FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

AND CLINICAL PHARMACOLOGY (ACPS-CP)

Wednesday, March 2, 2011

7:15 a.m. to 3:00 p.m.

Hyatt Regency Dallas at Reunion

300 Reunion Boulevard

Dallas, Texas 75207

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY MEMBERS (Voting)

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(Industry Representative)

Associate Director of Medical Affairs

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GUEST SPEAKER (Non-Voting)

A Paradox in Orphan Drug Development

Trevor Mundel, M.D., Ph.D.

Global Head of Development

Novartis Pharma AG

Basel, Switzerland

FDA PARTICIPANTS (Non-Voting)

Lawrence J. Lesko, Ph.D.

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(7:17 a.m.)

Call to Order

DR. VENITZ: Good morning, everyone. Welcome to the Clinical Pharmacology Advisory Committee meeting. My name is Jürgen Venitz. I'm the acting chair of the committee. I'd like to start by introducing all the members as well as the FDA staff that's in attendance. And maybe we can start from my right by introducing yourself, including your affiliation, please.

DR. MAYER: Phil Mayer from Pfizer.

DR. GIACOMINI: Kathy Giacomini from University of California San Francisco.

DR. THUMMEL: Ken Thummel, University of Washington.

DR. LERTORA: Juan Lertora, NIH Clinical Center.

DR. HARRALSON: Art Harralson, Shenandoah and George Washington University.

DR. CLOYD: Jim Cloyd, University of Minnesota.

DR. MCLEOD: Howard McLeod, University of North Carolina Chapel Hill.

DR. MAGER: Don Mager, University of Buffalo.

DR. COLLINS: Jerry Collins, National Cancer Institute at NIH.

MR. GOOZNER: Merrill Goozner. I am an independent writer.

DR. RELLING: Mary Relling, St. Jude Children's Research Hospital in Memphis.

DR. CALDWELL: Michael Caldwell from the Marshfield Clinic.

DR. REED: Michael Reed from Akron Children's Hospital and Northeastern Ohio University's College of Medicine.

DR. BARRETT: Jeff Barrett, the Children's Hospital of Philadelphia and University of Pennsylvania.

DR. PARISER: Anne Pariser, FDA.

DR. GARNETT: Christine Garnett, FDA.

DR. BASHAW: Dennis Bashaw, FDA.

DR. HUANG: Shiew Mei Huang, FDA.

DR. LESKO: Larry Lesko, Office of Clinical Pharmacology at FDA.

DR. VENITZ: Thank you. Let me begin the meeting by reading the introductory remarks.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these

proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now Dr. Waples will read the conflict of interest.

Conflict of Interest Statement

DR. WAPLES: The Food and Drug Administration, FDA, is convening today's meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative and guest speaker, all members and temporary voting members are special government employees, SGEs, or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and

conflict of interest laws, covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's

meeting, the members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of innovative approaches to development of drugs for orphan and rare diseases to support decisions such as dose and trial design selection. FDA will seek input and comment on how to optimally utilize mechanistic biomarkers and apply clinical pharmacology tools such as pharmacogenetics and modeling and simulation to facilitate efficient and informative drug development and regulatory review.

FDA will present and seek input from the committee on how lessons learned from other applications of clinical pharmacology tools in

pediatrics and oncology can be applied to orphan and rare disease drugs.

The committee will be asked to comment on the current status and future direction for clinical pharmacology studies -- for example, dose response, drug-drug interaction, pharmacokinetics in patients with renal and hepatic impairment -- as they pertain to drug development for orphan and rare diseases.

This is a particular matters meeting, during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with the meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the issues before the committee.

With respect to FDA'S invited industry

representatives, we would like to disclose that Dr. Philip Mayer is serving as a nonvoting industry representative acting on behalf of regulated industry. His role at this meeting is to represent industry in general and not any particular company. Dr. Philip Mayer is currently an employee of Pfizer.

With regards to FDA's guest speaker, the agency has determined that the information to be provided by the speaker is essential. The following interest is being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker. Dr. Trevor Mundel is employed by Novartis. As a guest speaker, Dr. Mundel will not participate in committee deliberations, nor will he vote.

We would like to remind members and temporary voting members that if discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such

involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. VENITZ: Thank you, Yvette.

Our first speaker is Dr. Lesko. He will give us some background and introduce the topic of today's discussion. Dr. Lesko.

Presentation - Lawrence Lesko

DR. LESKO: Good. Thanks, Dr. Venitz, and good morning, everybody. I'd like to welcome the committee to Dallas; thank the committee for coming to Dallas. This is our second offsite Clinical Pharmacology Advisory Committee. We started the first one last year in Atlanta in conjunction with the ASCPT. Everybody felt it was a good success. We had a lot of input both from the committee and from people that were in the audience during the course of the day. So we thought we'd try it another time. Besides, I think our advisory committee staff likes to get out of Washington once

in a while.

Well, some of you have been on the Clinical Pharmacology Advisory Committee for its entire life, I would say. This is our ninth or our tenth meeting. I couldn't quite remember them all. I remember a lot of them because it seemed in almost every one we discussed three topics -- drug interactions, renal impairment guidance, and clinical pharmacogenomics. So today we have something entirely different. The first meeting, by the way, was back in 2002, and today we're going to move into a new topic.

Today we're going to be talking about something new for this committee, rare diseases and orphan drugs. So just to sort of set the stage for today, I realize not everybody on the committee may necessarily be involved with rare diseases and orphan drugs. But I think the thing to remember is that what we're going to try to talk about today is really good, rational, incredible drug development, bringing the tools of clinical pharmacology to bear on a very special situation in drug development,

rare diseases and orphan drugs.

It's an ideal area I think for clinical pharmacology because it's one of those areas where we have to get the most out of the least amount of data when we compare it to conventional types of drug development. So the way we do that and the way we have done it employs a lot of clinical pharmacology tools. So think of this not only as rare diseases and orphan drugs, but think of it as a good, systematic way to develop drugs in general.

Before I get into the specifics of today, I'd like to just kind of refresh and review the past year. We met last year on March 17th in Atlanta, and we talked a lot about clinical pharmacogenomics. And 11 months to the day, the guidance finally came out. I've shown it on the top there, and it's now out for public comment for something like 60 or 90 days.

I hope you get a chance to go look at it and think about the discussions we had last year and in 2009 and 2008 over this guidance. And the little blurb on the bottom from the pink sheet indicates

the connection between the advisory committee and the draft guidance. And I think it speaks to the importance of this committee because over the years, the input that the committee has given us has been instrumental in us developing a guidance.

Even today with rare diseases and orphan drugs, we have the thought in mind that we might want to write a guidance on rare diseases and orphan drugs. We're mandated to do that, I believe, by NFDA, more general guidance. But we've been talking with Anne and Tim and others in FDA about possibly writing a clinical pharmacology guidance in this area that would lay out a blueprint for good clinical pharmacology as it applies to rare diseases and orphan drugs. So the input today is going to be very valuable in that context.

So this guidance is out as draft. Last year we talked about two other guidances. I'll give you an update. The first is the drug interaction guidance. Last year we talked a lot about transporter-mediated drug interactions. We've

created a new decision tree for the drug interactions that involve inhibition and induction. We've used a lot of our experience with PD/PK physiological-based pharmacokinetic modeling to look at multiple co-factors in DDI. We've added some drug protein drug interactions, how PGx pharmacogenomics data can inform drug interactions, and then something about the non-CYP enzyme drug interactions.

This guidance is basically complete. We have it in the process for CDER clearance. We don't know exactly when it'll be out, but we anticipate that in 2011 of this year, June, it'll be released for public comment.

Last year, we also talked about the renal impairment guidance. We talked about studies for non-renal routes, how to stage, which has been it seems like a year-long discussion now about MDRD versus creatinine clearance. We put both into the draft guidance; hemodialysis studies, renal studies of large molecules, proteins, labeling recommendations, and then we addressed many of the

2010 comments we had on the draft guidance and the comments that we had from this committee during the past year.

It's moving ahead, not as quickly as we'd like it to be. But, again, this year we anticipate we'll send it for clearance in June of 2011 and hopefully have it out and complete as a draft guidance for comment, or maybe a final guidance this time around, in 2011.

So that's the update of past discussions. But let me get into today's discussion and talk about what we're here to focus on.

So rare diseases is one affecting fewer than 200,000 people in the United States. Yesterday we had a symposium on personalized medicine, and it became clear from the discussion that most of the diseases of cancer that were discussed yesterday were in fact rare diseases. So rare diseases really are nothing new in that context, but there are 6- to 8,000 of these diseases that affect 7 percent of the population. Four out of five have a genetic basis, and 70 to 75 percent have a

prevalence of less than 100,000 patients.

An orphan drug is one that has been developed to treat a rare disease. More than 2200 molecules have been designated as orphan drugs. Thirty to 40 percent are for what people call rare cancers, and since 1993, FDA has approved roughly around 362, although that number keeps changing with time.

So I said in the beginning this is sort of an ideal area for the application of clinical pharmacology. And the reason I said that is because orphan drugs and rare diseases are characterized by these attributes. We have a large heterogeneity in disease pathophysiology. We have poorly understood natural histories and progression. We have relatively few patients to make the best of, in terms of clinical trials. We have uncertain appropriate durations of therapy for a durable response on these diseases. In some cases we lack appropriate endpoints that predict outcomes, or even clinical outcomes themselves, in which case biomarkers need to be relied upon more;

large heterogeneity in treatment effects, which means sorting out the causes of variability with biomarkers or generic factors.

At the end of the day, this particular area requires compromise, innovation, and tradeoffs. We can do business this way. We always do business with conventional drug development. So it's those compromises, those innovations, those tradeoffs, that are going to be really critical I think to what we discuss today; how can clinical pharmacology help in those tradeoffs?

Finally, we have difficult decisions to make in a regulatory agency in the absence of ideal information. So think about today in the context of extracting the most amount of knowledge from the least amount of information, and how can we do that in a systematic way to improve the orphan disease, rare drug development.

Now, February 28th, just around the corner, was Rare Disease Day. Rare Disease Day, this was the fourth one. It's an international event. And the whole purpose of Rare Disease Day is really to

raise public awareness of rare diseases and to try to engage policy-makers, scientists, clinicians to try to apply their knowledge to affect this area.

FDA, we've said it before; several people have said it, the development of effective medicines for rare diseases is a primary FDA objective. It's in our strategic plan for 2011.

Now, there's been a lot of activity in the area of rare diseases. I call these trends. If you watch what's going on in the landscape, we've seen licensing deals. I've given an example there. We've seen mergers. We've seen label extension strategies. Several government agencies have road maps. And several companies have now established dedicated research units to address the issues of rare diseases.

Finally, we have the Institute of Medicine calling for this national strategy to apply the advances in science and technology and innovation, innovations across the board in terms of trial design and so on and so forth. So there's an urgency here, as reflected by all of these goings-

on. And I think it's very timely then that we talk about this topic at our advisory committee.

Now, I've tried to categorize here rare diseases and orphan drugs to put them into little buckets so we can think about them better during the day. The only thing I'll ask you to sort of take with a grain of salt is the frequency of the rare diseases I've used as my example. I found when doing this slide it's actually very difficult to get the incidence of rare disease and define a rare disease specifically, so these numbers that I have up there for each of these examples are probably not entirely accurate.

But what's important in this slide is the categories. The first category is the NME, the new molecular entity, for, as yet, an untreated patient population with a rare disease. An example of this would be an enzyme replacement therapy for Pompe disease. It has an incidence of 1 in 40,000, as best I can tell. The disease is a genetic disease. There's a problem with lysosomal enzymes. GAA represents a substitute for the endogenous enzyme.

The symptoms I've listed there only to emphasize that these are serious disorders and people in real need of medical treatments, but muscle weakness, enlarged hearts, difficulty walking. That's one category.

The second is drugs for common disease that are also utilized in rare disease. The common term for this is repurposing, and an example would be sildenafil, a drug for erectile dysfunction, that has been recently approved for pulmonary hypertension in pediatric patients. It's a selective inhibitor of phosphodiesterase type 5. In its application, it comes along with a lot of different cardiac biomarkers that allow us to get to a proof of efficacy quickly that can correlate with clinical outcomes. And you'll see an example of that in another presentation. But, again, the symptoms are severe. The patients are in need.

Finally, there's the drug for rare disease that also has a line extension to a drug for common disease, Ilaris, canakinumab -- I can't say that very well -- Ilaris for Muckle-Wells. Trevor will

talk about that. As an example of that, it was approved for CAPS, and under CAPS is Muckle-Wells syndrome as one of the disorders.

Again, interleukin-1 beta is over-expressed in this disease. This is a drug that is an anti-interleukin-1 beta. And again, the symptoms and the severity are as I've shown them on the slide.

So orphan drugs, rare diseases, will fall into these categories, and think about when you see the examples during the course of the day.

This slide I've adapted from an article that appeared recently in the literature. And I thought it was sort of a visual mapping or a visual image about how orphan drugs come about. And on the Y axis, you can see the driver of drug development. Arbitrarily, it goes from a disease based on a molecular pathway to a drug based on pharmacological mechanism of action, sometimes empirical.

On the X axis is a range of populations, individuals to populations. On the left side, populations less than 200K, typical rare

disease/orphan disease, and gets into the realm of personalized medicine. On the right-hand side are populations with what we call evidence-based medicine, medicine applied to the general public over 200K.

So here are the orphan drugs. They're in that category, very much disease-driven, very much molecular-based, very much focused on individuals and personalized medicine, given the small subset of the general population. In contrast, we have in the upper right-hand corner the drug-oriented drug driver for development intended to apply to large populations. And then in the left-hand column is the emerging world of targeted therapies that we've seen predominately in oncology.

So here the visual mapping of blockbusters being repurposed for orphan drugs. That's a sildenafil example that I mentioned. Another way this goes is to expand the indication. As we'll see, some of the drugs used in orphan diseases, we'll see examples today about how knowing their mechanism of action, how knowing the

pathophysiology of a disease can help transfer that information to a much larger population and represents a nice, viable business model. And then we'll see that many orphan drugs, by nature of their cause, being genetic, represent in fact the ideal personalized medicine in terms of targeted therapy. So this is kind of the mind map of what we're talking about today.

Now, this is a general model for development of orphan drugs. And I have really three steps. They're fairly simple, but it gives you a sense of what we're trying to capture here in the advisory committee.

The first step is trying to establish a linkage between the biological mechanism of action of the drug and the molecular-based sub-disease -- marrying those two together, identifying a target, getting to cures, and not just symptom control. Unfortunately, many orphan diseases don't have cures. They only have symptom control. But I think understanding pathophysiology of disease and mechanism of action can get there.

This is just one example, inhibition of IL-1 inflammatory mediator. It's in the synovial fluid of joints in RA, not necessarily in CAPS. That's a little bit of a misnomer there. But it was first approved for CAPS, and it can be extended to RA because the mechanism and the receptors are similar, and I think the key part is the causal pathway.

The second step is really the world of clinical pharmacology, looking at changes in biomarkers that enable a rapid proof of efficacy concept. Sometimes this step in the process can represent supportive evidence of efficacy. Sometimes it can represent the blueprint for the subsequent clinical trial and increase its probability of success.

Step three is basically to think about innovative trial designs. Yesterday we heard, in the oncology discussion of personalized medicine, many examples of innovative trial designs, whether they're adaptive, they're enriched, things of that sort, to validate biomarker outcomes and to apply

quantitative methods, what we typically call pharmacometrics, to the analysis of dose response.

Just to represent the step on the left, we have PK/PD models and simulation being used in the case of Ilaris, looking at the interleukin-1 beta as a biomarker and looking at healthy volunteers to get a design of a trial from that information and optimal dosing. And n the right is another example of improvement in five clinical response criteria as observed with a function of dose.

One of the questions for today's discussion is, what type of clinical pharmacology package would one think would be important, particularly for new molecular entities that are being used for rare diseases?

So there's going to be a lot of thought going into this threshold of information and whether or not it does include good dose response, drug interactions, special populations, all that kind of stuff. But what does that boil down to in terms of an essential package, and does that include, for example, dose-response studies, and

how would they be done officially? So this is the kind of conundrums that we have to talk about today, and are looking for advice.

Now, development strategies for orphan diseases are really an evolving paradigm, and looking over the past approvals of rare diseases, basically I could say there's no consensus on what constitutes an ideal drug development program. There's no right way. FDA has seen as many different approaches to drug development as they have approved drugs in this area.

What we think, and it'll permeate our discussion today, is that the lessons we've learned from the application of clinical pharmacology and pharmacometrics and genetics to the areas of pediatric and oncology drug development can be also applied to rare diseases. We haven't done that, at least haven't done it to the extent we can to date, but taking those lessons learned and applying them to this area may expedite drug development.

Late-stage clinical development programs, whatever late-stage happens to be in the area of

orphan diseases, can be guided by early-phase clinical pharmacology studies. It's a truism. It hasn't been done in this area. It should be done in this area. And the question is how do we do that efficiently and what kind of data do we need?

Then, finally, in this area, because we have oftentimes to make do with so little, I think biomarkers, good dose response, PK/PD study data, are going to pay an essential role and could be in some cases persuasive as confirmatory evidence of efficacy when we can't do a full-blown randomized controlled trial program.

This is just to give you a synopsis of the orphan drug approvals and some recent successes. This covers the time period, as you can see, four years. You'll see something that is maybe a disconnect in one way because we have thousands of orphan drug designations, but we don't have thousands of orphan drugs approved. And that might be worth discussing today, and perhaps some of the other presenters will address that.

But over this time period, there were

34 approvals, 22 NDAs, 12 BLAs. These are, I believe, new molecular entities. Dennis can correct me if I'm wrong on this. But you can see where the action is in the therapeutic areas, much of it not a surprise, as in oncology.

But in the other areas, it's kind of interesting where the activity is in terms of GI and inborn areas of metabolism, rheumatology, neurology. And then a whole bunch, probably a dozen therapeutic areas, go into the little piece of that pie that is marked "Other." So there's a lot of one-off therapeutic areas and drugs used in those areas.

A further breakdown of this data indicates there were 34 approvals representing 27 different indications. So this is not a crowded marketplace by any means. Six indications had two approvals; 26 different companies were involved with the 34 approvals. Again, there's no lock on this area, no birthright to the approval process. No sponsor had more than three approvals.

You can see the trend lines on the bottom,

thinking about those buckets that I showed you in the beginning for rare diseases/orphan drugs; 38 percent over this time period were original approvals and 62 percent were those repurposed approvals that I showed.

This is a summary of orphan drug approvals in CDER in 2010. It gives you a sense of the indications that have been identified in terms of drug approval. You can see the time. One way to think about this in context if what percent of overall drug approvals over a time period have been for rare diseases. I don't know the number exactly off the top of my head, but I want to say probably one-fourth to one-third of drug approvals have been for rare diseases over the past decade. Anne or Tim can correct me if I'm wrong on that.

So the key features of the programs that were approved in 2010 when you analyzed our attributes, you can see, if you remember that slide, it was a diverse collection of diseases. There's no particular focus on this disease or that disease, and a diverse collection of patient

populations.

As I said, these are not large programs. The program size for those drugs approved in 2010 went from 23 patients to 540 patients. That's much smaller than a typically phase 2 trial or a phase 1 trial for a conventional drug development program.

The study designs and development processes were very broad and very diverse. Many of the approvals relied on novel and well-established clinical endpoints. We generally say that endpoints, whether they're outcomes or biomarkers or surrogates, need to be reliable, meaningful, well-defined, and fit for the purpose. And a wide range of study designs in almost every case reliant on a totality of evidence to make a regulatory decision for the approval.

So understanding the factors for success in orphan drug development is important, and this is almost like a checklist of what clinical pharmacology focuses on in drug development. And that's why I think this is a nice marriage between our science and also the needs.

Understanding disease pathology and identifies disease targets. The ease of demonstrating proof of concept -- there's a high probability the drug is going to work. Showing the linkage between the drug and target in terms of dose response, in terms of PK/PD. Delineating drug mechanisms of action and having clear and identifiable symptoms, knowing who to enter into the clinical trial to assure that efficacy can be demonstrated with small patient populations.

The key in all of these areas is mechanistic biomarkers. I think that's the foundation for good drug development in the rare disease area. And, indeed, many of the examples today, you'll see how mechanistic biomarkers facilitate a regulatory decision-making.

So what has brought us to this point? Why are we talking about it with the committee? Well, these are some of the reasons. Large randomized controlled trials and full clinical pharmacology program packages are just not feasible in developing orphan drugs. The patient populations

aren't there. The unmet need is crucial. We have to move quickly. Mechanistic approaches to drug development lend themselves to quantitative analyses, which is a hallmark of clinical pharmacology science.

Third, we've seen advances in pharmacometrics, that clinical trial simulation use of modeling can make important contributions to pediatric drug approvals. So I'm transferring experience from that world into the rare disease world.

Scientifically sound tradeoffs between full and light clinical pharmacology data sets have enabled oncology drug development. Again, we'll be reflecting on what's done in oncology, which shares many of the attributes with orphan drugs/rare diseases.

Finally, well designed clin pharm studies, innovative data analysis, can provide and has provided in pediatrics and oncology substantial evidence of benefit, and I believe it can do so in the area we're talking about today.

Now, one of the important challenges we may want to get into a little bit today is identifying safety signals with small populations. This isn't characteristic only of orphan drugs/rare diseases, but many clinical studies in drug development in general are underpowered to detect serious adverse events, but yet it's an important issue when we have unmet medical needs like we have today. So a regulatory agency needs a full assurance, or at least as best it can be assured, that benefits outweigh the risks.

We discussed the last bullet last year when Dr. Abernethy presented an approach to identifying safety issues by studying the off-target pharmacological mechanism of action of drugs. That program has progressed nicely in the past year. We had a workshop in January of two days with colleagues from industry and academia to talk about how to move the program forward. We won't talk about it very much today, but I want to put it on your radar scope for a possible discussion next year when this program becomes more mature.

There is a symposium at the ASCPT meeting -- I think it's Thursday -- that will more or less be an update on this program. But I see this as one of the solutions to addressing the safety issue with small populations.

So the goals for today are really to focus on the role of FDA, to focus on the role of clinical pharmacology to move this field forward. On the top is the regulation, and think about this. FDA is required to exercise scientific judgment to determine the kind and quantity of data and information that an applicant is required to provide for a particular drug to meet the statutory standards. That's 314.105.

In this area, however, regulations provide room for flexibility in the review of these treatments for rare diseases and the applications of standards and needs to use good scientific judgment. So I think today is all about flexibility in meeting the statute, and the role that modern clinical pharmacology can play in the application of its processes, its tools, to provide

the kind and quantity of data information that applicants need to meet the regulatory standard that I've indicated above.

The concluding thought I've borrowed from a website and a quote of Greg Simon, who runs an organization called Faster Cures, which is an advocacy organization for rare diseases. And this chart on the left came from a workshop that they held in Lake Tahoe not too long ago. And I kind of like the brain mapping that went on there.

It says, "Isn't somebody already doing this? No. Everyone is focused on the part, not on the whole system. It's not the train, it's the track. So we need action-oriented, not disease-specific. It's not the money. It's how we spend the money." And I think that's kind of a thought process for me in the area of orphan drugs. It's how we use our money to build a drug development program.

Then he closed the meeting with this thought. "Why does it take so long to find cures?" And he said, "Consider this. The potential speed of a high-speed train is 200 miles per hour, but

the average speed of today's train is 55 miles per hour. It's not the speed of the train that holds us back, it's the speed of the track. We need better and faster tracks for faster cures."

The metaphor here is that the train is the drug. The track is the process of drug development. And that's what we're going to focus on today. Thanks.

[Applause.]

DR. VENITZ: Thank you. Thank you, Dr. Lesko.

Are there any clarifying questions? And I would ask the committee to hold off the discussion till after the open public hearing. So right now we are going through the presentations one at a time, and I'm asking for any clarifying questions for Dr. Lesko's presentation.

[No response.]

DR. VENITZ: Since there are none, then let me go to the next speaker. Dr. Cote is going to talk about the FDA's perspective on rare disease drug development.

Presentation - Tim Cote

DR. COTE: Good morning, everybody. A beautiful day like this makes even an East Coast boy want to say howdy here in Texas. It's great to be here, and thank you all for coming. This is a very, very important day. Getting the advisory committee's input on this important matter will advance the field greatly.

You've already heard from Larry. He and I talked a great deal about today in advance of it, and his hopes and my hopes for today. The Institute of Medicine report you've all heard about. Many of you will also know that the FDA appropriations bill of 2010 required us, Section 740, to put out a report to Congress which is due imminently, within a matter of days or weeks, and we'll be moving forward on this important topic. But getting your scientific input on this is critical. And the time -- let's just say that the topic is ripe.

What I'm going to do today is give you a little bit of a historical perspective, set this

all in a context and talk about the Orphan Drug Act, what's happened over the past 27, 28 years since it's come about; the mega-trends, what has happened in America to this, what did it come out of?

This is a uniquely American experience. It's a result of our democratic system. And I want to show how the orphan drug movement and the orphan drug community -- and indeed, it is a movement and a community as much as a scientific problem -- has grown out of this, and what it means, and where we're going, hopefully.

So, yes, my name is Tim Cote. I'm the director of the Office of Orphan Products. I've been there for about three and a half years. We're going to talk about the Orphan Drug Act. Basically, for many of you, I assume there's a variety of understanding of it. So this is Orphan 101 for you, the promise and what it's delivered.

I want to go into a little bit of detail about this orphan drug designation bit, how does a product get orphan status designation, and some of

the little technical aspects of that because it has some implications for the future and what we can expect going forward in making new drugs.

Of particular interest is this question of medically relevant subsets, and when are they medically relevant and when are they what we call salami slicing? That's important and relevant to where we're going forward in the future with regards to making new, more personalized, and less impersonal medicines.

Finally, I want to wrap up with -- I'll give you some examples of orphan drugs. But I want to wrap up with a little bit about the relationship between the Office of Orphan Products, which I am the director of, which sits in the Office of the Commissioner, and the review divisions; and where do our various authorities lie, what do we work together on, what's their turf, what's our turf, so that everybody can understand how things work there in the agency.

So let me transport you back to 1983, when I was a new medical student, I guess. Things were

different then. The problem was that the basic, fundamental marketplace of drug development worked this way. A drug company puts a lot of money into developing it, and then gets an approval, and then goes out and sells it and recoups its money. Well, that doesn't work very well if you have very few people to buy your pills. And by definition, in rare diseases, we don't.

So the data are consistent with that, from 1973 to 1982, there were only about 10 new drugs for people with rare diseases that were approved by the FDA, so it was pretty paltry. And as you've already heard, we've got 7,000 rare diseases, and they affect 25, 30 million people. The numbers vary, but it's a lot of folk all put together.

Of just as much importance, congressmen and senators tell me, the ones that I've met, that every single week somebody is pounding on their door with poor little Sally with a really tragic disease and asking them, can you please do more? And it's tearing at their hearts and they want to do something about this.

So there was a lady, and her name was Abbey, and she was an art major, not a scientist, but a housewife from Danbury, Connecticut who had a couple of kids with Tourette's. And they were on a clinical trial, and the drug company pulled the IND because they figured they couldn't make any money at it.

Well, hell hath no fury like a mother who is in defense of her child. And Abbey realized that even though these individual diseases were individually infrequent, by definition, they were collectively very common. And she had a friend, an obscure senator at the time by the name of Henry Waxman from California, who came up with the Orphan Drug Act with her and several others. And Abbey founded NORD, the National Organization for Rare Disorders, which established my office and which really propelled the whole community forward. So patient groups are really the engine that's driving this whole thing forward.

So the new deal of the Orphan Drug Act was this. If you get an antecedent orphan drug

designation -- and to do that, you've got to show me two things, show with data that it's "promising," which is very, very far afield from the kinds of things that you all are considering here with efficacy, but promising; and that it's for treating a rare disease or condition, fewer than 200,000 people in the United States. So if you can do those two things, you get an antecedent orphan drug designation.

Then you go out and you do all the same things that you have to do for any other drug for a common disease. You do clinical trials and get marketing approval, and you received three main official incentives. The first is market exclusivity for 7 years here -- it's 10 years in Europe -- and that is really probably the single biggest carrot that has driven the system forward, by far more important than anything else.

Now, you might ask, why is market exclusivity important? It sounds a lot like a patent, doesn't it? But patents are realized very early in drug development, when the guy in the

laboratory holds up the test tube and says, "Eureka." By the time they get to marketing approval, they probably run out.

Additionally, patents have to be defended by these very expensive people called patent lawyers. And sometimes they win and sometimes they lose, whereas orphan exclusivity is enacted and defended strictly by the FDA, and we're the only group that can produce market authorization. You can't go anywhere else to get it. There are tax credits which can be carried forward and carried backwards, 50 percent tax credits, and fee exemptions. The PDUFA fee is waived for applicants for orphan drugs.

Well, it's been a major success, and everywhere I go, everybody tells me that there is no law that has worked to develop drugs so well as the Orphan Drug Act. We do have 362 approved drugs at this point, more than 2200 designated orphan products that have some promise on the basis of data, and, as was mentioned, about -- it varies from year to year, but in 2008, anyways, almost 40

percent of all FDA-APPROVED NMEs or new biologics were, in fact, orphan products. So things are changing. Things are changing big time.

Here is the numeric revelation of that. And Larry already mentioned that orphan designations have increased dramatically. Over the last three years that I've been there, they've increased 61 percent, in fact. But you can see that there is a rather constant level of approvals that have come through over that time.

Now, there is latency. Okay? It takes some time from the time of orphan drug designation, which only requires demonstration of promise, to full-blown marketing approval.

This chart shows you that the Orphan Drug Act has, in fact, worked to develop drugs for the rarest diseases. The Y axis is the numbers of designations in the black bars and the numbers of approvals, marketing approvals, in the white bars. The X axis shows you the population of the disease that is affected by the -- that is intended to be treated by the designated or approved product.

Okay?

So you can see that it's truncated over there at 200,000, appropriately. And over on the left, the largest bars are seen in populations between zero and 9,000 people. Indeed, we actually do have several diseases for which the prevalence is zero, and we'll mention that. We'll leave that as a little teaser for you for later. But that's a good thing.

This is a life table analysis that shows that, in fact, a very substantial proportion of designated products go forward to getting full marketing approval. It's about 24 percent. This is from an article that we published in Nature Review and Drug Development. And the halftime is roughly about four to six years for the different, various kinds of products.

So what's your typical orphan drug? Larry's already mentioned a bit about the heterogeneity, and I'll put a little flesh on those bones to show you that, in fact, they re really all over the map. Here's a pie chart of designations from 2000 to

2006. As you can already come to expect, oncology is that big slice of blue, light blue up there. But they're all over the map. All of the different forms of human pathophysiology, every organ system, every medical specialty, we're all affected by all these rare diseases.

Let me digress just for a moment to say that we have learned most of our materia medica from rare diseases. We all know something about hemoglobin from studying people with beta thal and sickle cell disease. We know amino acid metabolism from PKU, from homocystinuria, from all of those diseases. We know what the urea cycle is in everybody in this room, the normal urea cycle, because we have people with urea cycle disorders.

So these people with rare diseases, they've taught us a whole lot. I mean, most of what we've learned in our medical school texts has come from experience with these people with rare diseases, but they've been sort of left out of the drug development process. Well, that's something of an understatement.

So one of the first products -- there was a movie made about this bubble boy which relates to Adagen for ADA, adenosine deaminase deficiency, a pretty infrequent disease. This was one of the first orphan drugs to receive full marketing approval. It's between 1 in 100,000 and 1 in a million, and it's one of the causes of severe combined immunodeficiency. And there's your obligatory substrate and enzyme.

I did want to mention that this disease, things have moved forward over the 27 years of the Orphan Drug Act, and the science has moved forward. In January of 2009, there was a gene therapy reported for immunodeficiency and numbers of cures, flat-out cures, were reported. And this is not the only case of gene therapies that have come forward. They also have received orphan status designation, as have stem cell therapies and others. And we're extremely hopeful, moving forward, that gene therapy will have a lot to do about some of these single-gene problems.

Naglazyme for mucopolysaccharidosis type VI

is one of your classic orphan product diseases. Now, I mentioned that these are -- only about 5 percent of all orphan designations actually come from the inborn errors in metabolism, but they really are poster children. It's estimated that there are only about 100,000 people with this disorder worldwide.

But the drugs that treat disorders like this throughout the orphan drug spectrum are often the keys that fit into the lock so perfectly that they have absolutely transformative effects -- just like the ADA, just like the new gene therapy for Leber amaurosis. Some of these are just stunning drugs that raise the dead and make the blind see and make the lame walk.

Here's a picture of stuffed lysosomes that you see.

There are some serious ethical, social questions that all this has raised. These enzyme replacement therapies have become the single most expensive therapies in the history of humankind, bar none. And I said that they may be up to

400,000 per patient per year. In some cases it's $700,000 per patient per year.

Who pays for all of that? Well, we all do. Fortunately, it's a very, very small proportion of the budget because, as we define, these diseases are exquisitely rare. FDA does not regulate price, for anybody who is wondering, but they are radically transformative and beneficial to patients' lives.

The thing that we have to remember, the way that the Orphan Drug Act has worked is that the exclusivity, which has permitted drug marketers to charge whatever the market will bear, that exclusivity lasts seven years. But the drug wouldn't have been developed without the exclusivity, and the knowledge is eternal. It goes on. And we have numerous examples in which competitive forces have come in, and the prices have come down after that period has elapsed.

Okay. I mentioned that there are some diseases for which the prevalence is zero. That's a nice thing. And agents of bioterrorism,

thankfully, fall into that category in many regards. We have a couple of approved therapies for chelation agents for plutonium poisoning, and we don't have any plutonium poisoning; similar cases for some anthrax and other agents of bioterrorism.

I did mention that the criteria is that fewer than 200,000 people in the United States have the disease or condition. So one of the ironies of my job is that we have all these very unusual diseases that I didn't even hear about in medical school, and then we have the most common diseases of humanity, the neglected tropical diseases, African sleeping sickness. Eflornithine, is an example that we have an approved product for.

But malaria, schistosomiasis, tuberculosis, and onchocerciasis, on and on, all of those diseases which are common in other countries but rare in the United States are also eligible for treatment under the Orphan Drug Act. And there are your trypomastigotes. Is that what they're called?

Okay. So let's talk a little bit about

designation. It is a non-exclusive dyad of the orphan indication in the moiety. So you get designation for this moiety for that rare disease indication. That's what a designation is for. It's for the two of them, the pair of them together.

Those designations are regulatory incubators of tenuous ideas. They are often the target of venture capital. They are not prescribable. Once you get an orphan designation, a lot of people think, oh, well, if it's orphan-designated, FDA has approved. Well, it's not approved. We reserve that word "approved" for marketing approval, and designation, we use the verb "to grant" or "to award" designation. But it is a starting point for communication with the agency. My office serves in many ways as a welcome wagon to people who don't know what IND stands for.

The basis for designation, the first question, of course, is what is the disease or condition, and we'll talk a little bit about whether that disease or condition can be subsetted.

But given the disease or condition and/or its subset, there are two criteria that must be met. The first is the medical rationale criteria. Is there promise that your drug will treat it? And the second is the prevalence criteria. Is that disease in fact rare?

So this first question of what is a disease or condition sounds fairly simple. It sounds straightforward. But I'll give you some examples in which it's not very straightforward, and there are many, many that I'm not giving you right now.

For example, one of the very first things that was brought before me three and a half years ago was an appetite suppressant that was proposed for treating Prader-Willi disease. Now, for those of you who don't know, Prader-Willi disease is a pediatric disease in which there's a specific gene deletion that causes, at least in part -- one of the things it causes is these children lack satiety for food, so they never get full. They want to eat all the time. They eat the dog food. They open up the refrigerator. And they grow, and they grow,

and they become incredibly obese children. I mean, you're talking 200-pound 8-year-olds. It's really tragic.

So what is an appetite suppressant for -- what is the disease? Is the disease obesity or is the disease Prader-Willi? Well, it's a little bit of a puzzle, isn't it?

Another example is an adenoma regressing drug, a drug which causes adenomas to regress, which is proposed for use in treatment of familial adenomatous polyposis. Well, what is the disease or condition? Is it FAP, or is it adenomas? Adenomas are garden-variety; they're common. FAP is very different. Are they different?

Sometimes this changes over time. Lymphomas, for example, when the Orphan Drug Act was first put into place was considered all one disease. They were all lymphomas. And they were divided in to Hodgkin's and non-Hodgkin's, and the non-Hodgkin's were divided into B cell, T cell, and null cell.

I got there, and I'm trained in pathology,

so naturally I split them further according with the WHO classification. And so now mantle cell lymphoma, which is clearly very different from anaplastic B cell lymphoma, will in fact qualify as an orphan drug.

Okay. So the medical rationale criteria, just to give you a little bit of -- so you know a little better how we do it in the Office of Orphan Products for this purpose, it specifically states that we need to interpret this liberally because we're trying to create a little group of promising products here.

They can be data from clinical trials or it can be data from a few case studies, a few case reports, or it could be data from some animal models, if there's an existing animal model that shows use of that particular drug in the animal model for that disease in humans. And if there's no animal model, we'll rarely sometimes accept data from in vitro experiments; for example, some of the clotting factor orphans. But these are data, not theories. Okay? So we actually need to be

observable reports of observed data, not, this molecule goes up and makes that one go down. That's not adequate.

The prevalence can be found for each disease for the second criteria. It is an epidemiologic question. We consider all the estimates. We extrapolate when necessary. We need an actual number. That's how I was able to generate that previous chart. And when a range exists, we accept the highest.

We're pretty careful about this. You know, the Orphan Drug Act is an act which can be subject to abuse. This orphan can be abused. And so it requires eternal vigilance if it is to continue to deliver good drugs for people with rare diseases.

Now, the medically relevant subset, let me preface with the test that we apply to determine whether or not a medically relevant subset is truth or fiction. We would expect that the drug would be expected to treat only the subset of the disease that is proposed, and not the rest of the disease. So if you have the disease or condition, consider

it as a pie, a sponsor comes forward and says, well, this is the subset that is my medically relevant subset. Our test for whether or not that argument is true is, does your drug not work in the rest of the pie?

I know that's a rather unusual position for the agency to be in, to require sponsors to demonstrate to us the inefficacy of your drug, but in this particular case, that is how orphan status determination for a medically relevant subset is applied.

So we say no to salami slicing, yes to medically relevant subsets. Here are some examples.

A drug to treat hypertension among left-handed people with freckles? No. Okay? That's not going to work. A drug to treat renal cell carcinoma among those refractory to first-line treatment? No. That's not going to work, either, because your drug probably would treat the people who weren't refractory to first-line treatment. But a drug, a monoclonal antibody against a surface

antigen that can only be found in a rare subset of breast cancer cases? Yes, absolutely, because that monoclonal antibody would in fact be developed and only useful in those cases of people with that particular surface marker.

A drug used to be treating for stage 2B through 4 melanoma? Yes, because superficial melanoma is universally excised. A wide area excision universally cures superficial melanoma, and you would never give chemotherapy to people with superficial melanoma. And these more advanced cases, in fact, are fewer than 200,000. And pediatric Crohn's disease, yes, as well, because pediatric populations have always consistently been considered a different population.

I want to make just a couple of mentions -- I'm not going to read this whole slide -- a couple of mentions on our grants program. We do have FDA's largest grants program. In fact, it's larger than all the other grants programs at FDA combined, but FDA is not known as a bit grants-making agency.

It's incredibly successful, and we have a

recent inclusion in our most recent RFA of a pharmacometric component for that grants program. And I refer you to that.

Our grants program is about $14 million. It's exclusively for clinical trials, phase 1, 2, and 3, up to $200,000 for phase 1, $400,000 for phase 2 for three or four years. And we only have one receipt date. That's in February, for those of you who want to get started working on that.

Lastly, let me just wrap up with a little bit of a comparison and contrast between my office, the Office of Orphan Products, and the review divisions. My office considers claims for promise for the purposes of making orphan status designation. The review divisions are concerned with these dispassionate questions of safety and efficacy, this rather contemplative activity.

If you come to my office and get orphan status designation, you get bragging rights. And if you look at the companies out there, they'll proclaim it from the hilltops of their websites that they have indeed gotten orphan status

designation, and if you read it really fast, you'd think that they were out there on the market.

But in fact, you do get bragging rights. It is an official nod. It's an official action, and it's a good one. But if you go to the review divisions and they review your efficacy and safety data, they can decide to give you marketing rights.

We in Orphan Products are advocates for this process. We are proponents of making more products for people with rare diseases, and we do that in any way and anyhow that we can. So we're the cheerleaders -- appropriately enough, being in Dallas -- whereas the review divisions are more the monks. Their consideration of data are integral to their making good public health decisions. Their job is not to approve drugs. Their job is to make good public health decisions on this.

We are guests at the pre-IND meetings, the end of phase 2 meetings, all the other meetings. But the review divisions own them, and we go in support of them. My office is the only part which actually tries to calculate or evaluate the

prevalence claims of these rare disorders, and that's not specifically relevant to the review divisions' concerns.

Shortage issues, which many of you may have heard we had this last year -- a few this last year or two, a few rather tragic ones, which continue, actually -- are shared between our office and the review division.

So with that, I'm happy to take any clarifying questions, I guess, and we'll proceed. Thank you so much.

[Applause.]

DR. VENITZ: Thank you, Dr. Cote.

Any questions, clarifying questions, for Dr. Cote?

DR. GIACOMINI: A very nice presentation. The review divisions that review the products once they're ready for that, do they have people from your office on them? Are there somehow special considerations in the review because of the orphan designation?

DR. COTE: You'll hear later today from

Dr. Anne Pariser, who sits in the review divisions. She's in the Office of New Drugs, which is over the review divisions in CDER. And she'll tell you a little bit more about her activities. But, yes, I speak to Anne every single day, and we liase constantly with the review divisions.

After orphan status designation is made, the primary relationship of sponsors transfers to the review divisions, but that doesn't mean that our relationship is ended. We continue on. We work with them in an ombudsman sort of way, sort of fashion. And we do indeed go to several of these meetings as well. But the relationship shifts after orphan status designation has been achieved.

DR. VENITZ: Dr. Mager?

DR. MAGER: Thank you again for the nice presentation. I'm going to face this way for the question, and then I'll turn around for the answer.

DR. COTE: Okay.

DR. MAGER: So you described the orphan designation for single moieties. But I think the future for treating these orphan diseases are

likely going to be in combination regimens. And so I was wondering if there's any unique mechanisms or distinctions for combination products or combination regimens versus single moieties.

DR. COTE: Well, you're bringing up a challenge that the current regulation and the current structures don't really address. So you're absolutely right. This is particularly important for some things like tuberculosis, for example. We already know that we need combination therapies for that. But right now it's single moieties.

I do want to mention that there are provisions for breaking the orphan status exclusivity. If the same moiety is used in a different preparation which is found to be more effective or safer than that first, exclusivity can indeed be broken. But provisions for new combinations -- and I wouldn't extend that further to say diagnostic devices and drugs that are combined together -- those things really haven't been as well worked out in the rare disease bases. They will definitely need to be.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: In your slide where you review the medical rationale criteria, you've listed a lot of the types of data that would constitute a promise for a drug. But could you comment on the percentage of approvals where data other than clinical trials was the basis for an approval?

DR. COTE: Well, it's funny that you should mention that because we just recently did a review of 2009 data. We'll be publishing it shortly. Roughly about half of all of the products which received orphan status designation had some clinical experience.

That tells me that many sponsors didn't come in early enough. They probably could have satisfied the criteria for orphan status designation with only animal model data that they had antecedent to the time of their actual application.

So it's about half have -- a little more than half have some clinical trials information, clinical trials or case reports, in human

information, and about a third of them have animal model data, and the rest is in vitro data.

DR. VENITZ: Let me ask you a question. How many of those orphan diseases would you consider to be serious?

DR. COTE: Oh, virtually all of them. Now, this is an interesting question because, you know, we work very, very closely with the EMA. And the EMA has, in addition to our two criteria of medical rationale and the prevalence criteria. They also have two other criteria, one they call significant benefit, which requires them to require sponsors to show that their drug adds something to the armamentarium; and one example of things that would be important would be pulmonary arterial hypertension, for example. They look very closely at those because there are a number of products out there already. And the second is seriousness. And I really don't understand the European criteria for seriousness; they've never really turned on down on the basis of that because all of these diseases that these products purport to treat are real

serious. Real serious.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: So as we start learning more about disease, there may be a time when it's rare for a disease to not meet your criteria.

DR. COTE: You are so right. And people look forward and they say, oh, my God. Everything's going to be an orphan. And if everything's an orphan, then nothing's an orphan. Right?

So yes, you can look down that road, and you can see a time when personalized medicine has arrived, and we have no more of this impersonal -- we have no more diseases in which we have 20 million people with that disease because they just won't exist. But that's looking down the road.

We're dealing with today, and we started a quarter century ago. And today, the Orphan Drug Act is still responsive to the needs. And we still have a long ways to go with these 7,000 diseases that we already have that we know are rare before

we get into the business of sub-splitting and splitting up the common diseases into different entities.

But right now -- even though most cancers, for example, most cancers that occur are common cancers; lung, breast, colon, prostate. These are going to be, for the most part -- I mean, that's what most cancers are. Now, most kinds of cancers are orphan products. There are probably, what, a thousand, 2,000 different kinds of cancers. And those would be orphan -- excuse me, rare diseases which might be treated by orphan products.

But for today, the Orphan Drug Act is working. It's working incredibly well. In the future, will we shift in such a way that everything becomes an orphan? I guess it's foreseeable and conceivable. It really is, but it's not our present.

DR. MCLEOD: So my question is whether there's effort to change the way study design, and particularly the statistical component of FDA, views these, because often the hang-up that we've

got on the cancer side has been around the lack of rules for when something can be declared to be both safe and effective. Because of the small numbers, you can usually say neither with confidence.

So, sure, there's approval with 12 patients for an extremely rare disease. But with these more common rare diseases, if that could be said, how do we get a better statistical and clinical trial framework?

DR. COTE: Well, I mean, that's the million-dollar question. It's incredibly difficult for me to just sit and come up with something that's going to be stunning and everybody's going to say, oh, he's got the answer to that; the problem is solved. That's not going to happen today. However, Anne will tell you a little bit more about the flexibility that the agency has extended with regards to rare diseases.

We are exploring more some alternative biostatistical approaches, Bayesian approaches and adaptive designs, and we actually have a course that we've put on, now in our third year, for FDA

reviewers to learn about alternative approaches that are outside of the randomized, placebo-controlled, double-blinded trials because they have two things. They have pitfalls and they have evidentiary value. And you need to know what both of those are. And if you know what both of those are, maybe you can make better decisions about drug approvals in the future.

So that's one hope that we're looking for, is some of these alternative techniques for getting more out of less, which Larry already said, is where we have to go next.

DR. VENITZ: Last question. Mr. Goozner?

MR. GOOZNER: I notice from the chart that there is a handful of approvals for orphan drugs that are, say, in the 150- to 200,000 range. Is there a process -- you know, one can imagine through the magic of marketing that the actual patient populations are significantly larger than 200,000. Is there a process for removing orphan drug designation? And if there is, has it ever been used?

DR. COTE: There are processes for removing them. They're codified into the regulations. They're very specific and they are very discrete. And I'll refer you to them in the CFR.

However, one thing that does not remove a product from orphan status designation is if the prevalence should increase subsequent to the time of the application for orphan status designation. This was specifically written into the law at the time because, transporting you back again to 1982, it was the days of HIV, the early, early days of AIDS, and people knew that even though AIDS was then a rare disease, that it was likely to exceed that. And they wanted the provisions of the Orphan Drug Act to apply to HIV and AIDS at that time until such time as it exceeded the prevalence criteria.

So, yes, there are provisions, if there was malfeasance, or if somebody was lying about something, or we made a big mistake and we never should have given it, but those are written into law.

DR. VENITZ: Thank you again, Dr. Cote.

DR. COTE: Thank you so much, all of you.

DR. VENITZ: Our next speaker is Dr. Mundel, and he's going to discuss the paradox in orphan drug development.

Presentation - Trevor Mundel

DR. MUNDEL: Members of the advisory committee, FDA, it's my great pleasure to tell you about some of our work in this area of orphan and rare diseases. But as a disclaimer, I just have to say that I'm really here as a mouthpiece for many hundreds of scientists in industry, and their collaborators even more, in academia; but also, I think, importantly for patients and their caregivers who've participated in the programs that I'll tell you about.

I think Larry and Tim have set a very nice stage over here in the classifications and their thinking about rare diseases, certainly very instructive for me. But one thing struck me when I was thinking about this presentation, is that I've never heard of an orphan disease strategy, rare

disease strategy, and we don't have an orphan disease unit specifically. So that is immediately a factor which came up. Nevertheless, I have the tremendous good fortune to spend a lot of my time -- most of my time -- and a lot of my resources actually in studying orphan and rare diseases.

So how does that come about? Well, this is the conceptual paradigm that we've been following over here, and it fits very much into some of the questions earlier around what is serious, what is not serious, what is understood, what is not understood rationales.

So in the first instance, we want to study diseases where there's very high unmet medical need, which you can get into definitions around. But, briefly speaking, these are diseases with high morbidity/mortality for which there are not good treatments. Let's just put it like that.

But it is the other axis over here, which is absolutely critical for successful drug development, and that is scientific tractability,

which is a much more judgmental aspect of scientific judgment and looking at data, in fact, to come up with that assessment. So do we actually understand the mechanism? Do we have some human genetic evidence which indicates that an early compound is likely to be active?

I think that if you take this paradigm, you are very naturally led to study rare diseases because it typically is there where you have the understanding, monogenic diseases, for instance, a particular mechanism where you might be able to actually really prove in a rational way that your drug therapy impacts a particular pathway, as opposed to the more complex diseases where that may be more difficult.

So my contention would be that if you really pursue a scientific approach without a lot of other constraints, then naturally you will end up, in the first instance, at least, in the space of these targeted therapies, orphan diseases.

Now, that's the theory. But I wanted to take you through a series of case studies which

illustrate some of the things that we've heard about already and some of these concepts. And I was discussing this with Don Stanski, who works in my group. And Don was saying, this is a very compelling paradigm, first looking at very targeted populations, and then looking at the expansion going forward into other populations where the therapy might actually have an effect. And what I felt was that that is true, in theory. In practice, as you'll see from some of the examples, the path is much less linear and there are lots of twists and turns in this aspect and this approach to drug development.

So an example that we've already encountered here is this IL-1 blocker, canakinumab. So it blocks IL-1, and IL-1 is one of the beneficial cytokines in terms of defending against various infections, for instance, but it can also be very noxious in certain circumstances, leading to inflammation, which may be undesirable.

Now, at the time that we developed an antibody blocking a selective type of IL-1, IL-1

beta, there already were blockers, nonselective blockers, being used, particularly for rheumatoid arthritis. And we were trying to think about what indication would actually show us whether this was a promising drug, really promising or not.

To go into a disease like rheumatoid arthritis, very likely the results over there had been fairly modest, so you see 20, 30 percent of patients with a fairly good response. But then understanding what that patient population is, we didn't have that understanding. At that time, a result came up from London, actually, where somebody was looking at a rare autoimmune disease called the Muckle-Wells syndrome. And this is due to a single mutation in this cluster of proteins called the inflammasome. And in the cell, the inflammasome is responsible, actually, for processing the precursor of this toxic type of cytokine into its active form. And it looks like, in these patients, they are not able to shut down that process. And that process in them gets activated extremely easily, even by factors that

for us wouldn't trigger a big inflammatory response, for instance, exposure to cold.

So it was shown in a few of those patients -- and I think at that time there must have been less than about a hundred characterized families with that disease -- that it looked like an IL-1 blocker worked very well. And you would imagine, in fact -- you would certainly predict that an IL-1 blocker for an IL-1-based genetic disease would be the magic bullet.

So we went into that group of patients in London, actually. And what we had was in the very first patient, when we administered the blocker to that patient -- now, these patients have a variety of disease severity. There's an infantile form which really has fairly high mortality. In the adult form that we were studying, the patients are plagued by joint pains, troubling rashes, deafness, sometimes kidney problems, so a very disabling type of disease.

But in that very first patient, within five hours the troubling rash started to clear from the

patient's back. And by 24 hours, it was really a complete clinical response. It was absolutely remarkable. We were on the line to the clinical site in London and getting almost an hour-by-hour account of what was happening to that patient. And that entire proof of concept study was just four patients.

Now, the interesting thing about those four patients is that we were able to work out in considerable detail the clinical pharmacology of this block because they all responded dramatically. And what we'd gone in with was the highest safe dose that we could administer to these patients. We went in with that highest safe dose, and they all responded for roughly 180 days. They went into total remission for that time.

We were then able to set up a paradigm of re-dosing them on flare, and we did a type of reverse dose response. And we could sort out ultimately what it came down to was that actually varying the dose administered really just varied the time between flares. So from those four

patients, we had a very good understanding of the clinical pharmacology that we carried forward into the rest of the program.

Now, this is where the story gets a little bit non-linear because as we were doing this study in Muckle-Wells syndrome, data emerged, and there was a clinical study performed as well, that the IL-1 system, the same inflammasome system, was relevant to gout and that gouty crystals, these urate crystals, were a major trigger for the inflammasome. So the prediction was, in pre-clinical studies and then with the nonselective blocker in some patients, it would be that this would work extremely well.

That is exactly what happened. So we have now under review the same drug for gout, which is a much more prevalent condition. But that science only came out while we were in fact studying it for the rare indication. We didn't know that beforehand.

Now the puzzle actually grows even more interesting because, at the same time, while we

were studying the gout indication, data came out that cholesterol crystals, which are deposited in atherosclerotic lesions in vessels, also are major stimulants to the inflammasome, and the inflammasome and IL-1 may be a major driver of the highly inflammatory and dangerous type of atherosclerosis. So we have a program now looking at cardiovascular risk in a much broader set of patients.

So this was really a classic paradigm where understanding the mechanism and understanding the properties of the drug in that very defined set of patients was tremendously informative and opened up the prospect of this type of expansion.

Further non-linearity, though, is that at the same time as we were doing that, thinking about other populations that might benefit, we started to look at patients with this juvenile rheumatoid arthritis, or idiopathic arthritis, as it's now known, systemic juvenile idiopathic arthritis, what this adolescent onset of, effectively, Still's disease looks like. And we found that in contrast

to rheumatoid arthritis, this is actually quite a distinct entity, and the response over here looks dramatic as well.

So here this is a rare disease, not quite as rare as the initial Muckle-Wells CAPS disease, but it is very much a rare disease. But the results and the responses that we are initially seeing look very much like the Muckle-Wells. And there is a whole genetic puzzle to understand, a little bit more complicated here. But we have some indicators that one can unwind the genetics over here as well.

So we had the very nice expansion that Don was referring to, but then we had a twist in the path, and we are back here with a much rarer disease entity, but where this drug looks like it will have high therapeutic benefit. So this is the expansion in the linear fashion over here but, as I've indicated, a lot of twists in that path.

Another program that has come to the fore over here -- and I don't want to put up a lot of chemical pathways over here -- but this is a good example of -- I guess Larry would call this

repurposing to some extent because this class of drugs had been around for a while, used in the transplant area in particular, but the biology then only emerged later on that indicated it would have application elsewhere. And these are the mTOR blockers. Everolimus is the one that we have, and there are a couple out there, RAD001.

The story began over here that we were working with David Franz in Cincinnati, which is one of the leading centers looking at mTOR related to a genetic disease, a monogenic disease, called tuberous sclerosis, which is a fairly rare entity. But it is a disease where there is a mutation in some suppressors of mTOR. So this mTOR becomes over-accelerated and excessively active. So, once again, rationally, you would think that a blocker would be very useful for these patients, blocking the pathway and actually directly targeting the genetic lesion in this case.

So we were working there, and we wanted to test that hypothesis that this biology really played out, and we did a small study in tuberous

sclerosis patients. Some of the other blockers had already been looked at, and there were a lot of anecdotal reports that it worked.

So this was not surprising. This was well-known information in the community that these blockers potentially would be effective for these patients, although there was a lot of issues around what dose. This drug had previously been used in transplant, and was then being looked at in oncology. But these kids may be on this drug for a very prolonged period, so what dose would be safe? And the safety information came up over here.

Here we have a patient with some of the very troubling skin lesions, these hamartomatous angiofibromas that these patients get as part of the skin manifestations of the situation. And we saw some responses over there as well with the blocker.

But then David Franz came up with this particular population. And he mentioned it more as, this is a real need out there. A number of these kids have these giant cell astrocytomas in

their brains, and these tend to happen around the foramen of Monro, which gates the third ventricle.

So when these grow, as they frequently do, they get an obstructive hydrocephalus, which is very difficult to treat. And they treat it, and then it recurs, and then they have to be treated again. So it really is a disaster for these families, for these kids to have this condition.

It was clear that an mTOR inhibitor should actually work for this, but nobody was doing the study. So David really persuaded us, and we were working in the space, so we agreed to do the study. It was a small study I think, of the order of about 20 patients.

But they had the dramatic response you see over here, with the lesions that are lighting up over there on the right really dwindling here on the left, a dramatic response, and a resolution of the pressures in their ventricular system. And this was registered last year as an orphan drug for this condition of SEGA, and the difference it makes to these patients is tremendous.

What that has opened up for us is a whole different approach as well to other aspects of the disease because at the same time we were looking at this hard resolution of a tumor, it was noted by the families that there were a lot of behavioral improvements in their children, not only behavioral improvements, but they also have a very aggressive and very difficult-to-treat form of epilepsy, and that also seemed to respond. So now there is a whole new direction opening up around looking at the effects of this class of drug on epilepsy in these patients, but maybe in other patients as well.

I wanted to give an example which is a little bit opposite to those ones that seem rationally to start from a position of a rare disease and move forward, and this is in the immunology area again. One of the big excitements in the last 5 to 10 years has been the discovery that there is a new type of immune cell, the so-called Th17 cell. And it secretes another cytokine, which is essential for fighting

infections and other processes, but also has been implicated in a number of autoimmune diseases.

One of the diseases that it had been implicated in, and this was the first area that we went into, was in psoriasis. So our proof of concept over here was in psoriasis, and what we saw was a dramatic resolution of the psoriatic lesions in a fairly small cohort of patients, so giving us confidence that this biology of IL-17 and its relationship to some of these diseases was actually borne out. But psoriasis clearly is not a rare disease, and I didn't want to dwell on some of the negatives that can occur in a program.

At the same time, we were looking at some rarer diseases that also have had an implication of the IL-17 pathway. And one of those has been uveitis, so an eye inflammation which in its severe forms, particularly when it is posterior, or pan-uveitis affecting the whole eye, can lead to vision loss and permanent vision loss, so really a very severe eye inflammatory disorder, and difficult to treat, very high-dose steroids prolonged in these

patients.

So we went into severe uveitis. And what we found was the IL-17 blocker worked very well in this group of patients. But then we came to the issue of what is severe uveitis? How do you define that? That's not really a clear orphan designation.

So we started to look for what group of patients would be well-defined that we could study, and we found that one or two of the patients in this group of severe uveitis, from whatever cause, actually had Behcet's disease. Now, Behcet's is an immune disease. It can affect many organs. It affects the brain as well, in some cases, so a severe systemic disease. One of the manifestations is uveitis, and it's a severe form of uveitis.

So the idea was, let's segregate out -- and those one or two Behcet's patients didn't seem different from the rest of the group. So we said, well, let's study Behcet's. That's a well-identified group with classification criteria. It meets all the requirements for an orphan disease.

And we did that.

A couple of problems arose, and I've just indicated over here. I'm not getting into all the gory details. The first problem was where these patients are found. It's typically a disease of high prevalence around the Mediterranean. So suddenly we were looking at sites in rural areas around the Mediterranean in Turkey that had never been involved in clinical studies before, so there was that whole exercise of training sites to GCP standards.

The other thing is that there had never been a randomized, placebo-controlled study in Behcet's, so we had to define the design of it. And then the other thing was that clearly the patients could not be on placebo effectively. They were treated by high-dose steroids. So the paradigm was, really, our drug versus a placebo, and then attempting to actually wean patients off their high-dose steroids. Now, if anybody's been involved in these weaning types of studies, you know how extremely difficult they are to get a standardized protocol

across many sites, particularly in this case when these sites were in rural and inaccessible areas.

So to get to the end of the story over there, ultimately it looked like we had a negative study, and it looked like it was negative for reasons of high variability in that patient population. Really, the standardization of the protocols was not really adequate. Maybe there was a response, and maybe there was not in some subgroups. So going down this path can lead you into these blind ends over here.

We've continued to study patients with uveitis, with severe uveitis, and what we find is in those patients, it works extremely well. So we have now this conundrum to solve for ourselves, is how do we move forward in uveitis, having hit a blind end when we went into this one subpart or one slice of that population?

Another program which has attracted a lot of attention has been a program we have for mental retardation. That's the most prominent part of this program. So this is a drug which is a blocker

of a glutamate receptor, MGluR5, a metabotropic glutamate receptor.

The story here around fragile X mental retardation, which is the commonest genetic cause of mental retardation, is that it had been known, and there's even a mouse model whereby it looks like the protein, which is mutated or there's a triplicate repeat in this protein, actually is an inhibitor of mGluR5, of the receptor, of production of the receptor.

So that in the case where there's a loss of function of that protein -- or actual loss of the protein is what happens in these patients -- there is an over-ramping up of the mGluR5 system; so, once again, very rational that a blocker should be effective over there.

Now, this is a blocker that had started off its life, and there was a hope at one time, that the mGluR5 pathway would be a cure-all for anxiety disorders broadly or for depression, and might even have application in Alzheimer's disease. So there were very broad aspirations for the mGluR5

mechanism.

We came down to a couple of these rare diseases, like Fragile X, where we could more explicitly and rationally understand whether this mechanism was relevant to disease.

But the twist on the story with Fragile X -- now, it's maybe the commonest cause of monogenic mental retardation, but it's still a rare disease. When we looked at the study data overall, we found that there was a modest effect overall. But we'd already understood from existing work that there was an epigenetic component to this, that is, another way of marking genes to actually be transcribed or not. And there was a methylation status that one could determine for the promoter to this protein whereby if it were fully methylated, it would mean zero protein as opposed to various forms of partial protein production, so sort of partial manifestations of the genotype.

When we looked at -- and we'd already planned to look at this epigenetic marker -- when we looked at the population segregated full

methylation versus partial, we found a very dramatic response. So we've gone now forward potentially into a slice of the Fragile X population, and we'll probably see the results I hope end of this year or maybe early next year, and see whether the methylation status actually makes a difference or not.

There are some other populations that mechanistically have had suggestions that the mGluR5 mechanism may be relevant. We know that there's an overexpression of mGluR5 in the basal ganglia, and it seems to be particularly a problem with levodopa-induced dyskinesias; also in Huntington's disease, an overexpression of mGluR5, up-regulation of mGluR5 in the striatum, which is impacted in Huntington's disease. So we have some particular studies going forward over there as well.

Those are the case histories I wanted to bring forward for your attention today, and I think that they demonstrate quite nicely some of the categories that Larry mentioned earlier. But what

they've raised for us are a host of other questions -- and I've just put down a few of them over here, and I'll mention them -- as we've got into this area of drug development.

So I've shown you some of the successes we've had, and I've shown you at least one failure over here. But there are debates around what if we do have some very high responders, and they're just few in number, for a therapy that has no hope of progressing forward? What are we going to do?

Well, clearly, there is a need to provide those few patients who have a very good response, even though we may not understand why, with this drug that may be lifesaving for those few cases. But how do we do that in a way that makes sense from the entire business?

Now, we've committed, because I think that it would be the death knell of our working in rare diseases if we were to find some responses in a population, and terminate a program, and not provide those patients with the drug. But it does provide a lot of questions and issues for us.

There are the geographies. We have had to track down these rare diseases. In the Muckle-Wells case, for instance, we found a family that had moved from the U.K. back to their home in India. So suddenly we had some patients in India.

So we are doing these indications in many different parts of the world, with very uneven regulatory supervision in those areas. So that leads us to be very cautious in terms of being sure that we have adequate, good clinical practice actually exercised over there.

Then, finally, in terms of some of the incentives you've seen that are built into the Orphan Drug Act, so the ability to develop a useful business model, and the ability to have the freedom to actually pursue the scientific hypotheses which naturally will lead you to study some rare and orphan diseases, has been absolutely critical to us being able to do this.

I thank you for your attention, and I will take any questions.

[Applause.]

DR. VENITZ: Thank you, Dr. Mundel.

Any clarifying questions by committee members? Dr. Huang?

DR. HUANG: Thank you for a very nice presentation. I have a question about when do you ask for clinical pharmacology questions, like dosing and specific population of drug interaction, in various drug development paradigm? For example, you have talked about cases that expand from rare disease to a patient -- an indication was much larger patient base, or parallel indication exploration.

When would you consider specific questions on the clinical pharmacology dosing should be explored?

DR. MUNDEL: You know, I think that our approach on the dose side, which is the most vexing issue, never mind all the other questions one might ask. Typically, after doing a program, say a single dose program, maybe in healthy volunteers if the therapy permits it, and then a short multiple-dose program so we understand what the safety

limits are.

Our tendency is to be going with the highest safe dose we can in the targeted population to ensure that we effectively take out the question of, did it work or did it not work? And then we have an expansion of that program to then get into, a little bit retrospectively, now what is the minimal effective dose, often which is very difficult to characterize because you have very few patients.

But if you have a response which is so homogeneous and so very clear, then your ability to ask these questions around dose, for instance, are really much, much enhanced.

The other thing that we've found -- and I think, Larry, you showed some of the slides around this -- is you really have to put this into a PK/PD paradigm because you have a few sparse patients. You're never going to be able to do the usual kinds of statistical analyses, so you really need to have a model that you've built of how this is working in that particular disease.

Then you can add to that model. That is also particularly important when you are switching between indications. So you're going from your rare disease, where you understand the mechanism, then to cardiovascular risk reduction, for instance.

To have a model that you can actually change on the mechanistic end, and you can have various data that might indicate the effect in gout is 80 percent of the effect in Muckle-Wells and in cardiovascular, the population that is going to respond, that's homogeneous, is maybe 60 percent. So you can put these constraints in your model. But having that initial model is tremendously helpful in terms of making the dose projections that you need for the other indications. And we've used that extensively to jump between indications.

DR. VENITZ: Dr. Barrett, last question.

DR. BARRETT: You mentioned at the beginning of your presentation that Novartis doesn't have a specific rare disease or orphan disease strategy. But given the amount of effort and resources that

it takes to chase down some of these scientifically intriguing questions, how do you make decision points around which questions are going to be part of your strategy for the routine drug development, or drug development in which this would be a subset?

How do you justify the time and effort, I guess is my question?

DR. MUNDEL: Well, I think we've taken a very explicit approach to saying that there's an exploratory phase of work. And the investment in these studies is expensive in the periphery in terms of the production, say, of the antibody. But the actual proof of concept studies are much less expensive than any typical phase 2B kind of study, phase 3 study, by an order of magnitude. So we can do many of these small proof of concept studies.

As it happens with the rare populations, actually, your proof of concept study effectively might be your phase 3 study, much as in the oncology paradigm. So we can apply I think very much the same kind of thinking across the

portfolio. But as long as we make that separation, which there's an exploratory phase where all programs are gated by small studies, even for the larger indications, then you can see what happens.

So if you try and apply any of the business market analyses in that early stage absent of data, I have only seen errors made where people have gone down a path where something looks promising early, big disease population, let's go in that direction. Doesn't work. We've seen many, many examples of that.

So what you can filter out in that exploratory phase on the basis of actual data -- and I'd have to support that point. You have to see the data. It's not the theory that counts. And human data counts many X more than animal or in vitro data.

DR. VENITZ: Thank you, Dr. Mundel. I'm sorry, we are running out of time.

Our next speaker is Dr. Bashaw, and he's going to propose a clinical pharmacology decision tree.

Presentation - Dennis Bashaw

DR. BASHAW: Thank you, Dr. Venitz, committee members, and the audience today for coming to hear us debate and discuss different ways we can apply clinical pharmacology tools. Certainly, I am going to be presenting a decision tree today, but also I'm going to talk about some of the informational issues we go through on the new drug side.

Just like all typical FDA talks, I have my official disclaimer here because I will be presenting some data here today but will also be presenting opinion, thoughts on where we should be going. You have the slides, the committee member, in front of you. They are rather detailed. I want to assure you I'm not going to read the slides to you; they are detailed for your reference, and also, I believe, will be available to the audience on the FDA website.

Dr. Cote has already given us a nice introduction to the Orphan Drug Act. The only real issue I'd like to bring up here, of course -- he

has already talked about the incentives -- is the Orphan Drug Act does not comment on the issue of informational needs. It does not provide for a lower regulatory standard.

Now, Dr. Cote has indicated that the review side is very monk-like and dispassionate. I will try to overcome that in my personal presentation today because, of course, those people who know me know I am very monk-like in my nature. So we will move forward here.

But no, it does not address informational need. That is probably one thing it would have been nice if it did, but it doesn't. And I'm going to really focus on that somewhat. What are the informational considerations here?

Certainly we have provided here some estimates of orphan populations. If you look at JRA, which has been discussed already briefly this morning, right at 150,000. Pompe disease, which we have some effective treatment, we have some gene -- sorry, we have some treatments now for it, about 7300. N-acetylglutamate synthase, NAGS deficiency,

less than 250. It's very rare. It's a Krebs cycle. I will talk about that a little bit more. We approved a drug last year, Carbaglu, for that.

Really, the informational considerations, some of the things we need to think about as we deploy clinical pharmacology tools -- and in my presentation today and in the presentation that follows by Dr. Garnett, we're going to talk about how these tools can be used and how we can really use clinical pharmacology to advance this area.

Certainly, if we can use healthy subject data to define the pharmacodynamics, to define the pharmacokinetics, that's very helpful in development, but that's limited, of course, by drug toxicity. Obviously, for a lot of the drugs we develop for orphan indications for oncology, you really can't give those to healthy subjects. Maybe in micro-doses you could, but what can we learn from that information?

Of course there is the issue of how do you deal with special populations, orphan drugs themselves, orphan diseases, represent special

populations. But within that, you know, people may have a deficiency, but then that leads to renal failure. That leads to hepatic insufficiency. You've got that overlaying the initial stages of the orphan disease that progresses that we have to think about.

Let's think back. We talked about the beginning of the Orphan Drug Act, 1983-1984. Let's look back at clinical pharmacology. I dare say most of in this room were just getting involved in clinical pharmacology there. I came to the FDA in 1987, so I can speak clearly from that. 1987, we had five IBM PC XTs in the division. We had five. We were still using graph paper. We were still doing hand calculation, for the most part.

Today, you know, that seems very quaint. But that's the way it was, and that's the time frame when the Orphan Drug Act was first put in place. And you look at the revolution we've come through in clinical pharmacology, from using two-cycle graph paper to using supercomputing to using really advanced mathematical and computational

techniques. It's really quite dramatic.

If you look back at the original approvals, there were 27 orphan approvals between 1983 and 1987. Classification back then, we had 4 BLAs and 23 NDAs. You can see how it broke out. And back then, we didn't have the idea of a standard review clock and a priority review clock. But if you took today's standard to say, well, six-month approval versus ten-month or more-than-six-month approval, this is how it would break down. You had 6 that were standard review and 17 that were priority review.

The difference, of course, for those in the audience who don't know what I'm talking about there, in the FDA process now, your NDA is classified as a standard or a priority. A standard review clock at the FDA is a ten-month review clock. A priority review is a six-month review clock. So that's what we have. If we look back in 1983 with 2011 standards, that's how it broke out and how we handled the drugs back then.

Today, computing is quite a bit better. The

FDA has launched a computational science center whose mission is to support CDER in continually improving optimal drug evaluation to using more advanced, physiologically-based pharmacokinetic modeling, to do more pharmacodynamic modeling, to look at the pharmacometric aspects of drug disease, these models we're trying to develop to look at more informed ways to do drug development.

The days of taking thousands of patients and giving the drug and see what happens, really, we can't afford it these days. We've got to -- there's an old metaphor, work smarter, not harder. Well, we need to be both smarter and work harder. We've got to do better and got to do more.

The center and the agency have put a lot of effort and a lot of money into setting it up. This is something we're bringing online now. It's been online for I guess about two years it's been around. And we're certainly doing more and more with it, trying to be a resource so we can do this kind of work at the FDA. Right now the Office of Clinical Pharmacology, I believe, is about 140

people. And certainly we're trying to harness our knowledge base better and better and use the improved techniques.

Recently you can see, certainly, it is about the same. We've got 36 approvals in this time frame, and they represent 30 indications. Six indications had two approvals. They had two different drugs approved for the indication. Novartis and Genzyme both led the pack with three approvals each in this period.

You can see BLAs now, since 1983, they have certainly increased. As we get a better and better understanding, as our knowledge of disease state improves, we get these very targeted gene therapies. We get targeted biologic therapies. We're seeing a higher and higher proportion of those come into the system.

NDAs, still, we have a lot of priority reviews still. Standard review, these are simpler applications. These are sometimes -- these are repurposing to a degree. These are ones for lesser indications, but still they represent an orphan

population.

We'll hope to later this year break these numbers down a little bit more. We're starting to work on some internal publications on this, trying to look at what we've been doing and trying to address this issue. And my talk is going to primarily talk about informational need, and then how we can use decision tree to try to help bring the community into this.

But again, let's take one last look back at the past and compare, then and now, where the therapeutic areas were. And one thing you can see -- initially GI and endocrine and repro-uro led the pack. You primarily had -- these were your inborn errors of metabolism, and still today, 2011, that's still about 15, 17 percent.

What you really see a change here is oncology. Oncology represents 33 percent of the orphan approvals that we have at the FDA now. We've certainly seen a lot better understanding of tumor mechanisms, a lot better use of the targeted therapies.

To go back to the question from the audience that Dr. Cote handled regarding drugs like for AIDS, if you actually look here on this slide, you see 7 percent of the approvals back then were antivirals. Actually, that represents two drugs, if you do the math through. One of them was AZT, and other was DDI. So it's an example where, yes, at the time, this is the time frame where AIDS was just an orphan drug -- sorry, it was an orphan disease, a rare disease, and we were developing therapies for it. And now they are over here. The antivirals are over here in this area; they're in the "Others." It certainly has changed over time, but not unsurprisingly, the GI inborn error of metabolism is still a very predominate area, along with oncology.

Part of our project, what we've done, is we've gone back and looked at what was in the NDAS, what was in the products. Now, I'm focusing here on the clinical pharmacology studies. So for the applications -- and I see this was not the updated slide because it's got a math error here;

obviously, that's not 17, obviously. This was corrected. We didn't get the corrected slide set here. I'm sorry about that.

But, basically, you can see the class for this. For the priority NDAs, we had some radiolabeled studies, single-dose and multiple-dose. This includes both patients and healthy volunteers. For the dimensions of the slide here, I couldn't break it down into all the categories.

One thing that people -- when they look at this slide, they get really -- oops, this is not -- there was supposed to have been something here. Sorry. The other column here, people see it and they say, "Oh, my goodness; you've got 234 other studies. What are these?"

This is analytical reports. This is in vitro protein binding studies. This is in vitro drug-drug interaction studies. These are things that -- these are what the reviewer had to look at. This is the informational need. It doesn't represent a couple thousand more patients lurking out here. What I was focusing on when I made this

table was looking at what was the informational data set that the reviewer had to look at for those applications.

So, roughly, we would say for the 18 priority NDAs that came in, there were 259, so you could say there was roughly about 15 to 20-some-odd studies per application. But that included in vitro studies, analytical reports, single-dose, multiple-dose trials, et cetera, et cetera.

So there was quite a bit of information. But, again, it all varied because we have 18 NDAs. We only have four QT studies. Obviously, we do have some differing informational needs. FDA does have flexibility. People view the FDA oftentimes as a lockstep agency or a checkbox agency. You've got to have a QT study. You've got to have a renal study. You've got to have an hepatic study. You've got to have this. The FDA does have flexibility, looking at the population, looking at the informational need to meet the safety and efficacy.

We do have that flexibility, and we

encourage sponsors to come in and talk to us because we can't be flexible after the fact. But if you come in and discuss your program with us, we can help you define a better, more rational approach. So we do have flexibility here, and that's what this slide is trying to show with the fact that we aren't really keying on these studies so much here. We are keying on over here, where we're trying to see if we can get a mechanism, if we can get some safety information, we can get the efficacy information we need.

The title of my talk today was "A Straw Man" because we're putting out -- I think all of us in this room or around the table, if we sat down and considered orphan drug development, we'd come to the same models we're going to talk about today. But we just never had that conversation.

One of the things we wanted to do by having the AC meeting here today, especially with the ASCPT, where we have developers, we have researchers, we have patient groups out in the audience, is to bring this discussion to them as

well.

So we're going to talk about a pathway here. Some of this may be, "Of course we know this." "Oh, I've already known that." I understand that. But this is for everybody in the room to hear to try to broaden our experience here.

We really believe that the two paradigms that we would like to propose for our straw man are really based on the pediatric oncology experience. Pediatrics, as you know, through PREA and the pediatric rule and other aspects of drug development, has been very successful in its own right, where you take information that you've learned from the adult subjects -- you've defined the basic PK, you've done the drug-drug interaction studies, you've done the metabolism studies -- and now you've got a pediatric population that you can then go into and get the drug approved for it and help those patients. Very successful.

Oncologic. Very much so, the same way. You're using animal studies. You're using a lot of in vitro mechanism studies. You have to do it in

patients, most usually. You can't do it in subjects; so, again, trying to use a combination of these other pieces of information. Maybe there's not that pivotal dose-ranging trial of 40 subjects and escalating dose, but you've got some small proof of principle studies. You've got some animal data. You've got some in vitro cell data that, all together, gives you your world view that you can move forward with.

Repurposing has been touched on today. Sildenafil, I think, is the classic example that we use, where you've taken a drug that's been approved for an entirely different indication -- not like you're taking ibuprofen, which is approved for arthritis, and then getting it approved for JRA, which is very much -- it's not the same disease as in kids, but there's very similar elements to it.

But sildenafil, of course, a phosphodiesterase-5 inhibitor, you know, erectile dysfunction, late night TV. But pulmonary arterial hypertension, it just so happens the receptors are there also in the coronary bed, that we can use

this drug, and it's a wholly different purpose. It's not a related thing. It's related in that it's the same mechanism, but it's a very different disease system.

Again, it's the use of knowledge related to disease drug mechanisms to identify candidates at different stages in development, as much as Dr. Mundel talked about using the knowledge you've gained maybe in a larger population and realizing that there's some mechanistic understanding, or Dr. Cote talked about the fact that we've learned a lot of our basic science from these rare populations. Again, learning the information -- taking the information we already have and applying it in a new way is core repurposing.

A small commercial I will make now for FDA and the Office of Orphan Drug Products is that they have launched -- there's a beta version available now on the Web of the rare disease repurposing database, where you can go to the database and you can search under disease category. You can search it to see, well, what is being developed for maple

syrup urine disease, which was the first rare disease I ever came into experience with back when I was in training. You can go to it, and you can see what's available there. And it's a reconfiguration and cross-referencing of FDA-released information that's available to look for opportunities.

Say you're a researcher and you're working on Muckle-Wells or you're working in cystic fibrosis and you want to see, well, what else has been tried? You can go there and see where we have made orphan designations, or as Dr. Cote's brought up, it's promising. There has been promise there.

Let's try to make that information available out to the community, out to the researcher, because it may show where a dead end has been. It may show where there's a potential area for opportunity and cross-fertilization.

So I'm making a commercial here for the database and for its use, because I think, again, this is all trying to harness clinical pharmacology tools and clinical pharmacology information.

Decision tree, I promised you one, only 15 slides into it. We got to it. Basically, we've broken it down into the new molecular entity and the repurposed, which either can be a 505(b)(2), for those people who are familiar with the language, or, more classically, an NDA supplement.

We would view that. Of course, for this purpose over here, we would follow the repurposing. We'd follow the pediatric strategy, in that we already have a lot of clinical pharmacology information; why not harness that information?

Again, repurposing, as I said before, already approved for use in a pediatric model, in adult population. We already know the basic PK. We already can borrow all this information. For orphan disease, what's our informational need? That efficacy relationship in the population needs to be established.

Is there some special safety issue about the targeted population that needs to be thought about, that needs to be addressed? Is there a biomarker qualification or development we can use to help

verify the pharmacodynamics? This is where, say, at the FDA we could use our computational science, trying to look at some of these things, trying, again, to move the tools and the science forward.

Again, my example, which we've talked about already, is sildenafil. If you look back at its original approval for erectile dysfunction -- the clinical pharmacology section only; I'm not talking about the clinical database at all, I'm speaking today only about clinical pharmacology -- there were 676 patients. That's a very robust clinical pharmacology development program. You've got 82 patients in drug-drug interactions, 228 in single-dose, multiple-dose, and dose escalation studies. You do have some dynamic studies. This obviously had patients in it, but very much a very robust program.

We look at the repurposing example for idiopathic pulmonary hypertension. Again, we've already talked about that it's a rare disease. It was approved in 2005. And if you look at the database there, the clinical pharmacology section,

there are 15 postmarketing study reports, primarily DDIs and -- you know, we take the opportunity to update the label with information that's appeared in the literature.

There were three studies in patients with PAH, and one DDI study with bosentan. A total of 230 patients were studied in the clinical pharmacology portion; still a very robust program. Some of it did have healthy subjects in it, but there were also PAH subjects in there as well. But, still, if we think about it, that's one-third of what was studied for the original approval.

So, again, it shows that with repurposing, you can use a much larger -- you can target what you're looking at. And, again, a lot of it was postmarketing. And this would be the kind of things, when you saw my earlier table that said "Other." This is the kind of things that would be in the "Other" category, articles, journals, et cetera.

But let's talk about the new molecular entity side. Let's talk about a drug that we only

give in patients only. Well, that's going to have to be an oncology model, most definitely. Basically, we get our basic clinical pharmacology. We'd want to see -- since we don't have previous information, we would need some mass balance.

We would be able, however, unlike a lot of times, to use animal models. It's very established in oncology that animal models can be used to do studies you can't do in healthy subjects, you can't do in patients.

Basically, we like to work on biomarker development, just like we would for any oncology drug. Get the pharmacokinetics in the patients with the population-based tools. Special populations within the orphan population -- again, within any rare disease, there's going to be a spectrum. There are going to be patients who, they've got a bit lesser disease, they have longer time to develop the ravages, the renal function, the pulmonary insufficiencies, whatever, with the disease state.

We need to also think about prioritizing

drug-drug interaction studies based on mechanism. And, again, we recognize that the Orphan Drug Act does not allow us to have a lesser standard. But for us to come out here and say, well, you're going to have to do 30 studies, you're going to have to do 40, you're going to have to have 700 patients before you can -- that's not appropriate. We're not going to do that. We're going to look at what the need is.

I think this is a classic example here, Carbaglu. Carbaglu was approved last year for NAGS deficiency. What is the prevalence? That's a very interesting question. Estimates anywhere, worldwide, to a thousand to 200. Probably, in the U.S., maybe 50, because it's such a very specific defect.

The clinical pharmacology section, we had a total of 38 subjects. And, actually, some of the subjects were in both trials, but I put the numbers here just to show you what was in the clinical pharmacology section. We have to do with the information we have. There's no point in doing a

thousand patient studies here when there's not worldwide.

It does, however, require you to have to think about it a little bit. There's a bit of a paradox here, because people would say, well, you approved that drug with only data from 38 subjects. Yes, but that was actually a very high percentage of the population. Maybe that was 50 percent of the total population in the U.S.

Think about hypertension. If we were to study 50 percent of the hypertensives in the United States, I mean, you'd be talking millions, hundreds of millions of subjects; probably most of the people in this room would be eligible for those studies.

So actually, while we don't have, in terms of a volume of information that we have for a, let's say, hypertensive or an analgesic, in terms of the percentage of information and understanding the drug in the target population, we actually know quite a bit. But, again, we're going to have to accept that we just can't do studies or as many as

we'd like. But it's actually sort of a paradox here, to get your mind around a little bit, and the first time I thought about that, it was very strange. But then you do have new molecular entities that you can give to healthy subjects. You can give lower doses, or the disease state is such that you can give it and you don't really have a problem. You can get away with it.

Here we would do a very much more standard development program. We would try to use as much healthy subject data as we could, special populations, DDIs, again, prioritizing all this based on the population and based on the need, trying to just think about going into it, what would an appropriate plan be?

What's an appropriate informational need in terms of what's the kind of information, the quality of information, that we would need for making appropriate clinical pharmacology decisions, dose ranging, dosing; interval between doses, as in Dr. Mundel's experience, how much time between doses is a function of remission. You know, if you

gave this much dose, you could have remission for 180 days, this much 150 days, this much 210. Finding out what's the optimal dose-flare ratio was very important with that drug.

So Argatroban is a good example, used for HIT, heparin-induced thrombocytopenia. Again, you could do this study in healthy subjects. You could certainly -- you'd have to be careful with the dosing and watch what's going on and everything. But it had 293 patients in their clinical pharmacology studies. Certainly, in the clinical studies, they had many more subjects. But again, this represents -- Carbaglu, you had 38 subjects. This one, you had 300, roughly.

Certainly different informational needs by the population. Carbaglu, a very small population. HIT, it's very unsure what the actual population actually is. We're not really sure. It's hard to get a prevalence on that. But definitely an orphan disease -- sorry, a rare disease/orphan drug combination.

So coming here today, part of my

presentation and the presentation following after me, Dr. Garnett, it is a question of quo vadis. Where are we going? The Orphan Drug Act has had a major influence, as previous speakers have talked about. But I really view it, and we all should view it, is while we've had successes, it's very much like an iceberg. We have 362 approvals. That's really good. But we have 7,000 orphan diseases. I mean, there's a lot underneath the water line there. There's a lot more that needs to be done.

We can continue to go on and do it the old-fashioned way and just do study after study after study, but I think it's no longer 1983. We have advanced tools. We have better modeling. We have better therapies. We have better markers to look at and we can develop.

The FDA has certainly -- I can speak from example because I've been at the agency that long -- improved capacity for data analysis. But we also recognize that much more can be done. And that's what the challenge here today, to the panel

is and to the audience as well. And I would also like to make a plug.

On Friday, and I believe it is Landmark C, there's going to be another session on orphan and rare disease development at the FDA and NIH, which is going to be chaired by Dr. Ahn, who I see out in the audience. Please, if you're staying for the full meeting, come to that session as well and take part in that discussion, such that we can move it forward.

Certainly, we think these models -- again, there's nothing secret. I mean, oncologic model, pediatric models, people have written about them. We all understand them. But we're asking you to think about it not in the context of developing the next drug for pediatric analgesia, not the next drug for a pediatric tumor, but think about using those kinds of approaches to the developing of a drug for a rare disease/orphan drug population, to think about using those similar approaches to spur people forward.

The straw man today, there's nothing magical

about it. It's only I think 11 boxes. But, again, the whole purpose of it was to stimulate discussion. And with that note, I'd like to end my talk and take any clarifying questions. Thank you.

[Applause.]

DR. VENITZ: Any clarifying questions for Dr. Bashaw? Dr. Cloyd?

DR. CLOYD: A comment and a question. The data you presented regarding the relatively modest number of subjects and patients involved in orphan drug development is encouraging, and I would urge you to make that widely available, particularly for small companies and academic groups that are contemplating orphan drug development. Your thesis here is the mountain isn't quite as high as many might believe.

The question, and this might also require Dr. Cote to comment, one obvious use of the rare disease repurposing database is to find, if you will, the abandoned orphans, that is to say, the compounds that have an orphan designation but for which development seems to have lapsed. And could

that development be picked up by someone else other than the original sponsor?

DR. BASHAW: Well, I think you're -- I'll speak to the first point definitely. The second point I will start to address, and I will defer to Dr. Cote, as he is more familiar with it.

You're exactly right. We have started, and actually I've been going through the reviews, which is a very time-consuming process on top of my normal job, looking at these numbers and what's in there, trying to see what we've actually been doing. Because people are always saying, what does a successful program look like?

Well, it looks like lots of things. I mean, you can always say it's the Casablanca standard; you know it when you see it. But that's not helpful to the population. That's a very flip answer.

So we do have in mind -- and I think I referred to it in my talk. We are in the process of going through it from a clinical pharmacology-specific aspect and doing the math, working it out.

And we are planning on putting together a publication later to more disseminate this information.

That was also the purpose of having the discussion here today at the AC meeting, and also, unlike last year, spending the entire day on this issue because we saw it as a very important issue that needed to get the insight from you and also the researchers in more discussion throughout the meeting.

As for the repurposing database, you're exactly right. I mean, there may have been drugs that had an orphan designation that, for lots of reasons, the company changed the focus. A company was bought and it didn't fit in the new business plan. I mean, there are all sorts of reasons why drugs don't get developed. We all know that.

The aspects of going to the database, if you're looking from a disease standpoint, which you can search it, and you come up with 20 drugs for Duchenne's muscular dystrophy, see the ones that weren't developed and try to pursue that.

Dr. Cote, would you like to pick that up, please?

DR. COTE: Sure. Thanks so much for asking. Yes. We have 160 or so products that have received approval for a common disease indication that also have an orphan status designation, indication, up in that orphan -- RDRD, the Rare Disease Repurposing Database.

The biggest challenge is economic. A new rare disease indication will add almost a completely insignificant amount of new sales to a common disease indication. And there's a perception, which is unfounded, that it increases a sponsor's exposure to risk for new adverse events in doing additional clinical trials in a rare disease space.

Now, I have it on very good word from John Jenkins that that has never happened, that that has not led to any problems in the past, and that additional clinical trials for rare disease indications are very much encouraged, particularly for this repurposing, where the fruit is hanging so

very low. You've got something that's already approved. You know its toxicities. You know that it's effective in some clinical setting. We're just trying to retool it into something new.

To that end, recognizing that there are economic impediments, we have tried to do something with the public sector. We're working very closely with TRND right now, NIH's new initiative for rescuing abandoned orphans from their valley of death. And we are actually sharing commercially confidential information at FDA with NIH, under the rubric of specific memorandums of understanding, to better go through our FDA records to see which of these might be restarted, perhaps in the context of a clinical trial at the NIH Clinical Center.

So we are indeed working on that. Thank you so much for asking.

DR. VENITZ: I think we are deferring to the major discussion. Thank you, Dr. Bashaw, and thank you, Dr. Cote.

Our next speaker, and our last speaker before we take a break, is Dr. Garnett. She will

review clinical pharmacology tools in rare diseases.

Presentation - Christine Garnett

DR. GARNETT: Good morning. So my talk is going to build on what you just heard from Dr. Bashaw, and it's going to really focus on the clinical pharmacology tools that we could use for rare diseases.

So to address this topic, the way we approached it was first we wanted to go back and learn from our past experiences with applied quantitative approaches that had a direct impact on regulatory decisions.

So my first slide shows four cases where we've had success in applying quantitative tools that had a direct impact on regulatory decision. The first case is with Argatroban. Argatroban is approved in adults for HIT, and we wanted to be able to get an optimal dosing regimen for pediatrics. And to do that, what we did was we used both the adult and pediatric data. We combined them and used a PK/PD analysis to come up

with the derived dosing regimen. And that model-based dosing regimen is what was approved and is in the current label for Argatroban for pediatric use.

My second example that we've had successful use of quantitative methods is with tetrabenazine. Tetrabenazine is approved for Huntington's chorea. And in this program, what we did was we used exposure-response analysis as supporting evidence for effectiveness to support a single clinical trial. We also used the modeling, the PK modeling, to come up with a dosing regimen for patients who are 2D6 poor metabolizers.

My third case is levofloxacin. Levofloxacin, what we did was for pediatrics, and the indication we were looking for was post-inhalation anthrax exposure, where we can't really do clinical trials in this disease area. So what we did for pediatrics is we did PK simulations to match the exposures in pediatrics to that of adults for levofloxacin. And that was what is in the product label.

My fourth case is with sildenafil. This

is sildenafil IV. And in this case, we used physiological-based PK modeling, or PBPK, and this was used to alleviate the need for conducting another drug-drug interaction for the IV formulation.

So we now have to think about how can we use these tools in development programs for rare diseases. So in this slide, I'm just showing a schematic of the development process, from basic research through clinical development to all the way through postmarketing. And we can think about what kind of decisions we're making during the development process. So in the beginning, we're thinking about target identification, candidate drug selection. And then we move into understanding the ADME of the drug as well as understanding proof of concept, and then looking at efficacy and safety.

So the idea is, how can we apply these quantitative methods to inform the decisions? And especially unlike conventional drug programs, the challenge we have for development programs for rare

diseases is we have limited resources. So we really want to use these tools to help with the decision process.

So the first thing we can think about is the FDA process. The process facilitates interactions with sponsors, and recently we have included a new meeting that we can sit down with the sponsors and discuss quantitative tools, and that's with the end of phase 2A meeting, and that's specifically designated to talk about the use of quantitative methods.

So we think about the tools. They could be very mechanistic in nature or very empirical. But the idea is to use these quantitative approaches in combination with innovative trial designs so that we can answer questions about safety and efficacy during the development program. But, also, we also want to avoid late clinical trial failures because we just don't have sufficient resources in this type of development program to repeat studies. So we're trying to do two things, avoid late clinical trial failures as well as gain enough information

so the regulatory agencies feel comfortable with benefit-risk decisions.

So what I'm going to do for the remainder of my talk is I'm going to focus in on these quantitative tools, and I've pretty much categorized them in three categories. The first one is innovative analyses, then I have innovative designs, and knowledge management. And what I'm going to do is talk about each one of them in a little bit more detail and provide an example, a recent example, that we have used that tool as applied to a development program for rare disease.

So innovative analyses, these mainly are the exposure-response analyses for benefit-risk decisions as well as dose selection. And even though in the Division of Pharmacometrics we routinely do this type of analysis during our NDA and BLA reviews, but they are considered pretty innovative and a different way of looking at the effectiveness and safety data.

We could also think of innovative analyses as being these disease/drug trial models to gain

insights into biomarkers and clinical outcomes. And we've published a couple examples of that, such as with our non-small-cell lung cancer models as well as our Parkinson's disease models. So this would also fall under the class of innovative analyses.

We could also think about streamlining the clinical pharmacology package for development programs for rare diseases by prioritizing the drug interaction studies using both in vitro and PBPK modeling, and then we could also think about using more population-based PK approaches to understanding the intrinsic and extrinsic factors. And this is typically what we use for oncology drugs when we can't give those drugs to healthy volunteers. So the only way we're going to understanding the intrinsic and extrinsic factors is to evaluate it directly in the patients and correct PK in patients, especially in the late-phase trials.

So my first example that I'd like to go over is that of everolimus for SEGA. And I have to

thank Dr. Mundel, who's already laid the groundwork for the mechanism of the use of everolimus for this rare disease. And so I guess for my turn I'll just give the regulatory perspective.

So everolimus, we did consider -- if you think of Dr. Bashaw's decision tree, this is a repurposed drug. Everolimus was previously approved for renal cell carcinoma at a fixed dose of 10 milligrams. It's also previously approved for organ prophylaxis of kidney transplant at dose, as well as a therapeutic drug monitoring type of approach.

So the regulatory pathway for SEGA was a single clinical trial with 28 patients. And because it is repurposed drug, and we knew -- so we could rely on other indications for the clinical pharmacology information, the package for SEGA didn't include any new clinical pharmacology studies.

So the dosing was based on therapeutic drug monitoring, and the rationale for that was is there's a related mTOR inhibitor called rapamycin,

and there are some previously published reports that showed that rapamycin seemed to have some activity with SEGA tumors at the immunosuppressant concentrations. So then we could use the same immunosuppressant concentration range to target the dose for everolimus, and that's what they did in the phase -- I guess the single-arm trial.

So the tool that was used for the regulatory decision -- and in this case the regulatory decision was accelerated approval -- was exposure-response analysis. And we used that to demonstrate antitumor activity in a single-arm trial; in this case, we don't have controls. And we also used it to justify the therapeutic target range for TDM.

So this slide just shows the exposure-response analysis. As you can see, it's very simple. The Y axis is the percent reduction in tumor volume, and this is measured by MRI. And I'd like to say this is the first time the FDA has approved of a volumetric biomarker for an indication.

The X axis is the steady-state Cmin. It's

the observed trough concentrations. And as you could see, as you increase the exposures, as exposures increase, you're getting a further reduction in the tumor volume. And the minimum clinical effect size was considered to be a 30 percent reduction in tumor volume.

What this also showed is that when the patients' concentrations were within this defined target range, that we weren't getting a further increase in the reduction in the tumor volume. So it also supported the therapeutic range for TDM.

So if you think about going back to Dr. Bashaw's decision tree, this is for a repurposed drug. We were allowed to borrow -- we borrowed quite a bit of information from the previous indications, especially the clinical pharmacology. They allowed the sponsor to come up with a dose for the treatment of patients for SEGA. But, also, because the exposures in the patients with SEGA were comparable to the exposures in the other indications, we could also borrow quite a bit of the safety information. So it pretty much

streamlined the package for SEGA.

So my next category of innovative tools is innovative designs. And what I mean by that, we can think of the first one as making better use of enrichment designs in trials that are being used to look for drugs for rare diseases. So for enrichment, we can think in better uses of targets of genetic biomarkers that allow us to maximize the signal in clinical trials with small numbers of patients.

We could also think of making better use of crossover designs for these to show proof of efficacy. And this would be not good because in a crossover design, it controls within-subject variability. So we are able to detect effects with smaller numbers of patients.

We could also think about using dose response as the control instead of historical controls. And we could think about more using approaches for adaptive dosing and adaptive sample size, and this is going to be the focus of my second case and how we did that.

Finally, what I'd really like to see is more use of clinical trial simulation because clinical trial simulation will allow looking at the design, putting quantitative methods, models, around the assumptions about the pharmacology of the drug, about the PK/PD relationships, about what you think the design should look like. Simulate that design and see if your assumptions actually come true. And this will allow us to optimize the design, do a better dose selection, and maximize the power.

So this is going to be the focus of my second case. My second case is a blinded case. I'm just going to call the drug NuDrug. And NuDrug is being developed for a rare disease, and the prevalence of this rare disease was less than 500 patients in the United States.

NuDrug is not an NME. It's actually a new formulation of a reference product. And the clinical development program for this new drug was a pilot dose-ranging PK/PD study in 9 patients. And then based on the data from the 9 patients, the sponsor wanted to come in with the pivotal phase 3

study. And that study, what they proposed was to use approximately 30 patients. They were going to use a crossover design. The crossover was going to be with the reference product. And they wanted to use both adaptive dosing and adaptive sample size.

The way they were thinking about that is at an interim look at the study, they were going to say, well, is the variability estimates that we based our power calculations, is that what we're seeing, or if it's more variability, then they were going to recruit more patients into that trial.

Then for dosing, what they're going to think about is at that interim look in the study, are the patients meeting their pharmacodynamic target? And if they're not, they proposed increasing the dose 20 percent.

Now, for the endpoint, the endpoint is a biochemical biomarker. It's on the causal path of the disease, and the clinical colleagues felt very comfortable using that biochemical marker as the primary endpoint.

So the tool used for the regulatory

decision, in this case, the regulatory decision was the SPA or the Special Protocol Assessment. We used clinical trial simulation based on the data obtained in that 9-patient PK/PD study to assess both the dose selection as well as the size of the study.

So what we did is, again, the sponsor proposed at that interim look that if the patients aren't meeting their PD target for efficacy, that they were going to increase the dose by 20 percent. And given what we knew about the 9-patient PK/PD study, as well as we knew about the reference product, we didn't know intuitively that the 20 percent would really do much.

So what we did was, through simulations, we looked at a 50 percent dose increase for patients who weren't in their PD target. And we couldn't go much further than that 50 percent because we really didn't want to increase the exposures more than the Cmax of the reference product so we could actually borrow the safety data. So we were kind of limited on how much dose increase we could give. And then

in part of the simulations, we also looked at no dose increase.

So this is a result of the clinical trial simulation. We simulated 200 trials. And what we see here is that what the sponsor proposed is that 20 percent dose increase, that it only had about 25 percent of the patients reaching that PD target. However, with a 50 percent increase, is what the FDA was recommending, is that over 45 percent of patients would then reach their PD target. And those, again, is at the interim look for patients who weren't already there. So this is an additional 45 percent of patients who would get their target.

Again, in thinking about the sample size with 30 patients, the clinical trial simulation also showed that with the 50 percent dose increase, which is what the FDA was recommending, over 95 percent of the trials with 30 patients would meet that primary endpoint, would be considered successful.

So what we did was we made this

recommendation to the sponsor, and the sponsor agreed to incorporate that 50 percent dose increase in the revised protocol, and also our clinical colleagues also felt more comfortable with having only the 30 patients in the clinical trial.

So my last example for a quantitative approach is knowledge management, and this is relatively new at the agency. And the idea behind knowledge management is to build databases by pulling data across clinical trials. Leverage that prior knowledge to be able to inform future development programs.

What we could do with such a database, which is going to be the focus of my third and last case, is to evaluate biomarker outcome relationships across programs. Another thing we could think about doing also is we could develop these disease/drug trial models as a tool which we could also share with drug developers. This is similar to what we did for the non-small-cell lung cancer as well as the Parkinson's disease. So we can't share the data with developers, but we could share

the tools and the model approaches with developers so they could use it in their own programs.

So this is going to be my third case, which is pediatric pulmonary arterial hypertension. This is a rare disease in adults, and it's also more rare in children. And despite having several drugs approved for adults in different therapeutic classes, we have no drugs approved in children. And the reason, the challenge why we don't have drugs approved for children is that the primary clinical endpoint for PAH is the six-minute walk distance. And it's very difficult to get young children who are very sick with PAH to walk for six minutes.

So the idea for this project was to pool the adult trials across programs and look at the hemodynamic biomarkers, the relationship between those biomarkers and the clinical outcome, which is the six-minute walk test, and to see if we could use biomarkers in the pediatric drug development.

Now, this project was performed by a pharmacometric fellow by the name of Satjit Brar,

and he does a much better job presenting this, but I'll do my best in giving the synopsis of his research.

So again, he pooled several trials together. There were 13 trials in all, seven different drugs from three different drug classes, and also included the control group. And when we talked to the disease experts in PAH, they said that at least for the WHO Group 1 type of PAH, the data obtained in adults can be extrapolated to pediatrics. They thought the disease was similar enough.

So this plot showed the relationship from the pooled data analysis. So this is over a thousand patients, seven drugs, three different drug classes. And you can see the relationship between a hemodynamic marker, the peripheral vascular resistance index or PVRI, and this is the change from baseline. As you reduce the pressure, you're seeing an increase in the walk distance. And this was the most predictive hemodynamic biomarker that they evaluated.

This relationship, this slope -- and again,

this is based on the pooled data -- this slope was consistent between the treatment groups and the placebo groups. This relationship was also consistent between the seven different drugs as well as the three drug classes. So the relationship seemed to be quite robust.

So the way you would use this for pediatrics is this way. So, in adults, where the drug was already approved, based on the six-minute walk test, what you do is you develop the relationship between the six-minute walk test and the hemodynamic biomarker, PVRI, and you develop this relationship. And then you conduct dose-ranging studies in pediatrics. And you're looking at the relationship between the change in the biomarker, the PVRI, compared to dose. And then what you do is you pick the dose in pediatric that gives you the predefined clinical benefit from the six-minute walk test.

So this approach for pediatrics was presented to the Cardio-Renal Advisory Committee meeting in 2010. And the question posed for voting

was whether this approach can be used for PAH. And the committee members voted 7 to 6, yes, this can be. And so when you asked the ones who said no, this approach couldn't be used, why, what else did they want to see -- and most of it centered around looking at more data analysis, looking at additional biomarker relationships.

Since the committee meeting occurred this past summer until now, Satjit and his statistical colleagues have been performing additional analyses. PVRI is still the best-correlated biomarker. And we're just waiting for upper management to finally give the go that this is the type of approach that can be used for pediatric PAH.

So, in summary, I'd like to just conclude my talk by thinking about good drug development practices for rare diseases. And so the first step for a good practice development, and this is incorporating these quantitative methods, is to first understand the mechanism of action, when possible. Understanding the mechanism, as you

heard from the previous speakers, allows the selection of biomarkers, and the biomarkers are what we could use to demonstrate efficacy in our quantitative models.

We'd like to include those biomarkers for efficacy evaluation of drug response for benefit-risk decisions. We'd also like to use more innovative trial designs, including clinical trial simulation to support the trial design, the dosing assumptions, prior to embarking on that trial. And we also want to encourage sponsors to use more powerful methods for detecting this efficacy in small clinical trials.

So with that, that's my concluding slide. And I'd just like to acknowledge my colleagues in both OND and OCP who have contributed either as primary reviewers for the cases that I presented or to our working group within OCP. Thank you.

[Applause.]

DR. VENITZ: Thank you, Dr. Garnett.

We have a few minutes for clarifying questions, if anybody cares to ask a question.

[No response.]

DR. VENITZ: It looks like everybody is ready for a break, so let's take that very break, and we'll reconvene at 10:15.

(Whereupon, a brief recess was taken.)

DR. WAPLES: Before we start, I want to make one announcement. One of our committee members, Dr. Flockhart, is not in the room at the table at this time. He is ill. However, he is listening in to this presentation via webinar, and he may or may not attend this afternoon's session for our committee questions and discussion for this afternoon.

So for the announcement, Dr. Flockhart is not at the table; however, he is listening via webinar. Thank you.

DR. VENITZ: Okay. With that said, let's reconvene the meeting. We have our next and our last guest speaker for today, and that is Dr. Cloyd. He is going to give us future perspectives on academic, industry, government collaboration on orphan drug disease development.

Presentation - James Cloyd

DR. CLOYD: Thank you, Dr. Venitz. And I want to extend my deep appreciation to the FDA for allowing me to join this committee and to participate in this very important meeting.

One comment before beginning my presentation is that in offering my perspectives, I opted to consider a broader array of issues than simply clinical pharmacology as they pertain to the development of orphan drugs. So bear that in mind as we go through this presentation.

Now, my underlying thesis is that academic institutions can play a significant but complimentary role in orphan drug development, but are presently limited in this endeavor by resources, regulatory issues, funding, and I might say perceptions, and I'll address each of these in a moment.

The old paradigm for development of drugs, discovery and development of drugs, followed something like this, where discovery took place in the laboratories of the pharmaceutical industry,

and certainly in the laboratories of academic institutions and, to some degree, government. At that point, the industry typically takes over and conducts the preclinical work necessary, and then funds the clinical studies needed before submitting an NDA and eventually marketing their product.

In particular, with respect to orphan drugs, there is a new paradigm. And in that paradigm, academe continues to work on drug discovery, and if anything, that effort has accelerated over the last 20 years as major universities have invested literally hundreds of millions of dollars in infrastructure and faculty to understand the basic processes of diseases, identify targets, and then subsequently discover new therapies to treat these conditions.

But in addition to that, for a variety of factors, academe is now invested in clinical research as principal investigators and, indeed, as sponsors. This is driven by a number of factors. That pipeline that academe created needed to be further developed, and it was often hard to find

commercial sponsors to pick up these products and further develop them.

The economic situation in academe suggests that one find resources anywhere you can, and an expansion of commercialization and technology transfer has become important. In order to do that, you have to have a product to sell. And so you now see academic institutions and academicians involved in phase 1, phase 2, and phase 3 research in all areas, but certainly so with orphan drugs.

Now, with this in mind, I'm going to use two case studies to exemplify what I see are some of the challenges and to offer my perspective on the future of orphan drug development and the collaboration among industry, government, and academic institutions. In order to do that, I'm going to shamelessly tell you about my center, and I hope you will indulge me.

This center was created about five years ago. Its mission is to improve the care of individuals suffering from rare pediatric neurological orders. So in that rare disease

universe, we attempted to narrow it down just to that subset based on, largely, the expertise within our center.

Further, we endeavor to educate health professionals and scientists and students about rare diseases and orphan drugs, and, where possible, we serve as an advocate for expanded research in both rare diseases, orphan drug development, and access.

In our model, we first try to identify promising opportunities. And this slide was created some years ago. I've gotten a lot of helpful feedback from my colleagues. This globe is not covered by a piece of liver; that was supposed to be a screen, which apparently didn't work very well. And originally we thought we might look at any compound, including new chemical entities. Over the last five years, we've modified that model, and we are now looking largely at drugs that are already available.

Now, you have heard the term earlier today that that's called repurposing. And while it is

true, I want to amplify what that really means. Someone has estimated that approximately two-thirds or more of all available medications are generic, numbers in the thousands. And that essentially means there is no sponsor for those medications.

We have found that in some cases, there are opportunities to take a look at these generic drugs which might have a benefit in treating a rare condition. And I would submit to you that that is likely true across the broad array of drugs available as generics -- and there are an increasing number of drugs that will be generic -- that do not have a sponsor and cannot easily be revised in any way to either produce intellectual property protection or a market incentive, even if you have orphan drug designation, because a generic product will be available that's identical to the designated product, and there could well be a price differential working against the development of the designated orphan product.

We then would go on in our model, and had to do some preclinical work wherever that is

necessary. We would then conduct phase 1 through 2 or 3 clinical trials, where that's necessary, always looking for a sponsor where a sponsor is a viable alternative. Universities don't do a particularly good job in registering medications, and certainly not marketing them. Ultimately, our goal is to get medications to families and children afflicted by rare disorders.

Now, we, like a lot of large academic institutions, large medical centers, have an array of resources that in some ways mimic what a medium-sized drug company might have. And so within our center, we have expertise in these areas, and, as importantly, we can access the expertise across the University of Minnesota, which has a very large and capable group of faculty who are experts in a variety of areas that relate to drug development. This does give us a certain expertise and capability that would not otherwise be possible, given our very small size.

I'm going to give you two case studies that reflect some of the challenges and opportunities.

One is the development of an old drug, relatively old drug, topiramate, for treatment of neonatal seizures. And in that effort, we have a commercial partner who's looking at it for development in another related area.

The second one is an old drug, a really old drug, N-acetylcysteine -- some of you in the audience will know it as Mucomyst -- originally used for cystic fibrosis and now more commonly used for Tylenol or acetaminophen overdose. And we're looking at its use as adjunctive therapy in a rare condition, and I'll tell you more about that.

Let's talk about neonatal seizures. They occur in the first 28 days of life. The annual incidence is low. Fewer than 10,000 babies are born with this condition. Now, our mainstay of therapy are two drugs, phenobarbital and phenytoin. They are the oldest drugs we use, aside from bromide, in epilepsy. They are the most complex pharmacologically, and carry the largest burden of side effects known in the epilepsy field. And these are our drugs of choice for the most

vulnerable population you can imagine.

But that's not the full story. The basis on which we use these drugs is an uncontrolled trial -- well done, but nonetheless uncontrolled -- in which the active treatment was effective 40 to 45 percent of the time. And since there was no control, we do not know what the uncontrolled or placebo effect might have been. And as I pointed out, these drugs have not only short-term morbidity but also very long-term and serious adverse effects that may even affect the further development of the child.

Topiramate is a modified sulfa drug developed in the '80s and '90s, approved about 15 years ago, and it's in fact approved for various syndromes, including Lennox-Gastaut syndrome, a rare condition, down H2 as an oral product.

Based on basic research, neuroscience research, this drug looked promising as a potential treatment for neonatal seizures. So we took this on as a project, and we began with filing an IND and securing some funding to make the formulation.

We have completed adult studies. We hope to amend the IND after discussion with the FDA in order to move down in age, and that, of course, will be a question; how many patients at what ages need to be studied in order for us to begin research in newborn babies?

We hope to complete this work in older children and do pilot PK work in -- I say 2113; maybe that's the realistic date. Let's say it's 2013.

[Laughter.]

DR. CLOYD: And then if everything moves forward, we have a go decision, it is conceivable that we might have the completion of a controlled clinical trial by 2017, in other words, about 10 years after we started this project. And we're going to share this data with the putative commercial sponsor.

Now, what have we found in trying to do this from an academic institution -- and let me be clear. We are driving the development for this particular indication. First, our funding cycles

are short and often populated by gaps. This makes it difficult to organize a team and keep that team together, particularly with the appropriate expertise. Nonetheless, I'm grateful for the funding we do have, and there are expanding funding opportunities, as are listed here.

A challenge is getting early and timely guidance from the FDA. And I'm not criticizing the FDA; it's just the nature of the beast right now that you need to provide certain preliminary information in order to determine what the next steps are. But keeping in mind, until you know what the next steps are, it's really difficult to write a grant to get funded for the next step.

We're going to have a challenge in designing the appropriate trial, and Dr. Garnett gave an example of this of what trial designs are going to be informative but doable, particularly in the face of IRB concerns. And, lastly, some time out in the future, whatever time that may be, we will have to rely on a commercial sponsor to get this product to market.

So these are some of the challenges, some of which are regulatory, some of which are clinical pharmacologic in nature, and some of which are marketing-based.

Now, here's a different example. The first example conceivably leads to a commercial product supported by a sponsor that's been vetted by the FDA. That's probably the ideal scenario. This particular case is one of an old drug, N-acetylcysteine, for late stage adrenoleukodystrophy. This is another type of genetic, inborn error of metabolism disease. This one has to do with the inability of the cytoplasm, proteins in the cytoplasm, to transport very large strain free fatty acids into the peroxisome. It's a genetic defect that causes mutations or elimination of that protein.

It tends to affect boys, 1 in 20,000 live births of boys, or 1 in 40,000 births overall. The disease is hard to diagnose until you get to late stage. When you get to late-stage, mortality occurs at 3 to 5 years, and in the meantime, the

child has an ever-growing cascade of neurological disorders as well as decreased adrenal function.

In the early 2000s, our blood and marrow transplant group attempted an experimental procedure of transplanting hematopoietic stem cells as a means of trying to overcome this genetic deficiency, and I'm going to show you the results.

On this graph, we have survival on the Y axis and time in months on the X axis. The dashed blue line reflects the morbidity and life survival analysis after stem cell transplantation in a cohort of eight boys. All were dead in less than a year.

Because the accumulation of very-long-chain free fatty acids in the CNS is associated with oxidative stress, it was hypothesized that an antioxidant might be useful in improving outcome. And it was suggested that the antioxidant that might be most useful was N-acetylcysteine, which is thought to be a precursor to glutathione.

So these investigators took a look at the literature and said, let's try it. And what they

did was use the acetaminophen overdose protocol. And let me be clear here. That's 70 milligrams per kilogram every six hours for about two and a half days. This protocol was 70 milligrams per kilogram every six hours for 100 days, a significant increase in exposure.

Survival? Seven out of the eight boys are still alive. The one that died, died of a viral infection thought to be associated with the chemo preparatory regimen related to transplantation. We call this the wow graph.

While this is supportive, it's certainly not confirmatory, and there are certain shortcomings to this set of data that only suggest that N-acetylcysteine could be useful. We are pursuing an understanding of why it works, how best to use it, and can it be used prior, at an earlier stage in the disease, to modify outcomes.

Now, the issues here are as follows. The IV formulation, and you need to use an IV formulation early on – and, in fact, the oral formulation appears to have very poor bioavailability -- is an

orphan drug, so it has a sponsor. But that orphan designation expires this year. And even if you got an orphan designation for this particular indication, it is possible that a generic IV formulation at a lower cost would be available. What would your hospital choose?

Who funds the clinical trials for these long-term studies? Because ultimately you want to know both survival and quality of life and functionality, and these will take years to conduct.

If we did all of that without a sponsor, per se, is there a mechanism to change the label? And is there a mechanism to have a body such as the FDA to carefully examine the data so that it is adequately vetted?

By the way, does number 3 matter? Pediatrics and neonatology is populated with drugs that are used off label, and very successfully. And is there a pathway to commercializing this product, and if not, so what? Does it matter? There will be an intravenous formulation of N-

acetylcysteine readily available to most hospitals, so do we need to worry about that?

These are questions that I have in mind that relate to not only the clinical pharmacology issues but the regulatory considerations as well.

Now, challenges in getting academic centers involved in orphan drug development, and these are my top seven, starting from number 7.

Academicians really aren't interested in commercialization; they just want to know the truth and study science.

We do not operate GMP and GLP facilities, particularly animal toxicology. And while there are some exceptions to that statement, it is generally true.

It's hard to get money from the NIH, or at least has been hard to get money from the NIH, to develop drugs. It's just too pedestrian. And for repurposing of available drugs? That's 9 on the NIH rating score.

Academicians and faculty are generally unaware of the ever-growing number of federal

programs that support orphan drug development. Here's an opportunity. We can correct that problem.

It is very difficult to sustain development with funding gaps, and this is in marked distinction to the private sector, where there is sufficient capital to retain groups over time to conduct these kinds of long-lasting drug development projects.

There's difficulty, as you've heard, in finding industry partners interested in commercializing orphan drugs, for the reasons that have been stated. And the top reason why academic groups are reluctant to get involved in orphan drug development is the fear and loathing of regulatory requirements related to drug development and unfamiliarity with FDA procedures. And as was said in a conversation a minute ago, this looks to me like it's becoming a myth. And so the only thing we have to do is undo the myth, which could be a formidable challenge, but doable nonetheless.

On the other hand, there are enormous

opportunities for this community to accelerate orphan drug development if we harness academic institutions and get them appropriately involved in partnerships with government and with industry.

We possess most, but perhaps not all, of the personnel and facilities for discovery and development. We are increasingly involved in designing and performing phase 1 through phase 4 studies. We have expanding capabilities in the area of discovery and preclinical development. We are accustomed to competing for federal research funding, which will likely be the driver for early-stage development.

Many institutions serve as centers for patients with rare disorders, and so it's relatively easier to identify research groups and the patients they serve. And we are frequently collaborating in research consortia, which is almost an absolute necessity when attempting to conduct trials, particularly controlled trials, with rare disorders. So academe is positioned to help move forward orphan drug development only if

we harness it appropriately.

So what do we need to do collectively? We need to expand efforts to make academicians aware of the opportunities, funding, and what I'm now hearing as a spirit of collaboration within government, particularly the FDA, in orphan drug development.

We need to create mechanisms to ensure program continuity. I don't know quite how to do this, but it's illogical to start a drug development process and to seek funding on a step-by-step process where there are gaps that last months to years in that funding resource.

Enhance and expand government efforts to assist academicians in developing drugs for rare and neglected disorders. And this is already going on. There's FDA assistance with INDs; assistance in identifying and solving GMP and GLP issues -- some of that is also coming from NIH; guidance in how to identify and adhere to regulations. And this is all now being done in a spirit of collaboration as well as in regulation. And that

needs to be communicated to the academic communities.

Lastly, I think we need to integrate drug discovery and development into rare disease research. As an example, the NIH Office of Rare Disease Research now funds a group of consortia. So think of this as each group is a hub -- each rare disease is a hub -- with spokes out to several or more academic centers. Literally scores of academic centers are now engaged in understanding both the basic and clinical processes of rare disorders.

Let's integrate the notion of drug development and discovery into those processes to create efficiencies and to accelerate the identification of attractive, potentially useful compounds, and to carry out that development.

So my perspective is that academic centers can and should play a greater, albeit a complementary, role in the development of orphan drugs. I further see that early signs of growing involvement are encouraging.

The awareness about rare diseases and orphan drugs in the last two or three years is absolutely phenomenal, and you can see it everywhere. You can see it in the Wall Street Journal, in Time magazine. You can see it on 60 Minutes. You can go to the movies and watch something called "Extraordinary Measures." You can see the visibility of patient advocacy groups. You can see centers being established across this country in academic institutions, and you can see the emphasis that's now being placed on this by both the NIH and the FDA. These are all very encouraging signs. And it should lead, if we do it right, in a greater involvement with academic groups.

What does the future hold? Well, I hesitate to do anything more Niels Bohr, who thought it was darned difficult to envision what's going to happen, but I'm a glass half full guy. I think we're going to see not only an explosion of orphan designations, but an increasing number of drugs that are approved for rare disorders and an increasing number of drugs for which there is sound

scientific evidence of their safety and efficacy for the treatment of rare conditions.

Thank you.

[Applause.]

DR. VENITZ: Thank you very much, Dr. Cloyd.

Any clarifying questions? Dr. Giacomini?

DR. GIACOMINI: Yes. Very nice presentation.

Yes. I'm wondering how your center -- I mean, to have a center like yours, you have to either be endowed or have some money, at least, at the get-go. How was your center started in terms of getting it off the ground?

DR. CLOYD: I'll take a minute to answer this question. A former dean at the College of Pharmacy at the University of Minnesota by the name of Larry Weaver retired from his college position and went to the PMA. For those of you who are too young, that's the forerunner of what's now called PhRMA. And he became a vice president, and one of his missions was to get the pharmaceutical industry more greatly involved in orphan drug development,

and he had some success in doing that.

Upon his departure, he came back to Minnesota and set up a couple of companies. One was called Swedish Orphan. Another one was called Orphan Medical USA. He also brought in a very large gift to the College of Pharmacy, and his successor dean said, let's name a chair after Larry Weaver. And then a year or two later, she said, and let's dedicate it to orphan drug development in honor of his contributions.

So this was launched by an endowment, and that pays for about half of our operations. Most everything else requires extramural funding.

DR. VENITZ: Any other questions or comments?

DR. LERTORA: A comment, if I may.

DR. VENITZ: Go ahead.

DR. LERTORA: Thank you for your presentation.

With regard to the NIH role in repurposing, there may be some interesting things developing in the near and distant future, if you will. But this

issue is now part of a strategy that the NIH leadership is interested in, in terms of accelerating translational research and development of new therapeutic agents. And this actually includes the network of Center for Translational Research, the CTSA network that you may be familiar with, that has, in particular, an initiative dealing with repurposing. So there may be mechanisms developing in the future that may help in terms of funding these initiatives.

DR. CLOYD: The signs are encouraging.

DR. VENITZ: Dr. Lesko?

DR. LESKO: Jim, thanks for your presentation. As you were speaking, I was thinking about other collaborations that have borne some fruit, and I think of Critical Path Initiative and some of the collaborations through our biomarker qualification program.

I think we heard this morning that a lot of, let's say, the biomarkers that have been used in rare diseases could be qualified for many different indications, in fact, some other rare diseases.

And qualifying biomarkers under a consortium collaboration is one of the ideal mechanisms for doing that because it's so efficient and so timely, and it's something I'd like to see academia get involved with, and hopefully some funds would come along with that. But I think a lot of room for collaboration in this area, based on what we've already done with some of these other areas.

DR. VENITZ: Any other questions?

[No response.]

Open Public Hearing

DR. VENITZ: Thank you again, Dr. Cloyd. And that concludes the formal presentation part, and I'm going to open the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the

open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with a sponsor, its product, or, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the public open hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. One of

our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

I now would like to invite our first open public hearing speaker.

MR. EMMETT: Good morning. My name is Andrew Emmett, and I'm managing director for science and regulatory affairs with BIO, the Biotechnology Industry Organization. And with respect to conflicts, of course, I am an employee of BIO. Thank you for the opportunity to present the views of the biotech industry today regarding orphan drug development.

BIO represents more than 1,100 biotechnology companies, academic institutions, and state affiliates and related organizations across the United States and 30 other nations. And, indeed, the mission of many biotech companies is to bring hope and to meet the needs of patients who suffer

from rare diseases.

BIO members believe that FDA, in conjunction with the Orphan Drug Act, has made great strides to ensure the availability of safe and effective orphan products in a timely manner, but more must be done in order to accelerate the development of next-generation orphan products.

Given the significant morbidity and mortality associated with rare and orphan diseases, the unmet medical need, the societal costs, and the challenges of conducting trials in these patient populations, BIO believes that the current regulatory environment and FDA's review processes need to be reevaluated and modified for orphan products. The regulatory and approval pathway needs to be predictable, faster, and one that more clearly balances benefit and risk for these orphan disease patients and their families.

In general, the small size of patient populations is a crucial factor in clinical study design and demands different flexible approaches to FDA evaluation of trial design and statistical

analysis of results. Additionally, given these trials often necessitate global recruitment, protocols should be able to satisfy institutional review boards and ethics committees internationally.

More specifically, we have five recommendations for consideration.

First, BIO urges FDA to publish further guidance regarding orphan drug development to improve the understanding among both FDA reviewers and sponsors regarding novel study approaches and nontraditional clinical development programs so that we may encourage flexibility in scientific judgment and FDA's review processes.

For example, FDA guidance could address unique scientific considerations around study design, validation of novel efficacy endpoints in small patient populations, statistical analysis, development of patient-reported outcome tools, and challenges associated with postmarket studies. Additionally, FDA guidance should provide interpretations of current orphan drug regulations.

Second, we urge that FDA review the use of its standards for demonstrating efficacy of rare disease products. Given the small patient populations involved, BIO urges FDA to consider alternatives to demonstrating efficacy, including approval based on a single adequate and well-controlled trial at less than P equals .05.

In the many cases where it's not feasible, or even maybe unethical, to conduct a placebo-controlled trial, we urge FDA to consider the use of other data, including NIH-conducted studies using the same populations, the use of consortia between government and academia and industry, and the use of patient registries for rare diseases as part of efficacy considerations.

We appreciate the comments that FDA staff have made today in support of case-by-case, science-driven flexibility regarding approval standards, and we encourage the additional adoption of these views across FDA's review divisions.

Third, we urge FDA to support the use of scientifically validated surrogate endpoints for

product approval under FDA's accelerated approval regulations. Timely approval with adequate follow-up should become the norm for such diseases, of course, understanding that it will have to be based on credible scientific rationale, and will need to be assessed on a case-by-case basis.

We also encourage FDA to promote flexibility in the utilization of alternative surrogate endpoints and biomarkers. If data suggests that an alternative endpoint would be more appropriate than the established surrogate marker, then FDA should be open to discussing its utilization.

Fourth, BIO believes that FDA can improve communications processes for rare disease stakeholders. It's important that FDA encourage reviewers to establish more efficient communications processes that allow reviewers and sponsor researchers to discuss scientific issues based on realtime data.

There's no special priority given to rare disease products in current FDA practices regarding protocol assistance, informal communications with

the agency, the regulatory path, and other matters. Given the complexity and the special challenges of developing rare disease products, this impedes development and approval. It's also important that FDA consult with other review divisions and multidisciplinary teams well in advance of meeting with the sponsor so that all staff members are fully acquainted with the issue at hand.

Finally, we need to better understand the risk-reward ratios for these rare drug diseases. Addressing the tolerance for risk in drug development in the rare disease space is essential for advancing new therapies. Along these same lines, the agency may consider having medical reviewers spend more time with rare disease patient organizations to learn from their leadership and members of what they think and know of clinical trials, barriers to implementation, anticipated benefit, and tolerated risk.

So, in conclusion, thank you for the opportunity to present BIO's views on innovative approaches to orphan drug development. Thank you.

DR. VENITZ: Thank you very much.

Any questions by the committee?

[No response.]

DR. VENITZ: I don't see anybody. Thank you again.

Now I'd like to invite our second open public hearing speaker, please.

DR. KAKKIS: Hello. This is Emil Kakkis. I'm with the Kakkis EveryLife Foundation. My foundation is focused on improving the regulatory process for rare diseases. One of our goals, of course, is getting better access to the accelerated approval pathway, and I think it's one of the reason the oncology drugs have done so well in the last decade.

But I'm going to talk today about optimal dose or dose range determination in rare diseases, which I think is more complicated and needs further understanding and analysis. And my point to you today is simple. In a word, I think dose escalation designs are often more informative than parallel group studies in determining dose, and

there needs to be more consideration given, whatever the limitations are, to those type designs.

Both in industry and at FDA, there's a tendency to focus on parallel group designs as being superior because we will not have any effect of different amounts of time on dose effect. But the challenge is in rare diseases that there are often very heterogeneous and wide ranges, and it's very difficult to detect differences, and we end up unable to conduct the type of study with large enough sizes to be able to determine what's going on in those patients.

The other problem with these parallel group designs is that they're really very insensitive to individual patient differences, so I'd like to show you a couple examples that are -- in how things didn't work in rare diseases, and a couple examples how they did work, to help you understand these issues.

Aldurazyme is an enzyme replacement therapy for MPS-1, and a dose optimization study was done

as a postmarketing commitment in that program. Thirty-two patients were identified, which took an international effort, in fact, 8 patients per dose regimen. It doesn't matter what the four dose regimens were, but they were divided among four.

Well, we failed there. We were able to find no difference between any of the regimens, really, from an efficacy standpoint, even though it was very likely there should have been some difference between those regimens.

One of the sites took their 8 patients, currently on the label dose, and titrated them up to the alternate regimen, one of the regimens we studied, and showed that 3 of the patients had a dramatically better effect on that alternate regimen; 5 patients were the same.

But that's the kind of information you never see when you do a parallel dose group study. They had better results out of an 8-patient study than the 32-patient study we did, where we didn't discover those differences.

Elaprase is another example where a one-year

parallel group study with the walk test as one of the primary endpoints didn't really show a clear difference between two dose regimens; but, in fact, other endpoints in surrogate markers did show the difference. But if you had relied on the walk test in that design, you would have actually failed to appreciate the difference between what was good and very good doses. And I think that's where that subtlety is -- it doesn't work out very well with rare diseases. We need to understand those challenges.

Now, in dose escalation, there are a couple examples that are quite good. In the Kuvan, which is sapropterin, for PKU, this is a drug that lowers the phenylalanine level in patients with PKU. And in this situation, the FDA asked us to do a forced-dose titration.

We went through three doses, starting at a middle dose. We went to a low dose, high, then middle. And by analyzing that, we were able to show that each individual patient required different doses, and we put them on long-term

exposure at the right dose for each patient.

But importantly, there was a group of 8 patients that worked well at a 5 mg per kilo dose, not the 20 mg per kilo dose a lot of other patients were getting. And that would have been very -- if we had done a parallel group study, we would have only had two patients in that parallel group that would have responded, and you would have easily missed the fact that there's actually a good 10 percent subset that could tolerate a much lower dose and get a good effect. A similar problem now in -- so that study actually gave us an answer which we wouldn't have gotten otherwise. We've put patients on the right dose for long-term study.

The galsulfase example, I was at BioMarin at that time -- and I didn't mention my conflict, but I am an ex-employee of BioMarin, so I have some conflict because of my involvement there. However, they did not let me -- they didn't know I was talking about Morquio today. But the galsulfase program, we did a forced-dose titration -- I was involved in the design of that study -- going

through three doses, hit a top dose, and then back down to the middle dose. We showed that you got the best substrate reduction at the top dose, and when you backed down, the substrate came back, indicating the top dose was really the optimal dose.

But if you look at the walk test, the walk test was very noisy, and it created confounding information. But the truth is, I don't think you can rely on the walk test because with a 20-patient study, it's too noisy. And the truth is, even though it's a clinically relevant endpoint, clinically relevant endpoint noise is still just noise, and making good decisions off that is not smart.

So these are examples where dose escalation actually worked and gave us more information with a relatively small study and efficient use of patients.

So I think these studies can be better, and we need to be able to include them where they can be included, where there is a rapidly changing

marker or biological effect we can study. And we have to have designs that help evaluate what's known, to help control for the time of treatment effect. But we think we'll discover more unknown sensitive resistant subjects in these populations when you're talking about very small studies. So I think it fits the paradigm better of a complex disease.

I'll throw one other relevant point here, which is that these type designs I think will have implications for other diseases. And I cite here a couple examples of reports, by Carl Peck's group and another group, Heerdink, et al. And they showed that after approval, dose reductions are actually rather frequent, and that in fact of those 21 percent of drugs required dose changes; 79 percent were dose decreases, and 27 percent of neuropsych drugs, for example, needed dose decreases.

The truth is, because of desire to get maximal treatment effects, there's a drive with a parallel dose group study to end up driving doses

higher, and the means drive the groups and decisions to higher dose levels. What we fail to appreciate, then, is the tales of higher sensitive patients are lost in that story, and you end up with drugs that are probably being approved at a dose that are too high for the average patient; for some patients. Let's put it that way.

So I think what we need is better evaluation of dose escalation or titration methods in our design of these studies. And that is what I think would be effective in analyzing dose and establishing dose range in rare disease studies. And it's something that's not standard right now. It's not really well-accepted. And I think it needs to be not a difficult battle, but an accepted strategy on determining dose in rare disease studies.

That's it.

DR. VENITZ: Thank you, Dr. Kakkis.

Any questions? Dr. Cloyd?

DR. CLOYD: Are you proposing that this would be an alternative to an efficacy trial or

standard efficacy trial?

DR. KAKKIS: No, I'm not proposing that. I'm actually proposing that in the phase 1-2, many of our phases involve two studies anyways. So in the phase 1-2 study where we're looking at dose issues, by taking a small group of 10 patients through four or five doses, with the right caveats and right design, we can get more information than we would get trying to take 20 patients through three dose groups. That's what I'm saying.

So I don't mean to say that's going to substitute for an efficacy study.

DR. CLOYD: And then as a follow-up to that, the logical conclusion might be that in a controlled trial, you might have individualized doses, both active and placebo, for the population under study.

Is that something you would envision?

DR. KAKKIS: Well, I think it's something that would make sense. It is complicating to do in a placebo-controlled setting. In our Kuvan story, we actually randomized everyone to 10 mg per kilo

on placebo, and we did the dose titration after the placebo-controlled period, where we ramped them through. And then we put them on long-term exposure because of the difficulties of trying to do dose titration during the middle of the placebo-controlled study.

So that was the design we used in Kuvan. It worked very well in that program.

DR. VENITZ: Any other questions? Dr. Lesko?

DR. LESKO: Yes. I have one question while you're there at the microphone. Thank you for your remarks.

The question I had was in the dose escalation proposal or idea. Have you thought through how that might be analyzed, or how it might be analyzed differently, once you have the data compared to, say, what we do in a parallel situation, where we compare one dose to the other and somewhat get a lot of inefficiencies there? That is, some sort of continuous analysis of that dose escalation data, and have you any experience

with something like that?

DR. KAKKIS: Right. I think there's a lot of different ways you might go about the analysis. I think one of the things you can think about is some of the differences between dose has to do with differences in absorption, for example. So there could be parallel PK/PD data at different doses that could be used to normalize drug levels and dose effect, for example, as another strategy, because you have more data on each person, and at different dose levels you can actually use, maybe, that PK information to help analyze the PD information to get you a better understanding of how to dose; what are you trying to hit in terms of blood level?

So I think there's a lot of -- because there's connections between the patients at different doses, there's a lot more interesting ways of going at the data that allows you more insight in what's happening, and I think that's the general point. Thanks.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: I have a question. It's probably more for Dr. Lesko or Dr. Cote. Are there current guidance that is out that gives a preference to dose escalation versus parallel groups, or is it more just the way the industry has gone that is causing the parallel group to be preferred, maybe because of efficiency of time?

DR. LESKO: I was trying to think about that, going through my mind with some of the guidances FDA has put out, and two of them came to mind. I'm going to say I don't believe so, but we have an evidence of efficacy guidance that gets into dose-response and PK/PD analyses as a potential confirmatory evidence of efficacy. We also have a dose-response guidance that I haven't looked at in a while. But with these comments, I want to go back and take a look at that.

I think what we do feel is that a continuous analysis of dose response data with some PK and PD information in it is much more informative than a parallel design, where you're going to compare one dose to the other to see which one is better.

I think when we had the data -- and maybe Christine could comment on this as well because most of this is done in pharmacometrics -- but when we get the data, I think we tend to analyze it as a continuous variable as opposed to a discrete, categorical analysis. And it seems to be much more informative in terms of getting to the optimal dose, which you don't get, necessary, in the parallel dose design.

So I think it's a combination of both design of the study and the analysis being prospectively designed as well to address the questions.

DR. VENITZ: Let me make a comment. I'm in favor of your proposal. However, you do assume that you have a biomarker that changes quickly enough so you can actually adjust the dose. Usually, unless it's a symptomatic outcome, I don't see how you can do your individualized dose titration on outcomes.

DR. KAKKIS: Most of the time you're depending on the biomarker, and the design should help you verify that, in fact, you're not having

carryover effect or that you're actually dynamic, for example, by alternating high-low doses and looking at that issue.

So a biomarker is far more -- there are very few clinical endpoints, probably, that are going to be as responsive, but there may be. So I didn't want to prejudice it, but I do believe biomarkers are going to be more useful in this situation.

DR. VENITZ: Well, you mentioned this should be done early on, which I concur. But in order for you to do it appropriately, you need some information about the dynamics of that biomarker relative to time and maybe even to dose.

DR. KAKKIS: Very often we will have that information from, let's say, dog model and/or disease model studies where we kind of know what the marker is and how well it responses. And you can do some of those tests in the model to understand the dynamic relationship and how fast it turns and how what it relates to. So I think those are ways we can tap into other data sets to help us so when we enter the clinical study, we have a

better idea of what we're doing.

DR. VENITZ: Okay. Just one comment, Dr. Lesko, in terms of using the dose as a continuous variable. In this case, if you can actually measure the biomarker for each patient, you would have intra-individual dose-response groups, which would be extremely useful and obviously appropriate for orphan diseases.

[Dr. Lesko nods yes.]

Dr. Barrett?

DR. BARRETT: Yes. I think it offers some intriguing possibilities as well. I guess the question comes down to, if you're going to have sample size reduction with that type of an approach as opposed to a parallel group, you then have to weigh the issue of generalizability of the results. The analysis may be done in a continuous fashion, but if the basis for the approval was based on a comparison of dose groups, there again I think likes often the disconnect between what you can do from a pharmacometric side versus what constitutes language around an approval.

But I think it offers a lot of potential from the standpoint of an individualized recommendation. But I wonder if we can kind of couple that with the ability to extrapolate that individualized data to a larger population. Again, I think the pharmacometrics would be a great tool to explore that.

DR. VENITZ: Any other questions or comments?

[No response.]

DR. VENITZ: Thank you again, Dr. Kakkis.

Then I'd like to invite our third speaker.

DR. SHREWSBURY: Thank you very much. My name is Stephen Shrewsbury. I'm chief medical officer and full-time employee for AVI BioPharma. I have three questions or proposals for the committee, and I'll focus, really, on the first two, which is, the utility of mechanistic biomarkers; the use of class designation, perhaps specifically as applied to oligonucleotides, or in our case, oligomers; and then perhaps also a little bit about study design and statistical comparison

of primary endpoints, and perhaps some flexibility about how to design those.

Really, DMD, which is the disease that I'm focused on at the moment, is certainly a rare disease, and within that, there are very small subsets for the individual genetic deletions. You can see that within the U.S., there are under supposedly about 10,000 children, mainly all boys, with this disease. Very high annual cost, and therefore, drug development really has some challenges. You have to combine good science, ethics, and economics. And early discussion with all the stakeholders is vital.

Within those small subsets, particularly with the individual deletions, there is a lot of variability, both with age, disease status, concomitant medications, geographical location we've heard about this morning, genetics, and the natural history, in some cases not very well known. However, we have got some very good animal model data both in mice and in dogs, which has shown that with exon skipping in particular, you can restore

or you can start expressing the missing dystrophin protein.

This is a slide from a recently completed study we conducted in the United Kingdom, normal subject with dystrophin being expressed and shown on immunofluorescence. A particular patient pretreatment, and after treatment with 12 weekly injections, you're actually starting to see some of this protein being expressed, seemingly in the right place. The 12-week duration was not long enough, however, to see the functional benefit from that. And this was a child of several years, actually 10 years of age, and you might expect that it would take quite some time for that new protein to actually translate through to clinical functional benefits.

So, really, the use of mechanistic biomarkers, particularly when they are supported with animal model data, we believe should be encouraged for some of these rare and lethal diseases, obviously with ongoing clinical data being captured post conditional approval.

Question 2 or point 2 is about the use of a class designation. And as I mentioned, this refers to the oligonucleotides in general. Many different sequences will be needed to treat the various different subsets. However, each sequence can be built in the same almost identical chemistry backbone, and often the same length or very similar lengths.

Requiring traditional levels of proof of the clinical safety and efficacy for each one of those individual oligomers really would be not possible, and certainly not financially viable, for many small companies. So smaller programs, particularly for second, third, or subsequent candidates, should again be encouraged with some form of conditional approval and postmarketing follow-up, perhaps through registries or phase 4 studies.

Looking at the five most common exons that could be skipped in Duchenne muscular dystrophy, five drugs to target these would account for about 52 percent of the patients. However, only about half of those patients are going to be ambulant,

and the current endpoint is the six-minute walk test. A smaller number would also not have cognitive impairment, and as we've mentioned, a lot of the children might have difficulty with access to neuromuscular centers or would be outside of the current age criteria for the studies.

The PMO chemistry that we're using really has the same backbone for all the different oligomers. So, for instance, we have two that are in development, 4658, which is a 30-mer sequence, and then we have a second one which is a slightly shorter sequence. But you can see that the same chemistry backbone is employed, just with a different sequence of bases on that.

We've got a lot of preclinical experience with the PMOs, showing that there's no genotoxicity, no safety pharmacology issues, and we've got a significant amount of 12-week GLP data now. We've also conducted a number of different programs in different colors here with different PMOs in either healthy volunteers or in patients, and we've not seen any off-target effects as yet

with the oligonucleotides. And we've gone up to maximum cumulative exposures of over 10,000 milligrams and maximum single doses of 900 milligrams.

So, really, we would propose that where you're using a chemical backbone with different sequences, some thought should be given to treating these as a class, and more flexibility with particularly second, third, and fourth candidates within a class.

Those are the two main points that I wish to raise. Thank you.

DR. VENITZ: Thank you.

Any comments or questions? Dr. Thummel?

DR. THUMMEL: Yes. Thank you for those remarks.

I just had a follow-up on that. I mean, I could certainly see a compelling case with regard to safety, being a class designation. But with regard to efficacy, as I understand it, you really will be targeting a unique site. And so what could you provide with regard -- you know, to provide

confidence that you can extrapolate efficacy even though you may not test it in exactly the same way as, say, the first few compounds that you might look at?

DR. SHREWSBURY: Well, the paradigm would be that with perhaps more common deletions, you would establish both the mechanistic biomarker and some correlation with some clinical endpoints. And then in subsequent candidates where you are looking at much smaller populations, you'd be looking for that surrogate marker, particularly where it's a yes or no. It's a very distinct situation.

DR. VENITZ: Mr. Goozner?

MR. GOOZNER: A question. I'm the consumer representative on this committee, so I sort of have the same question, but looking at the safety side. I mean, in drug classes, we often see drugs that have problems. It's not a class effect, but it's one particular evolution of a common molecule. So in this case, why wouldn't that become a problem here as well, potentially, in some cases?

DR. SHREWSBURY: Well, the basis of this

chemistry is common across many of the oligonucleotides. They have a big chemical backbone on which the only changes are actually the sequence of the bases that you're actually linking to different RNA targets. So there is no difference in the actual backbone of the chemistry, and the amino acids that are used for actually the targeting are naturally occurring.

MR. GOOZNER: Just a follow-up. But very often these minor changes are precisely what cause, in broader drugs, rare side effects. So usually in a rare orphan disease, where the benefit-risk ratio is such that rare side effects are not an issue but it's conceivable that even a minor change could have some -- it seems to me a minor change could have some significant side effect.

DR. SHREWSBURY: Absolutely agree with you. And those are, in many cases, as with the more common blockbuster drugs, unexpected and unanticipated, which is one of the reasons why a conditional approval with very firm and clear guidance on registries and postmarketing approval

is probably the only way you're going to ever pick such rare side effects up.

DR. VENITZ: Dr. Lertora?

DR. LERTORA: Thank you.

Thank you for your presentation. My question was actually along the same lines as the previous speaker in terms of to what extent the traditional paradigm of structure-activity relationship can be applied in this -- or to these kind of products.

Again, I had the same kind of concern in terms of long-term exposure and the possibility of some safety issues arising due to these changes, as opposed to considering the whole class safe, if you will, in the way you propose.

DR. SHREWSBURY: Right. And some of the recent FDA approvals of rare orphan drugs have actually established the requirement to follow these drugs up for a number of years post-launch. And certainly we would support that because these children, once treated, they're going to be on lifelong treatment, and sometimes it's difficult to

predict when or how and in whom any idiopathic safety issues would be encountered.

DR. VENITZ: Dr. Lesko?

DR. LESKO: See if I understand the thought of this class designation. So in renal cell carcinoma, we see tumor-binding peptides being used, and they all sort of target the same region, let's say, of the tumor, but the peptides themselves have different structures.

Is that the kind of thing you're speaking about, so that a molecule would have slight differences in its sequence or whatever, but they're all working at the same site with a high degree of specificity, or am I misinterpreting what you said?

DR. SHREWSBURY: Close. So what we're doing is actually targeting the skipping of different exons within the pre-mRNA when it is actually going through the spliceosome in the nucleus and actually generating the messenger RNA. So we are using the same backbone and a different sequence of bases just to target different exons.

DR. LESKO: Has any other regulatory agency other than FDA considered this class designation idea?

DR. SHREWSBURY: We have yet to raise that question with some of the other agencies. But as I've indicated, we have now completed one clinical study in the U.K., and so we will be talking to the U.K. agencies about this issue.

DR. LESKO: And just to clarify on your comments regarding mechanistic biomarkers -- I think it was question 1 -- you were talking about subsetting. Right? And in cases where these drugs fail, sometimes that's simply a case of wrong subsetting.

So how do you propose in this kind of scheme, especially for the muscular dystrophy where there are no cures -- how do you figure out how to correctly subset so that when you have an effective drug, it actually is shown to be effective?

DR. SHREWSBURY: And thank you for that because that was a good point from your talk. These are very clearly defined subsets. So we know

with our lead product, which skips exon 51, we know exactly which genetic deletions we can actually target to skip exon 51 and restore the reading frame. We know that actually giving that oligomer to children with different deletions will not have any effect. And so we would specifically not use it for treating different genotypes.

However, again, we would obviously have to work very closely with the geneticists to identify the right candidates for the right individual oligomers up front.

DR. LESKO: Right. And just my last clarifying question so I understand your concept. So the qualification or validation or those subsetting biomarkers are done on the basis of -- certainly there's a hypothesis. Then is there a small efficacy study or some sort of small dose-response study? How do you actually say, yes, this a good biomarker for subsetting?

DR. SHREWSBURY: Well, the biomarker would be the expression of the novel dystrophin. So you can actually look at -- and indeed, we have done

that. We've looked at animal models. If you give the wrong oligomer, you do not generate the missing protein.

DR. VENITZ: Dr. Cote?

DR. COTE: If I could just make one brief comment. Our office has considered this very particular example and discussed it with the review divisions at CDER and the leadership at CDER. It is complex indeed. There is an urgency for producing cures for children with muscular dystrophy. They are dying. And once one of these oligomers is shown to be effective, if indeed that is what is going to occur, we can already foresee that there will be a hue and cry on the part of parents whose children have a different exon for that.

Having said that, what you're asking for is a complete and radical paradigm shift on the part of the agency to say that one product, which has one target, is equivalent to another product, which is chemically different in sequence and targets another product.

So I think that everyone -- the one thing that we can all agree to is that the race is on to find the first one that works. Let's do that first.

DR. VENITZ: Any other comments?

[No response.]

DR. VENITZ: Thank you, Dr. Shrewsbury.

Then let me invite our last open public hearing speaker, please.

DR. STOCKS: Mr. Chair, committee members, thank you for the opportunity to address the committee today. My name is Jim Stocks. I'm a professor of medicine at the University of Texas Health Science Center at Tyler in East Texas, or at least I am till the next Texas budget is established.

I'm a pulmonary internist with an academic career that's been focused upon clinical research, and drug development in particular. My special interest and experience has been in alpha-1 antitrypsin deficiency.

I am here today as an advocate of the alpha-

1 antitrypsin deficiency medical and patient communities. In particular, I'm currently the chair of the Alpha-1 Foundation's medical and scientific advisory committee, and the foundation requested that I speak today.

Alpha-1 deficiency in its most severe form is a genetic hereditary condition that leads to decreased circulating levels of the protein alpha-1 antitrypsin, and significantly increases the risks of serious lung disease in adults and liver disease across the spectrum of ages. Severe deficiency affects over 100,000 individuals here in the United States.

The pathophysiology of alpha-1 is that while the aberrant alpha-1 proteins are expressed in the liver, they are largely unable to be transported outside of the liver and into the bloodstream, from where the anti-inflammatory benefits of the protein are realized.

The awareness of alpha-1 disease state and the association with lung disease dates back to 1963, when the serum protein electrophoresis

technique was first being developed. The deficiency state is currently viewed as the leading identified genetic risk factor for COPD.

As a pulmonologist, I have spent much of the last 25 years subject to the bias of this history, believing that serious alpha-1 liver disease was primarily a problem in children and only affected a small overall subset of those with this genetic deficiency state.

As a clinical investigator, I have been involved in the development of all of the currently available plasma-derived medications for the treatment of lung disease due to this genetic condition. But having succeeded in helping to bring to the therapeutic table a menu of options for the treatment of lung disease in alpha-1, I am now finding myself humbled by the nature of the condition.

These now-available drugs have been able to slow the progression of lung disease. But while my patients may enjoy longer and less lung-disabled lives, I am thwarted by the recognition that

virtually all of them are now faced with the reality of progressive liver disease, liver disease such as in hepatitis, cirrhosis, carcinoma of the liver.

Having spent this last quarter-century developing pulmonary therapeutic agents, I am embarrassed to realize that while four new pulmonary alpha-1 drugs have been developed in this career, not a single agent is yet available to treat the liver condition, the true underlying problem in alpha-1 deficiency.

Here as a representative of an advocate of the medical and research community, I applaud the agency in its efforts to address the difficulties of orphan drug development. I and my colleagues are very much aware of the issues and difficulties of detection and education across the medical and patient communities as to rare conditions.

I would ask that this agency continue its pursuit of drug development tools such as the use of biomarkers and innovative trial designs. I would also ask that we remain focused on

facilitating the marriage of academics and industry. Our citizens need this help now, and our children will certainly need it in the future. Thank you.

DR. VENITZ: Thank you, Dr. Stocks.

Any comments or questions by any of the committee members?

[No response.]

DR. VENITZ: Okay. It does not appear that way. So that concludes, then, the open public hearing.

So the open public hearing portion of this meeting has now been concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand.

That doesn't apply because our task at hand is lunch.

[Laughter.]

DR. VENITZ: So much about reading scripts. So our task at hand is lunch. It's now 12:30 or thereabouts, so let's reconvene an hour from now,

at 1:30 -- 12:30, I apologize. I'm on a different time zone. So let's reconvene at 12:30 for the discussion and the voting on the questions. Thank you.

(Whereupon, at 11:22 a.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(12:31 p.m.)

Committee Questions and Discussion

DR. VENITZ: I'm officially reconvening the meeting. According to our agenda, we now have plenty of time to comment and discuss the preceding presentations.

I realize that I had to cut some of you short, so this is your time before we start getting into the questions that we have to discuss and vote on. Are there any discussion items, any follow-ups to the presentations that we've had a chance to listen to?

DR. RELLING: Is Jim Cloyd back? No? I guess I was intrigued by what Dr. Cloyd mentioned about what some of the challenges are for repurposing drugs. And I think he was getting at some of the issues that arise when drugs are only generically available.

It was also touched on briefly earlier in the morning. One of the main challenges that we have in pediatric oncology, particularly, but for

any "orphan disease," is the drug shortage problem in the United States. And for many of these drugs that are only generically available, there's no incentive for companies to make these drugs available because of the lack of profitability, and there's very little authority for FDA to even require that the shortages be reported, and essentially no authority that anything be done about the drug shortages.

So I guess I would just like to raise this issue of one of the big challenges, I think, for any orphan drugs with these very small markets is, even for the drugs that do make it to the approval stage, their continued availability is a huge problem, over 200 drugs unavailable in the last year.

DR. VENITZ: Does anybody on FDA's behalf want to comment on this?

DR. LESKO: Not on that per se, but just a follow-on question to that. The drug shortage area or drugs being unavailable, I assume when you were saying that it wasn't because of any issues

associated with manufacturing or raw material characterization. That would be kind of a regulatory problem, so to speak, as opposed to simply we're just not going to make more drug available for business reasons.

I'm just trying to think about what's behind all of that drug shortage. There are drug shortages because of manufacturing problems, I guess is what I'm thinking about, and how many of those are related to that.

DR. RELLING: But my understanding is that many of those manufacturing problems are attempting to comply with FDA regulations, and they're often in response to an FDA audit or visit that raises questions, many times preemptively shutting down production in order to avoid further problems.

I'm perfectly aware that it's not within a lot of what the purview of the FDA's regulatory capability is at this point, but I think it should be considered to be part of the FDA's regulatory authority because it's really damaging our ability to deliver effective drugs to children with life-

threatening illnesses, and adults with cancer in general.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes. One thing that wasn't raised today was the idea of -- I understand that when drugs are approved in Europe, for example, we also then have to approve those drugs here.

So what I didn't know, was there any link with orphan drugs, for example, that may be approved in Europe, and whether we could fast-track those here or do something in a more expedited way to enhance their approval here.

DR. LESKO: Yes. That's a good question. I wish I had numbers on that. The numbers would be how many products were approved in Europe and then came to the United States. And I'm thinking of other areas where this might be done, and usually what's involved is not reinventing the development program, per se, but doing some sort of bridging study, the bridging study typically being related to how much we understand the drug and the disease and whether or not something like pharmacokinetics,

PD, or something like that would do the job.

I think the other issue would be the etiology of the disease, are there any differences, if you will, in terms of genetic drivers of a disease in this population or this region of Europe versus the United States?

So I think there's a systemic way to think about that; that sort of has been thought through the ICH process for bridging studies for ethnic differences. So there's probably some lessons learned there that could be applied here. What I don't know is how many times -- I don't know if Dennis is here, somebody that's looked at our database -- how many times we've actually used a bridging study to approve an orphan drug for a rare disease in the United States. Maybe Anne might have some insight. I don't know.

DR. PARISER: I don't have a number on that, either. But most of the time, most drugs -- and I'm not sure of the percentage exactly, but most of the time drugs are approved here and Europe. It's really more the exception when it's one way or the

other. And a lot of times companies will come in, maybe not simultaneously but close in time, with an application. And sometimes Europe's a little quicker, and sometimes we are. But the majority of the time, it's not the case.

DR. GIACOMINI: It would just seem like this is a great opportunity for very much global collaboration in all the different countries to expedite that.

DR. LESKO: I think, as Tim may have said this morning, when you have such small populations. They generally come from all geographic areas to begin with. So you're not going to have a lock on the marketplace in, say, a European region or Japan or something like that, and then come to the United States.

But I'm thinking of our ICH experience, where products are approved in different countries. And I can't readily think of something in a rare disease that was done that way, although I bet there are some in the area of, say, oncology, where there's been an approval for a particular cancer in

one region but not in the other, and we somehow did something.

DR. VENITZ: Dr. Cloyd?

DR. CLOYD: Dr. Cote has just come in, so I'm going to defer to the distinguished gentleman from Washington, D.C.

But, Tim, the question had to do with collaboration between the U.S. and Europe with regard to approval of orphan drugs. But you might want to say just something quickly about the processes for designation in the two areas.

DR. COTE: Okay. Sure. I'll mention designations first off.

The Europeans and we are very, very close. We talk to each other every month on a monthly conference call. I go over to the COMP, the Committee on Orphan Medicinal Products, usually two or three times a year, and they come and play exchange student with us for at least a week in the summer.

We do regularly discuss applications that have come before us that have interesting twists

and turns. We do share a common application form. That is mostly symbolic because we have two very different application processes. We have compared our decisions on applications that have been received on both sides of the Atlantic, and in fact the concordance rate is quite high. In excess of 90 percent of the time, when they say no, we say no; they say yes, we say yes.

There are important differences, some of which stem from our differences in legislation, our controlling rules, but most of which actually are just grounded in the way that reasonable people in different places could look at the same information and come to different conclusions.

So there is a great deal of cross-fertilization there. Two independent processes. In the United States, a single person is empowered with making that decision; that's me. In Europe, it's a communitarian effort in which there is a -- people fly in from 40 -- 40 different people fly in from many different countries into London once a month and have a big discussion. And I think those

are reflective of our cultural differences between the two sides.

But the point is, it is a shared community, and we work very closely with them on designations.

DR. VENITZ: Dr. Mager?

DR. MAGER: I just had a quick follow-up question regarding actual approval of orphan drugs, actually. In thinking about what additional information might be useful in the development life cycle, I was wondering what the causes of attention were for orphan drugs, and are those causes similar to drugs in the traditional pipeline or not?

DR. COTE: The most appropriate person to answer that would be to my right, Dr. Anne Pariser. She'll speak to you later, but if she wants to address it now, she's more than welcome.

DR. PARISER: Yes. Actually, I don't think we have that data. I don't think that's been looked at separately. But as Tim has said before, the orphan designation usually comes pretty early in the process. So, I mean, there's just going to be a certain number of those that just don't work.

But some critical questions that it would be nice to know and we just don't have this right now is, are we losing people for financial reasons? Or they just -- as Dr. Cloyd brought up earlier, they can't do the GLP animal talk study or something. Are those addressable problems? And, unfortunately, we just don't know.

DR. VENITZ: Dr. Lertora?

DR. LERTORA: Yes. A comment regarding the general issue of drug repurposing, and of course, as it may also apply in the area of rare diseases, and that is that, of course, we have preexisting data that may help us in terms of understanding basic pharmacokinetics and safety information. And, of course, we have a dose range that has been used in the original indications. But the potential problem and challenge, of course, is that the effective dose for the new indication may be entirely different. And I think that's an issue that needs to be kept in mind in terms of exposure-response relationship studies that are applicable to repurposing drugs for rare diseases and in

general.

A case in point, one example of drug repurposing research done at the NIH clinical center has to do with tamoxifen, which has actually been studied and shown to be effective in patients with severe bipolar disorder.

Now, who would have thought of tamoxifen in terms of impacting bipolar disorder, but the study has actually been done, and the doses that were shown effective in this special group of patients is significantly higher than the typical dose in the context of breast cancer.

DR. VENITZ: Dr. Mayer?

DR. MAYER: I just wanted to follow up on Dr. Cloyd's comment about for N-acetylcysteine, I believe, where he said what difference would it make in the end for a repurposed drug? Why don't you just run the study, and if you have dosing recommendations, that may be just as good as the higher hurdle of an FDA approval.

So I think that's one route to go to, at least for repurposed drugs. We do it all the time

for compounds that have been approved, just to get publicity, to get a new -- not a new indication, but just to get a note out there for the real world.

DR. VENITZ: Dr. Cloyd?

DR. CLOYD: Well, now I have two comments. You know, pharmacotherapy is replete with circumstances in which we're giving medications based on well-done clinical studies that were published in reputable journals. Is that the same level of scrutiny that one gets when submitting to the FDA? And I submit to you that it is not. And, therefore, it may be at a lesser level of quality. And we ought not to settle for a lesser level unless we have to.

So your point is right. We'll do that because we have to; at least let's hope it's a well-controlled clinical trial. But I don't think it's the optimal way.

My other comment has to do with Dr. Bashaw's presentation, and it comes from the slide on Carbaglu orphan development paradox.

Dr. Bashaw, you state that in terms of the clinical pharmacology profile, the number of such a study was small, but relative to the target population, it was relatively high. Now, this brings up a very interesting question.

In rare diseases, we study a very high percentage of patients with a disorder relative to drugs for common disorders. Let's say there are a thousand people with the disorder. We may study 50 of them, or even a hundred. That's 10 percent of the population.

So if it applies to clinical pharmacology that we think we know more about the clinical pharmacology in a target group, even with a small number, what can we say about efficacy? Do you need to apply the same statistical standards when you're sampling 10 percent of the population, or 25, or 50?

DR. VENITZ: Do you want to respond?

DR. BASHAW: Sure. I think you raise the challenge. Certainly, I think we've also got to look at -- and it was brought up earlier -- that a

lot of these therapies, especially in the Carbaglu case, the NAGS deficiency, is very targeted. It's targeted to what you need there. So the response is quite dramatic. It's quite impressive. So you can easily see a change.

Now, certainly it does get into the issue of small clinical trials, the science of small clinical trials and innovative design, and so you've got to take the benefit-risk metric. You've got to look at these factors.

In terms of P values, et cetera, I'm not a statistician. I won't get into that. But I think that the FDA does have a recognition of the need for the patients and the population, and the fact that, yes, for these very small trials, you're not going to have hundreds of patients available to you. Even if they were, they're not -- they're geographically -- diaspora; it's all over. You're not going to have them in local centers. You may have -- you talk about international trials with a few patients here and a few patients there and all the statistical complications.

But getting back, if I could digress slightly, to the literature issue, very much using literature articles, certainly it's a different level of scrutiny. And when a sponsor comes into the FDA and they are using literature as primary evidence, we ask them to go to the authors and get the primary data, to have that submitted to us.

Most of the authors are quite happy to because they understand the value of the drug to the patient population, such that we say we'd use the literature, but the fact is, we've actually gone down and drilled down into the underlying data sets itself, not just looking at, boy, it's a nice six-page article in Annals of Internal Medicine, but actually seeing what were the numbers behind it and doing our own independent analysis of it.

DR. VENITZ: Dr. Reed?

DR. REED: Thank you, Chair. Actually, I was going to start in a different area, but I will opine on what we were just talking about now. And that is even though we are sampling a much larger percentage of a population, one might question the

greater degree of heterogeneity within that 10 percent of that population versus another disease process, which is going to lead me into the comment that I wanted to make. And that has to do -- about as we begin to think about study design.

I've heard stated at least once, if not twice, this morning that one of the things that we learned through the FDAMA and BCPA process is that there are certain diseases in children in which the expression and the etiology, the process, is identical to adults. And in looking at therapeutic design, it's really focused on exposure relationship.

I would like to pose to the committee that in fact what FDAMA and BCPA has taught us is that, in fact, the diseases may be different in how they express, how they manifest. And we have seen that with asthma, we clearly know that with GERD, relative to age, and potentially some other chronic disorders in children.

I bring that up because I think we should

think very hard about the dose-effect type of strategy design and how rich that gets us where we are targeting for that individual patient.

Furthermore, the importance of the registry comments I don't think we can overemphasize. If all of a sudden we are now modulating a previous process that had early mortality, and now we're growing through that because of our advances in therapy, we don't even know what that expression may be, as well as dose, which further underscores, in my opinion, the need of a dose-effect strategy that may need to be continually addressed as that child ages, not just because of body size but because of expression of the disorder.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: I'd like to actually build on what Mike just said, too, particularly when you're talking about the heterogeneity of some of rare disease populations.

You know, Dr. Garnett's presentation was wonderful in terms of showing the tools. And I think clinical trial simulation is something that

definitely should be explored with greater vigor in this area.

But one of the areas I think it's absolutely essential to be part of those models is an understanding of disease progression because therein lies I think where some of the heterogeneity actually falls, and also reflects the fact that these patients present at different stages, and they are not all -- even though the prevalence may be an N of a certain size, their response may be less than desirable because they're at different stages of the disease. I think you can look at failures in many of these past trials because the patient has already progressed far enough along where they were not going to benefit from the different targeted strategies.

So I think we need to take a look at the "to be enrolled" population in that sample size relative to the disease progression because they come into these trials, perhaps, at different stages, and that's also tied into why some of them don't work. So I think that would be a big

advantage in using or maximizing this tool set.

Having said that, I think again the situation of dealing with the small sample size is an issue. And I don't know, Dr. Bashaw. When I looked at your decision tree -- I think we all recognize the difficulty in the fact that all of these are unique situations. But at some point there should be I think some guidance that talks about what is the available population, at what stage can you define what that N is? Because I'm sure there are sponsors in the audience who are still struggling with the fact that the medical reviewers are still giving them guidance that they need to study bigger and bigger populations, when in fact it may be more difficult to enroll them than was originally thought at the surface.

DR. VENITZ: Dr. Bashaw?

DR. BASHAW: Yes. I'd like to go back to that. Certainly, the FDA, when we presented the straw man here, it definitely was a straw man. We weren't trying to say this was a do-all, end-all. And like I said, there's nothing new. I mean, if

you ask people and say, well, how do you develop these kind of things, they would take you down those same tacks. But it's -- hey, it really is the pediatric, just dressed up. It's the oncologic model dressed up a little bit, such that we need to use these.

Certainly, as mentioned by Dr. Cote, the FDA is embarking again this year on its training course for rare drug review for reviewers. And so we're trying to internally have these kinds of dialogues. And the AC meeting today -- not to keep blowing our horn here -- is to have this discussion with the community and to get everybody to come to give us their best input such that we can then go back and help start the process of writing guidances, of writing these kinds of white papers, if it be, that can advance this discussion more.

Because we can't -- if we're still looking at development, well, you've got to have 500 patients, you've got to have 600 patients, it's not going to happen. It's not going to happen for a myriad of reasons which we all know.

So that's, again, I think, the value of this discussion here today, and we'll move on.

DR. VENITZ: Dr. Relling? Okay. Dr. Collins?

DR. COLLINS: I think the FDA has got incredible examples of their flexibility of small sample sizes and completely novel designs that wouldn't have been even considered under other circumstances. I mean, the record is just very clear on that.

I think, if we go back to Dr. Cote's opening remarks about how much he learned in medical school from rare diseases, I think we could actually go the other way around in drug development, is that the experience with these designs and the success of the program calls into question -- or it's a laboratory. Let's just say it that way. It's a laboratory for trying things that we wouldn't ordinarily do in the course of business.

When you have a patient population of a million available, you don't think of the most efficient design, the smallest design. You've been

forced to do that as pragmatism, and I think there must be some great lessons learned from approving a drug with 28 patients or 9 patients or -- that just must be applicable to the ordinary course of business.

Particularly with the other point we made this morning about with personalized medicine, there are going to be, at least arguably, an explosion in the number of rare diseases. You're going to have to be more efficient. You don't have the staff. You don't have -- the workload's going to be high. The work flow is going to be difficult. You're going to have to be flexible in ways you never imagined.

I think you have the experience. I mean, you have enough approvals with out-of-the-box designs and sizes that that ought to feed forward to the ordinary stuff that's going to be shrinking as a part of your workload.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: To follow up on that, I was wondering whether the degree of benefit has been

quantitated in the approvals to date out of your office, Dr. Cote.

The reason I'm asking is that often in more common diseases, the big trial can be because there's a good prognosis and you're trying to find a rare event; or it can be because you're trying to find a small level of benefit that meets a predefined threshold, but really doesn't make a lot of difference.

We have some those -- you know, Pinker's (ph) cancer is full of examples where drugs have been approved based on clinically meaningless but statistically significant figures.

So I think one of the lessons learned might be that you're seeing odds ratios of 20 every time. And if we set the bar at a clinically meaningful level, maybe we could do small trials in common diseases, too.

DR. COTE: Thank you. I think that both of the two previous comments, Dr. Collins' and yours, are quite related in terms of what are the lessons learned in this laboratory. And one lesson learned

is when you've got a really good drug, you don't have to work so hard. You know? When you've got something that really --

I was reading a report the other day, just in the medical literature, of a gene therapy report of a cure for beta thalassemia. And, you know, if that's a real report, if it's a real true one and you've got electrophoretic results to show that you actually cured somebody who had beta thal, maybe you only need one person to prove the event. I mean, how do you do a clinical trial for the efficacy of parachutes saving you from jumping out of airplanes?

So I think that the real lesson is when you've got a really good drug, all of these nuances about -- all of the things that we spend most of our days thinking about, these methodologic issues, are taken care for us.

DR. VENITZ: Dr. Thummel?

DR. THUMMEL: Yes. I wanted to take it maybe in a slightly different direction, and it related to the decision tree for new molecular

entities. And this is addressed to Drs. Bashaw and Garnett and perhaps Dr. Lesko.

I noted with regard to drug interaction studies, renal disease, liver disease, numbers at least that you put in there were relatively low compared to the number of molecules being studied.

So my question is, was that a conscious decision to either delay or simply not conduct those studies, and does the agency really have a flexibility, in thinking about prioritization, to delay these, perhaps even to post approval on a case-by-case basis? So just clarity with regard to that.

DR. BASHAW: I'll take the first stab at that. Of course, that requires going back into the mind of the reviewers of that time, in the past five years. But I think what it was is a recognition of the need for the products out there. And it may be the situation where in that patient population, in the stage they were treating, it wasn't a factor you hadn't had. I think that's one of the points that was ably brought up.

You know, you have an orphan disease that maybe the life expectancy is three to five years. Now you've got a therapy that now makes it 10 to 15 years. I know when I started practice, cystic fibrosis, you didn't see many patients reach 21. Now you see them into their 40s, and you're seeing now they've got other things going on. The same thing with the orphan diseases. The ones who didn't get out of infancy, now they're getting older and older and you're seeing other ravages. You're seeing these other effects.

Basically, coming back to the question, it's a combination of seeing -- in those patients either renal or hepatic wasn't a presenting issue, that it was felt that the need for the drug -- I mean, a lot of the studies were there for drug-drug interaction. There were in vitro studies. But the limitations of the screen and projection, I couldn't slice 20 columns up there. I thought the table was overwhelming as it was.

But there were in vitro drug interaction studies that were done according to our guidances

that did provide us supporting information. But, basically, it was an attempt to -- you look back in your read reviews and you look at the administrative record. It was attempting to balance the benefit-risk ratio, and looking at the historical norms for that patient population and disease state and saying, this is what we need to do right now, and then, again drawing on other questions and speakers, the importance of the registries.

Because trying to get that -- now that we're modulating the disease, now its natural course is going to change, and everything that's written in the textbooks and the Merck manuals are now out of date because now we're going to have different patients who are now getting older, and they're going to start having other things happening to them that we need to follow long-term.

So it's a long answer to your question. I hope it helped.

DR. VENITZ: Dr. Mager?

DR. MAGER: I wanted to bring up a slightly

different decision tree, and that was the decision that a company might make in deciding to develop a large molecule versus a small molecule towards a new druggable target.

I was really struck by the presentation by Dr. Cote about the $400,000 per-patient per-year treatment that you'd mentioned in your presentation, and the concern that there could be populations that we're talking about that won't end up being able to afford the therapies that are being developed.

I was wondering if the agency is considering any changes to the regulatory approval process that could potentially influence the decision tree that a company might take to decide to make a large molecule versus a small molecule.

I was actually going to ask that as a follow-up to Dr. Mundel, and I don't know if Dr. Mayer would like to comment from an industrial perspective. But I think between the two -- and I don't know what could be done. I assume that large molecule is still often favorable because of the

wide therapeutic margin that's often available.

But is there an opportunity, for example, to work with patient advocacy groups to actually redefine these safety windows and look for ways to encourage small molecule such that the patients will be able to afford these medications?

DR. COTE: Thank you for your question. You remind me of a case example that Dr. Kakkis, if he's still here, put before us. There he is.

Do you remember, you put before us the question of Kuvan versus a large molecule and what would a drug company choose. I don't remember if -- we were speaking to some academic group at the time. And it is a good question.

Your other question was, is the agency considering revising its regulatory framework. I do know that the agency is right now under revision of all of its regulation. There's a massive regulatory second look going on right now that our Commissioner, Dr. Hamburg, has sent us all on, and I think that that's a good thing, and we're doing that.

But specifically with regards to these particular issues of orphan product regulations, I don't know if something with regards to our regulations, for example, on designations, is under -- we're reviewing them and trying to make them as less cumbersome as we can.

Referent to an earlier question about -- you're asking about access, about patients getting access to a drug. And earlier there were questions brought up about do we even need FDA approval. And I would contend that yes, FDA approval is the means through which access is best delivered.

I do know that there are off-label practices. I do know that the FDA doesn't regulate the practice of medicine, which includes off-label practices. But in order for patients to be reimbursed, in order for the world to know that this is an FDA-approved drug, this means -- what does that mean when you say it's an FDA-approved drug? It means that somebody's looked at it hard and has decided that it is safe and effective. It has a meaning that you can't get in any other

place. So I think there will always be a role for that in public health.

DR. VENITZ: Mr. Goozner?

MR. GOOZNER: Two comments. I feel like I would like to comment. One is that there are two types of orphan drugs. There are the type that have marginal efficacy, and those are -- I think you described it earlier today as it's like the key going in the lock. I mean, when Roscoe Brady discovered the enzyme that cured Gaucher's disease, it's because it was the missing enzyme, and when you have that kind of situation, it's very clear.

But I think it is instructive to take a look at what's been going on in the world of oncology, where you have marginal drugs that got approved in single-arm trials through accelerated approval. And now, when they go back, they're finding very often that the actual efficacy wasn't there. And, in fact, the Oncologic Drugs Advisory Committee, which met in early February, advised the FDA, the oncology division, that it ought to move towards two trials wherever possible.

So they're moving in the sort of opposite direction, and I think that that needs to inform the Orphan Drugs Division as it takes a look at this. And I think that the split really is between whether or not the drug is that slam-dunk.

I mean, a single-arm trial with a surrogate marker makes perfect sense in, say, an enzyme replacement situation. But where you're trying to mediate a possible cascade of events inside the body that is triggered by something where you're going to have potentially marginal efficacy, then you would have a different standard. It's very easy, I think -- it's not easy to turn this into a black or white question.

DR. COTE: Thank you for that. And I'd have to agree with much of the content of what you said.

I would just also add that there are some products which are somewhere in the middle, that it's not all a binary question of the slam-dunks versus the marginal one or two more months of life for pancreatic cancer. And even in oncology, I would take the example of thalidomide, for example,

which is the standard of care, and its daughters, thalidomide's daughters, that have resulted in the standard of care for multiple myeloma, a disease for which there really was no therapy when I went to medical school, and for which there is now.

DR. VENITZ: Let me make a couple of comments, and then I'll do one final round.

Let me maybe redefine orphan disease a little bit. I mean, right now, the way it's defined for purposes of the regulations, it's a disease that has a very low prevalence. But I think the discussion has also made it clear that it's usually a serious disease. And something that I don't think we've discussed a whole lot, most of the time there are very few, if any, alternative treatments available.

Okay? So there's a high degree of unmet need, which is obviously something that if you look at the big picture, not just the clinical pharmacology side of it, should affect the way the risk-benefit gets assessed as part of drug development.

So I think you have to look, in my mind, at least, beyond a little bit these decision trees that were put in front of us. And we heard the term accelerated or conditional approval a few times. And that to me seems to be a role or an approach that has a significant role in the development of drugs for orphan diseases that have very little alternative treatments.

That means there has to be some giving on the FDA's end as far as the proof to support that there's efficacy and equally on the safety side. And I would add to that something that you've heard before, that a lot of those orphan diseases, there are advocacy groups behind, and lots of them have registries. So you have a very captive audience in terms of the long-term safety that you could do or could get a sponsor to commit for postmarketing purposes.

So, in my mind, a lot of the issues that we are talking about beyond just the clinical pharmacology really deal with not how we develop it but how much proof do we need prior to approving

them in a conditional way, perhaps, and allow companies to market them.

I would make the argument -- and I guess I'm making the argument -- that there should be some leniency on the agency end as it relates to putting conditions on postmarketing development, not premarketing development, which is the paradigm that we use for the non-orphan diseases.

The other thing that relates more to the technical issues, a lot of those advocacy groups have medical boards associated with them. Usually those are the people that actually -- the physicians and healthcare providers that actually see those patients.

That's an invaluable resource, and again, a captive audience that I think should be taken advantage of as it relates to designing those studies, not only from a scientific point of view, but from an ethical and feasibility point of view; as well as, in my mind, one of the biggest issues in orphan diseases, coming up with meaningful endpoints. I'm not talking about biomarkers that

we all like in clinical pharmacology, but I'm talking about endpoints that convince the medical staff at the FDA that there's a benefit, not just a potential benefit.

So, again, I would urge that that's being taken advantage of, that there is some interaction, formal or informal, with those advocacy groups in the specific orphan disease areas to discuss what can be done to help drug development.

Okay. And I think one last round before we start questions. Dr. Mayer?

DR. MAYER: To Dr. Mager, I scratch my head with prices. Being from industry, I scratch my head as well with some of the prices for some of these compounds. But just because of the mechanism of action, they're almost going to be proteins rather than small molecules, and that's several log scales in difficulty, so the prices are really commensurate with how complicated the molecule is.

DR. VENITZ: Dr. Cloyd?

DR. CLOYD: As a participant in drug development for quite a while, I've come away with

the impression that at the time that product labels are negotiated, there is a general tendency to make prescribing information simple rather than difficult. And that may be driven by the industry. It may be driven by regulators. That I don't know.

But today I think we made a case for making prescribing information complex in order to maximize efficacy and safety. And so I ask this group, is there a barrier to putting forward complex prescribing information for rare diseases, because I would assert that the clinicians prescribing these drugs are capable of handling complex prescribing regimens.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: So coming back to the clinical trial design aspects, we talked a little bit about odds ratios or what is the level of benefit in there. But one of the things that we -- and we didn't talk about economics and some of these things that we're not allowed to talk about in terms of the FDA process.

But one of the things that I would love to

see brought in a little bit more transparently is the role of the level of willingness for risk by the patient population. And that's something that we don't tend to talk about. You're shaking your head, so I think you guys think about it all the time. But it really needs to influence the study design a little bit more. And maybe it does behind the curtain at the FDA. But there certainly is a higher level of risk in many of these extremely rare diseases, where people are willing for virtually anything, and in some cases will take their children to foreign lands to have unspeakable things injected into them.

So these sorts of levels of willingness and levels of risk, I guess, need to be put forward, because often we seem to take a common disease safety and efficacy framework and try to put it into something where the risks are much greater.

DR. VENITZ: Dr. Reed?

DR. REED: Mr. Chairman, I'd like to expand on one of the comments you made, and that had to do with aggressively embracing or enlisting the

medical expertise of the specific rare disease organizations. And I think that cannot be overstated, particularly as it links into a long-term registry.

As you stated, Mr. Chairman, about these are the specialists that are most likely going to be continuing to care for these individuals, I think embracing them early is very important. Number one, one can begin to establish even standardized physical assessment, data collection, type of evaluations that, for these diseases, much of this is through various critical periods.

Now that electronic medical records are maybe -- being legislated is not the right term in this forum, but secondarily being legislated, and recognizing the availability of those within the next two to three years in almost all quadrants, it would seem to me collecting this data and tracking it needs to be put into the vision of new paradigms going forward. Thank you.

DR. VENITZ: Dr. Caldwell?

DR. CALDWELL: Actually, it sounds like the

Michaels are on the same page here. I was just curious as to the thoughts that have gone into setting up some sort of postmarketing requirements that actually -- because these are small numbers of patients that are being treated -- that actually collects those data as a part of the approval mechanism, so that we -- I think many people would feel a lot more comfortable, because of the vagaries of assessing efficacy and safety in small numbers of patients in these trials, if we knew that there is an ongoing observation of what's actually happening with these medications in these patients over time. And it also helps us to understand progression of disease as well.

DR. VENITZ: Do you want to comment, Dr. Cote?

DR. COTE: The one piece of information I can add to that is there was a recent analysis by the Tufts group on drug development with regard to REMS being highly over-represented among orphan products in recent years. So at least on that safety metric, REMS are very frequently employed in

orphan product approval processes.

DR. VENITZ: All right. Are there any additional comments before we move to the questions?

[No response.]

DR. VENITZ: Okay. Then can we have the first question? I think we have a total of five or six questions. Two of them are voting questions.

So the first one that our FDA colleagues want us to discuss is in front of you. It's related to the mechanistic understanding of disease and response markers.

Any comments by any of the committee members? Dr. Mager?

DR. MAGER: I guess I'd refer back to Dr. Lesko's presentation that he briefly mentioned the work that's ongoing for multi-scale modeling and mechanism-based approaches for understanding drug safety. I would think that those methods would be very useful in leveraging preclinical biology and pharmacology and pathophysiology, and a focus clearly on the biology of the system that

would allow better extrapolation across scales of organization.

Of course, I'm biased. But, in any event, you cite very nicely the utility of physiologically-based modeling approaches for pharmacokinetics and its utility in understanding or projecting PK under different conditions. And I think that multi-scale modeling of data on that level, on the molecular and cellular level, will provide a bridge for that, help identify meaningful biomarkers. We could probably have another meeting on what we mean by meaningful biomarkers, but to help to identify targets, meaningful biomarkers.

Then also, the idea again of combination products, I think if we're going to think about how to integrate or to provide a mechanism for combination products, I think, again, multi-scale modeling is really the main mechanism for being able to evaluate the emergent properties of the system.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: This question says "how" as

the first word. So my comments really address the how. I brought a paper with me. This is in Nature Reviews Drug Discovery 2003, by David Horrobin. And the title of this is, "Modern Biomedical Research: An Internally Self-Consistent Universe with Little Contact with Medical Reality?"

Now, just bear with me a second. So the beginning of the abstract says, "Congruence between in vitro and animal models of disease and the corresponding human condition is a fundamental assumption of much biomedical research, but is one that is rarely critically assessed."

So I think we're kindred spirits in that we recognize the value of biomarkers. We recognize the value of animal models. But in terms of the how here, what I think I'd like to see the FDA embrace is really critically verifying whether or not these preclinical data and animal models are predictive, particularly in rare diseases.

There's no shortage of publications, and there's a replication of this fact over and over again. But I was struck by this paper when I read

it, and I highly encourage folks to take a look at it. It's a little bit more critical. He's definitely more the glass is half empty kind of author. But I think some of it is really very well deserved.

I think the one point that he makes here at the end of this is, "Is it really too much to think that a direct assault on human disease by studying humans might be at least as productive as the massive investment in the investigation of unvalidated animal or in vitro models?"

Now, that's, I think, overly critical for sure. But it comes back to the points that we were making here about maximizing the clinical experience with these rare diseases and pulling this information out of the caregivers who are treating these patients to articulate disease progression as best that we can, to understand it from the time of onset through its progression.

Then in this case we can use the preclinical data to verify, either through study designs or actually target investigations, one, can we come up

with an approach that is more meaningful; and, two, before we keep repeating this over and over again, where do we see the value? And then maximize that, and where we don't, just change things. Do something different.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: So during Dr. Garnett's presentation, you mentioned a number of examples where you took adult data -- or I don't know if you mentioned preclinical data, but I guess the same would apply -- , and modeled it, and then gave recommendations to the sponsor for how to move forward.

I guess in the context of how, one of the big issues that is unclear to me is, do people want help? And often those that are developing drugs are not necessarily asking for help. Certainly some of the -- I live in an area where there's a lot of small biotechs, some of which are developing orphan drugs. And the last thing they want is help, especially from the FDA.

So I think part of it is making it clear

that help is available, and part of it is by showing those examples in forums that have metrics like time to approval and issues that really matter. Because, as with all of us, help is available for all aspects of our life, but rarely do we ask for it. I think part of the way to answer this question is showing that the models that are out there can go forward.

Now, a number of the products that are being developed, there is no prior art. You can't really model them, and you're stuck there with the mechanism, mechanistic approaches that have been used in the past. But where there are examples, I think maybe you push that a little more.

DR. VENITZ: Dr. Cloyd?

DR. CLOYD: There may be a variety of options in terms of deriving what I would call preclinical information that can inform the design of clinical trials. And I'll talk about clinical trials in just a second.

But an example about which I know something is canine epilepsy, dogs with seizures. It's not a

model of epilepsy; it's clinical epilepsy. The electroencephalographic signatures are identical. The clinical symptomatology is the same. Drug response is the same, including refractory, drug-resistant epilepsy. And the side effects are the same.

So one would wonder if you could find clinical models of the disease in the relevant animal species, could you derive exposure-response relationships that then could be taken into clinical trials?

Then, turning to the issue of clinical trials, phase 2 and 3, what would happen if the agency strongly advocated concentration or exposure-controlled trials of an adaptive nature as being viable mechanisms to evaluate efficacy, and would be looked up favorably not only in the review but also in the development of the product label?

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes. I was struck by the presentation with muscular dystrophy, where they looked at the exon skipping. And I was struck

because of the fact that the presenter had highly mechanistic, first mechanism data where they actually showed the primary mechanism. In other words, the protein was being expressed on the plasma membrane, and although it may take time to get the clinical response, they had good mechanism.

So I feel like, based on what Dr. Cote said early on, that we've learned a lot in a lot of these rarer diseases. We know a lot about mechanism. But it's a very good opportunity to build models upward, starting with the fundamental mechanisms and then building models all the way to the clinical output, and seeing if that can be a way to enhance drug approval processes, et cetera. It just seemed like the mechanism was ahead of the clinical outcome by a lot in this case.

DR. VENITZ: I would just give the -- do you want to respond to that? Okay. Go ahead.

DR. LESKO: Yes. I just wanted to comment on several of the comments that went around the table And a little context for this question because I think one of the things we'd like to

drive towards is a more systemic, more efficient way to develop drugs in this space.

I think Don mentioned something that struck me, and it was about attrition in the area of rare drugs/orphan diseases. And I'm not sure we have the information to say that the pivotal trial, whether it be a phase 2 or phase 3, failed because of this, that, or the other thing. I think we need to get that data.

But I saw this week a study came out by an organization that does this sort of thing, and they found that at least in general drug development -- not rare diseases -- that the reasons for attrition in phase 3 -- 50 percent of those trials failed. That hasn't changed in about a dozen years.

The reasons for failure in the phase 3 was in two-thirds of the cases, 67 percent, was efficacy, lack of efficacy or failure to meet placebo or comparator. Twenty-one percent was safety, and 12 percent was other reasons.

So you think of those numbers, and it would seem to be, without data in front of me, that that

would not hold for rare diseases. In other words, the failure for efficacy should be much less because by comparison, we know -- and I think as Kathy just said -- more about the mechanism of the disease, and the drug being more tailored to the disease than it is with smaller molecules.

So if you were to think of what would cause attrition in rare disease and orphan drugs, I think what this question is trying to get to is, how do I sort out three things?

One is an ineffective drug, and maybe there's a set of studies that would be done to sort that out very quickly, maybe a dose-response study to begin with.

A poor strategy, so would a trial fail in a rare disease because I picked the wrong patients, or I picked the wrong endpoints, or I powered the study the wrong way, and started thinking about what can go wrong in this area, with efficacy being a given. So what else could go wrong? And then the third reason, of course, is the financial reason that people talked about.

So I can imagine a road map that would look at this and say, I don't need to worry about efficacy very much as a reason for attrition because the drug should work mechanistically. But I do need to worry about a failure of a good drug because of the wrong strategy and the wrong study designs, and begin to fill in the blanks about what the right strategy should look like for an effective drug.

That's not to say they'll all be effective. There's going to be some failure. But I think we can detect those pretty quickly in a relatively few. I mean, when Trevor was speaking this morning, I think he said 4 patients with Muckle-Wells. It was almost a perfect model; all of them responded. So efficacy wasn't an issue. The next question was, how do I get the dose right going forward, and how do I worry about safety in a unique way?

I think maybe that's the construct of this, to think about how to de-risk the attrition that is going to occur after the proof of efficacy concept

study is done, what kind of information will do that.

DR. VENITZ: Let me comment on that, which is what I was going to do anyway. And that has to do specifically to this question, which gets beyond just the other claims (unclear) of pharmacology because you're talking about phase 2 and phase 3 studies.

I think what you're talking about is the more you understand the biology and the more you understand the pharmacology of the drug, the better you pick your biomarker, and your biomarker is going to predict disease progression. And I think we saw some nice examples earlier today. But how often is that the case? Is that truly representative of orphan drug development? I don't know the answer to that.

So my caveat that I was going to raise here is the potential disconnect between the biomarkers that we can measure and help us perhaps with those recommendations, and the disease progression that ultimately has to provide a signal for clinical

benefit.

DR. LESKO: It would seem that there are two things at work. One is the disease pathophysiology and the other is the drug mechanism of action. It would seem that any molecule introduced for a rare disease should have a reasonably credible hypothesis for a mechanism of action. So it kind of leaves the disease pathophysiology as maybe the weak link, as it might be in, say, cancer or something like that.

So getting to the biomarkers that are the right ones for a disease state, that is differentiating biomarkers that are maybe prognostic versus those that are predictive, or maybe even thinking about the reverse causality of biomarkers that could be confounding in trying to figure out a disease, you know, this is really where maybe the intellectual piece ought to be focused, more on the disease as opposed to the drug.

Now, when Trevor presented it, and a couple other examples, it was pretty clear the mechanism

of action was well hypothesized over expression of IL-1 or something like that. But the question is, is that the right biomarker for the disease progression? And I think that's something that we need to think about in this question.

DR. VENITZ: Any further comments to this question? Yes, Dr. Reed?

DR. REED: I agree about the importance of disease progression because we are -- you know, we are most likely perturbating a process now that, at least as I said before, for fatal diseases we've not seen progress. And so we are going into unknown.

But Dr. Lesko, I would comment on the recent paper you reviewed with the 67 percent lack of efficacy. I think we have many examples when we go back that we have not performed our basic dose-response studies properly.

We don't know -- and particularly in pediatrics, we don't know what that range is. And, unfortunately, we are oftentimes anchored in pediatrics by an arbitrary adult ceiling dose that,

because of the nature of age and the disease difference, may have no relationship; which then comes back to, I feel, the importance of the dose-effect strategy, where you will then go forward and see how you're going to perturbate the process across any dose range.

DR. VENITZ: Any final comments to that question before we move on?

[No response.]

DR. VENITZ: Okay. Then let's move on to the second question. And the very first one is a voting question, so let's discuss it first to make sure that we all understand what it asks, and then I go on my script again or the task at hand.

Do you want to review it for us, Larry?

DR. LESKO: Maybe this will help just give a context because we're trying to anchor a direction to go forward, from the advisory committee forward. And the two questions under topic 2 are really related to maybe a lower-hanging fruit or an easier situation, when you have a repurposed drug with a fairly large body of information on prior

information, and the second case where you have the new molecular entity with some uncharted territories on the basic work about the molecule.

So we're trying to start with something we know in these questions. So in the first case, it talks about repurposing being analogous to the pediatric situation, where we have some prior information that's significant. But, of course, there are differences; it's adult versus pediatric. And over in the other case of rare diseases, it's one indication versus another. So they're not exactly alike. But they're similar enough, we think, to lead us to the next step of a systemic approach to drug development.

The second case, the new NME, really gets into a critical part of our discussion today because it addresses the threshold of information that would be optimal for a drug for a rare disease, given our limitations that we've talked about today, and ways of addressing information that is not there at the time of drug approval.

So they're two different scenarios, if

people can imagine it. In the second case, we tried to use the oncology drug development model for the second case, where you may not have the full package of clinical pharmacology studies, but what would you need? It's not the Cadillac, it's the Corolla, or something along those lines, and what would the Corolla look like, although that's expensive these days, too.

So that's being said. That's just creating a context for that, and any input on this would be very valuable for our next phase of discussion.

DR. VENITZ: Okay. Then can we go back to 2-1? I don't think I have to read it. Let me go on script so you guys can get ready to vote.

We will be using the electronic voting system for this meeting. Each voting member has three voting buttons on your microphone, "Yes," "No," and "Abstain." Once we begin the vote, please press the button that corresponds to your vote. You will have approximately 20 seconds to vote. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. I will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record, as well as the reason why they voted the way they did.

Any questions about the process?

[No response.]

DR. VENITZ: Okay. I have to read the question into the record.

"Are the drug development paradigms for regulatory approval of pediatric and oncologic drugs well suited as model processes for repurposing of approved drugs for new rare diseases/orphan drug indications, and for providing the substantial evidence of efficacy-clinical benefit needed to meet statutory standards for orphan drugs?"

Any question about the question?

[No response.]

DR. VENITZ: Then I'll open the vote. So you now have 20 seconds to press a button.

[Voting.]

DR. VENITZ: We're still waiting for the Jeopardy music.

Let's go around the room. Everybody please state your name, the vote that you gave, and any reasons that you might want to explain. Let's start with Dr. Giacomini.

DR. GIACOMINI: I guess you can guess what I voted. So I'm Kathy Giacomini, and I voted yes. I was impressed by some of the presentations today on the different methodologies that were being used, the modeling and simulation, the single-arm trial, the dose escalation. So I thought the methods were great. I voted yes.

DR. THUMMEL: Ken Thummel. I voted yes, for essentially the same reasons that Kathy stated. I think there are enough useful paradigms and approaches that have been developed for pediatric and oncology that would apply for ordering.

DR. LERTORA: Juan Lertora. I voted yes. And I was essentially persuaded by the information and the discussion that took place this morning in

terms of the potential utility of these model processes to guide drug development for orphan diseases.

DR. HARRALSON: Art Harralson. I voted yes. And I just think it's a more reasonable way to look at the whole process, and I think it's a great step forward.

I do have some concerns about modeling and that sort of thing. I love modeling; I've been doing that for a long time. But I wonder to what extent, if the FDA is advising, that they become vested in the model they're advising as opposed to the sponsor bringing the model to them. But maybe we'll discuss that more later. Thank you.

DR. CLOYD: I voted yes. Jim Cloyd. And I did so because it appears that a large percentage of the information available on a repurposed drug will be applicable for rare conditions, with the following caveat, that unique aspects of the disease or the patient population may require special studies, as well as those drugs that have been inadequately studied but approved, and they,

too, may require additional studies.

DR. MCLEOD: Howard McLeod. I voted yes. I think that the data from both industry and regulatory presenters made it clear that there is a path forward that works. The exception would be for drugs that no longer have a primary sponsor, where I think there's still some work to be done. But for the question that was posed, I thought yes.

DR. MAGER: Don Mager. I voted yes. I think we've had plenty of examples showing that these paradigms are useful for this purpose.

In terms of the question, new types of data, I don't know if we need new types of data. I think the bigger problem is that we have the tools and we have the approaches. It's the point that Dr. McLeod pointed out, that they often don't ask for that help. And it's really how do we bring those tools to the folks that need them as opposed to types of data, I think.

DR. VENITZ: Jürgen Venitz. I voted yes. It was a no-brainer.

DR. COLLINS: Jerry Collins. I voted yes.

In adult oncology, the vast majority of clinical work that's done is for supplemental NDAs for already-approved drugs. So they're essentially being repurposed, and that's the largest effort that goes on there.

Typically, it's a single-arm trial instead of -- a single phase 3 trial instead of multiple ones. There are essentially only rare cases where someone wants to reconsider. And accelerated approval -- out of 50 accelerated approvals, 10 percent, or 5, have reached a point where the sponsor or the FDA thinks that it should be -- the accelerated approval should be withdrawn in oncology. So that's a risk of 10 percent that most folks are willing to accept. And, of course, in pediatric oncology, essentially every drug is a repurposed adult oncology drug.

So the NCI is filing or is licensing the data for someone else to file an NDA this year for a drug that has a target population of 400 patients in pediatric oncology. That's very rare, that there's ever a primary indication for pediatrics.

MR. GOOZNER: I'm Merrill Goozner. I'm the consumer rep. I also voted yes, obviously. And Jerry stole actually most of the things that I was going to say, except that I would put a slightly different spin on it, which is to say that when you use the oncology paradigm, what came up at the recent Oncology Drugs Advisory Committee was that very often it's hard to get companies to follow through and do some of the after studies that are being require. And this becomes an issue once drugs are out there on the market.

That's something that you should take into account, especially if you're talking about validating surrogate markers and, you know, getting people to actually do the registries or to do the follow-up studies to make sure that the drugs are having the effect that the mechanism of action suggests they would.

DR. REED: Mary Relling, and I voted yes. I agree with what's been said. I'll reiterate what Dr. Giacomini said, that I think, whenever possible, the FDA should capitalize on data

generated from other countries.

We have an example in pediatric oncology of Erwinia asparaginase that's still not approved in the United States, although it's been used for 20 or 30 years everywhere else in the world. So I think there are plenty of examples where we could do a better job of taking advantage of foreign data.

DR. CALDWELL: Michael Caldwell, and I voted yes. And my biggest concern was not that we would be able to demonstrate efficacy with these types of study designs, but that we would have problems with truly evaluating safety because of the small numbers of patients that are involved. But when I've thought through this and sort of did some mental calculations, using repurposing techniques I think is extremely useful in this regard because the adverse events would have to be -- for you to be able to even see them in the orphan trials, would have to be so high that they'd be clearly obvious in the other trials. So, as stated earlier, it should be a no-brainer.

DR. REED: Michael Reed. I voted yes. I concur with Michael to my right, and the chair as well, that I think it's a no-brainer. In particular, capitalizing on what we've learned from our colleagues in oncology about rigorous dose-response assessments, and pushing that dose -- and again, I'll put the plea particularly in children -- without having a preconceived bias of an artificial dose ceiling and the presence of continued efficacy and in the absence of dose-limiting side effects.

I think that strategy we've learned very well from our colleagues in the oncology realm that can be brought into this process.

DR. BARRETT: Jeff Barrett. I voted yes. Again, as has been pointed out, there's significant overlap in these populations, so there's no reason to invent a new wheel. And I think the process is wonderfully flexible, so it does encourage the dialogue with the FDA. And I think you have an opportunity to use this process to deal with special cases on an as-needed basis. So it is a

no-brainer.

DR. VENITZ: Okay. Thank you. For the record, the final vote was 14 in favor and no abstentions and no votes against.

All right. Let's move to the second part of the second question. That's a discussion question, so here we are not talking about repurposed drugs, but we are talking about NMEs.

Does anybody want to make any comments in response to the question that's in front of you?

DR. COLLINS: I would make a pitch for just prioritizing the clinical pharmacology studies that you want to do, that I think there should be some more flexibility in terms of which clinical pharmacology studies are most important preapproval versus post-approval.

In the Argatroban study, there were 293 subjects were used. And, at least in my opinion, the dose concentration response curve for pediatric patients is still not very adequately characterized, at least in the published data. Maybe the unpublished NDA data is better, but in

the published data, it's certainly not very convincing. And certainly that's the whole reason we do all clinical pharmacology studies, is to get dose concentration and response right.

DR. VENITZ: I would second that. And I would add, especially the usual special population and drug interaction studies would have to be approached with caution in terms of making them preapproval requirements. Those are the kind of things, if they really end up being important other than being another check-off, they could, in my mind, at least, be put into a postmarketing commitment. So really identify -- as Dr. Collins just said, what are the pieces of information PK/PD that you need, preapproval, in support of efficacy, and everything else might be postponed, so to speak.

Dr. McLeod?

DR. MCLEOD: Some of the points that Dr. Reed made some earlier discussion were about the disease progression. And I think that's a part that is already taken into account, but needs to be

highlighted, in that there are some of these rare disorders where organ dysfunction is something that occurs in a fairly common basis as disease progresses. Others, it's more CNS-based deterioration and the organs are just fined.

So bringing that into account would also help with the prioritization that Dr. Collins and others have mentioned, where it may be that organ dysfunction studies prior to approval would be key in some disease states, whereas that could be a postmarketing event later, and I think that's an important issue.

The same with things like food effect. I think there's a number of areas where GI stasis and the liver blood flow, et cetera, are influenced by disease and need to be taken into account.

So I get the impression that the agency has the flexibility to change the prioritization based on the dynamics of the disease. But I think it needs to be more explicitly stated in future guidance, et cetera.

DR. LESKO: In thinking about, again, a

context for this point of discussion, what we had been thinking about is, yes, risk-based, priority-based recommendations on clinical studies. But the question comes up, what would be those studies that could adequately be done in healthy volunteers versus those that would be done in patients, and could we transfer that knowledge from healthy volunteers to patients and say something in labeling?

So, for example, if you had a new molecular entity for a rare disease, you could conceivably recommend that a renal impairment study be done, and then use that information to transfer to a dosing in the patient.

For example, like Dr. Mundel pointed out, Muckle-Wells sometimes leads to severe renal impairment. Okay. Then how do you adjust the dose, albeit in a small population, for that patient population, and can that knowledge then come from a healthy volunteer study and be transferred to the label for the purposes of dosing?

So that's kind of one of the contexts for this point.

DR. VENITZ: Can I just respond to that? The counter-argument would be, though, if you have some kind of a marker that you use to address dose anyways, maybe you don't need that information. So it depends on how the drug is given. Are you going to give everybody the same dose, or are you going to individualize it based on some market that you're measuring? If that's the case, then you may not be worried about those extrinsic and intrinsic factors.

DR. LESKO: The other angle on this that we've been -- and we discussed it last year in terms of in silico modeling, the physiological-based modeling, where you can make predictions about drug interactions or predictions about the effects of impaired renal function without doing the study that are, depending on the circumstances, reasonably accurate.

So that could also be another angle to this to say, look, ordinarily I might want to confirm

this, but given what we know and given our history and working with PD/PK, we can make some predictions and possibly include that in the label as an alternative to actually going out and doing the study.

So I think there's another innovative thought in thinking of it that way. And then the question becomes, under what circumstances can I do that?

DR. VENITZ: But I would make the argument as long as your label reflects the evidence, meaning either you have no evidence how to adjust it or you've got some models that suggest you should or shouldn't adjust it, you're fine. And that's why I made the argument earlier on to really work closely with the medical groups that work with those orphan disease advocacy groups.

DR. LERTORA: Mr. Chairman, I would like to concur with your previous suggestion that drug-drug interaction studies may be considered for implementation premarketing or postmarketing. And of course, it's being done with a case-by-case

analysis.

But if I may, in relation to that, to ask a question. In Dr. Bashaw's presentation -- and I'm looking at slide number 10 where we had informational content of NDAs and BLAs -- I was struck by the fact that there was no -- none of the 13 BLAs that were cited in this table had any drug-drug interaction data.

As I'm sure you're aware, there are published data in terms of potential significant interactions in terms of biologics and small molecules in terms of drug metabolism and perhaps also transport.

So would you comment on that? I mean, what is the standard requirement here in terms of biologics with regard to drug-drug interactions?

DR. BASHAW: Well, that's exactly right. When you look at the applications that were approved in that time slice, there were not. Those you're referring to, the classic pharmacokinetic drug-drug interactions, were oftentimes for the biologic agent. The actual biologic halftime in

the plasma is so short and so little that it's undetectable. So the classic level go up, level go down isn't seen.

Now, there were -- in the clinical trial database, again, they're trying to get very clean patients for the clinical efficacy-safety studies where they weren't on concomitant therapies, but we all know they would be in real life. And that is a problem. We don't have a specific recommendation.

I mean, look at -- Dr. Huang may want to speak on recommendations for biologic drug-drug interactions.

DR. HUANG: I'm not sure about, in the survey, whether we talk about whether there are drug interaction information in the submission or whether there are drug interaction recommendations in the labeling, because for some biologics, if we know there are certain cytokines, cytokine antagonists, we will put in the labeling about the possible interaction based on previous information. And we will put it in the labeling without specific studies. They could be generated from other drugs

in the class.

So some of other drugs may not be orphan indication, but because of similar mechanism -- so we put in information about warning of giving -- for example, this drug may affect CYP3A substrate, so be careful when you use this drug with CYP3A substrate.

So I'm not sure whether the survey indicates whether there are data available. But we have increasingly included the information about biologic interaction in the labeling of biologics without having actually conducted a study.

But based on what we know today about some of the cytokine effects on certain CYPs and transporters, we started to have asked, post-marketing, either commitment or requirement studies to help us to give more actionable labeling recommendations. But I'm not sure whether the survey indicated the labeling for studies.

DR. BASHAW: No. The survey, because of the mass -- when you started thinking about going through the clinical pharmacology reviews of 33

NDAs and look at what -- that's quite a -- this cut that is presented in the slide you're referring to is looking at what was submitted, what was the totality of information submitted by the sponsor.

Now, what may have been additional information learned from other drugs or what we can discern, we developed the clinical trials program that translated into actionable labeling, that is not included in that table, and that's a good follow-on for us as we continue on.

We're continuing with this survey and this research. We're still looking at the numbers. And I'll be very honest with the committee; the next time you see those numbers, they're probably going to change a bit because we're going back and reassessing what was submitted again.

There is some education here as to was this trial used, was it not used, et cetera. But we can certainly add into our database, just add a little more to it.

What eventually made it into the label as a good follow-on, we'll take that suggestion very

strongly. Thank you, sir.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: Yes. I think in terms of flexibility, clearly the agency wants to achieve the highest regulatory standards they can. So the issue really is at that first stage of the decision tree, will healthy volunteers be a reasonable population to extrapolate into your rare disease?

If the answer to that is yes, then certainly that opens up more possibilities for a clinical pharmacology package that allows you to have the actual experience in a relevant population. But where the answer is no, I think that's where the flexibility comes in.

So specifically we know that some populations are not otherwise healthy, and particularly some of the neurodegenerative disease, where patients are sitting or they're immobile, and we have some prior knowledge that the pathophysiology is not the same. So extrapolating from a healthy volunteer population may not be as meaningful.

Having said that, with the advances in in silico techniques and modeling, we can adjust some of these parameters to get some idea of what the expected performance is. And I think it gives us an opportunity, working with some of the caregivers and these registries, to actually populate those models with real data coming from the target population.

So there's an opportunity, I think, to refine this approach to maximize this information. We don't have to be limited by the difficulty in studying the population, and we can actually leverage the information that's out there and, again, use the best tools at our disposal.

DR. VENITZ: Last comment, Dr. McLeod?

DR. MCLEOD: So I can't remember from any of the talks from the agency whether -- there was mention about orphan drugs are subsequently withdrawn. And I know there's been at least one case, which I believe was an orphan drug in one of the GI disorders, which was withdrawn and then reintroduced, and I think withdrawn and

reintroduced one more time based on various pressures, one of the Glaxo drugs.

But how often is this actually a problem? Is there a case where a signal is missed and then subsequently brought back out? So I guess my question is are we worried about something that doesn't seem to be occurring, where there's no excess risk for drug withdrawal, or is there something where the signals are being found later that would cause us to reevaluate the way new drugs are brought forward?

DR. COTE: I don't know of many examples where drugs -- or any examples of drugs that have been withdrawn for safety reasons. I do know that there were issues on an orphan status designation being withdrawn for considerations that perhaps -- I know that there were circumstances with pancreatic enzymes -- perhaps that's what you're talking about -- which was withdrawn because there was reconsideration as to what the disease or condition was. And it was decided that it was pancreatic enzyme insufficiency rather than cystic

fibrosis, but those decisions antedated my arrival at the agency. But those are the only ones that I know about.

DR. MCLEOD: This was a hepatotoxicity example with one of the -- I believe it was inflammatory bowel disease drugs. But it may not have had orphan status.

DR. VENITZ: Okay. Are we ready to move to the next question? Let's do so because that's another voting question, and I'm looking at Dr. Lesko to maybe set the stage for us so we know what we're voting on.

DR. LESKO: I have to -- I don't see the copy here.

DR. VENITZ: Let me read it, and then you have a chance.

"Do the current drug development programs and clinical pharmacology studies for rare diseases/orphan drugs provide sufficient information on drug safety, that is, benefit-risk ratio, given the limitations that exist to conduct relatively large pivotal efficacy trials with

safety data collection?"

DR. LESKO: Yes. I'll just try to give a little context to this. We've given a lot of thought to, really, what's been discussed today with the committee, and that is, how do you leverage what you know to minimize the risk of safety? And questions were asked, and good questions asked, about what's been the history in terms of what happens when these products get into the marketplace.

I think it really circles back to what kind of information in the current programs or in an enhanced program can minimize and de-risk a compound even more. So, for example, one might think about a program in which a single dose is advanced. That would have a higher risk, let's say, and perhaps the limitations of a small population would be more significant.

We haven't talked very much about DNA collection in these trials. It's not surprising in that many of these diseases are in fact genetic-based, but they also in some cases can have off-

target effects in which DNA collection may be advantageous to give some insight.

So this is really a question to say, here's what we do now. Is it as good as we can do, given the tradeoffs with getting drugs to people that need them, or is there something more we can do in the context of today's drug development programs and as we look forward to the next couple of years?

DR. VENITZ: Thank you.

Any questions by the committee before I call for the vote? Dr. Reed?

DR. REED: Just a point of clarification. I do not know -- is there a requirement now for postmarketing registry or post-approval registry to track, as really we've discussed most of the morning?

DR. PARISER: There's no requirement, but it's very frequently done. And I think for the inborn errors of metabolism in particular, it's become pretty routine, that it becomes a condition of approval. And some of these registries are actually pretty longstanding. There's a Gaucher

registry, for example, that goes back about 20 years. And some of the more recent approvals, all of them have had registries.

DR. VENITZ: Any other questions or clarifications? Yes, go ahead.

DR. REED: Recognizing the rigor at which the agency approaches what it does, does the agency feel confident going forward having a voluntary process in this, recognizing the importance of disease progression as that goes forward, of either requiring that postmarketing registry, or you have enough confidence that even for new disease entities, the registry will just be voluntarily provided?

DR. PARISER: I'll clarify my comment a little bit. There's no regulation that you always have to have one of these things, so it would be something that would be negotiated with the Review Division. But if it is a condition of approval, then it is required, and they do have to do it. It's a postmarketing requirement.

So in those situations, it was a requirement

of approval. But there's no regulation there that says every time you approve a rare disease drug, you have to have this. But it's done a lot.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: So this is question that I'm probably going to get kicked for later. I think it was Larry showed a slide -- or maybe it was Tim -- that had a quote from the Faster Cures group saying that it's not the trains, it's the track. And yet when we hear the presentations, it seems like the track's pretty good.

So are we missing something? I mean, it seems like the track's in good shape. Is it the trains after all? Can you say in a public forum?

[Laughter.]

DR. LESKO: I don't know. The trains pass the hotel pretty frequently during the night here.

[Laughter.]

DR. MCLEOD: Yes. I noticed that as well.

DR. LESKO: I think it really boils down -- I mean, we sort of talked about this yesterday in the context of personalized medicine, and that is,

what is the expectation in the future for medicines to be personalized? When would you know that the genome analysis, the human genome, was a success? It isn't going to be every drug. It's going to be some fraction of drugs. So when do you sort of declare a win and go home?

In that context, it's like saying, okay, it's not been too bad. And Tim advocates, you know, with the designations and the number of approvals. Yet, on the other hand, there are still some significant unmet needs and diseases that haven't been addressed, or maybe haven't been addressed well even with approved drugs.

So I think it's more of a philosophical question for me that I think we can always do better. We have not seen the tools that Christine presented today, the modeling, the simulation, the thoughtful, systemic development. We haven't seen that.

So the question kind of is, if we advance this approach, if we even put it into a guidance, if we bring some efficiency to the process, is that

going to take us to the next level? Is that going to make things better? Are we going to have more drugs approved?

I mean, I think it's looking down a well in some ways and wishing. But I think it's worth trying, and I think that's why we're sort of advancing it for discussion at the AC as the next step forward.

DR. RELLING: For clarification, is this question asking whether current drug development programs and clinical pharmacology studies submitted by sponsors are sufficient? Is that what's --

DR. LESKO: Putting the question in that context kind of says, has FDA been approving unsafe drugs? So I think the question is more in the standpoint is that it's made the judgmental, flexible interpretation of the regulations to approve drugs. But do people feel more can be done? I think that's the spirit in which to take this.

While I have the microphone, I'll address to

the chair here.

Dr. Venitz, Dr. Cote just indicated he has a flight to catch, so if anybody has any questions that might want to be addressed to him, now is a good time to do it because he's going to catch the train or the plane back to Washington.

DR. VENITZ: Any burning questions for Dr. Cote?

[No response.]

DR. VENITZ: Okay. Thank you, Dr. Cote.

DR. COTE: Thank you all so much.

DR. LESKO: So getting back to -- I think the best way I can say this is from what you heard and what you read in the background or what you know about your area of rare diseases in oncology, given the tradeoffs that we have with the seriousness of the disease, the unmet medical need, what more do you think we could do to enhance the safety? As some people have expressed there are concerns maybe about can we do a better job with safety, whether it's preapproval, post-approval, or whatever. So we're looking for some kind of

innovative thinking here in terms of drug safety.

DR. VENITZ: Dr. Lertora?

DR. LERTORA: Yes. Again, in terms of clarification as I try to deal with this question, when we talked about the drug development program, do we include conceptually the postmarketing surveillance and potential studies that could be done in phase 4? Because that will help me.

DR. LESKO: I think it's good to consider the entire gamut of the life cycle of the medication because, as we see with accelerated approval, there are tradeoffs. We approve a drug on something less than the clinical outcome, and then we look what happens after it's in the marketplace.

So I'm thinking in the context of life cycle here. And therefore I would include in your interpretation the postmarketing as well as the premarketing, because certainly we've seen the last couple years with REMS, with PMC's postmarketing commitments --

We've taken care of limitations for just

general drug development. We've taken care of limitations for huge populations by asking for studies in the postmarketing period to fill in the gaps of information where it was deemed important to know that, but not at the expense of holding up a drug that can benefit people.

DR. VENITZ: Dr. Giacomini? Dr. Thummel?

DR. THUMMEL: We just want to make sure we're clear on the vote, I guess. It goes back to your question, do we think you've been approving unsafe drugs? I mean, is that the vote? Or is it more, are we going down the right path and -- you know, I'm looking at the second one. If yes, are there specific recommendations for how to improve it?

DR. LESKO: I think I could modify the question a little bit maybe to make it easier. And I think the question really is, can the current drug development program and clinical pharmacology studies be improve to bring additional insight into drug safety that would benefit the benefit-risk analysis?

Does that help? It doesn't say anything about the current situation, but it does say something about –

DR. VENITZ: That's not what the question reads, though. I mean, you're doing surgery on it.

DR. LESKO: I'm trying to give an interpretation for the committee.

DR. VENITZ: I think we're pretty much stuck with the language the way it is, and you have to do your best judgment to interpret it.

Having said that, are we ready to push buttons? Okay. Go ahead.

[Voting.]

DR. VENITZ: Okay. For the record, we have 10 yes, 3 no, and 1 abstain. And let's start to my left with Dr. Barrett. We need your name, your vote, and your rationale.

DR. BARRETT: I voted yes. I did. Well, I didn't really understand the struggle here because, to tell you the truth, as we discussed earlier, you look at the drugs that are taken off the market and the ones where dose-lowering was recommended, these

were for big trials where we had lots of evidence. So this hasn't been a place in orphan drugs or rare diseases where we have a smoking gun.

So maybe that's a combination of the protective nature or the specificity of the targets that we're looking for. But this is not an issue. And I hate to think we need to come up with some additional requirement to give us some perhaps false confidence.

I think everyone is very considerate of the fact that patient safety has to be an important issue here, and no one feels comfortable in making decisions based on limited data. That's true.

But as we talked about earlier, I think the best thing moving forward, the second part of this question, was to leverage the information about how this population has been performing in the absence of these drugs, and then look at it in a postmarketing sense. And I respect that the process will do that on the fly.

DR. REED: Michael Reed. I voted yes, though internally I was in somewhat of a quandary

in thinking about this. To qualify my vote, I want to underscore the importance relative to the postmarketing registry, as we talked, and even though it's not codified.

As you look at a guidance document, one might consider including in that document to request of the petitioner what is their postmarketing strategy, and if it's limited, to be able to substantiate in their petition why it either shouldn't be done or for such a short period of time.

The other thing I would like to caution the agency on that also caused some internal conflict -- I don't want to bring into my brain too much -- is reliance upon the data from non-diseased or healthy individuals. Again, these diseases may be very different than what we're used to seeing with respect to pharmacotherapy and the response, in particular, relative to the process.

So, yes, I think it can enrich what we have in that landscape. But we need to temper how much we depend upon that.

DR. CALDWELL: Michael Caldwell, and I voted no. I would have voted yes to the restated question by Dr. Lesko, but I voted no to the question that existed.

I have two real concerns. I really would like to see a registry and recording of the patients as a part of the approval process. I think it's the way, with small numbers of patients, we're going to learn the most about the process.

Also, taking the other side of the safety issue -- and perhaps the agency already does this. But I wonder if at the same time, when you look at these diseases, many of which are fatal at a very early age, if the longevity or likely longevity of the disease is taken into consideration as far as the risk, because patients and their families may clearly accept a higher percentage risk if it's a uniformly fatal disease at a very early age.

So I see both -- or just want to make comments on both sides of the safety issue.

DR. RELLING: Mary Relling. I voted yes. I agree, having postmarketing safety surveillance is

probably a good idea.

MR. GOOZNER: Merrill Goozner. I'm the consumer representative. I voted no. And it goes back to -- well, part of it's predictive. They quoted Niels Bohr earlier. I thought it was actually Yogi Berra who said the future was very hard to predict -- prediction is very hard, especially about the future.

But anyway, my concern has to go with that discussion I had this morning with Dr. Cote which had to do with -- you know, there are many differing types of rare drugs. There are some that are slam-dunks, some that are in the middle, and then some on that long tail that have marginal efficacy. And it's those that I'm most concerned about.

I think in an era of increasing emphasis on personalized medicine, the Orphan Drug Act could well become a vehicle for seeing more and more of those types of drugs trying to go through clinical trials and come into the marketplace.

So then your benefit-risk ratio is very

difficult to know in smaller and smaller population groups. So how do we get there? People have been talking about registries. I'm a big advocate of registries. I think that ought to be a requirement that somewhere along the line, that's certainly one way to go, and other forms of REM-style safety surveillance plans being requirements and going that route.

So it's not that it wouldn't be -- I would be yes in probably 90 percent of cases, especially in orphan drugs, but it's the tail that I worry about.

DR. COLLINS: Jerry Collins. I voted yes. My spin on all this registry, phase 4 commitment and so forth is that they shouldn't be viewed solely as things are being added onto requirements, but there would also be ways of delaying some studies, getting the approval and the access out earlier. So it could work either way. We certainly need more safety information than we get from 20- and 30-patient studies, but we also don't need -- we could also delay some of the other

studies until later.

I vote because not that it sounds like a good idea, but because there's actually data that shows that it works. Registries work, and after a few early bumps, phase 4 commitments work. And patient groups are increasingly well-organized, so they're practical. You can actually accrue patients to studies and get them done.

DR. VENITZ: This is Jürgen Venitz. I abstained because I don't know the answer to the question that you asked us, and I don't think anything I heard today allowed me to come up with an answer. I would have voted yes if you had submitted your question that you rephrased.

So based on what I've seen today, I don't see any major problems with the way things seem to work right now. One thing that I guess I didn't put on the record before, when I looked at some of Dennis's slides, I was surprised about the large number of clinical pharmacology studies. Now, I don't know how many of those were NMEs and how many of them were repurposed. But I didn't expect, for

an orphan disease, that that many clinical pharmacology studies would be necessary.

DR. MAGER: Don Mager. I voted yes, primarily for the reasons that have been stated already. I was encouraged by the question saying "sufficient" rather than "perfect." And there was a part 2 that allowed us to add, so I felt confident in saying yes here.

I just wanted to reiterate again, I think what could be added is active engagement in patient groups and clinicians, not only to define the risk-benefit ratio, but also to perhaps drive safety science as well in terms of drug safety assessment and prediction.

I like the example of natalizumab, for example, that was pulled from the market on PML. But then later we then moved the science forward and found factors available to help at least understand the determinants or the potential risk for such drugs. So I think that's a nice way to save a drug. And fortunately for the patients and clinicians, that one was pulled back.

DR. MCLEOD: Howard McLeod. I voted yes. I thought I was voting for the process that Drs. Bashaw and Garnett laid out in their talks in terms of having new science to try to do even better than we're doing now.

So I think that whether this question was asking that or not, I think that that's a great thing to move forward. And the drug I was talking about earlier was alosetron for irritable bowel syndrome, which had been pulled and brought back, which I don't think was on orphan drug status. But from what we heard from Dr. Cote, there have not been withdrawals in the orphan drug program. And so it gives some confidence -- small numbers, but -- that the current process is at least not adding risk.

DR. CLOYD: Jim Cloyd. I voted no. My rationale is that families who have a member with a devastating rare disorder need to have some appreciation for the risk of serious adverse effects. It is possible that we will have study cohorts that number fewer than several hundred at

the time of the drug approval. We may miss the occurrence of 1 in 100, or even more frequent, of serious, potentially life-threatening adverse events. Therefore, postmarketing surveillance should not be encouraged. It should be an expectation announced in advance when sponsors are beginning to develop their drug development program.

DR. HARRALSON: Art Harralson. Actually, that's the reason I voted yes. I think that you have to look at every situation individually. So each drug has its own risk-benefit ratio. And as Merrill Goozner said, there will be people out on the tails, but I think if you're able to make that decision in each case, you're going to address that, and so it won't slip through.

Obviously, for many of these diseases, the real risk versus benefit is not too hard because the severe disability or mortality, that's not a hard decision to make. And so I think it appears that you're absolutely on the right track, and I would be very much in favor of conditional

approvals that require certain things that would bring in the information that over time would allow you to make a better decision. And I don't believe you can actually make those decisions in advance, given the number of patients available.

DR. LERTORA: Juan Lertora. I voted yes. And as implied by my question before the vote, I believe that the question of postmarketing surveillance in terms of safety signals is very important and should be pursued.

DR. THUMMEL: Ken Thummel. I voted yes, heavily swayed by the second part to the question there. Beyond what was already said, obviously agreeing with the critical importance of registries and even the concept of delaying some studies to post-approval.

But I would also ask the agency to consider, as they begin to adopt new approaches to trial design, that these be evaluated rigorously as we move forward because I heard a lot today about perhaps changing the way the last number of drugs have been approved.

DR. GIACOMINI: I'm Kathy Giacomini. I voted yes. And I agree with the statements that Ken just made, and many of the statements that were made earlier.

DR. VENITZ: Okay. Thank you.

Then let's move to the next two questions, 3-1 and 3-2. So those are discussion questions. And I should point out that we are running a little bit late, so look at those questions and see if you have anything that wasn't mentioned or discussed in any level of detail that you'd like to contribute.

So the first one deals with using quantitative methods for repurposed or new drugs in rare diseases. Is there anything that hasn't been mentioned yet that anybody wants to contribute on that level? I'm just asking the committee. Is there anything else that hasn't been discussed yet?

[No response.]

DR. VENITZ: Is there anybody that wouldn't endorse using quantitative methods?

[No response.]

DR. VENITZ: All right. Then let's move on.

The second one, anything to add to that? Innovative tools, DNA collection, genetic analysis, biomarkers. Anything that we didn't discuss yet? Now is the time to speak up.

[No response.]

DR. VENITZ: Moving right along, our last task at hand. Any future recommendations for FDA? Anything that we haven't discussed yet that you'd like to mention before I turn it over to Dr. Pariser?

Yes, go ahead, Dr. Cloyd.

DR. CLOYD: Again, I want to emphasize the reality of drug development in rare diseases. And that is, it is likely the vast majority of drugs that are going to be used in a very vulnerable population will be drugs that are already available and without a functional sponsor. And we have to think about ways to ensure the health of the people who are going to get these medications. And I'm not convinced today that the current procedures ensure safety or efficacy.

I don't have an answer, but we can't just

ignore the elephant in the room. It's going to be a very common means of treating rare conditions, and that process deserves the same type of care and concern and oversight that we give to treatments for more common disorders.

DR. VENITZ: Dr. Lertora?

DR. LERTORA: I just wanted to emphasize, and essentially reiterate, the importance of addressing exposure-response relationships for repurposed drugs because we cannot make the assumption that the previously known exposure-response relationships for the original indications are going to be applicable for repurposing.

DR. CLOYD: Lastly, the quote from Yogi Berra is, "The future ain't what it used to be."

DR. VENITZ: Dr. Barrett?

DR. BARRETT: On this topic of collaboration, I read through the IOM report that was in our package, and I have to say while all of the points are covered, it's wonderfully vague and there's just really not a lot of detail on how, in fact, to pull that off. And maybe it's just to in

fact drum up an action item for what has to happen next.

But if you really want active involvement and collaboration, then people need to be collectively part of teams, not just showing up every year for "here's what I'm doing" kinds of meetings. So I think this really needs some thought for some tangible metrics on what collaboration would constitute. If you really want to leverage resources, then people have to work together.

So I would just encourage that while the items here are reasonable, the specificity and the detail is completely lacking and needs to be there.

MR. GOOZNER: This is very much on the nonscientific side, but it has to do with sort of the economics of this whole space. You know, NIH has launched this new translational science initiative. I don't know where that's going to go, or even if it's going to get funded in the current environment.

But I think historically, what's been

interesting as a student of this, as opposed to being a practitioner like other people on the panel -- historically, this has been a large part of government activity or academic activity. Industry really only came in in the last 20 years or so, simply because there were some really great things that finally came along in the rare drug space. And, again, I mean, all you have to do is visit NIH headquarters and visit the shrine that they've built to Roscoe Brady and all the work that he did on the lysosomal storage disorders.

I don't know where this whole field is going to go, moving forward, but I know the healthcare system can't afford $200,000-a-year drugs. So that model isn't going to work as a way of building incentives into the system. So I think thought needs to be given to collaborative models that take the economics and everything else into account. I'm not here to give an answer to all that. I have some opinions, but I don't know that they're so well-formed that I need to spend 10 minutes trying to formulate them off the cuff.

But I think that that's going to be a huge concern going forward, is just like not worrying just about getting the science done on this stuff, but getting the forces aligned in order to do it. It's going to be very, very difficult.

DR. VENITZ: Any final comments? Dr. Thummel?

DR. THUMMEL: So just to follow up on that, are there examples that one can point to where these collaborations seem to be effective? I mean, I'm sort of thinking about work my colleagues at the University of Washington are doing in cystic fibrosis. Are there enough examples where effective partnerships have occurred that that can be used as an example for other rare diseases and industry folk who are pursuing the development of orphan drugs?

MR. GOOZNER: I wrote about this in a book I did about the drug industry. And one of the things that I always found was fascinating is that when you found an industry really getting involved, it's almost because somebody came to them and really

beat them up over it. They had the drug, and so they had to be pushed to do it. And they said, well, yeah, you know, we could actually do that. And then worked on it, and then lo and behold, they had a drug that was fairly successful.

I mean, Gleevec is sort of an example of that. And, certainly, if you look at the history of Genzyme as a company, which just got bought -- but Genzyme was handed everything that they had, basically, on a silver platter by work that was done at NIH.

So I think that it just requires a kind of spirit. It's the spirit of collaboration. Industry has the tools, very often, but they really don't have the financial motivation, ultimately. And I don't know that the venture capital model is a good model for this, either, because, don't forget, the venture capital model ultimately says, we're going to do nine or ten of these things. One of them is going to really make it all the way through the pipeline, and then we have to get our 100-, $200,000 a year out of every single patient

for this drug in order to make all of them paid for.

So that's the business reporter part of me -- and I spent a lot of my career doing that kind of reporting and thinking, that's not a very good model, either, at least not from where our healthcare system needs to go over the next 10, 20 years, at least if what I read in the papers is accurate.

DR. VENITZ: Okay. Thank you.

Then let's proceed to our final presentation today. Dr. Pariser, she's going to talk about FDA's next step.

FDA Next Steps

DR. PARISER: Good afternoon. I'm Anne Pariser, and I lead the Rare Diseases Program in the Office of New Drugs at FDA's Center for Drugs. I've been working at FDA for 10 years. I've been working in the rare disease field all of that time.

I'd just really like to thank everybody for coming today. This is a meeting we wouldn't have had probably 10 years ago. And I particularly want

to thank Dr. Lesko and his office and the advisory committee for discussing these issues and really looking for efficient, deliberate, and more systematized approaches to trying to address these 7,000 diseases. Only about 200 of them actually do have targeted treatments, so the unmet needs are great. So I'm really seeing this conversation as, really, a step forward.

So I'd just like to spend the next several minutes just touching on a few points that were made earlier. I know some of these themes have come up over and over. I will try to be brief. I know it's getting late. And then we'll talk a little bit about some of the things that FDA is doing to try to address some of the things that have come up, and how we're trying to move these forward.

So as you've heard several times now, this is a rapidly expanding area, and probably the most rapidly expanding area. And it will continue to rapidly expand. There's about 100 new diseases being described a year. A lot of these genetic

diseases, in particular, that really had not been described are now being described, which is certainly very hopeful. But it does add diseases to the list. And the common diseases are now being divided into the medically plausible subsets that Tim spoke about earlier.

An example here is the non-small-cell lung cancer, which is certainly, unfortunately, not a rare disease. But the anaplastic lymphoma kinase-positive subset is about 5 percent of these cases. There's a target identified, and that now gives you a chance for intervention. But what that also does now is divide things into smaller and smaller populations, and we do have to find a way to efficiently deal with that.

Once again, these challenges have been stated several times. I'd just like to point out a few here in the middle. Two of the biggest challenges, at least in my mind -- and this is where the track slows down to that 40-, 50-mile-an-hour area -- would be the natural history studies and the specific endpoints and outcome markers and

the biomarkers.

So it's really the work in the translational space that seems to be one of the greatest areas of opportunity and really one of the greatest areas of need. And clinical pharmacology, of course, really can be a main player in this area. And I think we've heard that before, but if I had to pick a couple of things out of here, I think, where we could target some efforts, it would be here.

I think that question came up earlier as well, is what's coming through the door this day and age? As things are becoming more targeted and there's a lot more thought coming into these programs, are we seeing people walk in now with a better natural history and biomarkers and things identified?

I think the answer is yes and no. Some of these are very well thought out, but some of them not so much. And this is a major issue when you're trying to design clinical trials and you're trying to get to that level of evidence that you need to approve the drug.

Once again, we've heard about the successes. I won't go over them, but I just wanted to -- I'm from CDER, so I'll just point out that 90 percent of the orphans are in CDER. And one of the ways we're trying to really describe what needs to be done -- this is the successes, the barriers -- and where we can intervene, perhaps, especially, is by taking a look at our history.

So clinical pharmacology is doing a similar look. Dennis was looking specifically at where the clinical pharmacology level of evidence is. But we're also looking more comprehensively across the applications, a number of factors that go into this. So we're in the process of taking a look at the past five full calendar years, and the numbers are very similar to what Tim said for all of FDA, which would also include CDER.

But about 30 percent of NMEs and new biologics are orphans. They are for a broad range of indications. Out of the 35 drugs, there's 29 different indications, 28 different companies, and the prevalence is anywhere from all the way

down to 50 patients to about 180,000, but the median is somewhere around 43,000. So most of the new approvals are actually for very low-prevalence disorders. So the law is doing what it intended.

Here's some things that may be a little anti-conventional wisdom. By the time you get to a marketing application, an orphan application is just as likely as a common disease to be successful. About 75 percent of the orphan applications do get approved. Twenty percent of these -- and I found this to be a somewhat remarkable statistic; 20 percent of these are first in disease indications. Compare that to common, where it's about 3 percent. And 75 percent of these are in the small companies, and I think it was Dr. Cloyd who mentioned this earlier; a lot of this research is coming out of academics.

Well, for some of the very small companies, there's not much difference between an academic and a small company. It could be a couple of people. Maybe they started in academia. So this is where, really, the truly novel, innovative therapies are

coming from. It's usually the very small companies.

As has been mentioned before, there's two possible pathways to approval. There's regular approval, standard approval, full approval, or just approval; and then there's the accelerated approval pathway. I know this has come up several times, but the language says it has to be based on a surrogate, reasonably likely to predict clinical benefit. And that's kind of the key phrase there, is "likely to predict benefit." For a regular approval, orphan and non-orphans are held to the same standard. That did come up a little bit earlier, but let me clarify that in just a second. And we'll come back to this accelerated approval.

A question actually came up during the break, how many drugs actually have been approved as accelerated approvals? Well, since the passage of FDAMA in 1997, there have been about a hundred accelerated approvals. These all have to be for serious, life-threatening disorders with unmet needs. About half of those are cancer, about

30 percent of those were HIV, about 10 percent of those are bioterrorism, and the rest is really a smattering.

But the critical issue here is to have something act as a surrogate, it's really acting instead of that clinical benefit. So that implies that we really have to have a very good understanding of -- most surrogates are biomarkers. You have to have a very good understanding of all the mechanistic pathways around that biomarker, the intended consequences, the unintended consequences, and is that truly going to predict. Correlation is not enough.

That is really the limiting factor for a lot of rare diseases. We don't understand the disease or the biomarker well enough. So that's, once again, a plea for this natural history and really understanding the disease.

This is just a graphic showing that surrogates are a subset of the biomarkers. We use them interchangeably, but they're really not. Biomarkers are incredibly useful. We use them all

along drug development. We certainly can't do drug development without them. But there is a distinction there.

So in terms of are orphans and non-orphans looked at the same way by the review divisions, I guess the answer again is yes and no. You still do have to get to the substantial evidence of effectiveness for approval. But written into the regulations, there is this concept of flexibility, and I've heard it mentioned several times today, the scientific judgment and exercising flexibility. So the review divisions absolutely do take this into account.

So just one more thing to say on that. In looking at our database and looking at this level of evidence, which we're continuing to study, most of the orphan programs are unique. Most are nontraditional. Many of them -- last year, more than half of them were based on a single trial with supportive evidence of some kind, often clinical pharmacology. And there were a wide range of study endpoints. And this was even picked up by the Pink

Sheet last week. There was an approval in CBER last week based on a 14-patient clinical trial.

So then what are our plans for the future, and how are we going to incorporate some of these things that have been mentioned today, and the known challenges and where we need to intervene?

Well, this Institute of Medicine report, which Dr. Barrett was just talking about, it is a little bit vague. But I think what it is doing, it is telling us that we really do need to approach these differently than we have in the past, collaboration, timely advancement of science, and appropriate use of creative strategies.

So to put that somewhat graphically, if we're looking at a traditional drug development program, there's where the INDs and NDAs are. Drug developers can be involved anywhere along here, from drug discovery through to postmarketing. And FDA interactions typically begin here, with the pre-IND phase. It's about the point you're going into human studies. And then this is often described as that translational gap, and this is

where the track really slows down.

So where would we like to see this go? Well, here we have our same bars, and this is where we're building our scientific foundation. And I'd just like to point out, this space here for FDA interaction, we'll come to that in a minute. But some of the things that we're trying to do, we're actually trying to stretch everybody's involvement. And I'll tell you some specific things that we're doing for that.

FDA is really trying to reach down more into the translational space here. And the scientific foundation, meaning NIH and the TRND program especially, they're trying to move things however far they need to move them before they're going to be picked up by a drug developer and try to move these forward. So they're trying to step into that gap, and they're trying to answer a lot of these questions.

I think some of these things came up earlier as well, academic developers that can't get the animal toxicology studies done, for example, to try

to get their compound into development: Well, this is somewhere that the TRND program is actually looking to step in; the natural history studies, the biomarker identification, the endpoint identification, and this is an area where we are working with the patients groups and the experts in the field. They are very motivated to do these things. These are things that are often best done by patient groups, so how can we support them in that?

So clinical pharmacology, actually, all of these things really stretch down into this translational space, but also continue to be involved all the way through the clinical space.

So in terms of FDA interactions, there are many opportunities for collaboration. And I know that this has come up several times as well. But this has been looked at a number of times over the years by a number of different people, and one of the best predictors for successful programs, successful meaning working through to an approval, is frequent, early, and quality interactions with

FDA. And it doesn't mean we always agree, but at least if we're discussing the issues, we can usually get from point A to point B.

A couple of opportunities that drug developers are entitled to: These are milestone meetings, pre-IND, end of phase 1 if it's a serious disorder, end of phase 2A, end of phase 2, pre-NDA, and then there's type C meetings that can occur anywhere along there. But, once again, since a lot of the innovation is coming from the small companies, the inexperienced companies for the most part -- I go to meetings and I say this, and a lot of them tell me, "We can request meetings?" They don't know this.

So, really, we're trying to get the word out, and we're really trying to encourage people to come in. Things go a lot better, especially if we can anticipate what's going on. We can build that scientific foundation in advance. We can get what we need before we have to move to the pivotal study; so, in other words, going from the rickety bridge over the stream to the nice, solid bridge.

So I'll just comment on just a few areas of focus. I think we've discussed this.

Mapping out the clinical development programs, this is where the interaction is so important, and this is where interacting with patient groups, with NIH, with the academic researchers, this is where it's so important. And we have every intention of doing this, and we're actually looking for new ways that we can do this.

It can be started before you even have a candidate drug identified. And this is something also that working with patient groups to do this, if you can get the solid science foundation built, if you can identify your centers, once you have a candidate, then everything moves a lot faster because all the startup work has been done.

Making the most of the early phase development, I think Dr. Mundel gave a beautiful example of that earlier today. They had a 4-patient study. This is something we encourage everybody to do. These are unmet needs. The patients are very sick. There's always a sense of

urgency. Everybody really wants to get going very quickly. But going in blind to that pivotal trial is really a setup for failure, so even a very small phase 1-2 study can be enormously informative.

I think this point has been made as well; all the evidence will always be considered in a rare disease application. I think the effort here today is to try to use that to our best advantage possible and to collect our best practices.

So just to name a couple of the new initiatives, in addition to the Institute of Medicine with their report, this has also caught the attention of Congress, really, in the past couple of years. There was legislation about a year ago, the Brownback/Brown Amendment, that mandated FDA to form two committees, a rare disease committee and a neglected disease committee, and to come up with recommendations. So that report is actually due out this month, and a guidance has been mandated that will come out in September.

You've heard also we have this database analysis in progress. And what we are very hopeful

that will come out of this is more guidance, more advice, a much better recognition of specifically where the issues are. Where can we intervene? Where can we most help? Which trial designs work? What doesn't? Are there any predictors of what goes wrong? And I think at this point we have some ideas, but it would be really nice to get some data around that.

The New Disease Program was founded in the Office of New Drugs a year ago. That's my team. And if anybody has any questions, please don't hesitate to get in touch with either me or the Office of Orphan Products.

Then I'd just really like to say a couple words about some of our collaborations, and I think that was a question earlier, what specifically are you doing. Well, there are a number of workgroups, and I can't possibly name them all, but we do have one with NIH TRND program. And we meet on a regular basis. And some of the things that we are looking at, it's natural history studies. These are so fundamentally, critically, and essentially

important, we're actually trying to get a workshop together because it's the same question. What makes a good natural history study?

There are plenty of people that have done them. Some of them have been very good. Some of them haven't been. But if we're going to bother to do these, we really need to try to get the best information that we can, and the patients are very motivated to do these.

Workshops on scientific development, just to name a few, there have been a couple of biomarker workshops recently that actually FDA started. We're going to have one for spinal muscular atrophy, I think, in May that's cosponsored with NIH. And these are other things that we'd like to do.

There have been a few recently on patient-reported outcome development. This is all emerging science. We need to figure our best practices for all of these things. The repurposing database you've heard about. And then also I think this feeds into the comment Dr. Cloyd made earlier about

the reticence of coming in and talking with FDA. We don't want to scare people away. We do want to be approachable. We do want that information to be out there and easily accessible.

So we're working on trying to get one-stop shopping on our website so you can find these guidances because I have trouble finding things on our website. If it's in one place, it will probably make it easier. But we also started some training courses, and we started a course specifically for investigators.

We were going specifically for the small biotech companies. The first one was held last October, and we're going to do this again in collaboration with DIA and NORD again in October. But maybe we need to do one specifically for academics. I don't know. Maybe we can talk. And we're also training our staff as well. We actually have an ongoing training course right now in addition to the science of small clinical trials that Tim spoke about.

So I'll just close with the Rare Disease Day

logo. Rare Disease Day was on Monday, and their motto was, "Alone we are rare, together we are strong." So I think that I'd just like to really thank everybody for coming today. It's so heartening to see so many people willing to step into the orphan drug arena. We really thank you, and I really thank you, the advisory committee. Thanks.

[Applause.]

DR. VENITZ: Thank you, Dr. Pariser.

Any quick questions?

[No response.]

DR. VENITZ: Okay. Then I'm looking at Dr. Lesko to wrap things up for us.

FDA Closing Remarks

DR. LESKO: Okay. I have a feeling you want my usual fast wrap-up.

But, yes, we ventured into new territory today with the topic of rare diseases/orphan drugs. And we didn't know quite what to expect, but I have to say personally I'm very delighted with the advice we received from the committee, the

questions that were asked, the reaction to our presentations. It was exactly what I was looking for.

We had some goals coming into the meeting. We have a vision for developing a road map for efficient, informative, and systematic drug development in the area of orphan drugs/rare diseases, and I think we have the foundation of that from today's meeting.

We also wanted to raise awareness, particularly on the part of companies and others in FDA, about the tools that we have available on clinical pharmacology, especially those in the quantitative area, how we've applied them before, how they can conceivably be applied in the area of rare diseases/orphan drugs.

Thirdly, we have in mind the possibility of developing a guidance on this topic somewhere down the road, and we felt this meeting was a good spot to begin thinking about what the contents of that guidance would be. And I think a lot of the issues that were raised would really influence our

thinking in terms of what it would contain.

We also had a goal of hearing from the committee on things we didn't think about. And I think we succeeded there as well because we have quite a bit of ideas, issues, concerns, good suggestions that we had not thought of, and we really appreciate that.

Finally, one of our goals was to create a foundation for another advisory committee, as we usually do on the topics we bring before the committee, whether it's drug interactions or clinical pharmacogenomics. And we believe somewhere down the line we'll come back with a more specific set of recommendations that take into account a lot of what we heard today.

So on all counts, the committee, let me thank you. You did your job as public citizen-scientists and have given us a lot of good insight into the topic that we brought to the committee today. I want to thank the chair, Dr. Venitz. I wish I could manage meetings as good as you do. So thank you for that. I really appreciate it.

We have a production team behind this event from FDA. I'd like to thank Cicely Reese, who's behind me, I hope -- she was; Yvette Waples, who's right next to the chair over there; Christine Lee, working in the background liaising; and there was a gentleman that's working on this project I didn't know. So that guy, that anonymous guy, I want to thank as well. And, of course, I want to thank my colleagues from FDA.

Just looking at them and talking to them during the break, this advisory committee I think has actually brought us together, more so than when we were working back in Silver Spring. So I think with Tim and Anne and the team that we have at the table, we're going to go forward thanks to this event in collaborating much better on the things we heard at this committee.

Lastly, I should thank the audience. These events at the ASCPT meeting gives people an opportunity to see government at work, hear the debate and science that typifies regulatory science, maybe encourages you to become an

applicant for an advisory committee at FDA.

I know after this presentation and after this committee closes, we're going to get a lot of comments from those that are in the audience, and they can be kind of like a surrogate advisory committee or something like that.

But anyway, thank you. Appreciate it.

Adjournment

DR. VENITZ: Okay. Thank you, Dr. Lesko. Thank you, committee members. Thank you, audience. The meeting is adjourned until next year's ASCPT meeting.

I'm also asked to remind the people in the audience, there will be a presentation in a few minutes on how to become a member of an advisory committee. So if you're interested in serving as a member of an advisory committee for FDA, please hang around. You will have a presentation to attend in a few minutes.

Thank you. Meeting adjourned.

(Whereupon, at 2:49 p.m., the meeting was adjourned.)