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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE
CLINICAL PHARMACOLOGY SUBCOMMITTEE

October 18-19, 2006
CEDR Advisory Committee Conference Room
Room 1066
5630 Fishers Lane
Rockville, MD

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A P P E A R A N C E S :

Thursday, October 19, 2006
Jeffrey Barrett, Ph.D. FCP
Edmond V. Capparelli, Pharm.D
David Z. D'Argenio, Ph.D
Marie Davidson, Ph.D
Kathleen Giacomini, Ph.D.
Shiew-Mei Huang, Ph.D
William J. Jusko, Ph.D
Meryl Karol, M.D.
Larry Lesko, Ph.D
Howard L. McLeod, Pharm. D.
Joanne Mortimer, M.D.
Richard Pazdur, M.D.
Mimi Phan, Pharm. D
Atiqur Rahman, MD.
Mary V. Relling, Pharm.D.
Jurgen Venitz, M.D., Ph.D
Paul Watkins, MD
Sally Yasuda, Pharm, D.

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A G E N D A

THURSDAY, OCTOBER 19, 2006
Call to Order
Jurgen Venitz, M.D., Ph.D
Acting Chair CPSC of ACPS
Conflict of Interest Statement
Mimi Phan, Pharm.D., R.Ph.
Designated Federal Officer, ACPS
Topic 3: Using Disease, Placebo, and Drug
Prior Knowledge to Improve Decisions

Decisions in Drug Development and at FDA:
How Combining Prior Knowledge with Quantitative-
Based Decisions Can Improve Productivity and
Quality
  Bob Powell, Ph.D.
  Director, PM, OCP, FDA
Impact of Prior Knowledge on Drug Development
Decisions: Case Studies Across Companies
  Jacob Mandema, Ph.D.
  Quantitative Solutions, Inc.
Disease Models at FDA: Overview and Case
Studies (Diabetes and Obesity)

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A G E N D A (Cont.)

  Joga Gobburo, Ph.D.
  Team Leader, PM, OCP
Disease Models at FDA: Parkinson's Disease
  Atul Bhattaram, Ph.D.
  PM, OCP, FDA
  Ohid Siddiqui, Ph.D.
  OB, FDA
Open Public Hearing
Advisory Subcommittee Discussion
and Recommendations
  Jurgen Venitz, M.D., Ph.D
  Acting Chair CPSC of ACPS
Summary of Recommendations
  Lawrence Lesko, Ph.D.
  Director, OCPB, CDER, FDA

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P R O C E E D I N G S

CALL TO ORDER

CHAIRMAN VENITZ: Can everybody please be seated? Good morning, everyone, and welcome to the second day of the Clinical Pharmacology Subcommittee Meeting.

Today is our topic 3 for discussion, but before we go ahead and start our formal proceedings, I would like to go around this table and ask everyone to introduce themselves for the record.

DR. GOBBURU: Joga Gobburu, Pharmacometrics, FDA.

DR. HUANG: Shiew-Mei Huang, Office of Clinical Pharmacology, FDA.

DR. POWELL: Bob Powell, Clinical Pharmacology.

DR. JUSKO: William Jusko, Committee Member, and Professor at the University at Buffalo.

DR. QUANG: Brian Quang, Safety Solutions.

DR. DAVIDIAN: Marie Davidian, North Carolina State University.

CHAIRMAN VENITZ: Jurgen Venitz, Clinical Pharmacologist, Virginia Commonwealth University.

DR. PHAN: Mimi Phan, Designated Federal Officer.

DR. KAROL: Meryl Karol, the University of Pittsburgh.

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

DR. MCLEOD: Howard McLeod, UNC, Chapel Hill.

DR. D'ARGENIO: David D'Argenio, the University of Southern California.

DR. WATKINS: Paul Watkins, the University of North Carolina at Chapel Hill.

CHAIRMAN VENITZ: Okay. Thank you, everyone.

Again, before we start our official proceedings, as we usually do, we have the conflict of interest statement read, and Dr. Phan is going to do that for us.

CONFLICT OF INTEREST STATEMENT

DR. PHAN: Good morning. This the Conflict of Interest for today's meeting, October 19, on the topic of Prior Knowledge on Drug Development and Regulatory Decisions.

The following announcement addresses the issue of conflicts of interest and is made part of the record to preclude even the appearance of such at this meeting.

This meeting is being held by the Center for Clinical Evaluation and Research. The Clinical Pharmacology Subcommittee Meeting of the Advisory Committee for Pharmaceutical Science will consider the third new topic, the Impact of Using Prior Knowledge of Drug Development in Regulatory Decisions -- prior knowledge of disease change over time and covariates.

Placebo variation in drugs can be used to make better decisions and design more informative clinical trials. Examples will be used to demonstrate these principles.

Unlike issues before a committee, in which a particular product is discussed, the issue of broader applicability, such as the topic of today's meeting involves many industrial sponsor and academic institutions.

The Committee members have been screened for their financial interests as they may apply to the general topic at hand.

Because general topics impact so many institutions, it is not practical to recite all potential conflicts of interest as they might apply to each member.

In accordance with 18 USC 208.B3, full waivers have been granted for the following participants: Drs. Jurgen Venitz, Jeffrey Barrett, Edmund Capparelli, Marie Davidian, Kathleen Giacomini, William Jusko, Jacob Mandema, and Paul Watkins.

Waiver documents are available at the FDA document Web site. Specific instructions as to how to access the Web page are available outside today's meeting room at the FDA Information table.

In addition, a copy of all waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30, at the Parklawn Building.

FDA acknowledges that there may be potential conflicts

of interest, but because of the general nature of the discussion before the Committee, these potential conflicts are mitigated.

In the event that the discussion involves any other products or a firm not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement of any firm whose products they wish to comment upon.

CHAIRMAN VENITZ: Thank you, Mimi. And we have a new member that joined us. You want to introduce yourself, Bob?

DR. O'NEIL: Yeah. Hi. I'm Bob O'Neil. I'm the Director of the Office of Biostatics in CDER.

CHAIRMAN VENITZ: Okay. Welcome again.

Our today's topic is Using Disease, Placebo, and Drug Prior Knowledge to Improve Decisions, and the topic will be introduced and at least initially discussed by Dr. Bob Powell.

Bob is the Director of Pharmacometrics in the Office of Clinical Pharmacology.

DR. POWELL: Thank you, Jurgen. The -- talking about the -- analyzing and sharing disease, placebo, and drug prior knowledge really the case that we're going to hone down into is the case on Parkinson's disease.

And -- but it's -- we're really asking the question both in a specific and a genera way that in a general way, we're beginning to engage in analyzing this sort of information to help solve regulatory problems with people in clinical as well as with people in biostatistics.

And so, in that sense, it's kind of -- the questions have to do with how the data is put together; what data are used; how the data is put together and analyzed but in a general way, so that part sort of is technical.

In a general way, it's how to do this more routinely, and if you can imagine at the FDA, the vast amount of knowledge that's here in that, if this could be done more systematically, then the benefit that could accrue to people designing trials or making decisions based on this sort of knowledge anyway. Okay.

So I'm going to work to set the context for the work that we do. Jacob Mandema will provide an industry perspective of the same sort of work that goes on within the pharmaceutical industry. Jacob's a consultant in the industry -- to the industry.

Joga will present an FDA perspective for the more detailed aspect of the work that we do, and then Atul Bhattaram and Ohid Siddiqui will then get into the Parkinson's disease example.

Now, there's a second meeting on Parkinson's disease that will occur in the spring, and that will be more of a clinical meeting where the trial design and the

considerations around the trial design will be -- and that will be led by our colleagues in clinical and will also involve biostatistics at the clinical pharmacology meeting. So this is more of the technical one.

So the questions are: Is the overall approach reasonable to quantify in the various parts of the disease model? Is the approach reasonable for selecting the data to a model? Is the approach reasonable for quantifying the model? And how should this information be communicated publicly?

So I'm going to talk a bit about decisions in drug development and at the FDA and how combining the prior knowledge with quantitative-based decisions can improve productivity and quality.

I'll talk a little bit about modeling and simulation impact in general about how some of the work that we do at the FDA and pharmacometrics. I'll attempt to make the case for extracting and sharing this information, both for use within the FDA as well as outside the FDA.

And then talk about some future options.

So if you want -- so what I did was basically I Googled modeling and simulation, but you have to do that according to the application. And so if you look at weather forecasting, there's a huge amount of information on the Web about what's done with modeling the simulation in weather forecasting, and all the different engineering applications, whether it's airplane design or car crash testing -- Toyota, BMW. I mean these companies are into this in a very big way.

And basically, it's using prior knowledge to be able to make important financial decisions in making some sort of a product better than the prior product.

It's being used in global warming scenarios. I mean when you see people talk about what's likely to happen, it comes from modeling and simulation and running scenarios.

Homeland Security is using this in a fairly significant way for figuring out what to do with an anthrax sort of infection that's spread across some large area. The military, if I didn't list here, financial is where it's probably one of the largest applications.

Military, I'll expand on this a little bit is -- most of the design or the actions -- when they talk about scenario planning about what they're going to do, I mean to a large extent, it's being led through modeling and simulation.

Dealing with energy issues. Of course, medical it's being used in all sorts of areas, from teaching people how to do new complicated sorts of surgery or robotics surgery or creating artificial knees and hips. I mean the fundamental design has a lot to do with understanding the physiology and anatomy and then trying to design in the functionality.

Drugs it's -- modeling and simulation is being used increasingly in molecular design; formulation looking at

cross surfaces about what's going to impact a formulation's performance -- manufacture and marketing.

But really in clinical development, it's not used that much. It's beginning to be used, but I would say it's in the very earliest stages.

So if we look at the military, the -- people that are familiar with Louis Shiner's learn and confirm model are struck by it. So here's the ultimate maybe in confirmed if you're talking about one tank destroying another tank. And basically what the military is doing is not only designing their information systems that talk about how to get the tank to perform, but it's also being used in simulations to train people to use these devices as well.

There is an Office of -- in the upper right-hand

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corner -- the Defense Modeling and Simulation Office. I mean it's like I didn't -- I didn't know about these sorts of things , and it's -- not only is there this office, but each section of the military has a sub-office of modeling and simulation.

And when you look at what's -- is there a pen or a pointer? So if you look at these attributes here, they speak to what they expect to benefit in terms of using a technology across different applications and decreasing risk.

It's interesting to find out that from Congressman Randy Forbes has written to the President and they talked about the importance of modeling and simulation in general for our economy and our society in 2006.

So, you know, since I'm a government employee now it's nice to know that I'm aligned with my management within the government.

Borrowing -- this is a press release on a fighter that they were designing in competition early in this decade, and they speak to the -- I mean basically for products that we've heard about in the news for various types of aircraft being able to use modeling and simulation across commercial

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and military aircraft, using the prior knowledge that exists to more efficiently design these aircraft -- I mean very expensive sorts of numbers.

And then the fellow that was the head of this project -- I mean they really captured the importance of modeling and simulation in reducing risk can't be emphasized enough.

We were able to eliminate the majority of bugs before we ever built this new aircraft and then the aircraft worked in a fairly seamless way when they introduced it.

So why modeling and simulation?

Well, it's basically I think these sorts -- the reason there's so much interest in it is that it's a way of decreasing bias in risk and decisions, to overcome complexity when there are many more factors that are going to influence outcome than a human -- than one human can account for, to increase quality, decrease costs, and decrease time. I mean you can apply all these attributes to the design of clinical trials or making drug development

decisions or making regulatory decisions.
So the process has something to do with some action that you're getting ready to make, and whether it has to do

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with a decision of prediction, as in the weather; teaching design, in this case we're talking about clinical trials or making some sort of regulatory decision; or, in fact, in entertainment.
So the action generally should have something to do with -- there's significant risk; that it's expensive; and that it's important.
So really what we're talking about today is the collection of relevant information that is complex. It has multiple dimensions, and generally raw data is one of the things that you want to start out with.
So the next step is to organize the information into models. Now, I would say that at the FDA one of the things that we can't do is that we cannot share a sponsor's raw data. Only a sponsor can -- a company can say okay you can use our data to another -- to an academic or something like that.
But at the FDA, we cannot take a given company's data and just give it to some people and the public to use.
What we can do is we can summarize that information and that's what's done in an MDA and summary basis of approval, and so you organize it into models.

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And then once you have your models, then you can simulate different outcomes or scenarios. But as part of that, there has to be some sort of predictive check to know whether there's validity in the model that you've created. Then you can act, and then there's some of result and then going back to learning as a result of the results.
Now, let's go from the general to the specific and what we're doing within pharmacometrics and pharmacology.
Our objective is really to facilitate quantitatively-based regulatory decisions, focused on efficacy and safety and generally through a dose-response or concentration-response in the lab.
To do this, it really requires high quality partnerships with the physicians, statisticians, and people in clinical pharmacology.
Externally, we're working to define the pre-competitive space where knowledge like I'm talking about today can be shared more freely, and also to develop tools for doing this sort of work; likewise, within academics, of working on knowledge generation and training.
We're -- when we started, most of our work was opportunistic. In other words, an MDA comes in. You begin

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working on that problem, and -- or if there is end of phase 2A.
But what we've begun doing is working on planned projects, where there's solving some sort of regulatory problem, and that's what we're talking about today.
The work that we do in terms of NDA work, there's 42 NDAs and case studies were presented in the AAPS Journal

last year, and then this year what we're trying to do is to routinely summarize the work that we do so that people outside the FDA can learn this primarily NDA work.

So we've just submitted a publication for -- a paper for publication based on our '05 and '06 work, and here we've looked at the impact of our work in terms of -- from the perception of the clin pharm people, physicians, and pharmacometrics people.

Generally, and so we've asked questions around -- for the modeling that we've done on NDA decisions, for the approval decisions, but 85 percent of these 31 studies were felt by the people that worked on those projects either to be of pivotal or supportive significance.

With regard to what went into the labeling, it was about 89 percent felt that it was either pivotal or

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supportive. Another options were supportive. Unfortunately, we didn't score high there.

As I mentioned, another driver is end of phase 2A meetings, and we're preparing a manuscript there.

For the planned work that we're talking about today, this is where there's a regulatory question, and what we generally do is we will then acquire prior knowledge, usually within the FDA, as well as what's in the literature, and then perform some modeling and simulation on the question at hand and make recommendations to the group of people that are working on this.

We're talking about Parkinson's disease today, and the question really is how to measure a change in disease progression, which you could just as easily ask in a number of other diseases like Alzheimer's disease.

We're simultaneously working on small cell lung cancer, where the question is the imaging prediction, and what we have at had there is about eight prior NDAs where we could look across the data to begin to answer that question. We're getting ready to begin a project on osteoarthritis shortly, with a similar question.

Switching gears again, the -- so what's the problem?

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I mean the problem that everyone knows about is if you look at the declining success rate over time that was published in Science, I mean the 50 percent failure rate in clinical trials comes from this and some other data from Tufts so that what you would like is a high kill rate back here in Phase 1, but as you go onto a certain market, you would -- we'd like to know that your success rate, particularly because of the expense involved, gets greater as you move along. It decreases.

So with this 50 percent Phase 3 clinical trial failure rate, what's the root cause and what to do?

Generally, when you plan a trial, what we're looking for -- I mean it's okay to find a true positive and true negative, but if you can plan a trial and predict that you're going to have a true negative, then why do the trial?

So in terms of outcomes, what people are looking for is a good chance of coming out with a true positive, and if

you can predict not doing -- but you would indicate that it would kill a project, for example, not doing the trial -- or and -- and certainly avoid false positives for false negatives.

So the root causes are well known. I mean it's a lack of adequate efficacy and too much unpredicted toxicity. You know, the placebo effect, the baseline effects drawn down, and something to do with patient selection.

And that's what we're going to talk about today is quantitating this prior knowledge within a disease to be able to use that in subsequently making decisions on planning products.

So the way we're conceiving of this -- in this case, it's an example with diabetes that if you can understand the relationship of Hemoglobin A1C to relative risk or outcome for neuropathy by recording a function of stroke, then that could be a disease model.

What we're talking about today is looking at the time course of change in symptoms and functionality in Parkinson's disease over time.

The drug model simply relates the drug concentration to effect whether it's efficacy or toxicity, as well as the pharmacokinetics.

Now, if you simply just have that information, then you can use that to simulate those same -- you can answer a number of questions. You can bridge into pediatrics or special populations.

But there's this whole other piece of information around clinical trials that we'll talk about today, and then within a company this information can be used for trial design. It can be used for go/no go decisions, for projecting the labeling, the formulation, the combinations, pediatrics.

The list at the FDA is very similar except that what we're doing is we're usually checking. You know, it's like did someone adequately describe dose response, and so it's a similar sort of endeavor.

The modeling cycle is similar to what I talked about earlier is building the disease and the drug model, incorporating time to then extract the clinical trial information that you need to then design the trial and then you can begin simulating.

And so we could theoretically begin simulating -- in fact, we have begun simulating a specific type of trial design in Parkinson's disease. We can simulate other trial designs.

Then, when a sponsor submits the data, then we could be front loaded. I mean we could be ready then to take their information into the simulations and figure out the extent to which this trial that they're planning to do with specific drugs is likely to work or not or if there are alternative scenarios.

Our business is not to do this all time. It's really to have sponsors do this and submit this information to us.

I mean we're not actually staffed to do this for all the diseases and all the applications. But I think that if we can do it and show people, then maybe people are more likely to get this sort of function.

And then, as new information comes up, then you can update your models and simulations.

We think that -- everything other than the sponsor information could be available in some public form.

Now, let's look at placebos, for example. This is a recent paper in Annals of the Journal of Medicine where they looked at the duodenal healing rate in active versus placebo patients, active being Cimetidine or versus Ranitidine, and 83 trials.

So looking at the healing rate in placebo versus the healing rate in active treatment, then it would be good luck across these 83 trials if you happen to have a placebo that

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didn't have much effect; whereas, the drug effect was very effective.

On the other hand, it would be bad luck if you happen to have a placebo that was generating about as much activity in healing ulcer as the drug itself. And these are all the same drug.

Now, there's -- the other thing that's interesting to note here is that the magnitude of response of healing rate was related between placebo and active. Okay. So this sort of information can be used in a planning purpose, I mean just by taking account for the magnitude of variability in placebo.

Just looking at placebo response in depression, and this is a -- there's not really a good explanation for this but this is looking over time both so that the spores for active tricyclic anti-depressants versus SSRIs versus placebo in the dark triangles seems to be increasing over time.

But likewise, if you have a placebo effect in this case that's very close to the drug effect, then that's got a pretty high risk of trial failure; whereas, if the -- if about the same time zone, if the placebo is generating much

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less of an effect, then you might have an increased risk for a false positive, neither of which you would want.

Well, we wouldn't want it.

The -- looking now at Parkinson's disease patients that were treated with Levodopa plus Seligiline or placebo for five years, you can begin to see the nature of the issue with disease progression so that placebo over time looking at the functionalities for it for Parkinson's disease in the UPDRS score versus treatment over time.

And in this case, you can begin to see a slope change perhaps that it might be occurring, and it's hard to tell -- I mean you need to know something about drop-outs as well.

But to this point, there's not been all the drugs that are on the market to my knowledge or approved for symptomatic effects in the treatment of Parkinson's disease, but there is no drug to date that has received a claim for changing disease progression, although we think that there

may be people working for that.
Using this example, then the key questions -- asking a question about entry criteria and baseline effect. Well, what if the baseline was chosen to be much lower or much higher. If you begin to answer those questions, if you have

prior information.
To detect the disease progression change over time. Over what period do you look? Do you look over six months? Do you look over 18 months? Do you look over a couple years? What is the critical time in designing the trial?
Drop-outs you want to look over the entire time and understand what's the reason for drop-out in designing the trial.
Well, this work actually goes back in some time, so that Nick Holford [ph.] described this and actually this is a 2001 publication, but I think the original work in PNAS was in '92, and it was generated from Ritagramin [ph.], I think the first drug approved for Alzheimer's disease, where he computed the disease progression rate for Alzeheimer's disease using a similar scoring system for functionality and then looked at the Alzheimer's effect or the Tacrin effect in this case, which was to not change the slope, but to provide symptomatic relief, and then subsequently they plotted the effects of other drugs. And so it's a way of really looking at the effect of -- what is the drug doing and what's the quantity of effect that it's having.
Blasby and Shiner and others looked at AZT response

where they analyzed data from an early '90s study and HIV, and again it looked similar so that this is looking at CD4 counts over time, and this before people begin using bioload, and you can see this disease progression and the effect of AZT from analyzing this prior trial was that it bumped CD4 counts, but the benefit of disease progression was changed. Subsequently triple therapy changes that.
Now, the other thing, just for your information, to do this sort of work you have to have a software system that it helps you acquire the information and save the information. Peter Lee has been working on constructing this at the FDA, along with others and other -- George Rochester and people in biostatistics have been collaborating on the data warehouse portion.
But the problem is we get data in very disparate forms using different nomenclature so that we're looking at moving towards one form, a CDESK format, but that's not a rule yet. And so we have to be able to then convert that information, the variety of sponsor information when we don't get in CDESK format to be able to save and to warehouse it. We got to use it.
And so that we can then model the information and then

save the information back into the warehouse.
So the warehouse is set up to create and save datasets to save models and whether they're NDA models or disease models, and then what we envision is that we'll then be able to move this on out into reports.

Future options -- extracting information I believe that extracting information and problem solving is something that we're going to be with forever and that by taking information from within the FDA as well as the example that we'll show you today is getting collaboration from the NIH that these are goldmines of -- potential goldmines of information for disease, placebo, drug, drop-out rate, baseline information.

The benefits are that we could impact development strategies and clinical trial designs. We can in a quantitative way look more systematically and perhaps more efficiently at endpoints and biomarker evaluations. There's probably unanticipated benefits you construct in a system like this.

The beneficiaries are -- we believe that the industry's -- the FDA academics, and the public, and that we would waste less patient risk and money and time on failed

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trials, for example.

To do this, one way of thinking about is that you could dedicate teams to target the questions, where you have physicians, statisticians, epidemiologists, clinical pharmacologists, and depending on the question manage deliverables in the same ways as developing and rendering these models in the same way that people manage time. There could be learning efficiency and it could be a in sense -- you could think of it as a FDA product, and it could be a great opportunity for career development.

Now, in terms of sharing information, we're getting ready to have a public conference with people in the industry and academics in January where we'll be probing what is the competitive space and how can we get at some of the problems we discussed.

So my general recommendations is that we do have to spend more time in defining and developing -- in defining the pre-competitive space and developing mechanisms for systematically sharing -- that we do need to increase our -- to do this sort of work, we have to increase the investment, allowing physicians, statisticians, quantitative pharmacologists to mine and share prior knowledge and

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problem solving. And we also have to invest in these tools, and again requiring to see this as the format to receive data at the FDA, and looking at other sorts of tools as well. Thank you.

CHAIRMAN VENITZ: Thank you, Bob. Any clarification questions by the Committee?

Okay. Thank you, Bob.

Then let's move to our next speaker. He is Jacob Mandema, and he is working for Quantitative Solutions, and he is going to talk about the industry perspective.

Impact of Prior Knowledge on Drug Development Decisions: Case Studies Across Companies

DR. MANDEMA: Thank you very much. I'm very happy to present this morning.

I've been used to talk and to give a little overview of some of the applications in industry how we're working to

leverage better prior information. And, of course, prior information is something we always use to inform our decisions in one way or another.

Really the topic that I want to highlight today is how we can formalize that process a little bit better through the use of mathematical models to formally and maybe more in

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a quantitative way use the prior information to enhance our decision making.

So in general, what do models provide if we apply them and apply them effectively?

Well, they give two components to the results we can get out of it. One is an enhanced analysis of the data. Using models allows us to integrate a lot of information, and I'll actually talk about a few examples of that. By using more effectively all the data we have available, of course, we get better, more precise decisions about certain actions we should take, as well as we can put in assumptions through our structure of the model based on scientific knowledge that we have through enhanced analysis as well.

On the other side, if we get a better understanding of what we already know, obviously that will steer us into directions where the key uncertainties are in a particular development program, so we can focus especially early in development at proof of concept trials or other trials exactly into that direction. What's the key uncertainty in this particular program? What's an efficient trial to remove that uncertainty and then we can move along with the development process.

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And obviously, there's also the application in trial design, as Bob already alluded to this morning, because we better understand how patients behave in trials either through that time course of action or through variability from trial to trial response, and by better understanding of that we can enhance the trials that we design.

So how do models improve decision making? Well, they do that by combining pieces of information. And anybody who's working a lot in PKP modeling already is familiar with quite a few aspects of that. One piece of information that we could add is look at the time course instead of just the endpoint response, because as the disease moves along, as the response moves along over time, and we have an understanding, and, of course, that's an assumption we need to build in and we need to have some model that will describe the time course of drug action. Then we can use all that information to inform our decision making.

We can do the same thing with the cross doses. We often believe that there is an underlying concentration or dose response relationships that E-max model that has pharmacological basis, and we can use that to use neighboring doses to enhance our understanding of a

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particular dose of interest or to make predictions about doses that we have not necessarily studied.

But we can move beyond that. Actually, we can start integrating more and more data. The tools are there to do

that and actually include information across trials.

But, of course, once we start doing that, we have to worry about the assumptions. How are the patients similar or different from trial to trial, and do we have a mechanism to account for that? Obviously, just taking the mean from two trials can have -- it can either be correct or not depending on whether there are certain variables that make those patients different that you had in on trial versus the other.

We can expand that one more level by trying to include a variety of different drugs. That has two advantages because if they're analogues, if they have a similar mechanism of action, we can learn and we combine information maybe they share the similar E-max for a response. There's a clear pharmacological rationale for learning from one drug and applying it to the other.

But also, of course, in industry, that's a very important aspect, including all this information from other

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drugs, because there's a good understanding of what appropriate targets are of particular response, and we should look for to find an opportunity to better treat patients.

And lastly, and this is where unfortunately, I cannot talk about a lot of examples in detail, but in the end have some summary on is try to integrate across endpoints, and this is really where a lot of benefit comes into play if we understand and establish links between information we get in very early development, such as pre-clinical models, or from biomarker studies and project that out to what that means for the clinical outcome; so really establish these integrations across a variety of different endpoints and the assumptions that we will make is that certain drug may share similar relative potencies or efficacies that we would see early on in other -- in pre-clinical experiments and biomarker trials.

Of course, what I've said -- and if you'll listen carefully that that particular thing, we always have to make assumptions to get that particular advantage of making better decisions and applying models is always this trade off.

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I use a lot of data. I have to make certain assumptions to use that data, so the validity of those assumptions forms a basis for the value of our decisions.

The advantage, of course, is better decisions that we can make or precise decisions that have, and especially in early development, obviously we don't have the luxury of spending a lot of time or a lot of money to figure everything out, so we have to make some of these assumptions to make either a quick kill decision or a quick move decision on certain products.

A little bit more about the scope of data integration. I've talked about how we're trying to integrate lots of information that is out there and that can be anywhere from data from several up to the largest database that I'm working with has about 500 clinical trial data -- and

information in it.
      So it becomes quite large and obviously you should learn a lot of information from combining all that data. Anywhere again from one up to several endpoints, again scaling that from early pre-clinical biomarker up to clinical endpoints of safety and efficacy.
      And it includes data both at the summary level.

Obviously, we use published information that's out there or mine the summary basis of approval for information. That's all summary-level data, and we can combine that with actually patient-level data that we have internally available, and especially that mixing is of a great advantage because one thing that's lacking of the summary-level data is a good understanding of between patient variability and having and obviously disease severity often is impacting outcome. And having patient-level data as well as summary-level data together really enhances our understanding of the outcome and actually allows us both to use the individual patient data better as well as the summary-level data better.
      What is the scope of application? I work on this area quite a bit. In industry, it's the investments in this particular data, large-scale data integration and modeling of that of several of the large pharma companies across a variety of therapeutic areas. I don't think there's a limitation with respect to the particular therapeutic area, where it is more or less applicable and anywhere drug to development process. Obviously, we would like to build these models very early in the development cycle and

continuously update them as information becomes available along the way.
      One thing that I think Bob mentioned already as well is this requires a collaboration across a variety of different specialties and particularly clinical pharmacology, statistics, and the medical specialties because of the scope of the types of analysis so you need to understand much of these -- of integrating some of these large databases and analyzing that as well as building in the pharmacological reasonable assumptions and other aspects, as well as understanding the outcomes and differences in trial designs that we use of all the different trials that we're trying to integrate.
      So after that short introduction, let's look at some examples.
      And I want to start out with highlighting again the importance of accounting for differences between patient populations. If we look at an integrated analysis that spans or metaanalysis that spans a lot of trials, and this is one of the assumptions that I talked about earlier, and understanding between patient population variability and how to make an impact outcome is key. This is a particular

metaanalysis that I found in the literature, in which they made some conclusions about the specific net benefit of a variety of different treatment options, in this case

Fibrates and how they change LDL.

And actually, the LDL response of Fibrates is highly dependent upon the baseline lipid profile across patients, which is quite different in all of these trials. So if you ignore that particular aspect, you have this large variability in baseline lipids across the trials, and look at sort of an aggregate mean, you may actually get quite different discussions by different results if you actually account for that trial-to-trial difference, and these drugs will look quite, you know, the relative effect of these compounds can look quite different if you start to account for that.

And the next graph tries to highlight that. This is a picture -- I guess I'll use my pointer here -- this is a picture of summary level data from a [inaudible] where each doctor's particular trial is the mean response in a trial, and it shows the relationship between baseline triglycerides in this particular aspect and the LDL response for variety of different Fibrates.

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We can see actually that it goes from a reduction in LDL and lower triglyceride levels all the way to an increase of LDL at higher triglycerides level actually, so this spans an opposite response has been moved along that baseline level of triglycerides.

So not accounting for this very strong impact, of course, you happen to have a bunch of trials that are right here, you make a very different conclusion as if you would have a few trials that are on this particular location.

So, of course, this is the complexity, because not always would we know these particular factors that impact the outcome. But if we do know them in this particular instance there's a lot of data out there, of course, we get great, great power from applying that.

Now, we have a mechanism to normalize for the differences between these patients, and we can project the response for all of these compounds as if they had been studied in a similar patient population.

And that was applied in this particular example. This has been published. I guess it's in the same journal that Bob was referring to, in the same for his particular publication on novel lipid modifying agent, Gemcabene, and

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this particular point was of interest.

So we did such a metaanalysis and in that fact looking, combining data of a variety of different compounds to really understand the relative potency and efficacy and apply that in this instance to better understand potential combination products. So what can learn from all the data that's out in the literature and how the interaction would occur between a variety of compounds that modify lipid profiles.

One thing we learned, which may not be surprising giving us similar magnets of action is that all the statins share with respect to LDL a similar dose-response relationship. What this graph starts to highlight is that once we normalize for the differences in potency, so they

each have a difference in 80, 50 or the dose you would need to get a certain response, once we normalize for that difference, they fall on the same pharmacological concentration or dose response relationship. So no difference in their maximum response or shape of that relationship. And this actually we know quite well because this summary level data is from a large number of trials.

So again, each of these points are actually to mean

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for several trials in this particular instance.

Of course, that's with respect to LDL. I'm not saying all the statins are the same. I wouldn't say that. They differ quit a bit with respect to their other particular components or mechanisms or other actions that they would have.

But, you know, building in a pharmacological assumption in this case, which we would, the drugs share a mechanism; they would have a similar E-max potentially that would greatly enhance our understanding of the dose-response relationships of these compounds. If you would study neostaph and some are still maybe being evaluated, you can apply that.

In this particular instance, we used that to also look at the interactions between drugs. Here is shown the interaction between a variety of different statins. We have Atorvastatin, Lovastatin, Pravistatin, and them Simvastatin and their interaction with the cholesterol absorption inhibitor, Ezetimibe. And actually what we found is that a very simple interaction model that we could apply for these -- for this particular drug could describe this interaction across the whole dose range of statins as well as across all

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statins.

So we've reduced the complexity. If we study a new study, and we would -- a typically interaction study, where we have multiple combinations of doses that we would evaluate and what is the benefit of one combination over another, we've reduced that complex problem to a very simple one, where we may have to ask -- and made only a few parameters that would describe that particular interaction; in this case, actually there's just one parameter, sort of an interaction coefficient if we know the dose response relationships of the statin and the non-statin and simply there's one additional parameter that describes that whole interaction surface.

So that adds great value by just adding one parameter and actually we can give a certain meaning to that parameter as well, given when it applies for event therapeutic benefit. I will leave that in the middle.

But our particular knowledge was used there in an early phase 2 trial that was planned for this new drug, where we said, okay, let's analyze the data that comes out it, understanding that we hopefully can apply a similar model structure to understand the interaction between the

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compound we're interested in at that point in time, Gemcabene, and Atorvastatin and really enhance our decision

making about whether this particularly combination could be competitive against other drugs that were out there on the market. So wouldn't that be an additional benefit of using this since LDL lowering is still -- more LDL lowering is still an important therapeutic effect.

But we actually found that the very similar model could describe the interaction between Gemcabene and Atorvastatin. Here you see the dose-response of this particular compound at different doses of Atorvastatin, but you can already see that the type of interaction was actually quite different here. We see the two projected next to each other, where on the right-hand side, you have Atorvastatin plus Ezetimibe, on the left-hand side, you have Atorvastatin plus Gemcabene. You see that even though the interaction model was quite similar, the interaction coefficient is quite different. But here, the benefit of the combination diminishes the higher the dose we have of the statin.

So whereas for one drug, it was this additional benefit being maintained across the whole dose range. Here

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is was being diminished, and actually our certainty in these bands indicated a 90 percent or 80 percent -- oh, yeah, 90 percent confidence interval. Our certainty about that particular effect, even though we have only done a relatively small study, was quite high.

So we could do one thing is to increase our understanding of this particular interaction because we used that model structure, and we used all the data there is out there on Atorvastatin, as well as we were able to compare it against this study, of course, or another treatment that we have not evaluated at this point in time and make a clear decision about the benefit of one versus the other option.

So that's what I just said, so I'll skip that particular aspect and go to -- I have only a half an hour to go through a lot of stuff. I'll skip to the next one.

So accounting for patient differences is a key topic in what I am discussing, because, of course, that's always the assumption when you integrate a large variety of data. Here I am showing an example that's also been published before, in which we were looking at Eletriptan versus Sumatriptan and actually your premise for this particular study was -- this particular evaluation was understanding

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whether encapsulation of Sumatriptan would impact this response. In other trials, an encapsulated form of the drug was used versus the commercial form, and that could be an issue that encapsulation may change the performance of, in this case, Triptan.

Of course, normally, we may do a bioequivalent study to see whether that would be the case, but and migraine is changing the absorption of the drug, so how can you interpret that particular bioequivalent study would be an issue, as well as what if we find small differences and we could have a therapeutic effect.

So we took another approach and said, just let's look at all the clinical data that's out there. A lot of trials

have been studied with these drugs, and there is, of course, trial-to-trial variability, but if we have a mechanism of accounting for that trial to trial variability, we can make probably a good prediction as to would how Triptan in its encapsulated form versus the commercial form.

This shows just all the trials that were in there where we see for each of the different dose groups that were -- that we had data available; placebo on the bottom here.

The response, in fact, in patients that have pain

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relief at two hours. And one thing we see is there's a lot of variability. Bob already showed that in some of his graphs the variability in placebo response and actually we had a very similar thing as what he showed in his example. We found that this variability in placebo response actually correlates very highly with the variability in drug response. So if the placebo response is higher, the drug response is higher as well.

Or the difference between the two treatments is quite consistent from trial to trial. While there's a lot of heterogeneity or variability from trial to trial, the overall response shows a pretty good correlation between placebo is higher and, for example, these here correlate with where the drug response is higher as well.

So the placebo in this case is a valid thing -- it's an internal reference and by looking at the difference or relative arms in this particular instance between the treatment arm -- between the placebo group and the treated group, we can normalize for that variability and get a much better understanding and that's shown here. Here the data are now adjusted to all the same placebo response and what would be the response for each of these trials, given, you

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know, the typical placebo response of being -- is here, we can see all that variability that was there as we reduce and actually the outcome is very consistent with the mean model predictions.

Here, again, these dots are all trials with a 95 confidence levels, and here is the model prediction. So we've taken a variable component out of it; have a good rationale to believe that -- and this is just the equation to do that -- good rationale to believe that we understand what's causing the trial-to-trial variability so that we can make a comparison across trials and in this case, you know, we tested whether the treatment response by itself, the difference between placebo and active, whether there was additional trial-to-trial variability, and actually there was -- there was not.

So the difference in mean response could explain all the trial-to-trial difference that was there.

So we could project in this particular instance the time course of response of commercial Sumatriptan, here in the dots, versus the time course of response to encapsulated Sumatriptan, and we see early on, over time, actually there is no difference between -- we could not find any

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significant difference between these two forms, and, if

anything, encapsulated Sumatriptan -- or responds a little bit better that the commercial form actually. Those responses are higher than all the historic data on Sumatriptan.

So it was useful insight, but, of course, we learned so much more, even though that was the premise of that particular -- how it all started -- we learned a lot about the differences between those two treatments that can be used effectively to optimize patient care. We learned about the difference in speed of onset and magnitude of response between these two treatments so that we actually could project, what you see here, the difference between 40 milligrams Eletriptan and Sumatriptan over time was the anticipated differences in -- this is an absolute difference between those two treatments in patients that would give benefit from one drug over the other; and understand that as a course of time, we will there's substantial benefit in additional patients being treated of one versus the other, based on all the clinical data that's available.

So let's talk -- after I -- I think I've addressed that addition quite a bit. Let's talk a little bit more

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about maybe understanding a little bit the competitive clinical profile of a variety of different drugs.

Of course, obviously, that's from my perspective is also very, very important. By combining all this data, I learn -- hopefully very well -- what the targets out there of the compounds that we try to look to improve. And this example comes out of anti-seizure drugs looking at AEDs, where comparative trials are basically not done or very limited because of the sample sizes required to show certain differences, so our only way again, as I mentioned -- have shown before, to understand what potentially the relative effect could be of these treatments is to do a metaanalysis across all the trials that have been done, and hopefully find, and in this case actually we found a similar correlation, the variability in placebo response correlated highly with the variability of treatment response once you account for that. We've taken the trial-to-trial variability out of the equation, so the very different -- very consistent response in the difference between placebo and active, and actually you can get an adequate comparison of these treatments and look both at efficacy and safety so that we can understand if we put that all together -- we can

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understand what potentially the clinical profile would be of one treatment option versus the other.

Here this tries to put that together in one graph, where we have picked a variety of different doses, which is going to be typical doses of these treatments, we've plotted one of the tolerability issues that we looked at on the right-hand side and the patients that were allowed out of the trials due to AEs adversity. Then it's obviously quite different between these compounds. Sort of our assumption was that if the adverse event is bad enough to make people quit the trial, let's sort of put them on the same scales that would give a good relative comparison. And whereas,

here, on the Y-axis, we see the beneficial effect, the change in seizure frequency and really where you want to be is on this lower left-hand corner where we have very few drop-outs and we have a large treatment effect, up to 45 percent reduction in seizure frequency.

So we can see there are a few drugs that sit in that space -- Levetiracetam, Topiramate, and Pregabalin. There's just a few drugs that stand out due to high or low tolerability, and there's a few drugs that stand out due to pure-for efficacy at a typical dose that's being used.

So obviously, this gives us a good opportunity area to shoot for. We know that we want to be here obviously, but also we can understand how much effect we need to separate one treatment versus another -- and actually could use that very effectively to I think with a relatively small trial, because we also understand the differences from trial to trial in these outcomes. With a small trial, we get a good assessment of whether a new treatment option we would have in this space would give a benefit that's worthwhile pursuing.

One area where I think we can do a lot and hopefully also by using more of the internal data and it could be here at the FDA, so that's why I want it focused on a little bit is trying to link biomarkers to endpoints, and one of the key areas that I'm working in is exactly that particular space, and I want to discuss very quickly just at high level concepts the application of that to a novel anticoagulant that's being used for treatment of venous thrombus embolisms that could be there.

And here we did -- took a very similar approach. It's what you've seen before -- actually, combined the data from a variety of different compounds and different mechanisms,

all the way back to Heparin. Low molecular weight Heparin is a thrombin inhibitor. And, in fact, it's an A inhibitor. All the data that's out there after having knee surgery to understand the dose response relationships of these compounds with respect to the outcome of venous thrombus embolism, as well as the outcome on bleeding. Of course, if you give too much of the treatment, you'll get the adverse events, which is bleeding.

So that set a good target for a normal compound and identified opportunities to improve treatment in this particular area.

One thing we really wanted to do here is use the biomarker data that we could accumulate that we'd understand and that gives information about the relevant potency of these compounds with respect to their clotting, or anti-coagulant effect, and actually effort was undertaken to generate that particular biomarker data across all of these compounds internally and use that to scale from the biomarker data out to the clinical outcome so that we could optimize the design of the phase 2 trial so that an understanding of how the biomarker may link to the particular outcome was used to optimize the dose range as

well as the targets for the particular phase 2 design.

But we could take that even a little bit further. VTE prophylaxis is just one indication for these types of compounds. They're actually also being used in the treatment of VTE as well as in AF and R-2 relation and in other therapeutic areas. So another link we made is to say, okay, can we use what we learned from VTE prophylaxis to VTE treatment? Is the relative potency that we see of all these different treatment options with respect to one particular outcome correlated with differences in effect in the treatment of VTE? The reason to do that is that the treatment of VTE at very low frequency of responses, it's hard to do dose finding in that particular area, even use trials if you want to do that.

So if you have a good rationale that we can pick a dose based on one endpoint that would be correlated with the response we would have in another one, we can validate the selection of the particular doses for treatment in that area.

So that was -- that approach was taken in this particular instance as well.

I have a few other examples that relate biomarker to

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endpoint models. One that we use a lot is, of course, about compounds that have a similar mechanism of action, which was applied in a novel PDE5 inhibitor for male erectile dysfunction. Of course, what I showed previously those compounds have quite different mechanisms of action in how they impact the coagulation.

And in this particular instance that was -- a similar approach was taken and used the information from the biomarker studies. We could test its predictive performance because we have other compounds out there, and use that to optimize the dose finding in phase 2.

Here there was a particular complexity because the disease has changed over time. More less severe patients were included in later trials versus early trials. Early trials really those severe patients were mostly included. This time and on less severe patients were starting to come in these trials, so we needed to find a way to scale for the difference in base populations so that we compare the response that we find now was a response in the trial that had occurred a while ago. And actually could establish I found it a very -- a close correlation between the baseline disease severity and the magnitude of response.

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In this particular instance, patients respond better if they have more disease, which is ultimately good. That's what you would like.

Then analyzing the phase 2 data by using all the prior information so, of course, if you believe our assumptions -- in this case we did -- we can really enhance our decision making power and could express that in, for example, the relative sample size. Basically, we do sample size from 350 to about 200 to have a similar ability of decision making and distinguishing features.

So using the prior information basically reduced the

involved in the outcome enough to get to that particular level.

I'll skip the last example really to highlight a point and continue some of the things that Bob said this morning. What are the opportunities inside -- and maybe the FDA from my perspective?

And, of course, it's important there to engage with industry, 'cause this is a complex area. We're trying to interpret a lot of information. It requires specialties -- for a variety of different specialties to be involved in that particular effort, and if it's used in the drug

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development decision making, of course, it's good to have that engagement and discussion of methods that are being used.

But also, and the more highlight of this, of course, there's a wealth of information to mine that can be used to patient benefit. From my perspective, what would be very, very useful is understand this trial-to-trial variability. What are predictive covariants, such as disease severity, that would explain variability in response from trial to trial so we can account for it? That is a non-competitive situation maybe. It's not focusing on any particular drug per se, but it helps us really understand if we have this particular aspect how can we compare responses in certain trials versus other trials, whether it's random -- so how much random trial-to-trial variability is there -- as well as may be explained by covariance.

Of course, safety modeling is a key aspect as well. And there's a wealth of information on that particular aspect. We're not focused on advocacy. We're focused on understanding the safety concerns in some of the drugs.

For me, it's always an important question to ask is it the drug that's causing the concern in a particular

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therapeutic area or is it the dose, meaning is it because the dose that was selected that we may find more concerns in one treatment over another or is it something specific about this particular drug that it has a narrower therapeutic index.

Of course having the data available also a variety of drugs in a certain class can answer the question. Can we get rid of the problem or minimize the problem by changing the dose versus something intrinsic to this particular treatment that makes it less valuable than other treatments and especially in this instance a safety concern for patients.

And the last one that I want to highlight again is really this biomarker linking. By having a lot of information available on actual clinical outcomes of treatment options, and I put it into maybe not as much competitive aspects but the other safety concern on QTc by having the data available for both clinical and pre-clinical situations and with clinical outcomes we can really establish that correlation very effectively and use it to the benefit of everybody.

I think that was what I wanted to highlight. I have a

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full summary towards the end. I think a key thing there is there is a tremendous opportunity, there's a wealth of information out there that we can use. We understand a lot of the pharmacology and underlying physiology so we can use those models that mimic that to analyze the data and really have the models, obviously that's a trend where things seem to be going, and use the models as our knowledge repository to provide the quantitative basis for drug development as well as certain regulatory decisions. Thank you very much.

CHAIRMAN VENITZ: Thank you, Jaap.

Any questions by the Committee members at this stage?

DR. JUSKO: Jaap, that was very impressive how you did the metaanalysis for this data and some of the other drugs and summarizing all this information.

It's -- I think you indicated that the summary basis of approval was one of your primary sources of information, and I wondered if you could comment on the adequacy of these summaries. It seems like it's the only public access to this wealth of information that is given to the FDA.

DR. MANDEMA: Yeah. It's actually quite good if the only thing you're using is the mean responses of the

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outcomes for the trials, because they are listed. So we know the means of the patient populations with respect -- they're important -- covariance that may affect outcome, as well as the mean response; and often maybe have available data that has not been published may include fail trials that I want to include in the analysis as well. And so that's why it's a useful source.

Obviously, having individual data would help a lot. That will not happen on that particular aspect, but especially more understanding of the correlation between some of the outcomes that are there, which is done as well. Cuts are made of the data by particular covariants and tables have been produced that show difference in response by gender by other particular outcomes, so give a little bit more granularity than actually you may find in a scientific publication.

CHAIRMAN VENITZ: I have a related question related to published literature as opposed to the FDA information. How much covariant information did you get?

DR. MANDEMA: Of course, the covariant information is limited, because you just have the mean in the group, and in the case of the statins in some areas we have a lot of

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trials that have been run on Fibrates, as what I showed you.

So across all these trials, we span the differences in patient covariance; you know, the means of the patient populations in those trials differs anywhere from very low and certain baseline values to very high certain baseline values.

So there that information is available. In therapeutic areas where we do not have as many publications that is, that's lacking. And if one these outcomes, of

course, affect you're published over time. For other aspects, one of these outcomes could impact outcome. That minimizes your ability to use that particular data.

CHAIRMAN VENITZ: So it's basically the range of the mean variance that allows you to resist?

DR. MANDEMA: Right.

DR. KAROL: Understanding variability is, of course, very important, so I was interested in the association of variability in the placebo effect to that of treatment, and I wondered if you could offer some explanation of why you think there is this association and could your modeling help inform the staff perhaps of why there is this association?

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DR. MANDEMA: That would be hard to understand why there's an association because those patients are stratified or, you know, it's one set of patients, so if I do not have individual covariants that may be able to correlate with that, they're probably pretty similar in those two treatment groups. They're being evaluated in on trial, so I do not have the information to really separate what could explain that.

You could come up with a variety of rationales of why that would be the case. It could be the inclusion criteria that are set that makes the overall response a little bit higher or a little bit lower in each of the groups as if it's a regression to a certain response.

It could be that it's just a patient population that's more sensitive to treatment and it correlates with placebo response as well. It's a variety of reasons why that could be the case.

But it's always good to know that at least the difference between those two is not very variable from trial to trial, so the information we learn in these trials can be effectively compared.

DR. BARRETT: Jaap, I was glad to see the comment

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about biomarkers. They could be a real advantage to doing -- you know pulling this off successfully.

But I was struck by your example of the thromboid embolism modeling, because many -- pulling the data across all of those different mechanisms and a lot of those biomarkers are very mechanism specific as well. So it's more than just methodologies obviously.

So my question is in your experience, when you're making decisions on including or excluding data adverse studies that you find that given -- it's really an issue of generalizability obviously and your objective of the model in the first place.

Do you feel that there's still an opportunity to use a lot of that data on biomarker specific to certain mechanism or have you had success needing the skills across mechanisms?

DR. MANDEMA: There I cannot comment on particularly how successful it was to scale particular biomarkers, but, of course, you learn how well it works in one way or the other and you can account then for if I does scale very nicely, of course, you can reduce the complexity based on

trials because you're quite predictive with respect to the doses that you would have.

If there's poor scaling or a lot of variability in the scaling across these compounds, you can use that information as well, 'cause that will mean that -- you know, have to study a wider dose range in your particular trial to account for an uncertainty in that scaling.

Of course, when I use the models, we always take uncertainty in the components into account, and especially with biomarker scaling we may in certain areas across mechanism might be very tight correlation. In other areas, there may be no as tight a correlation, and we take that into account in designing the trials to basically not be hurt by assuming something whereas, in fact there's still quite a bit of uncertainty in that relationship.

So it's affected one way or the other. Of course, you use it in -- you know, your next trial is going to account for that and optimize with respect to that component.

DR. D'ARGENIO: Jaap, this morning of the boxes involves model development cycle, in other words the building of the disease model. And I'm sure later on we're going to talk about these specific applications.

But from some of your applications and looking into the literature, how much can you pull out of that in terms of trying to build a relevant disease model and how generally would that be going forward for other compounds?

DR. MANDEMA: You know I focused more on difference between placebo and response. I focused on interpreting action, interpreting safety and efficacy, so the disease model is more, if you think about that in the placebo response, for me, it's more nuisance factor that I have to deal with than a particular goal of the outcome.

I think there's an incredible amount of information out there that we can use, even with just having mean data available, which, of course, is a limitation. You can do a lot better if we have also the patient-level data.

But I think there's a tremendous amount of information available that can be used very effectively and can understand and can actually get quite predictive models on outcome.

DR. POWELL: My recollection on the statin information that you showed was that a company -- you actually predicted -- there was a company that did an outcome study of their drug versus I think it was Atorvastatin, and the trial in effect didn't go the way the company wanted, but you had predicted that that could -- would occur based on the model that you had.

DR. MANDEMA: That's, of course, a little too vague to comment on specifically on that, but, yes, what we could do is also link the biomarker profile, which the lipids would be, to ultimate cardiovascular events, which, of course, the outcome, ultimate outcome of interest, and try to understand how, you know, modifying our lipids will give a certain benefit on outcome and use that to predict relatively

treatment comparisons and my experience is that actually is quite successful.

DR. POWELL: Well, my question is with regard to relatively rare adverse events, like, let's say Rabdomyalisis across statins. Did you do something similar as you did with anti-convulsants and look at the -- in effect the benefit-risk across the statins?

DR. MANDEMA: Not that I can really show you much about at this point in time.

CHAIRMAN VENITZ: Okay. Thank you, again, Jaap.

Our third presentation for today is given by Joga Gobburu. Joga is a teacher in pharmacometrics, and he's going to show us a few examples in diabetes and obesity of

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using disease progression modeling.

Disease Models at FDA: Overview and Case Studies (Diabetes and Obesity)

DR. GOBBURU: Good morning, everybody. As they say, we're from the government, and we're here to help.

Let me tell you what we meant when MDA made a cognizant commitment to improve drug development as reflected in the critical path initiative, which is a public document.

And one of the specific approaches that is identified under this initiative is using quantitative tools based on clinical pharmacology, advanced biostatistics, and pharmacogenomics, et cetera, to improve the success rate of clinical trials; thereby allowing us to have access and the public to have access to it sooner and also to contain the avoidable losses.

But we cannot do this alone, and that is why we're here today, to share our experiences with using quantitative clinical pharmacology information to predict regulatory actions and then seek feedback and also increase the awareness of this approach to improving drug development.

I specifically have three points that I will claim to

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make in my presentation. The first one is that I will try to impress upon you that in general quantitative clinical pharmacology/innovative biostatistics approaches are being used to make important regulatory decisions.

And the second point I would like to make is that from our experience over the 74 NDAs and then the other 20 or so NDAs currently under review -- so net a hundred NDAs -- our experience is that ignoring the value of ignoring the planning trials analysis well in advance will lead to more failed trials. I will show you examples to impress upon you on that aspect.

And the final point I will try to make is that -- is to give a perspective, our perspective on what we really mean by disease models, a slight extension to what Dr. Powell has presented and Dr. Mandema has presented; and also to walk you through a couple of examples to really see what we mean when we say disease modeling and its role in drug development.

So with that introduction, I would like to first present the results of a pharmacometric survey. There were

two surveys that we conducted. One is with the NDAs that needed pharmacometric reviews or analysis submitted and

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reviewed between 2000 and 2004 and another survey of the NDAs submitted and reviewed 2005 and 2006.

For each of these pharmacometric reviews, which are the consultation from this analysis, came from -- to the clinical pharmacology primary reviewers or, in several instances, the medical team members. And we asked the customers in this case either the clinical pharmacology and the medical partners to rate the impact of the pharmacometric analysis for a given NDA. And we asked them to specifically rate them on the role of pharmacometric analysis on drug approval, approval meaning approval-related decision. It could be an approval, non-approval, or approval, and labeling decisions.

We gave them three ranks to choose from for each NDA and each category -- total, supportive, and no contribution. Total meaning the decision -- the regulatory decision would not have been the same without the pharmacometric analysis, and supportive is the decision was well supported -- I can't find any other word to define that -- corroborate or increase the comfort level in making the decision.

As you know, confirmatory evidence is also equally important for regulatory actions. And the third category is

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no contribution.

We could be doing something else more useful. So this is the slide showing the results of the survey of the 42 NDAs submitted and reviewed between 2000 and 2004.

As you see here, you have the impact -- the type of impact -- total, supportive, or no contribution -- and the category -- approval and labeling. And if you, for practical reasons, if you consider total and supportive as equally important, then about 90 percent of the cases or so have contributed to very important regulatory decisions.

And this trend is similar in the latest survey of the NDAs submitted and reviewed between 2005 and 2006. Now what we have here, different from the previous one, is we have expanded the disciplines from which we sought the survey. So we have the pharmacometrics reviewers. You have the Division of Clinical Pharmacology, primary reviewer, and his or her team leader as well as the medical reviewer.

As you see, consistently, still, that pharmacometric analysis led to a large number of cases important regulatory decisions.

Now, this is a forest view of the impact of pharmacometrics, and I will show you some of the examples

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where -- to give you a better appreciation of what we really mean by total or supportive for approval and labeling.

This is the first NDA where we have approved the monotherapy of Oxcarbazepine in pediatrics, which is indicated to treat partial seizures using prior clinical data. So we have alleviated the need for any further control trials in monotherapy for pediatrics.

The way we did it is we used the data from the others,

whose indications were approved based on empirical clinical trial data in both for adjunctive as well as monotherapy. And for pediatrics, four years to 16 years, we had clinical trial data for agent therapy treatment, but we don't -- we did not have data for monotherapy and then, yes, you might surmise the conduct of monotherapy trials is challenging in pediatrics, given one the resistance to give -- to put these patients on placebo and also a wealth of information is already available.

So there is the law that supports approval of pediatric per indications, especially monotherapy, if we had reasonable prior information. That's what we exactly did. We used export response analysis across these three boxes, clinical trial boxes, and then tried to fill in the fourth

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box, and it is approved right now.

So this was an NDA where the different disciplines within the FDA -- clinical pharmacology, biostatistics, clinical -- as well as the sponsors worked together to produce this product.

The second NDA is on the lines of the importance of establishing the biomarker outcome relationship, which, in our opinion, would have allowed more efficient future trail designs.

The sponsor in this case was pursuing an accelerated approval for a drug to prevent a life-threatening disease based on the biomarker, even though clinical endpoint analysis failed for two pivotal trials.

Now, in our opinion, the -- if the data from the first trial was -- were used to develop a relationship between the change in biomarker with or without the drug, and the relative risk of the disease, which is plotted on the Y-axis, if we had known this relationship with what our certainty that would have allowed to better design the next trial.

And as you see here, our retrospective analysis, when the NDA was submitted, clearly showed that there is strong

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relationship between the change, the suppression of the biomarker in this case, and the relative risk of this disease event, which we don't want.

So the lower the events, the better.

So if you had, if you just to illustrate the role of the -- of this relationship, if you had a drug which, is light blue, and if you have an increase in the biomarker level by 50 percent, 1.5, then the risk of the event is about 60 percent. Yeah, it increased by 60 percent. Versus if you had a decrease in the biomarker, then you will reduce the risk.

So you can use this relationship to better power the studies; also, more importantly in this case, to choose the dose.

In our opinion, the dose was too low. Now, the sponsor is pursuing like 10-fold higher doses than what was studied previously.

Now, we can stop here and ask now what would have been the outcome of the second trial if we had done this at the

end of the first trial.

Similarly, this is the NDA -- third example -- NDA number three. The sponsor is pursuing an indication, which

is again very debilitating and life-threatening, and the sponsor has conducted pre-clinical trials without regard to any sub-populations, and there was equal evidence of effectiveness. Essentially, like we could say that all three trials failed, but if we -- in our review, NDA review, tried to understand why the trials failed so that we can give more specific recommendations to the sponsor and next time the sponsor can do more efficient trials. And this is a disease where there are not many drugs available for the patients to -- for use.

Now, clearly, as you can see, that there was a baseline condition, which is just the baseline disease severity scale, which differentiated the patients who responded and who did not.

So if you see the right-hand side box here, you can clearly see that patients who had more severe disease responded very well. In fact, there is a clear dose response, which, in my opinion, is the strongest evidence that any drug works.

On the contrary, if you look at non-responders, there is literally no dose response individually here, and this can be used -- could have been used, should have been used

as a stratification variable, and then maybe that would have improved the chance of trial success.

Similarly, so what I've shown in the previous three examples is using prior information so in a narrow view rather, though, so using trial data from first trial to the second trial. But we are talking even -- there are much more important uses if you look at across NDAs. For example, it might be meaningful for us to understand that females in general have steeper slopes in terms of concentration in QT change relationships. We don't know what this means in terms of drug risk today, but what we wanted to show you is an example of the power of comparing across different drugs. These are four different drugs and what you have in the box plots for the males and females and the Y-axis is the slope of the concentration of QT response.

As you may see, that females in general have higher slopes than males.

Now, that goes back to accruing more data, again, having data from the outcome trials; in fact, from drugs like Circulol [ph.] or other, you know, class three anti-diuretics and then relating the QT change to that may

again alleviate the -- or give us an opportunity to go in a different path for assessing broad medical risk.

So across these four examples I showed you, there are questions that deal with, you know, like optimal design to show this is modifying effects. This goes back to some of the examples that Dr. Powell has shown, and you would ask probably what is a good biomarker survival benefit for

cancer patients. Why are 60 percent of cancer trials failing?

So that's an inquisitive drug development question. And what would -- how would we maximize the chance of success that should be chance of success, not change -- for a two-year obesity trial? Obesity trials are very large and start to lot of troubles. How do we use prior information to design them better?

And given that about 85 percent of depression trials fail, can we not learn from these trials to design our next depression trial better? What would be the best dose to -- for an anti-diabetic, let's say, based on 12-week data for a 26-week endpoint? These are some of the questions that pondered in our minds during our experience across these almost one hundred NDAs, and then we have only one hammer in

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our hand and everything is a nail that's quantitative to clinical pharmacology approaches.

And we believe that that's a very powerful tool to answer questions like this, which is of interest to both sponsors, public as well as the FDA.

So this is what we're talking about. We're talking about managing and leveraging knowledge across NDAs, across clinical trials. So we get all kinds of information, in different forms, shapes, colors, and then we have this mill here, which is the quantitating, quantifying these -- this information and churning out the knowledge.

So what do we mean by these placebo disease models. We specifically are referring to biomarker endpoint relationships. The time course of these biomarkers and or the endpoints, and the drop out. What is -- we need to quantitate -- quantify the drop-out rate. Why are they dropping out? And the inclusion-exclusion criteria. What would be the distribution of, for example, the Parkinson's disease rating scale at baseline in males, in females, in age, unless we have these pockets of information we cannot simulate future trials and power them to -- and connect this to the analysis.

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So that's the impetus for us to consider this approach. And we are, in my personal opinion, calling this approach loosely as disease modeling, but we don't have a better word. Maybe if you have, please let us know.

So disease modeling is -- encompasses a lot of different activities which are, you know, which are based on quantitative clinical pharmacology and advanced biostatistical methods, and the type of questions we're asking that's in my opinion the more important -- the one I showed you in the previous slide that's the type of question -- those are the types of questions we're trying to answer.

And we have to date experience with Parkinson's disease, obesity, diabetes, and tumor survival in non-small cell lung cancer, rheumatologic condition -- I actually showed you an example -- HIV, epilepsy, and pain.

Now, and each of these area had different questions -- objectives to answer, and some of them needed mechanistic models. Some of them required empirical models. So I hope

you can appreciate the diversity of objectives under the umbrella called disease models.

Now, the ultimate goal, what we envision, the utility of these models is the following: we'll show you -- focused

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on one example, testosterone suppressants to treat prostate cancer patients.

So let's imagine that next year we come here again, and we have this wonderful disease model across different drugs and types of drugs and trials for this indication.

So at that point, if the drug developer has access to this model, then they may be able to conduct a gene assay early on into this story and feeding the potency of the various compounds maybe through this disease model.

So you can appreciate the disease model is now in this, as shown on this slide, is -- it has many more dimensions. It's not just human data. You are talking about pre-clinical, in vitro, and so on.

This is a dream so it is -- so we dream that. So we feed that information into this disease model. Then the output we're saying would be the choice -- the range of doses that can be tested in the pre-clinical models and then -- and the design of the experiments -- what to measure, when to measure. For example, in this case, the concentrations of the drug, GnRH, the luteinizing hormone, testosterone, et cetera.

Then once you have -- that's what we call the PKPD

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data, then you again update your model and then come up with the output to design the future trials. We're, in fact, asking that we take a debrief, and stop here, and conduct local trial simulations to understand what type of designs, doses, will maximize the success rate of these trials, which are long, expensive, as well as it's very hard to recruit prostate cancer patients just like that.

So keeping those challenges in mind, if you use the quantitative approach to design the trials, then you can come up with the optimal design for dose finding in cancer patients and ultimately the registration trial by the total trial.

With that -- with those points -- one the survey; the second one is four examples from NDAs of the value of looking into prior data and the vision, the application of disease models. I will now show you two examples of disease modeling activity for obesity and diabetes.

This is a project that was initiated by a need, so there was a sponsor who came to us for an end of phase 2 meeting with questions related to design and dose of for an obesity indication, and, as you can see, the team is mentioned here -- Dr. Zhang, Dr. Qui, and Dr. Hae Young Ahn.

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They were the core group that developed these models.

So going back to Dr. Powell's slides about the different pieces of the disease model, what you see here is the distribution of baseline body weights; the endpoint is body weight for obesity. So you have the distributions for Caucasian males, females, African American males, females,

and other races here.

As you see, the distributions are very different. And this is a case where the change in body weight is related to the baseline. It's proportional to the baseline. Heavier people lose more.

So this is important for us to know the heterogeneity in the population so that the recruitment is done accordingly and the doses are chosen accordingly.

Now, as a technical matter, you would like to make sure that these distributions are reliable and you can use them to reproduce in the future, so what we have done simply are -- we have looked at the QQ blocks to ensure that these distributions indeed roughly reasonably follow a large number distribution. So if I give you the mean and the standard deviation, which we did in the background package, one should be able to reproduce these distributions

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reliably.

Now, coming to the drop-out model, as you see here, the X-axis in the different time events, 0 to 12 weeks through 36 to 52 weeks, and at this point it's focused on the Y-axis labeled drop-out percent. And, as you see, the drop-out percent in each -- over the time decreases from the initial period to the end, so you can assume that the total drop-out will be the cumulative of all these drop-outs across the time.

Now, it's not important -- it is not merely important to know that this is the drop-out rate, but we would like to know why.

If you look at the body weight change -- that's this axis, the green axis here -- in patients who dropped out it's pretty much flat, so there is very little or none change in body weight in those patients who dropped out. So it's lack of effectiveness essentially.

But on the contrary, if you look at the patients who remain in the trial beyond each of these time periods, clearly there is a greater impact of the drug in lowering the body weight.

So this an information that's very important if you

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really want to conduct an informative clinical trial simulations or scenario planning, as Dr. O'Neil refers to.

And we have covered the patient demographic model. We have covered the drop-out model. This is the time course of the placebo effect. As you see here, it's -- the X-axis is in days, and the weight class, in kilograms, is on the Y-axis.

So weight loss, just imagine this is negative, meaning you have to -- it's a decrease in body weight. So it's a convenient relationship. It's an empirical model which states that in about one year or so you reach about 1.6 kilograms on an average.

So the value that this integral to drug development is the effective use of prior data for designing future registration trials and also might lead to alternative dosing recommendations, especially if you know that people are dropping out because of lack of effectiveness maybe we

should build in a titration scheme rather than a fixed dose to see if that helps.

And that is important because maybe that's the way it's going to be used in the patients ultimately when it's approved. And it allows designing useful short duration

trials. Now that you know the shape of the body weight change, the reasons for drop out, and the distribution of the baseline covariates, you might be able to do proof of concept trial, more informative trials, early on, and predict -- or choose doses more efficiently.

The second example is diabetes. Again, please keep in mind, the purpose of this is to give a flavor of what we're trying to do with this initiative here, and, as you will see, this is -- in most of the examples -- they're not in a shape that's fully developed that people can go and use them today. But they're important pieces of this disease model puzzle that, still, people can use and probably build upon that.

So this is again the need for this arose from an end of phase 2 interaction with the sponsor.

So the key question was how to reliably select doses based on a short-term study for a long-term study, which is the registration trial. Here, the short-term is 12 weeks, and the long-term is 26 weeks.

That's exactly what I have mentioned. So the effect size let's challenge on HBa1C at 26 weeks was not available, but the effect size on FPG at 12 weeks was available.

So what we did was we -- this is as close as you get to mechanism today. So this is the mechanistic model relating the fasting plasma glucose and HBa1C. It is irrespective of whether they're on drug or treatment. This is a biological model. And this is the drug model that we used.

And, as you can see here, the drug concentrations reached steady state at some point, but the fasting plasma glucose and the HBa1C concentrations in plasma reached steady state at a later time, which is empirically observed and that's the impetus for this type of a model, which was originally proposed by Dr. Jusko, and there are other groups from Upsala, Dr. Causen [ph.] and from Leyden working on expanding the diabetes model to include placebo effects and so on, which we're not going to discuss today.

So given the truncated or abbreviated data from this new drug, and how can we predict the 26-week change to allow more level dose selection?

So we used the relationship between FPG, fasting plasma glucose, and HBa1C from other NDAs, internal NDAs, to fill in the gap through 12 to, let's say, 36 weeks, and then predicted what would be the most likely change for a given

dose of the new drug at 26 weeks.

So this, in our opinion, led to a more informed dose regimen selection and could lead to, you know, increased trial success. Quantitative analysis, in my opinion, was critical here, and the effective use of prior data supports

conduct. So once we know this model, you can routinely design a shorter clinical trial early on to pick the doses and so on, and screen compounds.

So this is my last slide, which I don't think it's needed; the reason is we have specific questions for the advisory committee, and that will be the end of my presentation.

CHAIRMAN VENITZ: Thank you, Joga. Any questions by Committee members?

DR. JUSKO: A very nice presentation. I have a question on your early slides where you did the survey of customer satisfaction. I wonder if there's any element of what we commonly encounter in academia. If we give students "A" grades, they usually give us raving reviews of a course, and the students that we flunk give us poor reviews. Were you able to assess that type of potential bias in your study's assessment?

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DR. GOBBURU: Yeah. Well, I don't think that there is an easy way to get rid of the bias, because it's a team -- everybody is involved from the beginning of the NDA review, and the outcome I would say has some stake for all the team players. So there is going to be some bias. I don't think we can get rid of that.

The more important feature here is that no matter what the review says, the survey says, the regular reaction is what it is. So there is a concrete action letter that will attest to the usefulness of this analysis. For example, the OCTs have been examples. It's approved. People are using that drug, so that is its testament to the utility of this analysis, and I hope that helps.

DR. POWELL: If I could add to that, the -- we also do surveys, internal and external and end phase 2 at our meetings, and the results are quite different, so that the data on those meetings would indicate that the sponsors like the meetings a lot. It's on five-point scale.

And but you can say, well, bias there, and are they going to say, well, that was terrible meeting.

But to get to your point, though, that the FDA responses are a fair bit lower in terms of the value, and I

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think that probably also has something to do with asking people to do something in addition to what they're already doing in a fairly short period of time. But also they may be -- they don't -- for an end of phase 2A meeting, we may not -- the FDA see -- gain the actual values so much as what the industry does.

So, you know, but your point is well taken.

DR. DAVIDIAN: That was an excellent presentation. I'm certainly in favor of using prior knowledge as a way to help with the understanding of what you're studying first of all, and designing trials to identify what's going on.

I guess I -- and this may be too much of a sensitive question, but it may come clearer in the more detailed presentation, but I just had a question in terms of how you think about drop outs and how you think about the actual response between obesity because the time course of the

placebo effect. How did you come up with that increasing model in the face of the drop-outs that you had in the trials in which you were able to use the model?

DR. GOBBURU: Yeah.

DR. DAVIDIAN: Do you use, you know, modeling of the drop-out effect, and incorporate that into the statistical

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modeling to identify this relationship? How is that -- or is it more of something that's chosen -- funding or?

DR. GOBBURU: That's right. You see there are two parts of that -- at least two parts of that placebo model. The first one is the structural, which is the trend of the change in body weight over time. Now, being a clinical pharmacologist and, you know, having been with PKPD, we almost believe that most changes, biological changes, follow a certain process. Now, not to say that this has anything to do with the biological process of weight loss, but we use the loss model to describe the time course of body weight change.

Now, the very fact that we've shown you the drop outs are because of observed events, not because of unobserved events, so there is people who did not respond to the drug are the people who dropped out. So naturally, the trend in the body weight change over time is -- need not be -- you don't have to have a special drop out model when describing the structural model because you're saying that the model itself is taking care of the drop-out phenomenon. You're saying that if you keep going -- changing on the body weight, then you're dropping out. So that's an exception

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that we made in the model. So that's what it is.

DR. DAVIDIAN: Well, I was just wondering, you know, I mean you have data from folks who dropped out, and folks who didn't drop out. I was just wondering if this is a correct model for empirical studies, then similarly it took into account the drop outs according to the models that you have there. You should be able to cover that relationship.

DR. GOBBURU: That's exactly what I was telling you.

DR. DAVIDIAN: And I was just wondering if you actually tried that for an empirical model?

DR. GOBBURU: Okay. In this case, we did not. But you will see that specifically in the next case study, Parkinson's, we really did that. So what specifically we did was we had built the structural model, the variability component, as well as the drop-out model. Then we put all the pieces together to make sure that we can reproduce the time course of the disease progression and have slides on that, and you'll see that.

DR. DAVIDIAN: Yeah, I didn't want to get into that.

DR. GOBBURU: Yeah. No, but that was a good question and we need to take that.

DR. MANDEMA: This may come up later in regard to any

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of these models, but I imagine your thinking about also moving towards a little bit more mechanistic approach to some of these disease processes. For example, obesity, when you're measuring total body weight, body weight is a

function of caloric intake and metabolic utilization of calories.

So quantitating both either and both of those processes in addition to body weight would provide much more information, and then drug effects can act by virtue of drugs reducing appetite or reducing calorie intake or increasing energy utilization.

So we all know that if we eat too much or we don't exercise enough either condition results in someone being overweight. So it would be good to move towards what you described, plus adding these mechanistic elements to these kinds of disease process models.

DR. GOBBURU: Yeah, I agree with that -- that's a very good recommendation, so we would need some very rich trials early on -- where you can control the intake and even exercise, which is important; and understand the impact of those on the change in weight loss, because for these registration trials with thousands of patients having that

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kind of very detailed information might be challenging to procure.

DR. POWELL: The context of the Parkinson's disease model and the obesity model that Joga described are a bit different. The Parkinson's disease work has been going on, as they'll describe, for over a year; whereas, the obesity voices in the context of an end of phase 2A meeting, that information was extracted over a couple weeks, like three or four weeks, so that the level of rigor in developing the two pieces of information is a bit different.

The other thing about the obesity information is it's contextual in the sense -- to the extent of how the trial was designed. Those trials are generally designed with a diet and exercise so that the drug effect is layering on top of that. I mean you would expect -- people did what is in the trial. You would expect them to lose weight anyway, and the drug effect is on top of that. It's not just the drug versus placebo.

CHAIRMAN VENITZ: Any other questions? Okay. Then let's take our break. We are running a little bit behind, so let's reconvene at 10:45 a.m. Thank you, Joga.

[Recess.]

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DISEASE MODELS AT FDA: PARKINSON'S DISEASE

CHAIRMAN VENITZ: Okay. Our last speaker for today is Atul Bhattaram. Atul is going to tell us as we've already heard about before about a Parkinson's disease model-based approach. Atul.

DR. BHATTARAM: Thank you, Dr. Venitz, for your introduction.

Good morning, everybody. We have heard from three presenters, Dr. Bob Powell, Dr. Jaap Mandema, and Dr. Gobburu, about the ability of creative thinking and how integrating prior information can be useful in drug development.

But it's even more critical to really understand all the prior information if you're dealing with approval of a drug or understanding what do we need for something which

has never been done before.
As what was said by Dr. Powell earlier, there is no drug which has been approved for changing the progression of the Parkinson's disease.
So it's very important for us to understand what are the various components in this which are normally encountered in clinical trials in Parkinson's disease, and

how we can learn from the past experience in designing potentially trials which can show disease modifying benefit.

And as you can see in this slide, this work would not have been possible without the collaboration from the Office of Biostatistics, Dr. Hung, who will be presenting the findings from the clinical translations and will focus on where we are going next with this work.
Very briefly, I really want to acknowledge the following external and internal members who really contributed a lot. Clinical -- Dr. Stanley Fahn, the Parkinson's Study Group, and Dr. Karl Kieburtz and the NET-PD Steering Committee for giving us access to their study data.
And statistics -- Dr. David Oakes from the University of Rochester and Jordan Elm from the Medical University of South Carolina. Also Dr. -- also Arthur Watts, a programmer at the University of Rochester, who helped us in understanding all the aspects of the database.
And internal -- also there was a big group which really helped us to focus on this project -- Bob Temple, Dr. Russell Katz, Dr. John Feeney, Dr. Len Kapcala from the

Division of Neuropharmacological Drug Products; Dr. Jim Hung of the Biostatistics, and Dr. Mehul Mehta and Ramana Uppoor from the Office of Clinical Pharmacology; and, of course, our Pharmacometrics Group for their valuable additions.
As was briefly stated with Bob -- Dr. Bob Powell before -- the object of this part of the presentation is really to show how the application of disease models. As was mentioned, in the spring of 2007, there will be much greater discussion on the prior design and endpoints, where potential issues -- this is model's implication will be discussed.
I also want to mention here is that I slightly rearranged my slides compared to what you have; that is, bear with me and please do focus while I'm presenting on the screen.
So the impetus -- why did we really start this project? Drugs to slow the progression of disease, such as Parkinson's and Alzheimer's, are under development. And innovative trial designs, endpoints, and statistical analyses as using somewhat more model-based are being proposed to discern protective drug effect from symptomatic. And FDA is asked to comment on the acceptability of these

trial designs and pre-specified analyses.
So it's very critical to understand the disease baseline characteristics and what was shown in all the

presentations before. Disease progression that is the size and the variability of placebo drug effects and statistical issues as opposed to currently, which is the missing data.

So I will give you a brief overland of what we spent on this project and because that will really give you flavor of how things -- how we operated at the FDA on this project.

So it really started with a concept in January of 2005 where when a sponsor proposed an interesting methodology for validating one of their treatments.

And based on what was submitted with the sponsor, we are [inaudible] with the clinical and the statistical groups, and we came up with what do really know about this disease and why are these being proposed and what can learn about them here and before waiting for the results of the trials to come in.

So we are, in fact, that we really need to have good data to be collected. So we'll get the NDA, NDA sources of what we have in house, and we looked at and requested access

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to the data, and they were grateful in letting us access to the data. And we completed our data collection almost for about six trials by September of 2005.

And along, as we were planning and trying to execute this project, we are now requested to organize the session on drug development strategies for Parkinson's disease -- how the difference here -- protective and symptomatic effects at the American College of Clinical Pharmacology, where we had three speakers. One was a clinical doctor being delivered, followed by an imaging expert, Dr. Ken Maring [ph.], and Dr. Bodwell, the lead statistician.

So they shared their findings and we had discussions with them as to what are the potential problems they have seen so far.

And all these things went into -- we kept on updating our -- what we were trying to do, and we had our last meeting on August 2nd of 2006, where in general there was a buy in of the kind of approaches what we are doing and how we are going to address these problems, and so there was also considerable feedback. And we are working on it.

And so today, we are here in October to present some of our findings and the approaches what we used.

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And we hope that by the spring of 2007, when we are going to have the clinical and statistics meeting, we'll have a much clearer understanding of what are the expectations of the FDA for approving disease modeling models.

So we started first the project with identifying the key scientific questions, and the scientific questions were from the different groups -- clinical, biostatistics, and the clinical pharmacology group.

So naturally, the first question was what are the influential demographic factors influencing the baseline clinical response, the UPDRS in the progression. So UPDRS is actually -- it's a disease rating scale, which is used to follow the longitudinal course of Parkinson's disease. It's

made up of three components -- mentation, behavior, and mood -- attributes of daily living, and motor sections.

Then the next big item was how do we describe the progression of Parkinson's disease? Is it linear or is it non-linear.

And we did refer to the publications by Nick Holford [ph.] and others in the field where they published studies to get the feel of what we were really getting into. And

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third was exploring really we didn't understand why patients drop out of these trials, because that's helpful in really designing and also in understanding how the trials should really go on.

So this is the snapshot of the database that we collected, and, as you can see, we had data from three NDA sources and from two external sources. And I won't really mention here, but we are a combination of the latest trial presented. We had titration designs. We had fixed tool studies, and we also had information from another trial.

So and -- the graduations of -- of different durations. You can see there are four years follow-up to where nine months on year in the clinical trial, and we had one and a half years.

So we had about 2,000 patients in the longitudinal information on the UPDRS course, along with that baseline characteristics and drop out information.

So the first step in our project was to really characterize the patient population model, because we really wanted to -- we wanted to understand across different trials where the inclusion [ph.] with the baseline distributions of the various covariants influence which kind of potential

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influence the baseline UPDRS scores with this. So we did simple regression techniques, evaluating age, gender, disease duration; that's how long they have the disease; smoking and caffeine intake on the baseline scores.

And we found that age and disease duration -- disease duration were influencing the baseline UPDRS scores. And this is pretty much in line with what has been reported in other epidemiological studies, too.

And one of the reasons for us to do this is if later on in our -- when we are doing the drug effect models and then understanding the progression if some of these covariants are potentially important, we really have to include them at baseline to think about sort of heterogeneity in our simulated population.

So as I mentioned, the most important item was how do we really get the shape or you can call it a shape or a trend to the Parkinson's disease population.

I'm going to show you information from what is published in the literature, but we did a similar kind of analysis based on the mean effects as well as we look at individual time courses of events, because we had access to all the data.

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This is a trial which was done with Selegiline as -- showing the mean of the total UPDRS score with patients all

the way up to five years, and with the four weeks of washout base. Let's not focus too much on washout phase right now.

So as you can see here, first a certain time period here after the initial symptomatic effects, you can -- the mean effects can reasonably be served by a linear model.

The same as for another trial which was done with Levodopa and Pramilpexole, where you can again see symptomatic effects the trends are approximately linear, and this was for four years.

In this trial, just published in Neurology of 2006, they studied for up to one year creatinine-minocycline was in a regulated trial, and, as can we see, the placebo, minocycline, and creatine, the shape still falls the line of what is already done before.

So one of the reasons why we wanted to look at the different reasons in the literature to in-house is we wanted to make sure that similar kinds of trends are seen across drugs and also wanted to understand how different prior designs can influence the shape of the progression.

So we think that based on the evidence that we have

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seen a linear model can reasonably describe the UPDRS change post eight weeks. But it's also important that the time post service [ph.] needs to be understood well in early dose-binding studies. Typically, one can measure UPDRS scores every four to eight weeks, and you get the value of dose-binding studies.

So the next item which was very important to understand is the missing data mechanisms in these trials. So the way went about it is we first generated some graphical displays to understand the patterns actually of these drugs. So this is, for example, we -- when patients are roughly let's say 0 to 16 weeks versus 16 to 32 weeks, and then we looked at how are they being produced in these groups of patients.

And consistently, you'll see in the patients who discontinued earlier had worse symptoms compared to those who stayed in the trial, and this is also -- is present in the -- in various literature sources that patients who discontinue have in general higher UPDRS as compared to those who remain in the trial.

So naturally, the question is what is the specific risk factor for drop-outs and is there any way that we can

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burden some form of a quantitative thinking.

So we thought let's attempt to do some parametric hazard models and we looked at all the trials for what we had, and this time we -- we were looking -- interested in looking at three important covariants, which I'll show you pictorially what I really mean by that. That is, we asked the question is the change in UPDRS scores in the last office visit, what is important? Is it related to the baseline or is it related to the previous visit?

Our reason for doing -- is it related to the rate of change between the first and the last office visit? That's kind of its slope.

So if you see at this for a hypothetical subject what

I'm showing here, but these are the kinds of things you will see the real data to look at individual profiles.

So if you look at the change from baseline UPDRS for those times, let's say for at 24-week study, and this patient here at 40 weeks tends to drop out of the trial, because it's the same doctor has not been -- and it's a mutual between the physician and the patient that the drug is not offering him benefit, so they decided to take him off and put him on some gold standard treatment.

So naturally what we are saying on this end is what has been related to drop here. So the first question what we asked was is the probability of drop-out related to the change in scores from the baseline visit? That is sort of duration I just quoted. It's just an average. So that means he spent 20 weeks in the trial and his change from baseline is more -- so you could deviate by 20. That's sort of a duration I just said, so is that important?

Or is it really how he was doing before, two weeks before, and what is the score that really changed him. So here's change by six weeks, about six units, and about two weeks, and you really see those kinds of trends in some other patients.

Or can we really put some sort of -- we can get this number from linear fixed models and see whether he's a candidate to spend the probability of trouble.

In addition to these three covariates, which are related to the UPDRS score, but we also looked at the other covariants like -- related to demographics like age, how long they were on the -- how long they had the disease, et cetera.

And in order to qualify our models to a better model

we are trying to -- using statistical methods, can it really reproduce our data. So this is -- I'm just showing you one graph where you can see a very clear drop out pattern -- this is under certain assumptions, so you can really see that my model systemically deviates from the observed. This is just to show you pictorially how we are going stepwise in model assumptions we can use.

We then looked at another trial, which was a drug unrelated to the previous one, and really understood what is making people to dropping those trials, by using certain combination of parameters and assumptions.

And reasonably our simulations varied from the observed pattern, which you see here. So to summarize, the predominant reason for drop-out in these trials is worsening of symptoms that depend on the duration of the trial and how good are your drugs.

But based on some of the initial statistical analysis, we see that the duration is just a change in rate of change in UPDRS scores from the visit are -- for this fluctuation.

But we are not stopping there. We also want to ensure that our model adequately predicts the discontinuation rates well across varied drug designs; that is, fixed versus

titration dosing, and we have some reasonable ideas as to

why -- what kind of an effect size will be observed in a certain person with a problem, so we are still sort of confirming it with other datasets.

So, so far, in my presentation, you have really seen the two models here. One is the key portions that we identified based on our discussions with the clinical biostatistics and the clinical pharmacology group, and then the second step is we extracted the clinical trial information, where we looked at the baseline of a model, the placebo models, understanding the drop-out models, and understanding the drop-outs, and also their designs; that is, fixed dose, titration designs -- what really happens. What is the progression of them, and importantly the patient demographics across these trials?

This is -- now Dr. Siddiqui will show you how we integrated this information to simulate trial designs in various scenarios.

CHAIRMAN VENITZ: You're going to be introduced. Dr. Siddiqui he is a reviewer in the Office of Biostatistics.

DR. SIDDIQUI: Good morning. I'm going to chat with you about this -- how the baseline data has become important

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for [inaudible] the progress of disease at the baseline as well as the progression of the disease. I'm here to discuss how the drop-out, the more of the drop-out progression, what is the probability of -- and why they are dropped out. That is, those are -- the similarity is the higher -- and they are both likely to drop out -- that is from the in-house data.

Now, I'm sharing with you three key questions: Does a linear model -- a linear disease progression model can be applied to model the progression of the disease? The second question is what is the reasonable trial design and endpoint? And how do we integrate the clinical pharmacology findings and statistical findings to address the regulatory issues? That's the first question.

So the longitudinal -- here in Atul's presentation you saw that if the drug has a symptomatic effect, that it showed up in eight weeks, and after that the progression is going on. So, and after eight weeks, the progression seems to be linear, and it's supported by the published data as well as the in-house data. And these are so since it is -- it is approximately linear after four to eight weeks randomization, so we can model -- to model the progression

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of the disease.

So together, we applied the -- monitor whatever the progression this seems to -- and observed and with the progression we can render some judgments.

Also we get some other exploratory on how the model -- what the guidance -- and if we take this longitudinal model that -- is close to the observed, so that confirms that the model, the linear model, is a good candidate to generalize what the progression of the disease is.

We have seen simulation differences, so here what we are trying to do is that in-house data where on particular trial is the distribution of the UPDRS score -- and so we

are trying to get the information from this real data, this like mean vector of variance -- and the information we are trying to -- simulated that, and after simulating the data, you see that the distribution of UPDRS scores and all the data is -- so if confirms for us that, yes, we are applying the real characteristics in the simulated data.

So, again, now what are the trial-to-trial -- is it possible trial to -- symptomatic effect often to -- that is -- as symptomatic effect issue. After that is progression of disease is going the same significance of the symptomatic

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effect, but in symptomatic trials, many -- and -- so -- is different from the -- and you are -- but we don't know how this -- to the symptomatic, and what happens -- but there are lot of -- these are the cases -- it is impossible to differentiate the projected effect.

So -- develop the drug for the protective effect of Parkinson's disease, and the -- it has two parts -- the placebo phase and the active phase. In the placebo phase, the patients are -- and -- that -- and we can see this is active phase -- we can say this is late starter group, and so this is a late starter group. This is an early starter group, so they started from here.

So in many -- even if they're so, the difference between these two are -- significantly -- then we can say that the -- some protective effect on the drug. But this is a -- this is a longitudinal trial, that will be missing that. This type of trials there are -- so and -- regular -- we need the statistical analysis based on ITT, intend to treat analysis, that means for all the randomized version's information here. So the main question is how we refute the -- can we get it over to him here. And if the data score is here? No, because he's already getting the placebo phase,

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placebo drug under the placebo and here is the drug. So it's not possible to refute directly.

Now, we are exploring one possibility is that we can do some slope phase analyses in the place of this. We can compare that slopes are understood -- the slopes are different and not in the rest of the phase. If the slopes are different, then that means the paths are not parallel; that just indicates that it's not evidence of protective effect. To reconfirm this, we can analyze here the available case and compare the mean, the difference, on the available persons, and but we are planning to think that this will be our primary support, and here in this analysis, we are -- models -- so all the ITT core samples are included, so it ITT analyzed.

So let's summarize what we are trying to do. We are trying to export that -- or whether it is possible to compare the slope difference between the placebo and drug group at the placebo phase, and then in active phase, we compare the -- the mean difference between the early starter versus available, early starter versus late starter at the endpoint.

So we did some simulations based on this under -- that

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the drug has for symptomatic effects; this is just symptomatic effect, no protective effect.

So I will show you what is -- what I mean by -- level. Now, if you give 500 persons, two groups, one to randomize and one to one; 72 weeks plus 26 weeks is phase, then the active phase, and we also consider -- and we also consider in simulation different drop-out scenarios -- equal drop-out between two groups. So what do mean by this knowledge? Here you see that there is no difference between the area under the late starter and early starter. That is the -- but there is a symptomatic reversal, here separated, so that is the product symptomatic effect -- no -- so simulation is -- we are interested to -- so the drop-out scenario is drop-out not related to drug or disease. That means statistically we see it completely at random, and drop-out due to -- so what our thinking is that in the placebo phase the slope analysis you see that at least drop-out scenario with control type -- however, in active phase, since we are mainly interested in the end of the active phase and often people propose that instead of YTT, you can analyze available -- instead of -- how you see that -- except the fast scenario -- and also recently I reviewed two NDAs -- to

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analyze ITT at the endpoint of the active phase, but -- if you see that the how is -- has already been started.

So this simulation, simple simulation, it confirms that if we analyze in the -- analyzes the -- it controls the rate.

So this work -- we realize that -- we need to understand the demographics of the patients, time scores of the disease -- and this work -- it is not possible to understand completely by individual areas like, either pharmacologists or either by statisticians, so joint work is important here, and collaborative work, and this is the work -- in the morning, you heard about the collaborative -- the importance of collaborating work and this is the one impetus of the importance. Thank you.

CHAIRMAN VENITZ: Thank you. Any questions for Atul?

DR. MANDEMA: Thank you for a very nice presentation. I'm glad you showed that nation selection along the way in the trial could lead to a type one error, and I do agree with that.

I do agree with your assumption that it's preserved in the placebo phase basically because that was your assumption

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you put in, the way you analyzed the data or the simulations you set up assumes that the linear trend was the trend that everybody is on. So, yes, you will get a preserved error rate in that phase because that's what you simulated. But at least you can that the delayed start design gives problems with it.

DR. SIDDIQUI: So, yes, in the placebo phase, that is symptomatic effect, but the protective effect is -- effect. So the simulations performed this, and you are analyzing this in the placebo phase. If you took up a different slope, then there will be -- the two have different

significant stroke, then there will be within subjective effect and the endpoint. So we are thinking that it's one to one correspondence so the net mean product here we can get this so we can analyze this -- available at the -- and to we confronted how that is to -- is finding it in the evidence of the protective effect, we analyzed the available rates of the endpoint.

DR. MANDEMA: No, no, I understand what you did, and you showed that patient selection along the way and due to drop-out will impact the active phase comparison and will lead to a biased conclusion at that point.

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But during the placebo phase, obviously your model is assuming a certain linear trend that you simulate on, and there the error rate should be exactly what you put in if your sample size is big enough due to your simulations, because that's specifically what you put in. There's no difference in slope, and there's no mechanism to be able to deviate from that in your simulations, so you should pick up the exact error rate if you should do your test.

DR. SIDDIQUI: Not necessarily. If the -- up until now, we are saying that I simulate this slope because zero, so that will be reflected. But I applied here a different type of missing data mechanism, so if the missing data mechanism would affect it differently, it might be not the type for another rate.

DR. MANDEMA: Well, if it's linear and the drop-out is not happening all very soon, it should be pretty accurate.

DR. SIDDIQUI: No. We're here about 45 percent or above.

DR. MANDEMA: I know. But if it's a linear slope. Of course, your ability to distinguish is whether you can actually estimate that slope good enough with the data that you have early on, because you're projecting those patients

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go on and that's the trajectory in your analysis. So if you have enough data, then it should be very well protected.

But I think it's just a minor point to show, but the important part is it's probably better to compare in that early phase than in the late phase, because the late phase definitely could give you problems.

That brings up just as one more question, how do you distinguish between a drug that's truly protective and a drug that just has a slow onset of action, because both may impact the slope of that relationship?

DR. BHATTARAM: Yeah, that's -- we had a discussion on that conduct what you are talking. We have a drug which has got a very slow onset of action. What we think -- although we have not seen any drug so far which has such a slow onset of action, but we think that when you do this -- the analysis in the active phase, and do the analysis -- you can do the analysis at each time point and see if it becomes a crossing regional, and we're also looking at putting some sort of margin for ensuring that the slopes are at least part of the region. So those kinds of metrics we're putting in just to make sure we don't have goals, which are trying to -- work at some point. So we will be looking at those

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kinds of things.
DR. GOBBURU: Yeah, just on the previous point that Dr. Bhattaram pointed out. Yes, you can argue that if you use this same model to simulate and analyze the data, you're going to get expected theoretical decisions, but I would encourage you to keep in mind that this is not -- the model is not just out of the blue, but it is based upon data substantiated by qualification, and so there is a basis for using that model, and, yes, sure, and as Dr. Siddiqui pointed out, which I completely agree with, the point was to also perturb the system from what we observed in the trials to see what happens under different scenarios, if that falls apart.
DR. JUSKO: These graphs that you show have a placebo having a slope starting at 0 at time 0. Some of the profiles that I've seen plus one of them shown by Bob Powell, slide 20, shows that there's a pronounced placebo effect. It looks just like your drug curve.
Do you have more data? Is your analysis accounting for changes in both slope as well as intercept or some early part of the curve?
DR. BHATTARAM: Yes, I can address that. Actually,
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the curve that was shown by Dr. Powell, filling into this curve, it's actually not placebo versus those patients that were on Levodopamine. It's added on. We see the placebo added on to Levodopamine. Selegiline added on to Levodopamine. So that is the reason why you see this curve, and the other question whether -- we also looked at in placebo groups what kind of effects you really do also, and we empirically estimated that when we included them in the solutions. So, you know, simulations of placebos just don't start at the 0 point. They have some very minor, but the effect is very real.
DR. DAVIDIAN: I'm going to repeat my question from the last round. So, as you progressed through this first, you talked about developing the model, which appears thoroughly a totally empirically model, a straight line model for change, and then you talked about drop-out and undoubtedly the trials on which you base your disease model had drop-outs. So I was just wondering how you developed the model in the face of that drop-out? Did you use drop-out modeling there as well?
DR. SIDDIQUI: Okay. This Parkinson's -- we have up to last observed if your UPDRS score was higher from here to
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there, presented higher -- that means an absolute that is by definition that's using a -- and this situation is true that we used the likelihood based analysis. Likelihood based analysis has two parts. One is the -- another part is the -- so when we can estimate the parameter, and up to this part -- so that takes care of this, but if it is not reaching up at random, then yes.
DR. DAVIDIAN: Well, my thing is this analysis will work as long as the assumptions that you're relying on the graphs.

DR. SIDDIQUI: Yes.
DR. DAVIDIAN: In terms of whatever you normally distributed and so on. So I was just wondering have you looked at possible deviations from that?
DR. SIDDIQUI: Yes. We are aware of those.
DR. DAVIDIAN: Then that's okay.
DR. SIDDIQUI: Yes, we are definitely aware.
DR. DAVIDIAN: Just a follow-up question, too. Drop-outs from toxicity. I mean you obviously have information on who drops out. What's the rate on that?
DR. BHATTARAM: Yeah, actually, I'll briefly mention about the three scenarios of what we chose for simulation or

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the basis.
The first one where you saw that there were equal drop outs in placebo and treatment groups. That was from one group that we saw the placebo effect [ph.]. The second one was where we saw very less drop outs in the treatment compared to placebo. One of the drugs was Levodopa, and that's the case. And the third one we looked at was where in the creatinine trial, we observed in the creatinine level, a 30 percent drop outs in the observed.
So we thought let's also integrate that into our simulations and see really in this design how it happens, because if it -- because the interesting part you have these two pieces. If patients drop out due to -- in the treatment arm, then the people who switch from the placebo to the treatment also have to be dropping out due to this. So how do these contrast to the overall simulation?
DR. O'NEIL: Yeah, I just wanted to follow up on what Marie Davidian has been pushing a point on. The whole issue of missing data in clinical trials is critical to virtually every area that we're dealing with at the NDA; right? It's a deal breaker in many situations because it's not clear whether the information on the individuals who have left the

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trial or left exposure is informative or not and the statistical methods that are available to handle this problem depend upon the assumptions of whether what you haven't seen yet is informative, and there may be, in fact, a need for some design changes here, and I -- we're asking for your general advice in a number of areas.
First of all, as Bob Powell indicated, there is no product that has a disease modifying claim yet, and one of the reasons is just think about what kind of study design you would need that would allow you to say there's been a permanent change in something, and it lasts for a while. And this is hard to do in chronic progressing diseases, where you have to follow individuals for a reasonable amount of time, and you also know that if you follow them for a reasonable amount of time and you also know that if you follow them for a reasonable amount of time, they may or may not stay on exposure, so how do you take both of those guys into account at the same time, because we deal with this problem in just your vanilla version symptomatic trial where there is withdrawal. So there's two things going on here: one is trying to put a lot of emphasis on shape of what's

progressing over time. The other issue is how do you deal with that in the face of individuals who are withdrawing from exposure either because of toxicity or lack of effect or aggravation -- I've been in this trial for six months. I'm out of here. It's not that I'm -- I just don't like coming in anymore.

So the issue is what kind of changes in the protocol have to be implemented. Let's say a different informed consent saying this is going to be a two-year trial. We understand you may not hang around for two years. What would it be that would likely cause you to leave? And if you leave, meaning that you don't like to be on the assigned treatment anymore, will you allow us to measure you after you go off of that, because we want to measure everybody for two years. Do you agree to that at the entrance? Because if you don't have that in place, you're dead in the water with all these assumptions.

So we're talking about a major culture change in how a lot of trials are actually carried out. We do not, in most symptomatic trials, measure someone after they have withdrawn from exposure. The intent to treat philosophy says you sign up for a one-year trial. You measure outcomes on everybody at one year, and that can be done on mortality trials or where you can actually get the outcome.

Where you have repeated measures longitudinally progressing people where they're not giving you information at some point later on in the trial, that's a different kind of an issue, and that's what Marie has been hitting on.

And we don't expect a magic answer on this, but I can tell you that we need to be making some major changes in how we address, both from a design and analysis, what kind of diagnostics are needed. I think Joga indicates that the empirical data that is behind this model is pretty impressive -- four or five or six or seven studies that repetitively have shown the same progression. But as Jaap pointed out, it's not clear whether everyone has a random slope and a random intercept, meaning if you and I have a different onset of where start, our curves start to go up, then that needs to be taken into the model.

Your comment about everybody -- the typical clinical trial because of the highlight effect is you come into the trial and everybody drops down right away. That's because everybody is being monitored, and then that's not a placebo effect. That's a design effect. That's essentially because you're in a clinical trial.

After you get by that -- and so that's why this linearity is not being modeled from time zero in a clinical trial. It's being from -- it's being modeled from what is assumed to be some delay of let's say four weeks, after which everybody has gone through their highlight effect, and now they're on some progression, and it looks like it's linear.

And as you state, these are all very model-dependent, but they're empirically based upon how much weight do you

want to put in all of these six or seven trials in the past.

So where FDA is is a sponsor is coming in and essentially asking for a handshake, and they're saying we have this design, with this support a disease modifying claim; and that's the point where we are as a society. That's the point where we are in these drugs, and that's why we're sort of raising this, and there's sort of the modeling and simulation as a quantitative approach to address whether this disease model claim is doable in any sense, so I think that's behind the kinds of questions that we're asking you, and the missing data mechanism is really probably the deal breaker here in terms of whether you can believe that the

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people who hang around are the same as the people who don't hang around and whether their paths follow the same, and that's why all this effort has gone into this. And we're trying to, you know, get you as a sounding board as to whether this makes any sense at all.

DR. BARRETT: Yeah, I really appreciate your presentation on the topic, and as I was listening to this, what was in my mind was when you started out; you listed the trials that were part of your database. I'm sure there were probably additional trials that you could have chosen to be part of this as well, so you really can't decompose the model from the data, from the design using those trials. They're all part of the signature of information that went into this.

What I think you're highlighting is the fundamental problem that would be true of any study moving forward. I think the question for me and probably others is, you know, how generalizable is -- do you think this will be for, again, these new class of agents that could potentially have this disease modeling claim. I think I mean it really underscores the relevance of what you're doing, but I'm thinking as I see or hear the dialogue, too, the designs

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that would be potentially studied in the future may have to be very different than those that have been studied as part of your historical data, so I'm seeing some elements of what you're doing that would absolutely be portable and others that may not be.

Do you have a sense of that?

DR. BHATTARAM: Yeah, actually, we only have experience from one study -- that's the delayed studies. And given that more and more sponsors are proposing those kinds of designs, our main aim is to -- for this particular design what are the likely problems that one can encounter and what are the statistical issues that's worked, and how this can be magnified at this level. So that's our aim.

We do agree that there are -- there could be alternative designs which can be done, but this is one of the designs that we are currently working on to solve the issue.

And if I may just comment on the -- one more aspect is that in our simulations, it's not that everybody gets to the maximum event only by eight weeks, so we have a random

component, so people can go -- we have a certain degree of variable dose, and then we are -- so when we are testing

what happens if you cut everybody at eights weeks onwards, that will also help you to evaluate the effect of that parameter. If somebody gets to the maximum benefit with 16 weeks, and how does it affect your whole -- that's what's being developed.

DR. MANDEMA: Thanks, and ask one more question. Now, don't get me wrong with my earlier comments. I think what you're doing is very insightful in how to understand changes of disease over time.

What would be really good for me to look at is are those slope estimates that you get to across these trials are they very similar or are they quite different? You haven't shown a particular component of that. Was your analysis based on just on one trial you highlighted or was it based on a joint analysis of all the trials, and if it was a joint analysis, did you allow for random differences between trial in the intercepts and slopes that could occur?

DR. SIDDIQUI: One is -- and the other are parallel groups.

DR. MANDEMA: No, I mean the slope with time, not the difference between treated and placebo.

DR. BHATTARAM: Yeah, I can answer it. Actually, the way we did was we analyzed these trial individuals, and then we looked at the rates of progression in the placebo group just to make sure the trials which have been done earlier or the trials which have been done now has anything changed with background which can impact the progression.

So across what we have seen is that the placebo -- progression in the placebo groups are pretty much similar. And the second is we also looked at the progression within for each drug also, but we haven't shown the effect sizes. But we did do each individual -- I mean the analysis was done at each trial level, and not combined.

DR. MANDEMA: So it would be very good to show the distribution of slopes across these trials. That would be very helpful in continuing that -- our understanding of the validity of the disease progression models.

DR. GOBBURU: Two comments -- actually one is, you know, Dr. Bhattaram has already spoken to -- this is about the question about the assumption that it's linear, and then you use that to simulate, of course, you're going to get 85 percent, but, as he pointed out, there is this component of non-linearity and variability on where patients have this

inflection to progress, so it does, in my opinion still account for any model re-specification, if any, between linear and non-linear. That was the first comment.

The second is to throw out the description of the drop-out models and model your qualification validation. Dr. Davidian, would you agree that given the model for the progression of the score over time, the structural component, and the variability has left the drop-out model

from the parameters of this model -- and you put them together and you reproduce the data across the six trials, would that be a reasonable validation tool to feel comfortable that the model is performing reasonably well.

DR. DAVIDIAN: Well, it would certainly help. I mean I think as Bob pointed out, okay, you can never tell if you've got an importance to drop out, because you don't get the data that you don't get if you don't have responses after drop out, you have no way of knowing the drop out depends on this response, but you can never validate that assumption.

DR. SIDDIQUI: In this case, it is slightly different, because, although people discontinued -- I mean as Dr. O'Neil used the word -- discontinued exposure, they still

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got UPDRS measurements in each patient.

DR. DAVIDIAN: Okay. That wasn't clear. I mean that was one of my questions.

DR. SIDDIQUI: Yeah.

DR. DAVIDIAN: Okay. So if you have data like that, then that certainly helps a lot.

DR. SIDDIQUI: Yeah. So that is -- there is --

DR. DAVIDIAN: Yeah. And what you've done I think, you know I don't want to sound negative here, because I'm actually very supportive of such a plan. I think it's wonderful, and it makes great sense. And I think the more you can do to look at can you stress your models to see how differently things would turn out, the better, you know, so that you gain an understanding of the extent to which this whole exercise is going to be useful.

CHAIRMAN VENITZ: Bill?

DR. JUSKO: When you use the linear models, the expectation is that the score can continue in a linear manner, is there an upper limit to the score that can be achieved in these patients so that if there is, does the linear model respect that type of upper limit?

DR. BHATTARAM: Yes. Actually, the upper limit of the

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scores is 199, but none of the patients really go to that level, and we haven't seen anybody going up there, the real thresholds. People go from 70 or 80.

OPEN PUBLIC HEARING

CHAIRMAN VENITZ: Any other questions? Then I want to thank both of our speakers. And our next order of business includes the open public hearing. We have nobody signed up, but I want to make sure that anybody in the audience that wishes to speak.

You need to read something before you can start. So I think that it's the sense that we should not give him -- or asked to disclose any potential conflicts.

DR. PECK: Right. My name is Carl Peck [ph.]. I'm an adjunct professor at the University of California at San Francisco, the Center for Drug Development Science. I participate in a consulting I founded in the partners, and I work with John Burkhart in a company called Arnex.

I first of all want to congratulate the FDA and this advisory committee for these two days of remarkably

cutting-edge discussions on the application of advances in clinical pharmacology in drug regulation and drug development, and so for Larry Lesko, Bob Powell, Joga Gobburu and all of you.

What I want to say briefly was it's also I believe great that you are attending now to trial design issues that would seem to improve the interpretation and maximize the learning with respect to deviations from the protocol, seeking, of course, also information on the actual trajectory of the response. And you focused on a major observable deviation from the protocol and that is drop outs. Of course, protocols are violated all the time, but another major source of protocol violation is deviation from the assigned medication regimen.

And just as drop outs can be observed and documented, it's now possible to document reasonably using the date and time -- it's now an electronic form -- the extent to which patients actually adhere to the assigned drug regimen.

So my challenge to you is to -- is the question is that another protocol deviation that you're interested in developing techniques for minimizing bias or maximizing outcomes for trials where that kind of data were captured?

CHAIRMAN VENITZ: Thank you. Anybody else in the audience that wishes to speak?

ADVISORY SUBCOMMITTEE DISCUSSION AND RECOMMENDATIONS

CHAIRMAN VENITZ: That concludes our open hearing, and I think we're now moving to the deliberation part of our meeting that goes to questions for the Committee so we can -- or whoever has the slide?

Okay. So let's go step by step. Let's discuss each question, and I'm going to try to summarize the Committee's sense.

So the first question that we're asked to discuss is the overall approach to modifying various parts of disease models reasonable? David?

DR. D'ARGENIO: First, I'll start off by echoing the comments of several others about the importance of this work and obviously the FDA is in an unique position to do some of this and make these contributions.

Just a couple of specific comments about the first point, and maybe then some general comments.

Perhaps the biggest impact of all the work that heard presented today and related work would certainly be in developing models for placebo and drop-out. We're absolutely in the best position to do that, and it's going to have the biggest impact on I suspect sponsors who want to use these models as they consider trial design issues that would have a dramatic effect.

One of the more difficult parts of this whole modeling cycle that Bob put on another slide is the disease modeling part or the building the disease model, and most of the models that we've seen and others that I've seen have been obviously extremely empirical, and that's a clear limitation of going forward. Now, that's the hardest thing, and I

don't expect the folks here to be able to really do that, but that's a very important, and Bob mentioned the analogy with the use of modeling and simulation in other areas, in particular engineering and design of physical systems.

When you look at the successes of modeling and simulation and adhering to physical systems, and you look at the models, you find very few empirical models or equations of convenience, and we have to use all the time.

And that's what makes those -- and one of the reasons that makes those very successful, for example, in evaluating aircraft now we do very few wind tunnel testings. That's just not done anymore as it used to be. That experimental approach has been replaced by computational fluid dynamics. Now, those are models that have assumptions in them. There's no question about that, but they have very few of

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these equations of convenience that we unfortunately we have to use.

And that's the biggest difficulty that we'll be using in modeling and simulation in the whole schema that Bob presented, the disease modeling part. It's not hopeless, though, and there are people who are developing, for example, in models of insulation action that include insulin signaling and look at the effect of insulin on glucose transporters. Those signal transduction models are available. People are using those to take a look at the effects of lipidphosphotases as drug targets and while you folks can't really perhaps focus on those, but as you develop these models for these particular applications, it's useful to cite what's out there in that regard so others can do that.

One thing that's also been missing a bit -- we talked about it -- it's validation. I haven't seen a lot of focus on the validation of these models that even placebo and drop-out, and that's got to be integrate in what we're doing here.

And some general comments -- while we've been presented with several examples that really illustrate the

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possibilities here and some concrete examples, what was missing is kind of a systematic schema for how you're proposing in the agency to go about this process in the future, and I know you're at the beginning stages here, and you can develop that after you get input from these specific examples. But I think that's going to be very important, and in a sense a flowchart as to, you know, how you're going to develop these various models, how you're going to mine the data, all the things that you've discussed, but it's got to be put together in a framework and associated with that is how you're organized to do it.

And that's probably more issues than just question number one, but I think they'll come back again and again in the other questions.

DR. POWELL: David, you raised excellent points. Let me respond to a couple of them.

With regard to mechanistic models or empirical models, I'm reminded of an English phrase, "horses for horses," and

that I think mechanistic models, in other words, the models have to be set up according to what the use is going to be, and the mechanistic models I think are primarily useful at this point in time in the discovery and R&D process.

I mean if you -- so FDA's decision-centric point at -- based on clinical data, and I believe that our models really have to be burdened and what the primary endpoints are.

And then mechanistic models start from biology and move forward. At the FDA, we have to start with what the primary endpoints are, and then move backwards.

So you would imagine over time that they ought to be able to delay it. We have used mechanistic models. I think with HIV it's available, and I think Bill Jusko's model is kind of like this somewhat I guess.

Okay. With regard to validation, the tools speak to that. I think there was some qualifications.

In terms of future, to my knowledge, I think Carl some years ago convened some people to look at best practices and modeling and simulation. What we're talking about doing is in the next year or some time reconvene some experts on this so we can -- I'm not sure whether it's best practices or good practices, but I agree with you that we have to -- and if we're going to be doing this more systematically than within the FDA, we need to understand how we're going to broaden this, but also be able to speak to sponsors so that people understand what we expect as they bring, for example,

for an end of phase 2A meeting their justification on what the trial is that they're going to use.

DR. BARRETT: I had a similar comment to Dr. D'Argenio about just being able to answer that first question, but let me follow up on some points that you made, Bob, too. And these really stem from -- and Joga had mentioned this in terms of the need what do we call this disease progression model. Maybe that's where some of the problem lies, because I think if you set out the objectives and you laid this out -- and I think nicely, Bob -- you're really focusing in on this -- I see this as more of a decision support system around the critical decisions that are made in a late stage clinical development. It benefits from all the prior knowledge from preceding stages and from data that's on the marketplace, either from related compounds, but it is obviously very specific to the underlying data that's a part of it. But the disease piece of this I think this could be an essential element in that disease progression model that maybe had the benefit of more longitudinal epidemiologic data, so I think there's value in being able to look and marry that up. And in cases where you can do that, I think you really should plan for it. So because of that, because

disease as we're calling it for this decision support system is very much dependent on how these diseases or indications are studied.

And you rightly focused this on you know there is an attempt to align these models with what is the current basis for an improvement. What I saw from the Parkinson's disease

model is maybe this interface where things are changing potentially in this therapeutic area, where you have a lot of historical data that forms the basis of this model and allows you to answer or ask targeted questions, but the assumptions that are tied to it are also tied to that data. There's an element of it that's true just because we're evaluating patients who, over a long period of time, and the issue of drop outs is fundamental to that kind of study. So there's value I think in the portability of that.

My concern is really the issue of generalizability when you have a new mechanism of action or you would like to be able to make some extrapolations beyond this clinical evaluation period. I think if you lay out the objectives, and this is a tool to do clinical trial simulation effect then we could do the most informative trials, then it's all I think in the right vein. But extrapolating beyond that to

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really talk about disease progression or performance on the marketplace that's a little bit more dicey, and I think really requires those kind of bridges to built.

And keep in mind, you know, you have the pooling criteria. I think that's what I was looking for when I -- if I was able to make an assessment of approach, I would like to see what your thoughts are about the data that you allow to form the basis of these models, you know, and really see, as David suggested, what is this kind of decision tree or flow charting maybe of disease progression model for lack of a better word.

DR. O'NEIL: Yeah. I think the last two comments that both of you gave are really right on target, and, you know, how do you put a more systematic approach on top of this whole thing. And we're pressured on that by the industry and by others, and the critical path document that went out a few years ago sort of said we know that there are some obstacles to the success rate of clinical trials these days, and we think we can put our finger on a few things that we can fix, one of which is providing some more systematic guidance in certain areas. So we're sort of committed, for better or for worse, to three or four documents that we're

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supposed to put out over the next year, and embedded in those documents is a lot of what we're talking about here.

This is -- modeling and simulation is 2006 modern protocol planning, if anything else. I mean if you don't think about it this way, you're back in the 1960s. You're just not -- you're not using prior data. You're not using epidemiology. You're not -- and its' the deal breaker. I mean I think clinical trials have gotten off in a very amateur way for a long time because they haven't had a system and a science behind it that is actually sort of -- and so now what we're faced with is a series of tell me how to do it better, and these are guidances. So at least from the biostatistics perspective, we're committed to developing a guidance on missing data, which is going to include all of this, and this is bigger than us. This is the whole community -- the academic community, the pharmaceutical community, the clinical trial culture community. A lot of

people have to buy into this.
In fact, we had a discussion with the National Science -- National Academy of Sciences about two months ago about how would we like to do a big study for you guys to help out in this area. Well, if we have the funds, we might be able

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to do that. But this is a big-time issue. And it probably needs to be done in conjunction with the Institute of Medicine and other folks in play.
So that's just dealing with missing data and the whole and clinical trials and how does this disease modeling issue get embedded in that whole thing.
The next thing we're committed to is doing a guidance on non-inferiority trials. Now, if there's any area where you wan to make sure that you have repeated information on the effect size in clinical trials -- everybody is talking about I'd like to see this slope from these five different trials presented. That problem is in spades in a sponsor coming into to us and saying I want to do a non-inferiority trial, because I can't justify do ethically a placebo control trial. But in order to do that, you have to look to historical data and look for all the clinical trials on the active control that you're going to use in a current, and you need to essentially establish that you have a repeatable effect size that you can count on because you're going to use that effect size in your current study to be able to indirectly infer that you have efficacy on the new product that you're testing.

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And so, so much goes into those assumptions. You have to make sure that the conduct of your current study is the same as your past studies. You have to assure that the patient population is the same in your current study, as it was in the past. You have to assure that you have built into your margin the study to study variability because you don't know which one you're going to be dealt with in this time.
So all of those concepts that Jaap was talking about have to be embedded in this non-inferiority guidance that we have to put out, because it's very much providing guidance of how do you quantify the effect that you're going to be able to use in your active control trial.
So that's one other thing that's going on. And so I say this in terms of there's pieces of this general problem embedded in at least three or four things that we're being asked to do to bring some order to the system -- the non-inferiority, the missing data. There's another area of adaptive designs going on, and the other guidance is multiple endpoints, because what has not received very much attention is why did you choose these two endpoints as the endpoints to characterize the effect of the disease? And so

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if you are fuzzy on that, where in essence you say, well, I can't characterize the disease by one endpoint. I need to put two or three in there.
So if you're talking about Alzheimer's disease, traditionally, the Alzheimer's disease has been a joint

bivariate endpoint, a clinical global evaluation on whether that patient has had a benefit, as well as some objective scoring data that is at the patient level, we may be getting into MRI stuff in the future or whatever, but the more endpoints you throw onto the win criteria, the more you challenge the system in terms of whether you're going to be able to make that.

And so the industry is very interested in how do we provide guidance to sponsors on multiple endpoints, and up until about three or four years ago, this has not been on anyone's radar screen. They'll throw primary endpoints on the pile. They'll throw secondary endpoints on the pile. There won't be any pre-specified thinking about what's the win criteria. What is the win criteria in terms of how this has to play out?

If X goes in this direction, doesn't Y have to go in this direction? Can I win on either X or Y? Do I need both

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of them together? Do I need X and Y and any one of A, B, and C. And that's essentially the criteria in arthritis right now in terms of how a win criteria.

So what's different about the example that you've been shown is that the win criteria is on the model itself, not on the endpoint. It's essentially on the model and whether the model is correct in terms of the slopes, essentially establishing disease progression or not, the intercepts and what not, and that's a little different wrinkle than the endpoints that have traditionally been used which are essentially endpoint or time specific at the end of the trial, not the shape of the trial, not the shape of the progression, but where you are at the end.

So just summarizing, we are on the fence in terms of delivering publicly, to bring some order to, through guidances that will have public comment before they're vetted and finalized in missing data, multiple endpoints, non-inferiority trials, and sort of the modeling and simulation is really embedded in all of these. And so we're at a very critical stage here I think, where quantification is now being appreciated in having to be the bedrock for any planning because if you don't have the planning right, you

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can't do the inference. You can't do the conclusion part of it. And it's really at this stage of where we need to be in terms of modern decision making and using all the data and everything else.

So that's what I felt was critical with this set of presentations sort of giving some flavor for what we are meaning. Everyone has heard all this buzzwords about modeling and simulation and -- but I think what you're getting is an appreciation for the level of planning that has to go on behind the scenes, including bringing the epidemiology to the table on what do you know in terms of stuff outside of the trial to be able to even say I think I got the endpoints right. I think I need as a minimum to characterize this disease by at least these three outcomes or these two outcome, or I think I'm better off using this composite endpoint rather than these three univariate

endpoints that I might put out there on the table.
So enough said. I mean this is really in the context of where we are going as an agency and what we're being pressured to do in terms of trying to bring some systematic approach to this problem.
DR. JUSKO: I would like to join some of the other

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Committee members in complimenting you and your leadership efforts in this area of disease progression modeling.
Some people have suggested that a better name is disease process modeling because it might better respect that fact that there are multiple components that control disease mechanisms, and, although Bob indicated that your viewpoint is primarily for making best use of endpoints, I would urge you to continue advising the companies to develop the more mechanistic insights into the disease processes that will further help evolve these models in the future.
DR. BHATTARAM: I just wanted to answer a few comments. the one is the -- regarding what kind of data is relevant. I mean we looked at the trials all in the literature, which have been studied from the '80s to onwards right now, and the kind of population studies that will be case for patients who are newly diagnosed with the diseases. So, so far, there were eight trials which have been done so far, and we have six of the eight.
So we think we are reasonably collecting good information.
And the second thing is that although I was not sure how much time I had to show everything, but the way we

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started to develop these kind of missing data models is we started with a simple study like this, design study model, for 15 weeks and then we tried to simulate and to see how many patients will keep this covariate, let's say the duration or some other covariate is really responsible, how will it predict in another trial which has been done for almost two years , if a similar mechanism is really working. How would it then reveal toxicity-related problems? And the -- so we are -- and the third thing is regarding the mechanisms of action, because all the drugs that we tried to look at and have been reported to have different kinds of mechanisms like the Levodopa or creatine, which they say it's free radicals, and other drugs which inhibit morphine and things like that. So we are trying to look at across different kinds of mechanisms to come up with similar kinds of parameters.
So I mean we haven't fully presented that in detail, but definitely the points that you have raised are correct and they are being integrated in the whole process.
DR. BARRETT: This I think is true of any therapeutic areas. You know, you're trying to bump this kind of information and get a signal, and that's why I think Bob's

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-- what he was framing this about -- you know you have the basis for an approval based on the existing knowledge about a therapeutic area that may accommodate several mechanisms.
But again, that potentially changes over time. You

think differently about this, and UPDRS as a score. You've got a composite matrix. It's got a lot of noise associated with it. There's other things you could do to decompose that and maybe to get more resolution. There's lots of possibilities if you are focused on trying to understand the subtle nuisances, but if your objective, as I think everybody was hearing, is to really complement the approval process, indeed this decision support tool, then, you know, I think it sounded like it was going in the right vein, with all of the limitations on assumptions and being in this pooling criteria.

But things change, and, you know, new mechanisms, new indications, new ideas about study design occur that, you know, I think make you have to rethink about that foundation that is part of the model. I think that's really the issue here is you're really identifying the fact that it's a constant reevaluation that has to occur. This is almost like an SOP that needs to be reviewed every year, and, you

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know, looked at and decide whether or not it's still portable or its value is the same.

CHAIRMAN VENITZ: Any other comments on I guess question one.

And I think I can summarize the Committee is very appreciative of the efforts and encourages you to continue. I think we talked about some of the limitations, and obviously you're pretty aware of that.

Okay. Then let's move to question number -- excuse me -- to question number two: Is the approach to qualifying the models reasonable? Any discussion?

Well, let me start perhaps. I know that you used the term qualification as opposed to validation, which I do appreciate, because I think it implies that it depends on what you want to do with the information; right; the intended use is really going to drive your qualification.

And I would definitely encourage you to do that. I mean we have to identify what this takes or are you using this model to design a trial or to improve a drug or to justify a dosing regimen or change indications to a different population of patients. Those to me are worthwhile objectives. I think the kind of approach that

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you're using in terms of disease modeling can help you to do that, but the stakes are very different. Okay.

Not only that, depending on what your overall objective is, you might be more worried about false positives or false negatives. Okay. So it's not only that the error rate per se, it's the direction of the error that you might be worried about. How should you design the trial? On the other hand, maybe you're worried about a false positive?

Okay. And the second thing, given the fact that in my mind what you're basically trying to do is use one data method for risk assessment is think through what the consequences are if you go wrong either way. In other words, not only the error rate again, but how bad is that? And this is something that depends on who looks at it. Is

it the sponsor or is it you? And that, to me, is as important as the technical stuff that we've been talking about -- a lot how to statistically modify, validate, whatever the term you're going to use to these models; agree on what the objectives are and what the stakes are, and that has to be done in a prospective way. And then let the horses run.

DR. BARRETT: I think my answer to this is similar to the first. You know I don't know that we've seen the details of the approach. We've seen -- and I know you've done a lot of work to qualify the Parkinson's disease model; that's obvious. But in terms of what you would say is an overall approach, I know you pointed out, Bob, the best practices paper that came out before, and I'm assuming that's, you know, what you're relying on here as far as that goes, but if you're looking for feedback on what the approach should be, I think you probably should have a -- and maybe after this meeting that you're having, there will be more discussions about specifics. And we didn't get behind the curtain to see all of the qualification work that was done for this. But, you know, and it's obvious that quite a bit of it was there in order for you to get that far. Qualifying the model has to be there, so -- it's obviously a key component of this. It has to be there.

The extent to which you show transparency for modeling qualifications, though, is something you'd put out for public distribution. Obviously, it's an important factor in this as well. And again, I go back to the similar comments -- qualification will probably have to be revisited as these models are similarly reevaluated.

CHAIRMAN VENITZ: Any other comments? Joga?

DR. GOBURRU: I would like to briefly mention our philosophy to model qualification. Dr. Venitz, you have indicated that this is the criteria for model qualification. It's healthier to respecify our prospectively identify, and it is different from what Dr. Barrett has said. And that's our -- or actually it's to -- it's very hard to identify prospectively how to validate a model. It has to be an evolution of criteria.

So broadly, we do -- we use two mechanisms to qualify models. One is the most powerful in my opinion mechanism, so if we have the model for the fasting plasma glucose and relating grades B and C, then the best validation you're going to see in the parameters estimated are reasonable accordance with the biological literature, signifying those rates.

And the other type of validation is for -- which is more important for empirical models is can you reproduce the rate? And what happens when you per W receptions. So it's that sense to the analysis, and these are the probably two types of approaches we're embracing at this point.

CHAIRMAN VENITZ: And I don't disagree with that, but I'm saying you have to take a step above that, you know, before you even get into this exercise. You have to

identify what your primary objective is. What the stakes are? Which way you don't want to go wrong or what the penalty is for being false positive or false negative? And then decide what technical on the mechanistic side or the empiric side support you need to justify that.

DR. GOBBURU: Well, we agree completely.

CHAIRMAN VENITZ: So I'm talking about more philosophical than I am talking about technically. I mean.

DR. D'ARGENIO: Yeah, just to bring a couple of things together. I understand what you're saying, but that's extremely difficult, that kind of validation and let's make it more concrete. Suppose you want to look at some of these placebo and drop out models. You've got so much data here that you can develop the model based on some of those data and validate the instrument. You don't need to go out in the literature and so, as Jurgen was saying, your validation approach depends on the particular part of the model, the particular application, and I would focus on that seemingly simple task, but as I suggested before one that I think can

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have an extremely big impact on the industry. To put simple models like that out there would help so many people and then you can do the validation and it seems there's a lot of ways to do that.

CHAIRMAN VENITZ: Any other comments? It looks like question three has been answered in advance. So let's talk about question number three: What appropriate forum does the Committee suggest for sharing these advances with the public? Bob.

DR. POWELL: What other -- I mean our thinking has been evolving. I mean what -- today, what we were trying to do is to use this forum to get the comments that we have gotten from you and improve our practices, but also it's a way, because we put the background package to you, and then it's publicly available to then make this information available generally. So that's sort of going into the future one could imagine as we complete pieces of work like this then being able to come back and do the same thing, kind of like a disease-centric model that would be presented to a committee like this. That's what I'm thinking.

DR. WATKINS: One thought is there is this new clinical and translational science support network that two

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weeks ago the first round of winners were announced of all the institutions that have bio -- strong biostatistics components in the network, and one of the goals of the network is to develop a national clinical research network to do a multi-center trial, so that may be another, you know, forum to both get feedback and to publicize and enact new models and things like this.

DR. BARRETT: I think a couple points, but just maybe to ask initially clarification on what the public is in your question, because, you know, among the lay community, I can't imagine this being the initial target, although an appreciation -- I see your point as far as just starting the dialogue and allow this material to be more visible. That's all I think in the right vein.

As far as the sharing of the advances, one of the things I know it's been said before is we should really find a way to get to the specific critique areas so that this can be appreciated at the level of the clinical research community, and also I think you'll have always that potential audience so the patient having it as a part of that as well. So presenting this in the clinical pharmacology community I think is, you know, we're somewhat

like minded in this, and you're amongst the peer group, and it's safe, but I think it's good from the standpoint of evaluating what we're doing, but from the standpoint of getting the appreciation of this advance within the public, I would strongly encourage that as you develop these targeted models in certain therapeutic areas to make sure that they penetrate those communities.

DR. GOBBURU: Just a couple of comments. What is obvious that we're doing and we continue to do is to use these approaches to advise sponsors when they come in with their questions regarding a protocol or some kind of an issue. So that is going to be some kind of a public sharing, because that sponsor will get benefit. But that's -- actually the motivation for this question so that more sponsors who are not knocking on the doors how can they access this information.

The second comment is, you know, just to know we have talked about the subsequent meeting to discuss Parkinson's trial design endpoints and both criteria.

There is a conference that is being designed with the three different players in this camp -- the clinical disease experts, biostatisticians, clin pharm. And there will be

mixture of people from this committee essentially, the background of this committee as relates from the clinical to comment, discuss the details of that modeling experience and the recommendations. So I hope that's something what you're implying.

DR. POWELL: Jeff, the public that I was referring to is really the public of potential users in that -- and I -- going back to model qualification, I think you know you can -- you should do as good a job as you can while you're constructing the model, but you have to expect that a model is going to change as new information becomes available and as the community of users begins using it in whatever their own situations are and then you have some sort of a mechanism to learn, which gets to the second point of having disease-centric meetings which get at how do you measure change based on whatever the contemporary and historical and contemporary technology provides opportunities for measuring, you know, new -- coming up with new ways to measuring change, and then adding that in a quantitative way.

I think meetings where you mix the clinicians in neurology or statisticians and clinical pharmacology will go

around that -- those sorts of questions.

DR. KAROL: I think one of the best ways of reaching a

diverse public is to think about presenting a roundtable or discussion at some of the meetings of professional societies. There are some societies where you have both academicians, physicians, and government together with industry, and I think that plays a very informative type of role and exposure.

DR. BARRETT: This is one other comment on in terms of the communication part of this. I think some of the things that Dr. O'Neil brought up in terms of activities that are going on in parallel with respect to guidances are also very important to communicate here. I mean this is the first that I'm hearing of these things that work, which I think is so clearly aligned with what you're doing on the pharmacometric side. I think it's valuable. Certainly on the sponsor side, they should know that this is coming, and it's going to be something that they should anticipate and also potentially have a stake in.

You know the public comment period that the guidance will be there, and they will get a chance to evaluate, but sometimes this occurs in such a tight window that you don't

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necessarily get the comments you could with a little bit more foreshadowing when these things are going to occur.

DR. POWELL: The -- I should -- when Atul had laid out the timeline over the last year and a half or whatever, that they were doing this work, they've actually been primarily doing NDA reviews and protocol assessments, and so this work was done fitting it amongst what their primary job is, and so the if -- I would say that one of the things that I've been amazed at is kind of do this and the remarkable effect. I mean it's like the main metric is different times, and if you look at the different times, FDA must hit 99.5 percent of the times. I mean it's really had a big effect on the culture, and what we're talking here -- about here is coming up with knowledge that affects quality and that the space needs to be created for people to be able to do this sort of work. And that the strain that people are under with the multiple meetings makes this difficult. So I put that out there as something that really needs to be addressed over the long term.

CHAIRMAN VENITZ: Any other comments or questions? Then I think since Dr. Lesko was unable to attend, Shiew-Mei you want to give us?

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DR. HUANG: On behalf of Dr. Lesko, I'd like to thank all Committee members for your excellent input on this very important topic in the last day and a half, and we'll take back your thoughtful comments and suggestions, while we continue working on those. And I'd also like to thank the FDA speakers, the invited speakers, and a lot of individuals who helped develop the work that was presented in the past one and half days, and I'd like to thank the Advisory Group, especially Dr. Mimi Phan, for the fantastic and endless reminders to make sure we're complying with the law and also within our office, Dr. Fena Lee [ph.] for making sure that we submit and encouraging all these paperwork and time, and I thank you, Jurgen, for your excellent leadership for

meeting the time; and have a safe trip back. Thanks again.

CHAIRMAN VENITZ: Okay. Thank you, everyone. The meeting is adjourned and have a safe trip home.

[Whereupon, at 12:30 p.m., the meeting of the Advisory Committee was adjourned.]