Therapies for Rare Diseases

EXCERPTS FROM THE DISCUSSION

Following are key excerpts from the day-long discussion at the Summit. These excerpts were edited somewhat for clarity. For full transcripts of the morning and afternoon sessions, contact NORD.

Slides from the presentations and a video summary of the Summit are posted on the NORD website (www.rarediseases.org).

The Stage is Set for Change in the Drug Development Paradigm

DR. WOODCOCK: 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. Dr. Collins is talking this afternoon about how we can accelerate discovery, how we can fill the pipeline up better. 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.

The 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. There's nothing like a crisis in a business to focus the mind and to make people more open to alternatives.

There's a need for new development models with better predictive capacity. In other words, 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 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 the diseases of interest to them.

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 disease treatments.

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.

DR. GROFT: We have a tremendous amount of information about a lot of rare diseases. There's a lot of research ongoing, information is available, bioinformatic sources and processes are available. . . . How do we utilize that information so the physicians out there in practice and the other healthcare providers really know how to dose, what to use?

DR. COLLINS: 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 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.

DR. WOODCOCK: I think that what Francis (Collins) has proposed, which I agree with, is a broader initiative, which isn't just disease by disease. . . . 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. What we ought to talk about is new development pathways, new partnerships, new initiatives. And 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.

Drug Development is Changing

- Blockbuster model no longer highly viable
- Productivity crisis in pharmaceutical industry
- Need for new development models with better predictive capacity; yielding high value drugs
- Nonprofits and disease advocacy groups participating in development, not just research
- Thesis: orphan drug community can take advantage of these changes

Source: Woodcock presentation

MR. SASINOWSKI: One thing that struck me this afternoon is that I heard Dr. Barer talking about, for instance, that there hadn't been a drug for multiple myeloma in 30 years. Then, Celgene developed one and now there are several others being developed. I commented on that phenomenon earlier this morning, with pulmonary hypertension, because the first approval reduces the regulatory uncertainty. I heard the same thing from Dr. Meeker's talk about the value of knowing natural histories, so that if you know the natural histories, then we may have endpoints that can reduce the regulatory uncertainty. Just think about what that may mean.

We have 200 diseases for which there are drugs approved. That means there are 6,800 others for which there are no drugs. Yet companies are willing to go out there and develop a second multiple myeloma drug because of the reduced regulatory uncertainty to developing a drug for this condition since the first drug has been approved and blazed a regulatory trail for others to follow. That means companies are willing to forego having an orphan drug monopoly that they would have if they develop a drug for one of the 6,800. Talk about a business model! Think about that! Corporations are willing to forsake the opportunity to be a monopoly drug. Instead they would rather try to take market share away from another product. This is because the regulatory uncertainty barrier is so high that it's more attractive to get the second orphan drug in a disease like multiple myeloma than to fight through the

regulatory uncertainty of blazing a trail for the first drug to treat one of the other 6,800 rare diseases that today lacks any drug therapy.

So that's why I was captivated this morning by all the discussion about how important it was for patient groups to work with the scientists at FDA and NIH and with academics to try to develop natural histories, and to try to develop pivotal study endpoints. It's like "Field of Dreams." I'm picking up on that third brick wall that Francis (Collins) talked about: the clinical endpoints. If we can reduce that wall by developing natural histories and pivotal study endpoints and, thereby, reduce regulatory uncertainty, then maybe we as patient advocacy groups will be able to draw more companies in to begin to develop therapies for those other 6,800 diseases.



The traditional study designs and analyses, 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. ”

— Emil Kakkis, M.D., Ph.D.

The Benefit-Risk Balance for Orphan Drug Development

DR. JENKINS: The first part of the (drug approval) 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 clinical trials that we usually think of when we're thinking about the blockbuster model.

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 from 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.

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.

DR. YETTER: We understand that for these types of studies, for these kinds of products, we have to have flexibility. As John (Jenkins) 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.

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.

“De-Risking” Orphan Product Development: the 3 “Brick Walls” of Assay Development, Preclinical, and Clinical Development

DR. COLLINS: There’s 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 the academic community is hungry to begin to be a broader participant in this but needs some tools, some support.

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 bio and pharma companies who are going to play a critical role here.

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. 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.

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



My bottom line is that we can come up with a model that de-risks these kinds of projects in a way that makes them more attractive for commercial development ...



— Francis Collins, MD, PhD

My bottom line is that we can come up with a model that 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 begin to be more appealing.

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

and so many steps involved in taking a promising initial compound and bringing it to the point of having something that could go into an IND.

The clinical effort needs attention as well, and I think the bottom line here is that 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 when 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 are often not in place are 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.

“ 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. ”

— John Jenkins, M.D.

DR. KAKKIS: The traditional study designs and analyses, 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 how to design studies for very heterogeneous complex multisystem diseases.

What I want to very quickly go through is the fact that surrogates are very hard to use. You have a defect. We treat the model, but 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 based on the surrogate. Now, that process is never going to happen with some of the rare diseases.

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.

We need to figure out how to get qualified surrogate endpoints, and these qualified – not validated, qualified – are reasonably likely to predict clinical benefit, if we can accept what those criteria would be.

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 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 what really is there.

We need to be able to evaluate multiple endpoints, which is not done today. 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.

MR. SASINOWSKI: In listening to the various speakers, I picked up a common thread that was reinforced by my experience. Almost every day I'm involved helping sponsors develop new therapies. I heard 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.

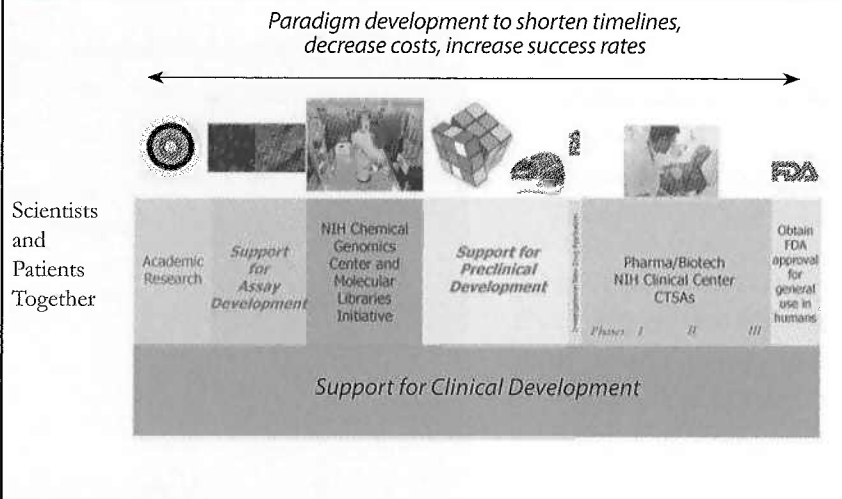
Natural histories are something that we – now I'm speaking as vice chair of the board of NORD – we in the patient or advocacy community can help develop, together with the academics and the physicians dedicated to treating those patients with rare disorders, to address that third barrier.

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, to take the lead. That's what Emil Kakkis was talking about with his work at BioMarin. Companies like

A New Public-Private Partnership

An innovative, integrated and generalized drug development process for rare and neglected diseases



Source: Collins presentation

BioMarin have been the ones who have been 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, we have

“ 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. ”

— Francis Collins, MD, PhD

FDA, NIH, the scientists who understand rare diseases like Sami Said, the head of the NORD Scientific Advisory Board, and lots of other notable experts. 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. WOODCOCK: Frank, that's one of the things I was suggesting -- that the public-private collaborative partnerships not only look at natural history, but construct to the best of our ability a quantitative disease model where we actually quantify all the different endpoints.

DR. COLLINS: 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 in which 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.

Simplifying SSA's Disability Determination Process

Social Security Commissioner Michael Astrue described the Quick Disability Determination and Compassionate Allowances programs during his luncheon presentation.

MR. ASTRUE: We had a very small pilot (for speeding the processing of disability claims) tested in a few states in New England, with a planned 10-year rollout that would pull out cases for triaging, but really just highly probable cases. That was something that we could make much more robust and roll it out much more quickly, which is what we have done. So now we have something called QDD, quick disability determination, where we take the cases that are highly likely (for disability) -- and we still have to go through our five-step process -- but at least we put them at the head of the queue. And we can decide those cases extremely quickly.

But we had never embraced the notion that we could essentially have categories of diseases or conditions that would be presumptive, where basically our only job was to confirm that someone was eligible for Social Security and that, in fact, there was a correct diagnosis, which saves us an enormous amount of time and effort. So we created a category called "compassionate allowances." And it is not necessarily a restriction of the system, but I think pretty much everything in compassionate allowances is, in fact, a rare disease and pretty much everything that comes out in the QDD model is also well under the orphan drug guidelines, even though we don't explicitly restrict it to that list.

So first we started with the QDD model and we made it more robust and expanded it. And we have pushed that out nationwide. And then about six months later, we got a parallel system for essentially an even faster, more presumptive category called compassionate allowances. As we speak, about 4 percent of the 3 million (disability) cases that are decided this year will be decided in an average of 10 days. That will be about 100,000 to 125,000 people. They will basically all be people with rare diseases and conditions. And they will be picked out. And they will get benefits much faster than before.



I think it's important for all orphan drugs to be reimbursed equally, regardless of modality...I think reimbursement of off-label has to be looked at very carefully.



— Sol Barer, PhD

Off-label Prescribing and Reimbursement

DR. BARER: Practically speaking, a drug goes generic after seven years, so there's just no benefit for any company to develop a drug for more than one rare disease. We need to understand the influence of orphan drug exclusivity. The Office of Orphan Drug Products at the FDA has been fantastically successful, with the Orphan Drug Act and NORD, in bringing this to a new level. But I think we really have to examine whether there is a way for us to go to the next step....

In a quote that was in The New York Times, a brain cancer patient said, "Because it was a pill, I had to pay, not my insurance." I'm sure many of you know, especially in terms of Medicare Part D versus Part B, that if you take an oral drug – and sometimes that's the only thing that's available – a patient has a higher co-payment and a patient also has to pay through the doughnut hole. This is thousands of dollars for a patient with a rare disease....

I think it's important for all orphan drugs to be reimbursed equally, regardless of modality associated with it. I think reimbursement of off-label has to be looked at very carefully. There are a lot of implications. But for example in the area of cancer, if it's listed in a prestigious compendium like the NCCN, the National Comprehensive Cancer Network, and has peer review publications, then that should be something that is good enough as a basis for reimbursement for some really rare diseases.

MR. VLADECK: If there is good data suggesting that there's an appropriate indication, then why is it so difficult for a manufacturer to get those indications approved? Is that a function of the inadequacy of the bureaucracy, or the inadequacy of the process? Or is it more profitable for them to promote off-label use?

DR. KESSLER: While that is happening, the patient is stuck in the middle.

MR. VLADECK: But there is not a perfect answer. If you

look at the incredible bureaucracy that CMS and others have set up to determine which off-label use is okay, and which off-label use is not okay, and which compendia do you use and how many peer review articles do you have to use, this is a surrogate for an FDA that is not functioning the way the FDA is supposed to function.

MR. SCHULTZ: I don't know the data for orphan drugs, but I think you have to look carefully to see whether the problem is that it's too expensive to do the trials, in which case you need to try and find a policy that identifies off-label uses that at least have promise. I would not advocate a policy that just reimburses for all off-label uses. But somehow you need to find something in between an FDA approval and simply no data.

Lifetime Limits/Catastrophic Coverage

MR. VLADECK: Our problem with healthcare costs is not what we're paying for 20 percent. It's what we're paying for those other 80 percent. As my successor Tom Scully used to say, it's not the real life-saving drugs that are killing us. It's Nexium that's killing us. It's not the rare biotechnology products that are killing us. It's the brand-name statins. That's where the money's going in this system.

I think if to the extent that NORD and its constituent organizations are worried about somehow being singled out in cost containment because of the visibility or the unit costs and so on and so forth, I think there's a relatively easy case to make that it's only thoughtless, dumb cost containment that focuses on a very small number of cases. The big money is in the middle of the distribution.

DR. KESSLER: So that's the policy? No cutoff, no lifetime cap, for patients with rare disease.

MR. NOVELLI: David, I know what you're trying to get us to. It just seems to me that Bruce (Vladeck) is correct, and that it has to be a given, a going-in position on NORD's part, on the community's part, that this reformed system has to bear the

burden for vulnerable populations. We cannot have care being rationed in any way. I don't think the public would stand for it.

Genetic Testing & Pharmacogenomic Labeling

MS. JAVITT: What we want is access to genetic tests that are valid and reliable and informational, informative, and also information that is truthful and not misleading to consumers and patients. And also access to interventions and therapies informed by those genetic tests. And of course, once we have those tests we want to make sure they are paid for, but without the baseline valid test, there is nothing to pay for.

There also is a need for high quality laboratories to perform those tests and get those diagnoses, and those laboratories must have personnel that are adequately trained to communicate the information about those tests. Then access by whom gets us to the issue of privacy of the information that's provided by genetic testing.

In terms of how many genetic tests there are to do all these things that we want them to do, there's been a huge growth in genetic tests. There are now tests available for more than 1,500 diseases, but I say that number advisedly because there is no requirement anywhere to register if you are performing genetic testing. So these numbers are based on a voluntary system of registration. There are likely many more but we may not know about them because there is no obligation to be transparent.

So who's in charge? That's a complicated question and there are many potential players. There is not a lot of coherence, and a lot of things are falling through the cracks right now. So to the extent that there is oversight of genetic tests today, the locus of oversight is within the Department of Health and Human Services, and specifically FDA and the Centers for Medicare and Medicaid Services, which we think of usually as the payer.

But CMS is kind of stuck in 1988, when there is a need to update the regulations to ensure the quality of genetic testing laboratories.

We are doing a study right now to try to figure out what is the pathway by which pharmacokinetic information should get into the drug label. What we are finding is it's really not very consistent or coherent. If personalized medicine's going to

succeed, you need tests that work that you can be sure of, and you need a pathway to get the information into the label and to physicians.

In April 2008 the (HHS) Secretary's Advisory Committee on Genetics, Health and Society, which Dr. Collins was on, issued a report saying there are real gaps in the oversight of genetic testing that have potential risks for patients. They recommended updating proficiency testing requirements, having a mandatory registry so that if you're offering a test you have to show your work, show your data. Oversight by FDA based on the level of risk of a test but not how the test was performed. More enforcement for noncompliance, and a way to assess the clinical utility of tests. All excellent recommendations.

Just to recap my recommendations for this Blue Ribbon panel: We need test oversight that's based on the level of risk and not the method by which the test is performed. And laboratory oversight needs to make sure that we get accurate tests, and we need to have data to measure whether we're getting accurate tests. There needs to be transparency in the data that underlies the tests that are being offered. We need pharmacogenetic information to be rapidly integrated into drug labels. We need to demand truth in advertising and claims about genetic tests, and GINA of course should be quickly and rationally implemented.

There really needs to be a rethinking of what kind of data the agency is going to be willing to accept for pharmacogenetic claims.

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