FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

WEDNESDAY, MARCH 17, 2010

7:30 a.m. to 2:50 p.m.

Atlanta Marriott Marquis

265 Peachtree Center Avenue

Atlanta, Georgia

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

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Merrill Goozner (Consumer Representative)
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Roxane Laboratories, Inc.
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Philip R. Mayer, Ph.D. (Industry Representative)
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GUEST SPEAKERS (Non-Voting)

Perspectives on Pharmacokinetic Studies in Patients with Renal Impairment

Richard L. Lalonde, Pharm.D.
Vice President and Global Head of Clinical Pharmacology
Pfizer, Inc.
New London, Connecticut

Perspectives of Transporter-Mediated Drug Interactions in Drug Development

Joseph W. Polli, Ph.D.
Director
Preclinical Drug Metabolism and Pharmacokinetics
GlaxoSmithKline, Inc
Research Triangle, North Carolina

FDA PARTICIPANTS (Non-Voting)

Lawrence Lesko, Ph.D.
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(OCP), OTS, CDER, FDA

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I N D E X

P R O C E E D I N G S

7:30 a.m.

DR. VENITZ: Good morning. My name is Jurgen Venitz. I'm the acting chair of the Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology. I will now call the meeting to order.

We will go around the room and please introduce yourselves. And we will start to my left with the FDA. Dr. Lesko.

DR. LESKO: My name is Larry Lesko, director of the Office of Clinical Pharmacology.

DR. HUANG: Shiew Mei Huang, deputy director, Office of Clinical Pharmacology.

DR. ABERNETHY: Darrell Abernethy, associate director for drug safety.

DR. ZHANG: Lei Zhang, Office of Clinical Pharmacology.

DR. CAPPARELLI: Edmund Capparelli from the University of California San Diego.

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

DR. STEVENS: Lesley Stevens, Tufts Medical

Center, Boston.

DR. CALDWELL: Michael Caldwell from the Marshfield Clinic.

DR. KEARNS: Good morning. I'm Greg Kearns from the Children's Mercy Hospital in Kansas City, Missouri.

DR. COLLINS: Jerry Collins, National Institutes of Health, National Cancer Institute.

DR. MAGER: Don Mager, University of Buffalo.

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

DR. FLOCKHART: Dave Flockhart, Indiana University School of Medicine.

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

DR. DOWLING: Tom Dowling from the University of Maryland Baltimore.

DR. LERTORA: Juan Lertora from the NIH Clinical Center, Clinical Pharmacology Program.

DR. THUMMEL: Ken Thummel, University of Washington.

DR. GIACOMINI: Kathy Giacomini, UC San Francisco.

DR. MAYER: Phil Mayer, industry representative from Pfizer.

DR. AGRAWAL: Mukul Agrawal, industry representative, Roxane Laboratories.

DR. VENITZ: Okay. Thank you. Let me then proceed with the official reading.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care

their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about those proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, Dr. Waples will read the conflict of interest statement.

DR. WAPLES: Good morning again. My name is Yvette Waples, and I'm the Designated Federal Official for this meeting today.

The Food and Drug Administration is convening today's meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and temporary voting members of the committee are special government employees or regular federal employees from other

agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetics Act is being provided to participants in today's meeting and to the public.

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

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees

with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda involves the following topics: (1) General scientific issues related to the application of pharmacogenomics in the early stages of drug development. Pharmacogenomics examines the genetic differences that influence a person’s responses, both beneficial and harmful, to certain drugs;

(2) A new patient-centric clinical pharmacology approach to drug safety;

(3) The design and analysis of clinical pharmacology studies focusing on how the renal function changes in the way the body absorbs, distributes, metabolizes and excretes a drug in patients with kidney impairment; and

(4) Scientific considerations and recent developments in transporter-mediated drug interactions. These interactions are between two or more drugs that either inhibit or enhance the roles of specialized proteins known as "transporters" and, in turn, the interactions can affect a drug’s safety and/or efficacy.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

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

With respect to FDA's invited industry

representatives, we would like to disclose that Drs. Philip Mayer and Mukul Agrawal are participating in this meeting as nonvoting industry representatives, acting on behalf of regulated industry. Both doctors' roles at this meeting are to represent industry in general and not any particular company. Dr. Mayer is employed by Wyeth, and Dr. Agrawal is employed by Boehringer Ingelheim.

With regards to FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any presentations and/or comments made by the speakers.

Dr. Richard Lalonde is currently employed by Pfizer, and Dr. Joseph Polli is currently employed by GlaxoSmithKline. As guest speakers, Drs. Lalonde and Polli will not participate in committee deliberations, nor will they vote.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the

agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. VENITZ: Thank you, Yvette.

We will now proceed with the FDA opening remarks from Dr. Lesko, and I would like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request by the panel.

Dr. Lesko?

DR. LESKO: Good morning everybody, and welcome to the Clinical Pharmacology Advisory Committee. I want to thank again each of the representatives around the table up front here. I felt like we should have had a red carpet when I was coming in here. It reminded me of the G-15 meeting or something like that. And I want to welcome everybody

that's in the audience there as well.

In case I don't do it later on, I just want to emphasize the effort that it took to get this meeting off-site, not in Silver Spring. And a lot of people worked hard. We have six people down here to pull this together with Yvette and Cicely and all the other people. So thank you very much for doing this. I know we drove you crazy with the logistics, but we're finally here. The big day has come.

Nevertheless, my job right now is to set the stage for the advisory committee meeting today with an introduction to the topics. And let me start by saying this is a first for us in many ways. This committee, when it was formed -- I'm not sure when, maybe eight years ago or so -- was a subcommittee of another committee. And as a subcommittee, it didn't have all the privileges of voting and full membership on the committee.

A short time ago, we were able to get the charter amended so that this committee is now a full committee and has all the voting privileges and all of that, that other committees have. So that was a big

step for us.

It does have the same purpose. And all advisory committees are committees that provide advice to the FDA Commissioner through the discipline or the office that supports the meeting.

The charter for this committee meeting was really focused on a number of topics. And I've outlined them in the box there on the right-hand side. Given clinical pharmacology is a discipline, the focus of this committee was on general topics as opposed to drug-specific topics -- things having to do with dose response; PK/PD quantitation; the science of clinical trials, especially in early drug development; pediatrics; special populations; mechanisms of drug interaction and innovative methods that relate to drug development -- critical path projects, if you will. And the complete agenda today falls into one or another of these topics.

So the role of the committee, then, is to review and evaluate the scientific and clinical issues related to the benefit/risk of medicines, especially as it pertains to the clinical pharmacology, and also

to review intramural and extramural research programs and critical path initiatives. So that is what the committee does.

There is another first. And as I mentioned, this is a full committee, and we scheduled this meeting here in Atlanta as really an experiment. By meeting during the opening day of the ASCPT annual meeting, we thought this might be a good time for members of the Society to see what an FDA advisory committee is all about, what the process of science is in the context of regulatory decision-making. So we have taken it outside of the Washington area for that purpose, and hopefully you'll enjoy the day.

It isn't the first time an FDA committee has moved out of Washington. The first time that I was aware of -- that this happened was with the Oncology Advisory Committee, which met at the ASCO meeting in June 2006. Coincidentally, that was in Atlanta as well.

Having a meeting like this in association with the annual meeting of ASCPT represents one of our, I would say, strategic initiatives in our office,

which is to reach out and work with external stakeholders, including this society and other clinical pharmacology societies as well.

In a broad sense, having the advisory committee here again is to expose as many people as possible in the clinical pharmacology community to the regulatory decision-making processes.

Now, it's been not quite but almost two years since this committee met. And I thought it would be worthwhile to look at the impact of the advisory committee on regulatory science and decisions.

What I've listed on this slide in the left-hand column is some of the meeting dates. It may not be entirely conclusive, but these were the ones that stuck in my mind as milestones for what we accomplished in terms of the committee meetings. In the middle are the topics that were presented and discussed at the respective meetings.

Then on the right-hand side, probably all-important, is what the outcomes of those meetings were. And I'll just pick a few of them to give you a

feeling for how the process of moving from science to a discussion of policy to a final decision works.

The October 2002 meeting, for example, discussed the TPMT pharmacogenetics and the dosing of 6-MP. And that label was eventually updated, using the advice from this committee, somewhere around 2004.

Today, we'll be talking about transporter drug interactions. And you can see that this was discussed way back in 2003. And it kind of reflects the evolution of science and how rapidly the science is moving forward with our discovery of the role of transporters in drug disposition. With regard to the exposure response guidance, that guidance is now finalized.

November 2003, we proposed a new meeting for FDA and industry called the End of Phase 2A Meeting. We described its purpose, the motivation behind it. And this past September 2009, we released a guidance for industry on the End of Phase 2A Meeting. So again, we move from idea through the committee discussions to a final product.

As we go down to the last meeting that we

had, the clinical pharmacogenomics concept paper was a key part of that meeting, and the renal impairment guidance. And since that meeting, we've been working on both of these topics. And today we'll be discussing some elements of what will eventually be a draft guidance that we'll be issuing for the public.

So these are the topics for today. The first is clinical pharmacogenomics in early drug development. And this will be a continuation of the concept paper that we presented almost two years ago. We're not going to go over the whole document again. What we'll focus on is primarily the issue of DNA sample collection. And we have more information now than we had back in the original discussion to share with the committee and look for some input on it.

We're going to be talking in some specific ways about the use of genomics to assess variability in drug response. And one of the motivations for this topic is to create a sound basis for late-stage drug development and prepare the way for integration of genetics into late-stage drug development in a credible way.

Where we're going with this discussion: We hope to eventually develop a draft guidance. After the committee meeting discussion today, we have a working group that's meeting on this topic on a regular basis.

Now, moving to topic number 2, this is something the committee has not heard before. With all of the focus on drug safety, we've developed a concept for a new safety program that's rooted in clinical pharmacology principles.

We think of this as a complimentary approach to drug safety, complimenting all of the other programs that FDA has -- things like the Sentinel program, the Safe-Use program, post-marketing surveillance. But one thing those complimentary programs don't have is a systematic way to get to the mechanism of adverse events.

So what we're trying to create in this program -- and it is relatively new; therefore, it's a work in progress -- is a mechanistic approach to understanding adverse drug reactions. And the goal of the program is to be able to map off-target effects of

drugs and predict adverse events before they happen, to the extent possible.

So you'll be hearing about the feasibility of a systems approach to drug safety. And we recently implemented a pilot study that you'll hear about from Dr. Abernethy just recently. And this will be a high-level presentation; we won't present any examples at this meeting. We hope to do that at the next meeting. But nevertheless, from a conceptual program standpoint, we're looking for feedback from the committee where they see this fitting, what might be part of it, and how we might move forward on the design of the program.

Now, the third topic is the area of renal impairment. And we've discussed this before in the committee. We are working on a guidance, which would be a revision of our existing guidance. And this will be a continuation of our previous discussions.

You'll see today a proposal for a decision tree for conducting studies, including drug elimination by a non-renal route. And this came about because of our collecting data, evaluating data, and

our observation that renal impairment affects drugs much more widely than we might have thought five years ago when the original guidance was developed.

We'll also be talking about what are the appropriate extremes of renal function for a reduced study design, as we call it in our guidance. And we refer to this as the worst case scenario. And you'll be hearing today about some new concepts on what a reduced study design might look like.

Next, probably one of the more complex issues that we want to bring to the committee is the proposed use of the MDRD and Cockroft-Gault equations, two different approaches to estimating glomerular filtration, which we think can predict, fairly closely, the clearance of a drug based on area under curve. And either one might be suitable for application to dose adjustments.

This is a fairly important advancement for inclusion in a future draft guidance. So we'd like to hear the committee's views on these metrics and whether or not they represent improvements, especially the MDRD over the current way we adjust doses.

Then finally, we're going to be talking about approaches to conducting studies in dialysis patients, with some new information.

Our last topic for this meeting is transporter-mediated drug interactions. As I showed you in that earlier slide, we've been discussing this over the last eight years. No surprise that additional evidence has emerged from the literature from applications that we see on the significance of these interactions.

At the same time, the number of transporters is growing exponentially. I think we now have catalogued probably over a thousand transporters, although we don't know the role of each one of those in drug disposition. It's obviously a growing and important area.

So the question for the committee is really going to revolve around, what does the regulatory agency say to industry with respect to the growth in the transporter area? Are we at a tipping point, so to speak, on recommending specific studies that might be done during drug development?

So these are kind of the four subset questions we'll be thinking about as we approach this topic. What are the clinical questions related to transporters that are important in terms of anticipated use? If somebody does a study, how is that data going to be used? What transporters, of that whole world of transporters, are mature enough that they should be studied, in fact, during drug development?

Then once we get through that decision, how to evaluate new molecular entity transporter substrates. And we have a decision tree that we'll share with the committee to discuss that, as well as NME inhibitors of transporters. How do we study those? What is the relationship between in vitro and in vivo studies? Things of that sort.

Then finally, once the information is available, we have some questions related to label information. What label information would be most useful to prescribers? What label information will be most useful to patient care? And these are the kind of decisions that we'd like to arrive at through the

discussion with the committee.

So that's an overview. The expectations of an advisory committee are to freely share your expertise, your insights, your advice on the topics that we'll be presenting. What you'll see in the presentations are going to be several questions where I'll ask for votes. And if people are comfortable in voting, then they should do so. And we look forward to hearing more what you say.

So with that, hopefully I've given you the overview of the meeting, and I'll turn it back to the chair.

DR. VENITZ: Thank you, Dr. Lesko. Any quick questions by any of the panelists for Dr. Lesko?

[No response.]

DR. VENITZ: Thank you again.

Now, I've been advised that our first speaker is not present yet. So we're going to have to do some minor surgery to our agenda. And we're going to have to start with our second topic first.

So what I'd like to do is I'd like to ask Dr. Abernethy -- Abernethy, I apologize -- for his

presentation on mechanistic systems approaches.

DR. ABERNETHY: Thank you very much. I'm delighted to have the opportunity to present a new program, as Dr. Lesko mentioned, that we've been working on very hard since last fall in the Office of Clinical Pharmacology. And we look forward to your critique, your criticisms, your comments and we hope, your collaboration in helping us to build this program in the very best way.

There has been a huge emphasis on safety and drug safety at the FDA over the past few years. And at the moment, much of that effort has been based in the arena of epidemiology and pharmacoepidemiology. And I think that the various alerts to safety problems, and in some cases changes in the way drugs are made available or whether they're made available at all or not, are a tribute to the effectiveness of these pharmacoepidemiological approaches.

However, at the same time, we believe that safety is still an issue. And what I'll discuss with you are some concepts and really, a hypothesis that we have that if we can better predict safety problems,

perhaps we can avert some of the difficulties that have come from time to time.

So these are the questions that we put forth listed on this slide. How can a mechanistic understanding of drug safety evaluation help the empirical or the pharmacoepidemiologic safety assessments both pre- and post-market?

Are there ways that we can fully utilize the information each step along the way to look forward in predictive safety assessment? And if this is true, then can we learn more about how to not only predict safety for the population, but to identify subgroups that may be particularly benefitted by a drug therapy or particularly harmed by a drug therapy in order to optimize the use of the drug and optimize the benefit/risk relationships.

The unifying theme is to identify variability in response, not a new theme for a clinical pharmacologist. And we think that the real problem is to figure out the predictive factors that patient subgroups, however the subgroups are segmented out -- by genetics, by particular environmental

exposures, or what have you.

Then we need to work closely, particularly in the pre-marketing arena, with the various review groups at the FDA -- that would be primarily in the Office of New Drugs -- to understand, as they get an increasing understanding of what a pre-marketing development program and the data in it look like.

Finally, working closely -- and I apologize for these acronyms, but if I didn't, there would be too many lines in the slide -- with the Office of New Drugs -- that's OND; the Office of Surveillance and Epidemiology -- that's OSE; the biostatisticians and other activities.

DSOB is the Data Safety Observation Board, and this is a board that's been set up across CDER to evaluate and bring particular safety programs to the fore. And finally Safety First, which is yet another new initiative at the FDA to help improve drug therapy at the patient level, an area that FDA has really had very little activity in, in the past, but a real emphasis by Dr. Woodcock and others at CDER.

There are a number of new tools that are

coming along across the scientific community, and we think that these tools have been in rapid development over the past decade. And I guess the real question is: Are they ready at this point now to begin to pull together, into a package if you will, to utilize, to predict drug safety?

Data mining algorithms are increasingly sophisticated, and we've been reviewing the large number of companies that are evolving these. We'll discuss one very, very briefly this morning. The area of systems biology of course has been at the fore in research for a while.

Then more recently, our chemical biology friends are talking about chemical systems biology now. But that's really simply saying, can we put chemical structure into the equation? And if you think for a moment, that's particularly pertinent to thinking about drug safety, particularly in the small molecule arena.

We're working to understand how we can be very proactive in the development of uniform approaches to post-marketing commitments and post-

marketing requirements. Again, the acronyms. Part of the FDA legislation in which FDA, when a drug is approved, comes to an agreement with the sponsor as to what needs to occur post-marketing to better understand the best use of the drug.

There are a number of current tools that have been developed in the Office of Clinical Pharmacology and in laboratories around the world that are already much more mature than some of the areas that I just mentioned; for example, the pharmacogenetics arena, modeling and simulation and other approaches. And the challenge will be to incorporate and meld these different lines of thinking into a predictive approach.

When we say pharmacological mechanism, we're thinking beyond what we'd think of as the usual definition, which I would posit really has to do with on-target or desired therapeutic effects. Of course, part of drug safety has to do with extension of the desired therapeutic effect or excessive desired therapeutic effect. At the same time, an important part and probably where many of the surprises come are

in off-target effects.

Now, there's much information available with regard to the biotransformation, disposition and elimination of drugs. We're learning much more about the genetics of disposition, and at an earlier stage in learning about the genetics of effectors of drug action or pharmacodynamic genetics.

At the same time, as that knowledge evolves, we believe that that can be very useful in identifying subsets of individuals again who may benefit or be harmed by a particular therapeutic approach.

This then needs to be and will be integrated into modeling and simulation approaches that have been evolving rapidly and maturing in the Office of Clinical Pharmacology under the direction of Dr. Gobburu.

As I've mentioned, we believe that at the moment, much of drug safety is what we'd call retrospective. That is that you really do the best you can with regard to understanding preclinical toxicology. You learn as much as you can during phase 1 and phase 2, of course.

But in fact, you monitor for adverse events. And you in essence wait until they happen, and then you count them, and then when there is a perceived signal, begin to work to understand what the mechanism of that adverse event might be.

As I say, that has certainly served us well. At the same time, if one could prospectively identify areas in which adverse events were likely to occur, at the very least one could be monitoring more closely. But at best, one could focus a drug development program, perhaps even in phase 3, to alleviate the risk or to minimize the risk and focus on patient populations that would most benefit.

I simply listed a few of the -- what I would call retrospective pick-ups that have resulted in drug withdrawals in some cases, and in other cases, are current areas of interest and investigation. If we look at No. 3, for example, the tyrosine kinase inhibitors, a new and dramatically effective class of drugs for specific diseases -- at the same time, a class of drugs that have really a wide variety of targets that we don't fully understand at the present

time.

The various kinase inhibitors are brought forward as specific inhibitors of a particular kinase. And I think those of us who have spent a good amount of time in biochemistry and pharmacology understand that specificity in that arena is a relative term on a good day. And so, how can we better understand and predict what the potential toxicities of this class of drugs might be.

Finally, there's been recent activity and some labeling activity with regard to clopidogrel. Was there a way that we could have known up front, before a number of large clinical trials needed to be done, that there would be subsets of patients or patients on concurrent medications that simply would not benefit from a drug?

With regard to the patient populations we're talking about -- well, in clinical pharmacology, the mantra has always been individualization of therapy. And what we think, looking toward the future, will be the individual patient characteristics we can better understand, be they genetic or other characteristics.

And as we gain information about that and how that interfaces with exposure to drugs, that will be part of our predictive equation.

We'll discuss in a few minutes more, but the concept of developing molecular risk targets in much the same way that we currently develop molecular targets for desired therapeutic effects. The targets for efficacy have evolved in our view much more rapidly than the targets for toxicity. And so, now it's time to bring forward the evolution of an understanding of molecular targets for toxicity.

Of course, then that leads to dose selection. And in the past and at the current time, the approach is based on PK/PD characteristics, in some cases using pathways of biotransformation genetic information to better select doses.

So the question will be: Going to the future, are there ways that we can further refine dose selection to again enhance the benefit/risk ratio for particular groups, either to inform enrichment designs during preclinical marketing evaluation, or perhaps in some cases, to identify groups that should be excluded

from a particular therapy, either because of lack of efficacy or an increased likelihood of adverse event.

We think that these approaches, as they evolve, can be very helpful and very synergistic with pharmacoepidemiologic approaches. At the present time, a huge issue in the world of pharmacoepidemiology is the matter of false-positive signals. When a drug gets out into the marketplace, there are all sorts of side effects that get reported.

The question is, when do you cross that threshold from when a series of reports is something other than background noise and becomes a real signal that one then needs to further evaluate?

We believe that if we can do predictive safety evaluation, that we can offer the epidemiologist prospective hypothesis to go into their considerations when they're looking at this mass of adverse events that have been reported. And so our hope is that we can evolve this in a way that will be very synergistic with pharmacoepidemiology.

Moving toward the future, as I mentioned earlier, this really, we think, is going to be a

synthesis of chemical systems, biological pathway systems, and then adding genetic information in and other sorts of individual variability that will impact on drug response, either adverse or beneficial.

So as I said, we believe that this kind of approach will compliment the pharmacoepidemiologic activities; and at the same time, as part of this approach, to do data mining and other sorts of activities in an informed sort of way, we think, can expand our understanding of the potential for adverse effects.

Over the last few years, the various approaches to gleaning information from the masses of data that are in the literature have improved rather dramatically, so that one can hone in on probabilities for associations of a drug and a potential adverse effect that wouldn't really be possible if one were simply using their own knowledge and reviewing the -- reviewing literature.

A huge challenge in this effort will be communication and collaboration, as it always is. The arrows you see here are certainly not new in the

pharmaceutical industry.

During my entire career, the challenge has been, how do you get pre-clinical to talk to clinical? How do you get the various steps of the development process to really communicate with each other so that they don't exist in silos and operate in inefficient ways? Here, I think one of the bridges will be the mechanistic clinical pharmacology collaborating and communicating with the pharmacoepidemiology community.

A challenge to the sponsors of drug candidates and the pre-marketing will be to develop methods of prospective safety data collection, and then monitoring with pre-specified safety analysis plans. That would be the idea of moving into later stages of drug development with hypotheses about what one should be looking for.

In the post-marketing arena, a real challenge when understanding how to evaluate safety signals, of course, is having adequate phenotypic information. In the kinds of safety data that one gleans at the present time, the phenotype of the potential safety signal is often very loosely

characterized.

FDA, and particularly the Office of Clinical Pharmacology, is developing relationships with a number of healthcare providers that work in more closed systems that much of the U.S. healthcare system in order to have a better handle on phenotype as safety signals arise.

So the synergy we're talking about -- this would be within FDA and then of course outside of FDA -- but what's listed here, we think, will happen and will develop in-house with collaborations.

We talked some about what we're calling safety systems biology. That's linked tightly, we think, with genetics, and then linking with chemistry pre-clinical tox and modeling approaches.

These four boxes you see at the present time -- I'd say the three boxes on your right and at the lower are currently working at FDA and have offered really considerable understanding and benefit/risk and protected the public in many ways. We think if we add the upper left box, innovations and safety prediction, that can enhance the whole process.

Now, at the bottom you see this word, "Sentinel." That's a developing activity at FDA to have a much better, active surveillance system out in the community. There'll be a symposium later in the week that addresses this initiative and others directly.

But the concept here is to again have the capacity to assess early safety signals in a rapid way, and hopefully in a way that there's enough phenotypic information to really have a better understanding of the meaning of an early safety signal with then the capacity to do something about it.

Now, when we use this buzzword or buzzwords, safety systems biology, what are we really talking about? Well, this is kind of the current way of thinking about safety in my view. And you put things into the organ boxes.

Then we have these screening laboratory tests that we use to evaluate the various organ boxes. And then, to the extent that we can, we think about interactions among the systems.

Now, again, this has served well. But quite

frankly, it's not a terribly directed or informed process. If we were to look at a safety evaluation program across a variety of classes of drugs, I'd posit they more or less look all the same. That's not saying that those are bad programs. It's simply saying that it's a fairly generic screening and not focusing on where real risk may be with a particular drug candidate.

So our thinking goes more along these lines, that if we can better understand and predict at a molecular level, then if we move up through increasing levels of complexity, that by the time we get up to the organ level, we have a reasonable understanding, we hope, of what pathways may be important, how those pathways may be important from one organ system to another, and then of course how they might interact with each other.

This is simply looking at the same thing turned upside down. But the real challenge is to develop, if we look at that lower box, a taxonomy for molecular and other aspects that relate to safety in much the same way that we have a taxonomy, if you

will, to understand targets, molecular targets for drug efficacy.

Now, this is certainly not news to this group. But it's simply saying that this, the drug itself is a very complex part of this equation. To understand from the structure of the drug to then its -- the various aspects of its biotransformation, its formation of metabolites, reactive or otherwise, and then route of elimination, are all part of this equation.

This is looking at the same thing a little differently, and I think brings home our thinking about the necessity to understand what these molecular toxic targets are. At the present time, we have a pretty vague understanding of what these, the various targets are, and as we evolve that understanding, then that we believe will be very useful in making predictions.

So the challenge is shown here that we've been talking about. How do we do this? How do we understand and make distinctions between the effect of a drug or an underlying co-morbidity when trying to

make these predictions? How can we link classes of drugs or mechanisms of two classes of toxicities?

How do we go beyond the obvious? This is an area that we're working very hard in right now because, of course, there are always these rather straightforward likelihood issues. But if we think about it, the surprises we've had in drug safety, particularly in the post-marketing arena, have generally not been so obvious.

Now, when we look in retrospect, we can create all sorts of hypothesis to say why a COX-2 inhibitor might have particular cardiovascular effects or what have you. But at the same time, before we went into that door, it wasn't so obvious. And a question is: Should it have been, if we would have thought carefully about the target of this class of drugs?

Now, there are a variety of approaches that one might take. This is simply using an example of a whole number of approaches that are out there. But the biomedical literature now is being organized and collated in such a way that it can be accessed and one

can create, really, relationships that are not at all obvious.

This is one particular example that takes the entire database for PubMed and the U.S. Patent and Trade Office and extracts these into categories and concepts that relate to genes, pathways, diseases, model organisms and so on, and then connects concepts in a way that really allows one to see what all the possibilities are, with a weighting toward the strength of the association based on what's in the published literature.

Then, of course, the informed observer needs to work with those sorts of relationships to better understand what makes sense, what doesn't make sense, what might need to be explored further to create associations between drugs and potential toxicities.

This is just a very simple-minded view of how one might make such an association that wasn't totally obvious. And that would be, really looking -- in this case at gene relationships, drug association with gene. How does that associate then with other potential genes that relate to adverse effects? And

then stepping back for a moment, applying as much knowledge and as much collaborative input as possible to understand: Does that association make sense? Is that something that we need to look further into, to better understand and predict a potential drug toxicity?

The key here is to think beyond, then, extension of therapeutic effect of the drug and to think of the off-target effects that aren't really off-target if we understand the entirety of what's known about that drug and its target.

Now, here's just a snapshot that we're developing at the moment, and it is, in the current -- currently being further worked through. In the variety of statin trials, both in phase 3 and then in post-marketing that have been done, it was brought to our attention by people in the Office of New Drugs that if you really look across these trials, it's fairly clear that the risk of developing diabetes mellitus goes up actually, some in people who are on chronic statin therapy.

The general view at this point has been that

the benefits of statin therapy far outweigh the risk of developing diabetes across the population. And so that's something that's of interest and to be observed, but certainly does not alter one's view of benefit/risk for this class of drugs to a large degree. At the same time, are there subsets of patients that are at particular risk of developing diabetes? And that's the question that we posed.

Well, it turns out, when you go through a variety of data mining exercises, there's a fairly clear molecular mechanism as to why this might happen. And it has to do with isoprenylation and other things that statins do. And that has to do with impairment of insulin signaling.

Now, are there populations then, that might be at particular risk of developing diabetes with statin therapy? Well, if one goes through further, looking across data trying to understand, are there subgroups that have elements of their disease, their underlying disease, that would put them at particular risk? Well, it turns out that there are -- that one can identify hypothesized subgroups.

So this provides a hypothesis that one can go forward. And in-house at FDA and then in the public domain, there is a huge database that will allow us to test such a hypothesis across statin trials to understand: Are these predicted subgroups the ones who do get diabetes? Can we understand a very small part of the entire population that receives this particular therapy, identify them either for closer monitoring or for potential alternative therapies or what have you based on this kind of approach? And so we'll see.

What are the pieces that need to be developed at this point? Well, as I said, a systemic database for molecular toxic targets. That needs to happen, and that's going to be an important collaborative effort that we undertake.

We're in early discussions with NIGMS and the systems and integrated pharmacology activities going on there. And then out in the community, there are a number of people who are beginning to look at this issue. A key thing for us to do will be to pull these groups together in a way to really move this

effort forward.

Linking the molecular toxic targets to organ-level toxicity will be key, then linking, of course, the molecular toxic targets to those kinds of terms that adverse events get reported in, so that we can make that linkage with what happens in the clinical reporting arena.

Linkage of chemical systems biology and biological pathways databases: Well, this is the silo problem. The chemists live in one world, biologists live in another world, and it seems like never the twain shall meet. Of course, that's nothing new. I suspect everybody in this room has confronted that from one time or another.

We believe that there's a huge opportunity because the approaches are really not so different in what's trying to happen. And so we believe that we can make some real progress in bringing these approaches together so that starting with a molecule, we can move to the predictions that we need to do.

Now, an important piece to be developed, and we hope to be reporting these sorts of things to you

over next year and in the next years, are examples of how this has evolved and how it can work because, of course, the proof will be when we really have concrete examples that demonstrate that the predictive safety approach has added value to understanding and optimizing benefit/risk.

So with that, thanks very much.

[Applause.]

DR. VENITZ: Thank you, Dr. Abernethy.

Any quick questions by any of the panelists? We will discuss the questions that OCP asked us to answer after the break. Go ahead.

DR. MCLEOD: Darrell, the idea is a good one. Currently, the type of data that you would need for to do this is not generated in a consistent manner, and there's really not a structure for doing this.

It would be quite an added expense to add that. So what is the carrot for generating the quality of systems data that you want to have to inform this process? I know you're wanting to stay at 60,000 feet, but I think that is a 60,000-foot

question.

DR. ABERNETHY: You're meaning the carrot to the sponsor?

DR. MCLEOD: Yes. You know, currently the type of data you get that you would need to ask that is often available ten years after a drug has been on the market. You're talking about bringing that in hopefully earlier than that.

In some cases, like in cancer, there is a lot more work being developed. But in other areas, it's just not needed with the current paradigm. So how do you make it so it's worth the significant added expense to start thinking the way you're presenting?

DR. ABERNETHY: Well, I can offer you some thoughts. If one can identify the patient group for study in phase 3 that has the optimal benefit/risk, that the development program should go forward more efficiently if one takes a substantial piece of risk out of the phase -- the groups who are highest risk out of phase 3 for study, for example, or modifies dose, or so on, then one could argue that, that should accelerate the development program.

In post-marketing, one can certainly argue that the liability that goes along with the safety surprises that occur are not something that anybody wants, either with regard to patient safety or to financial aspects.

So I think those are just, you know, a couple of carrots. Now, are those so kind of conceptual that it's very hard to put that into concrete terms? Well, I think a mission that we'll have to have will be with examples to demonstrate that indeed, you have brought value or carrot to the overall program by implementing these kinds of approaches. And I think the burden's on us to do that.

DR. VENITZ: Dr. Lertora?

DR. LERTORA: Thank you very much for that very interesting presentation. I have a question in terms of the example of statin exposure and the risk for diabetes mellitus. And I'm sure all of these issues are being considered.

But when you look at the subgroup depression, I mean, are you controlling or are the

people looking at these associations and tools for the fact that patients with depression may be on SSRIs that lead to weight gain, and that in turn increase the risk of diabetes mellitus in that population in terms of associations that may be of a mechanistic nature related to the statins themselves, or perhaps to some sort of interaction, drug interaction, or the effect of other drug that is being prescribed concomitantly to that subpopulation.

DR. ABERNETHY: I think that it would give them something to shoot at, and they will. This is an early hypothesis that needs to be tested. And I think what you just described points out one of the challenges that we're hopeful that Sentinel and some of these other activities that are in more closed health care systems can provide.

That is how to best get the phenotype of the individuals and have a fully characterized phenotype to address exactly those issues you have, because oftentimes now, you don't have that. You have either a laboratory value that changed or you have some other bit of clinical information. But you don't really

have the fully characterized phenotype to understand what -- how real that association may be.

As we go forward, we'll just have to have, when we test hypotheses, as much information as possible because it clearly would be in error to be raising many, many flags that shouldn't be raised, that are false signals. That doesn't really get us ahead of where we want to go.

DR. MCLEOD: Thank you.

DR. VENITZ: Let me allow two questions. I think, Dr. Lesko, you're next.

DR. LESKO: I just wanted to comment on the question about data gathering. And one of the ways we've been thinking about this program is forward-looking clinical pharmacology and reverse clinical pharmacology. If you think about it in a preapproval setting, you have information that comes in, in the NDA, both from clin pharm, pre-clinical, and the clinical trials themselves.

We think it's possible to identify at-risk populations based on data that would include things like the dose/response relationship between benefit

and risk, potential for drug interactions, patient demographic factors, observations of co-existing disease in the pivotal trials, and then move towards a hypothesis about drug safety that would be looked at in more targeted surveillance approach, rather than what I would call maybe a hit-or-miss surveillance approach.

Then if you can identify at-risk populations, do the surveillance piece and identify risks earlier, you could then move into possibly some risk management strategies. That's the forward-looking approach.

The reverse approach for data gathering -- and by the way, in the forward approach, there's a fairly large number of post-marketing requirements and commitments that FDA is rendering. And one could imagine collecting data that is missing in the forward approach through some post-marketing requirements or commitments if that data is missing on drug safety.

The other way to look at it is a risk occurs after the drug's approved. Now you get into a reverse clinical pharmacology approach. What are the

characteristics of the population? If I go out to that incident or event, what kind of data would I collect? Then I'd go back and look at the mechanisms that I knew prior to the approval and begin to put together hypotheses.

This isn't just sitting in the office, either, of course. We have some software we're playing around with that connects concepts and ideas, some of it hypothesis-free. Just to give an example to bring it to life, we recently looked at the ototoxicity of cisplatin in children, and this was reported in the literature out of Canada based on surveillance.

What did they find was the biggest predictor? It was the genetic polymorphism and TPMT and COMT, with odds ratios of 5 and 17 respectively. Well, who would have predicted that? I mean, there's no mechanism involved there.

But if you reverse analyze that ototoxicity, you realize that most of the principles of toxicity, which is about 60 percent in kids with solid tumors, relates to their age, their concomitant therapy, prior

treatment such as brain irradiation, the size of the dose, the duration of the dose and the genetics, all of which you put together in a systematic explanation of that risk, which then leads you to how to manage the risk.

You can identify people earlier. You can deal with the disability in terms of the tradeoff with efficacy earlier. You could possibly do some preventive treatment for ototoxicity. So that's kind of a picture of an example that we think could be expanded to other toxicities rather than saying, oh, it's 60 percent of everybody getting cisplatin, and that's just the price you pay for the efficacy of the drug. And I think we can do better than that.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: [Shakes head negatively.]

DR. VENITZ: Okay. Dr. Flockhart?

DR. FLOCKHART: I guess I'd like to thank FDA. I'm still recovering a bit from this presentation. It's kind of like inhaling jet fuel. There's a lot of stuff in it and it takes you a while to recover.

I'd like to address two points raised by the other questions. One is the expense issue. And I think actually, what this provides is an answer to a big problem, which is the money on safety is not really spent in any comprehensively organized way at all. And this kind of comprehensive vision provides everybody, particularly sponsors but also reviewers, in all aspects, in all divisions of medicine but also across the FDA, with a much more organized way of thinking about it.

I think, in thinking ahead, though, I have to just make the editorial comment that I think the stability of proteomics is a problem that is rapidly being solved, and the word didn't come up. Similarly, the stability of microRNA, I think, is established. And these are markers that we will be using as well as genomic markers.

So I think the technical inclusion of those to the critical role they play in systems biology is really going to be important. And those are partners, technical I guess, and scientific partners that should be part of this looking forward.

I'm interested in the partners that you're interested in engaging early on in this process. And I wondered if you might address that, because that would give us all some insight into how you envisage building this large -- implementing this large, comprehensive vision.

DR. ABERNETHY: There is a very important bioinformatics piece, and that really has to do with linking the various approaches. Bringing the chemical biologists into the fold, they have kind of been out there, very much more thinking about QSAR activities as it relates to effectors and so on; but bringing that group of people who have a tremendous understanding at the chemistry into biology level into the kinds of work that we're more familiar with.

Then I think, really, if we think of the systems biology community at the moment, these are -- that activity really is mostly in the arena of biological pathways. And there hasn't been a huge amount of effort in what happens when you lay a drug molecule on top of those pathways -- some, but not a huge amount. And so I think linking kind of the

pharmacologic mechanism with those groups as well.

So what we're envisioning, really, are consortia working together. And if you -- I suspect you are familiar. But if you think of what NIGMS has been working toward in their systems and integrative pharmacology activity, it's -- we're talking about those components coming together in a collaborative sort of way to put this concept of, first, the taxonomy of molecular toxic targets, which I frankly think is a huge piece of it at the moment.

The way I've kind of thought this through is that safety may be about where efficacy was in 1962. I'm not so sure. That may be a little harsh, but I'm not so sure it's far off. I think that we've come a long way in understanding how to assess and think about efficacy. Now it's time to go a long way in thinking in the same much more careful way about predictive safety.

DR. VENITZ: Let me defer all remaining questions until our next presentation because we've got some extra time. Okay? So I have Dr. Caldwell, Dr. Barrett, Dr. Lesko, and Dr. Kearns listed as the

next questioners. Let's proceed after the next presentation. Okay?

So we're now going back to our original topic 1, which has become topic 2. And we've got Dr. Zineh talking about clinical genomics in early clinical drug development.

DR. ZINEH: Thank you very much. Good morning.

My name is Issam Zineh, for those who don't know me. My group is the review group within the office who is charged with dealing with pharmacogenomics as well as applied biomarkers across the drug development landscape.

Today I've been charged with trying to create some preamble or context to the two, hopefully three questions, time permitting, that we'd like to receive advice on with respect to the optimal way to apply pharmacogenetics in early drug development, meaning those studies in which clinical pharmacology play pivotal roles in general.

So our purpose within FDA, within the Office in particular, is to provide pragmatic,

methodologically sound advice in terms of pharmacogenetic applications in all phases of drug development. To that extent, we'd like to receive the opinions of the committee on how best to do that on several key questions that remain unresolved.

For the purposes of this talk, I'll be using pharmacogenetics or pharmacogenomics interchangeably. For the most part, I'll be focusing on the use of information on DNA variance, whether it be germline or somatic, and how they correlate with variability in pharmacokinetic parameters, pharmacodynamic endpoints, or clinical response.

There might be some slight modifications from the original version of the slides. They're not dramatic. They're meant to be more -- they're meant for clarity.

So why do we care about pharmacogenetics at all in the drug development space? I think this slide here gives the answer. What you're seeing on the left-hand side of the slide are the numbers of new drug applications and biologics that have been approved over the years. And what you can clearly see

is that there's a decline in number.

What people should appreciate is that, that decline in number is not due to some changing evidentiary standard that FDA has, but rather to the abysmal attrition rates across all phases of drug development. And that's shown on the right-hand side of the slide.

You can see that even for drugs that make it into humans for the first time, only about 60 percent of those go on to what has been historically called phase 2. A little more than a third of those go on to phase 3. And then of those, about 50 percent go on to approval.

So when you look overall, you're seeing that there's about a 90 percent attrition rate for compounds that go into humans for the first time. And when one looks closely at those reasons for attrition, they're due to lack of efficacy, lack of differentiation from a comparator, or a safety signal that we found to be notable, either that the sponsor found to be notable or FDA found to be notable.

Interestingly, we have pharmacogenetic

examples where genetic variations play a role in efficacy, in safety, and in differentiation. And these are just a couple of examples where in one paper, we see genetic determinants of response; and in another paper, we see genetic determinants of unmet medical need or of differentiation in effect; and in another paper, we highlight some concepts related to the pharmacogenetics of adverse events, including serious adverse events that are on the rarer side.

So FDA has always -- FDA has been an enabler of pharmacogenetics in many ways. And this goes back to the early 2000s. This slide gives a brief history of -- it's not even early history any more -- of pharmacogenetics at FDA; it comes to the present time. But let me just walk the crowd through this slide quickly.

Essentially, in the early 2000s, Dr. Lesko and Dr. Woodcock identified that pharmacogenetics can be an important tool in addressing some of these bottlenecks in development, the reasons for attrition that we highlighted in the previous slide. And so it was felt that it would be important to get some

stakeholders together and maybe flush out some ideas on how pharmacogenetics dialogues can occur between FDA and developers.

So there was the first in a series of workshops on pharmacogenetics and genomics in development. And at that meeting, a key concept of the safe harbor came out. What's meant by that is that drug companies felt that there needed to be some kind of mechanism whereby they could bring their genomic or genetic or biomarker information to FDA without the fear that FDA reviewers would somehow look at these data and compel the company to do additional studies or to take regulatory action.

This was meant to be purely instructional and purely a scientific exchange of information so that sponsors could get some thinking about where FDA is on this science. And FDA reviewers can get some experience on the practical applications of genomics in development.

So that safe harbor principle, if you will, evolved into what was called the voluntary genomic data submissions program or the VGDS. It's now called

VXDS. And in 2004, the first VGDS came to FDA, and the program has been growing ever since.

Since that very first workshop, there have been several workshops. And recently in 2010, in February, we had our fifth workshop, which dealt with the impact of genomics on the product label, the question of co-development of diagnostics and therapeutics, the acceptable parameters around which one can use retrospective analysis of prospectively collected data to make claims about genomic subsets, and the issues of sample collection.

This workshop was sandwiched between two key events in the pharmacogenetics space, at least as we see it in FDA. In January we updated the Coumadin label again to include specific dosing guidelines based on VKORC1 and 2C9 genotypes, and we also just recently updated the Plavix label to include a boxed warning notifying patients and clinicians that poor metabolizers at 2C19 may not achieve full benefit from Plavix.

So the VXDS program has been, really, a flagship program that was developed within our office.

And since that first VXDS, there have been over 40 face-to-face meetings with sponsors. These include not just drug companies, but they include academic researchers, diagnostic companies, platform developers, and those kinds of folks.

This slide is really meant to show that there is a diversity in the therapeutic areas in the particular topics that we've been dealing with in the voluntary submissions. And this is really what's led to a lot of the thinking around pharmacogenetic applications that we'll get to in a moment.

So I want to switch gears just briefly and talk about how genomic information is being used in drug development currently for those who may not be following it closely, what we're sort of doing well and what's not being done so well.

In the discovery space, the pharmaceutical industry is for the most part no longer investing in genome-wide association studies of complex disease. It's felt that academic researchers are actually doing that quite well.

So what the pharmaceutical industry is doing

is looking at the multitude of published genome-wide association studies. To orient you to this slide, these are the 22 chromosomes and the sex chromosomes. What you're seeing in these pinpricks are low side that reach genome-wide association significance. And the colors represent the different phenotypes of interest. They range from everything from Coumadin dose requirements to LDL cholesterol concentrations.

So companies are looking at these regions to see if there are potentially druggable targets here for them to develop. There is no doubt that there's a genomic revolution, and that this information is being leveraged by both the pharmaceutical industry as well as FDA.

This is not just limited to the area of complex diseases. We know, for example, that genome-wide associations related to drug responses are clearly here. And these are just some examples.

The idea would be: How do we find the balance between these exploratory, large-scale, genome-wide methodologies and more focused hypothesis testing in the different phases of drug development?

The Office has recognized recently in 2009, January, that there needed to be an integrated approach from a clinical pharmacology perspective to dealing with these complex issues, genomics and other.

A manual of policies and procedures was developed that for all new molecular entities, pediatric supplements, and new biologics, that the pharmacogenomics team, the pharmacometrics team, and the clinical pharmacology team would all get together and scope out, if you will, the submissions to see what the opportunities for modeling and simulation, clinical pharmacology analysis, biopharmaceutics, pharmacogenetics would be and what would be the defined roles.

That's actually led to a tremendous growth in review work for the genomics group within OCP. This gives you some numbers from 2008 to 2009. What you could see is that for INDs, for biologics, and for new drug applications, there's about a 250 percent growth from 2008 to 2009 in the number of reviews that the genomics group is doing within the office. And this is mostly related to genomics, but it also

includes non-genetic biomarkers as well.

We've also recognized that there needed to be an integrated skill set for a pharmacogeneticist doing this work within FDA. We've coined this phrase, the clinical pharmacogeneticist, which is an emerging regulatory scientist at FDA, to orient the members of the committee as to what we're actually talking about when we're talking about genomic science.

We really divide it into two phases. One is the advice phase, or the IND phase, where we're really trying to instruct companies how to best do the science so that when they do do the science, the results are unambiguous. They're interpretable. One can extrapolate the results to the broader population in which the drug is being approved.

The second thing that we do is analyze the data when they come in. So this in the NDA and the BLA space. And we concern ourselves with all products of the genome, not just somatic or germline variations, but we look at RNA protein. We look at expression. We look at -- we can look at metabolomics if it's appropriate.

We consider all genomes. So in areas like HIV and HCV and oncology, where you're concerned not just with the patient's genome but also with the viral or the tumor genome, we approach questions slightly differently. And then we use our understanding of biological pathways and pharmacology to make an informed regulatory viewpoint that we call translational analyses.

So we've identified opportunities, but we've also identified gaps. So how is genomic science being applied across very diverse areas in development? Clearly, in drug target identification and validation, genome-wide association studies have revolutionized the way that companies approach those questions.

I'm going to skip the conversation around predictive models of efficacy and safety. But of course, what we're most interested in is prognostic and predictive enrichment strategies or patient selection strategies. And a big unanswered question is: What is the role of pharmacogenetics in early drug development, in the clinical pharmacology studies?

So to conceptualize the question, I think that this slide modified by David Katz really gives a fairly accurate description of how we are seeing clinical pharmacology pharmacogenetics, if you will. And so I'll sort of orient you to this slide.

This is all the phases of drug development, as they're classically thought of. What's done is in the pre-clinical development. Companies spend resources in identifying the metabolic pathways of a new chemical entity in terms of what drug transporters or what drug metabolizing enzymes might be important.

Based on that pre-clinical information, they may choose one of several strategies on their first in-human studies. These include excluding patients based on genetics, particularly if there's some safety concern or some thought that there might be a narrow margin in those patients; sample collection on all patients, and perhaps analyzing the data if some outliers are uncovered and identified later in the development programs; or enriching the study with certain genetic subgroups.

The idea, irrespective of what approach is

taken, is that one could inform their population models or their PK information, PD information, based on what they're seeing in these early phase 1 studies, which include the first in-human studies and the multiple dose/rising dose studies.

That information is built upon in phase 2. And ultimately, the decisions that are made, the critical decisions that are made in the pivotal space are dose selection and formulation decisions, patient selection for phase 3.

What's also being done along the lines of what Dr. Abernethy mentioned is a retrospective analysis in these late-phase clinical studies to identify super-responders, if you will, population subsets in which a drug company can make claims about a group that's more likely to respond to their medications, or to elucidate the basis for changes in biomarkers that one might think are adverse event biomarkers. Those are done in the late-phase studies. And all the while, multiple marker analyses, exploratory, if you will, are being conducted.

So this creates, I hope, some context for

Question 1, which we won't answer now but we'll describe. This question, the choices are slightly different than what you're seeing in your dossier. So I think we'll vote on the questions as they appear in the packet.

This is an earlier form of the question that is meant to highlight the different areas in which one might collect DNA. But in 2008, the AC reached consensus that DNA samples should be collected from all patients in all clinical trials in drug development. So there was a thought that this should be mandatory across phase 1 through 3.

Since then, drug developers have stated that this is not a practical or feasible thing, and I'll show you some slides about why we're hearing that's the case. After I've sort of provided you with that information, really, the question at hand is whether or not you still feel the same way as you did in 2008, or is there something more prescriptive that we could provide in terms of advice. There's also some question as to the utility of this wholesale collection of DNA samples when you haven't even really

established efficacy of your drug yet or a dose/response relationship.

So this is part of the reason why companies say that mandatory collection across all phases of development is impractical if not impossible. What you're seeing here in the colors -- I hope they're projecting well -- is the -- across the phases of development -- this comes from the industry pharmacogenomic working group -- across the phases of drug development, what you're seeing is that for many phases, there's actually high sample acquisition on the order of 70 to 99 percent. And for the majority of these bars, I think the 50 to 69 and the 70 to 99 percent sample acquisition are represented. And that's these here.

So there's a high number of samples that are being acquired across development. But there's a reason why the sample collection is incomplete. Part of it is because when you look at how the -- we're focusing on DNA here -- how the samples are collected, they're collected through optional participation. So the companies are no

One of the other reasons for missing samples

is in the context of global drug development, we are told that different countries have different regulations about what can and cannot be done with respect to not just sample acquisition, but storage of the sample and even testing hypotheses.

So there may be some health authority rejection of the DNA sub-study. There's a lot of heterogeneity, even within the United States, amongst IRBs and ethics committees on their requirements or what they allow for genomic sub-studies. Investigators may choose not to participate.

The investigational staff may not be encouraging or may even be discouraging participation in the genomic sub-studies. There may be some issues in terms of wording on the informed consent. Because this is voluntary, subjects themselves may be opting out or not consenting. And we have been told that in the group settings where multiple patients are consented at the same time, they influence each other as to whether or not they will be participating in the genomic sub-study.

So again I come back to the question. The

choices in the dossier are not all these -- or they're not broken down in this granularity. The question is: should it be mandatory to collect DNA in any of the following drug development scenarios?

Exploratory clinical studies in the preapproval phase of drug development, so these are the phase 1 and phase 2 studies; confirmatory clinical trials in the preapproval phase of drug development; these are the pivotal phase 3 studies, the registration trials, if you will; and (c) is post-approval studies required by FDA to assess a safety signal.

Another question for the committee is, if you don't have any priority pharmacogenetic hypothesis, does that change your answer?

A second question is, we know that in drug development, just like in patient-oriented academic research, investigators have several options on how they want to approach the pharmacogenetic question. They can do it in a focused, targeted genotyping strategy, or they could use these more high-throughput ADME panels to ask the question, or GWAs to ask the

question.

So Question 2 is really meant to ask the committee is there anything unique about the drug development context where one might choose a candidate gene approach over a genome-wide association approach, or vice versa? What are the advantages and disadvantages, if you will, to those strategies? And if there's nothing unique about drug development, we would still like to hear from the committee as to what they feel the advantages and disadvantages of those approaches might be.

Question 3 goes back to the sort of landscape that I painted, whereby the pharmaceutical industry is using pre-clinical information to make decisions about how they want to approach pharmacogenetics in their first in-human studies and their subsequent studies.

Without reading the details of this question, the question is: How do we use, how do we best leverage those pre-clinical data, whether they're in vitro metabolism studies or they're in vivo animal studies to inform things like first in-human studies

or drug interaction studies?

There's a follow-up question where drug interaction -- pharmacogenetic studies can tell us a lot about drug potentials for drug/drug interactions, and vice versa. So what's the relationship between knowing the genetic information and how that might inform whether or not you need to do a drug interaction study and how might one do that, and vice versa? If you pick up a signal in drug interaction studies, does that tell you anything about potential for genomic subsets of patients differentially responding to medications?

What sparked this question is a decision tree that was presented at the previous AC in 2008. This is not a decision tree that we necessarily are endorsing today, but I think conceptually gives you an idea of the question, of what's behind the question.

So the idea is that there would be some pre-clinical workup of the molecule in terms of whether or not it's a substrate for a polymorphic pathway, a well-characterized polymorphic pathway. And if it's not -- excuse me -- if it is, but less than

25 percent -- this was the number that was put forward at the time, then it was considered that maybe this is not really likely to have a clinical relevance, and one may not choose to do any evaluations from a pharmacogenetic standpoint.

If it's greater than some threshold in terms of how much of the compound is metabolized by the polymorphic pathway, then a series of questions and actions are put forward, which include collection of DNA in the early phase clinical studies, and assessing whether or not there is pharmacokinetic or pharmacodynamic variability that's sufficiently different where a decision-maker might want to explore the genetic underpinnings of those differences. And then based on what the answers to those questions are, one would handle that in labeling.

Of course, there are many iterations of this. One can choose to do prospective genotype-stratified studies under certain conditions. And we'd like to hear from the Advisory Committee on, conceptually, how one could use pre-clinical information to inform what you do along the lines of

these decision tree-type thinking.

Now, here are some potentials for -- potential considerations as you think about what a decision tree or something along -- a tool along those lines might look like. One, is there any significance if we're talking about a variation in drug metabolism versus transporters? Does that sort of change your answer?

What is the balance between the in vivo pre-clinical information and the in vitro microsomal data, for example? Which one do you believe more? How do you balance the information that's coming off of those experiments? Does the number of major metabolic routes matter for the drug?

Is there some threshold? Here we had 25 percent, what had been previously presented. Is there a clearance threshold via a single polymorphic pathway that the committee feels should be considered to trigger subsequent actions in terms of prioritizing pharmacogenetics?

Does the PK variability -- is there a particular PK variability? Are there parameters

around PK variability where one might think that there's some clinical relevance to that variation? And does it matter whether or not a PK-PD relationship or an exposure/response relationship has been established for the molecule of interest?

This is our current thinking in terms of what we think is important to convey to drug development communities and outside communities. Essentially, we'd like to convey information about why -- the history of pharmacogenetics at FDA and why we think it's sort of important. We'd like to introduce the concepts and provide regulatory background.

Then we'd like to talk about clinical evaluation of pharmacogenetics, essentially all the things that we're talking about today, both in terms of general considerations, providing value, examples of value of pharmacogenetics with a couple of examples. By the way, all of these examples have been sort of developed post-approval and in a non-optimal way.

So the idea is, can we take any lessons

learned from these post-approval label changes, for example, or drug development actions and regulatory actions to more prospectively in drug development tease out the clinical pharmacology questions as they relate to genomic variability and have more informed decision-making?

We will also talk -- we hope to convey to people our thinking on applications of pharmacogenetics in different types of studies, so in PK/PD studies in healthy patients, in healthy folks, in patients, in dose response and some other types of clinical pharmacology studies.

Then we'd like to discuss with the public specific considerations in study design. So here, we're talking about study populations; the importance of phenotype; how one approaches this from a statistical standpoint; if it's exploratory, what are the considerations from a data analysis and an interpretation standpoint; and of course, what the impact would be on labeling.

With that, I stop and I welcome any clarification questions.

DR. VENITZ: Thank you, Dr. Zineh.

Any quick clarification questions by any committee member? Dr. Giacomini?

DR. GIACOMINI: Yes. Very nice presentation and nice update from what went on in the last Advisory Committee meeting.

I guess the question I have is, at least what I'm hearing, is there's been a little bit of pushback in terms of sample collection. And the question I have, are pharmaceutical industries who have collected samples, are they actually using those samples in their data submissions, or are they just simply collecting?

DR. ZINEH: Right. So there are really two camps in the pharmaceutical industry. There are those that feel we should make sample collection mandatory, to the extent that we can. It's still unclear whether or not we even have the authority to mandate that sort of thing because it makes their job within the industry -- these are the pharmacogenomic groups -- it makes their job within industry much easier in terms of being able to answer some of these questions.

There are others, though, that feel as though the value has not been demonstrated yet for routine collection across all development, that whole development landscape. If there's a specific hypothesis or if there's a reason to believe that genetics would be important, then companies feel as though there could be value there, and they're actually doing the experiments.

We are seeing pharmacogenetics a lot in different applications, very innovative applications, that range from the exclusion of patients in these first in-human studies to get a better feel, an estimate of the PK, all the way to identifying genomic subsets at the end of the day that are super-responders. So it is actually being done, and being done in pretty unique ways.

In terms of the -- I think your second question was just about value in how it's being done. What we're hearing from different companies is that they're -- I think in a sense I answered it -- this is not a -- this is not trivial in terms of resource consumption, and there are a lot of competing

priorities within development. So it's not just the collection, but it's the banking as well.

So it's felt that again, unless you have -- by some companies -- unless you have a specific hypothesis, that it's not justified to do this across all phases of drug development.

DR. VENITZ: The last question. Dr. Lertora?

DR. LERTORA: Yes. A somewhat related question. But again, I think there's a potential concern in terms of mandatory DNA sample collection, from a regulatory standpoint. Then the pharmaceutical company will try to implement in terms of their clinical trials.

Again, you have the issue of volunteer patient autonomy. A patient can always decline to provide such sample after going through the informed consent process. And then you may run the risk of some recruitment bias that is being introduced that then may impact on data interpretation at a later stage.

DR. ZINEH: Yes. That is true. There could

be a bias whereby you're selecting out people that are, let's say, genomically inclined. On the other hand, we're dealing with some real issues here in terms of data interpretation when the samples are collected in a voluntary way.

So, for example, when you have 50, 60, 70 percent sample acquisition, how generalizable is that information from that genomic subset? In a sense, there's bias there in the people that have consented to do the genomic study.

In addition, if samples are collected, not at baseline, but they're allowed to collect DNA any time during the course of a study, if these are morbid or mortal events, then we run into survivorship biases and things like that.

So I think that there are very large questions about how sample collection impairs or limits how you interpret the data and how you extrapolate those. But your point is absolutely well taken and appreciated.

DR. VENITZ: Okay. Thank you. Then I suggest that we take our scheduled break, and we

reconvene at 9:25. And I am to remind the committee members not to discuss any of those topics amongst ourselves.

[Whereupon, a recess was taken.]

DR. VENITZ: Okay. Welcome back.

We don't have any speakers for the open public hearing, so it looks like we have an extra 30 minutes. And with the committee's consent, what I'd like to do is use that time and add it to the renal and the transporter topics, topic 3 and topic 4. So I'd like to stick with a one-hour discussion on topic 1 and topic 2, unless I see violent opposition.

Okay. Then I would suggest that we go back to the schedule. Our next order of business is to discuss the questions that we were asked to answer. And I think our first question relates to the genomics topic. So I'd like to start off our discussion of the genomics topic, Question 1 in particular. Let me go first, then.

I think I enjoyed your presentation, and I understand the dilemma that you're facing in terms of not having the generalizable-type information that

you'd like to have, and think about mandatory collection and announces of those samples. However, I would tell you as an IRB member, I don't think you can mandate that kind of information.

I think it is up to the individual subjects to decide whether they want to participate in the collection of DNA samples, regardless of their participation in the study, and that's the way it's usually handled.

I can see if you have an a priori piece of information that would tell you to exclude patients because you think it might be a safety issue, that that's defensible. And I think that happens all the time. However, I don't think, at least in phase 1, phase 2, and I think even in phase 3, that it would be ethically defensible to mandate collection of a DNA sample in order to participate in the study. And I think it becomes even more ethically problematic if there's any potential for benefit from participating in the study.

I think what, in my opinion, might change that a little bit is your add-on to the question.

That is, what is your a priori hypothesis? So if you're looking at exploratory DNA sampling, from my perspective I don't think you can mandate that. And I'm talking about just from an ethical point of view. If there's an a priori hypothesis and you can make an argument that collecting that information improves the risk/benefit for an individual patient, that is a different story.

The second comment that I have is related to your decision tree, and that is specifically looking at pharmacogenetic differences relative to drug-metabolizing enzymes. And as far as I can tell, it is perfectly permissible right now under current guidances to substitute genomic information by drug/drug information. Is that correct?

That means if I know that I have a 2D6 substrate, it is either by demonstration that there's a genetic difference or by demonstration of a drug/drug interaction consistent with that. So again, depending on the information that you have, it may not be necessary, then, to "mandate" a collection of 2D6 genotype because you've got other information that

tells you what the exposure changes would be.

So unless, in my opinion, there's an explicit hypothesis that you want to test, maybe related to exposure response or outcomes, I don't think you should mandate. And I'd be happy to give you --

DR. ZINEH: No. I appreciate the comment. I guess, to your second point about the drug/drug interaction piece, what we are finding to be increasingly problematic is that the genetics is pretty unambiguous. If you're a 2C19 poor metabolizer, genetically you are that 24 hours a day.

On the other hand, if you have a drug that's a 2C19 inhibitor, it's really -- many times it's hard to know whether that's really a pure 2C19 inhibitor, or does it have some sort of inducing properties? Is there a temporal relationship between the concomitant administration of the drugs?

So I think, in some ways, the genomics informs the drug/drug interaction a little bit more than the drug/drug interaction data informs the genomics, for those reasons.

Is that clear? I hope I made that clear.

DR. VENITZ: Dr. Harralson?

DR. HARRALSON: Yes. I guess my question would be, in the early studies where you have very small sample sizes, I don't see how you actually can evaluate the pharmacokinetics if you don't know the genotype if it's a substrate for a major enzyme.

I've reviewed a lot of studies with an n of 25 or 30 with outliers, and it would seem that that would be basic information, and that as you're looking for volunteers for a study, why wouldn't you ask, would you be willing to -- because you're selecting them anyway, why wouldn't their willingness to participate with their DNA be part of that?

DR. VENITZ: Dr. Flockhart?

DR. FLOCKHART: I guess I'd like to address this question in a little bit of a legal -- I'm sorry; did you say me -- in a legal way. And that gets to the definition of the word "mandatory."

Because I think when the committee originally did this, we were maybe naive in thinking that people would assume that this meant mandatory for

patients without consent. Of course that's not what the committee meant. But I think the language could be modified in such a way that it's clear that that's not what we meant.

Now, having said that, I think that the idea that people should be strongly encouraged, which is where we were coming from, to do it has been communicated. I mean, it's been done now, and we've got -- Kathy's right. We've got some pushback.

But I think the FDA's leadership in this arena is now clear, and their intent that it happen as much as possible be clear. I don't actually think that given infinite resources, there's any scientific argument not to do this. But I think it is very difficult to argue that it be federalized, if you like, like this.

I would prefer that we offer advice and guidances in which it was, rather than being federally driven in the sense that everybody has to do it for whatever, that it be scientifically driven on the basis of either statistical considerations when that's possible, or when a reasonable scientific argument can

be made.

Not to go on too long, but a scientific argument can be made either if you do know a really clear candidate pathway or, on the other hand, if you don't because if you don't, you can argue for a genome-wide association look.

So I think you can make scientific arguments in both cases. I'll stop there.

DR. VENITZ: Dr. Kearns?

DR. KEARNS: Thank you. Just a few comments, and some of them will bleed over to Darrell's talk.

Back in the late '40s/early '50s, in pediatrics we always remember bad history. And there was a tragedy called the gray baby syndrome. And I posit that had we understood the similarities in how bilirubin was metabolized and we understood something about that drug, that we understood the children were indeed different, that their phenotypes are different, that perhaps that whole tragedy could have been avoided.

But we didn't understand that then, but we

do understand it now. And certainly during human development, at certain points, susceptibility to drug effects is different. We know that about adverse drug reactions that occur more commonly in young infants than adults. And we also have very clear understanding now that drug disposition is different, although we may still not totally know the reasons why.

That having been said, the inclusion of DNA samples in a study to characterize either an adverse event or the clinical pharmacology cannot assume a fixed phenotype. And much of this, of what I've heard today, has that seemingly as an inherent assumption because the phenotype as we all know is never fixed. The genotype may be, other than if you have an epigenetic phenomenon that occurs, and those do happen, I'm told. But the phenotype does change.

One of the real difficulties we are seeing at our institution in trying to look at some of these studies is how fuzzy phenotypes are. You know, people think they do a good job of characterizing a phenotype, and people try to take a dichotomous, do

you have/do you don't approach, and that just doesn't get you anywhere at the end of the day, largely because the numbers of subjects that you have, especially in kids, is small.

If you look at the frequency of the number of allelic variants that may be of interest, those are low. And so at the end of a study with maybe 50 or 100 patients and you've got DNA from everybody, you wind up, not with a turkey dinner, but with turkey scraps at the end of the day, and you can make no sense of it.

Even studies now exploring new techniques to look at gene/gene interactions, while those hold some real promise, even the most recent things that are out there, like the use of MDR analysis, don't control for gene frequency. So until we can get those things hammered down, some of this stuff is going to be difficult.

I think the last comment I'll make about collecting DNA -- I agree with our chairman, especially in kids. If I go to my place and I say, I want to do a study and oh, by the way, I want DNA on

everybody, then I know who the guy on the IRB, one of our chaplains -- I'm not going to say his name here publicly -- but will put me against the wall and say, what are you going to do with it?

His point is always, there has to be some direction. You can't just take it because you have maybe some good ideas five years from now. It can't be exploratory. You have to have a direction.

So we have to state that the reason we're getting the sample is because we want to investigate more about, you know, X or Y or Z characteristic of a drug. So it's directed. It's not exploratory. And I think if it's done in that way, it's very, very powerful.

Lastly, you know, at the end of the day this is all about trying to quantitate the variability in drug response or disposition or concentration/effect relationship. And I think the FDA can be -- especially this office, Larry -- can be very useful as it continues to interact with sponsors in coming up with ways to study drugs. And if this technology is important to helping describe variability, then

recommendations like that can be made. But for the sake of getting it for purely exploratory science, I just think it's a mistake.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes. I guess I'll disagree a little bit with that because I feel like the case that Larry made with the cisplatin-induced ototoxicity and what came out subsequently, some genetic variance in TPMT and catechol aminomethyltransferase.

When you're doing an exploratory study, I mean, I feel like the purpose of an exploratory study, part of the purpose, is to identify populations at risk and patients who may be at particular risk for safety. And so, for example, if you did a study and somebody had ototoxicity or they were deaf but you didn't have their DNA, you could never go back and get that DNA if you hadn't collected it or banked it. And that would concern me because then you can't identify those populations. So I'm not sure what you're exploring.

I do understand that you can't mandate patients to participate in trials and give their DNA.

But I'm not sure if you couldn't mandate the companies to include that in their study design, and if the patient opts out, still allow that patient in. But I would be for, when you do an exploratory study, to really try to explore everything to try to identify these populations.

DR. VENITZ: Dr. Thummel?

DR. THUMMEL: Yes. I'd like to echo what Kathy said. I think you can in fact make it very clear what the purpose of the DNA collection is for. It's to help understand intra-individual differences in safety and efficacy. It's not to explore other issues.

All of the questions won't be known. In fact, that is the whole point of the investigation. And many of the issues may not emerge until later. And, you know, my colleagues who do, you know, pharmacogenetic studies on drugs that have been approved really understand that one of the biggest limitations is trying to mount this retrospectively, where the clear place to do it is during the development process.

So to me, you know, getting that information, genetic information, is no different than any other type of data that might help understand intra-individual variability. And leave it at that.

DR. VENITZ: Dr. Caldwell?

DR. CALDWELL: Well, I want to add my agreement as well to the last two comments. Take case, for instance, of warfarin. At the time that the first genetic variants in 2C9 were known as far as this regulation of warfarin metabolism, if we had not had DNA on patients who were on the warfarin subsequently, we would not have understood VKORC1. We would not have understood CYP4F2.

Other clear regulators of warfarin metabolism and our ability to adjust the stable therapeutic dose of warfarin were discoveries based on the fact that we had DNA in patients who had been exposed to that drug.

I agree that this -- at least so far, this is not a country where we force people to give us their DNA. But I also agree with Kathy that study design can be constructed such that the study design

mandates DNA being collected. Having established a biobank of 20,000 people where we've collected DNA, it's very easy to have an IRB approve that, even for exploratory processes.

I don't think it's unethical to collect DNA from patients for that type of study. Can patients opt out of the study? Of course they can. I'm not forcing them into the study. Therefore, I'm not forcing them to give me their DNA. But if they're going to participate in this study, and this is the basic study design, then DNA is a part of the contribution for the study.

Should there be exceptions under that system for scientific reasons or for other reasons? Fine. That can be done as well. But I think a major emphasis on collecting DNA as a part of the studies is still a worthwhile process.

I would like to be able to comment at some point on Dr. Abernethy's talk as well.

DR. VENITZ: We will.

DR. CALDWELL: Thanks.

DR. VENITZ: Go ahead.

DR. KEARNS: Just, I want to make sure that my comment's not misunderstood. I agree with what Kathy said, Kenny said, and what you said. Okay? My only point is when we collect that information, we have to be able to say the reason why.

The reason why might be if there's a safety concern, or to evaluate. But what we can't do is say, we're going to collect it, and if we're asked why and we don't have a reason, that can't be done in children.

DR. CALDWELL: But it's easy to come up -- I mean, it's easy to explain the reason.

DR. KEARNS: I agree. But I'm just being a little pedantic here in terms of what has to happen. And I just want to be clear.

DR. VENITZ: And I would second that. I think what bothers both you and me is the term "mandatory" more than anything else.

Dr. Barrett?

DR. BARRETT: I think if this becomes an exercise in trying to think up a genetic hypothesis before every study, it just really undersells the

value of the data, though. I mean, I hear what you're saying as far as wanting to come up with a good rationale and certainly appreciate the difficulties in dealing with the IRB.

But all of this information will have different value in terms of its content. And it's very difficult, I think, to construct this on a study-specific basis. I think it also undersells the value in looking at this across studies. Compounds are going to die at various stages of development, and you will not get the same value out of some of them.

But the ones that move forward when you have the ability to construct a longitudinal data set that grows and then leaks into an eventual patient population data set, there will be tremendous value in having that look-through. So I think we up-front have to appreciate that some of this process will not offer the same amount of clarity, and that it's something that you have to buy into on a larger plane.

Notwithstanding the difficulties in the word mandatory here, but I think at some point you have to recognize that this does have value beyond the

individual study, and then solicit buy-in on a much bigger scale. And we still have to educate.

DR. VENITZ: Don?

DR. MAGER: I think in the area of the confirmatory studies, there's a lot of incentive for this to be done already. And I think the marketplace has caused many groups to, if not make it mandatory, at least strongly encourage it throughout their clinical trial system.

There are some situations where companies, the sponsors, have felt so strongly that they have mandated it with very strong scientific rationale for that. And so I think that having a -- and the FDA use of the word mandatory is not necessary because of what we're trying to accomplish.

Where I do think that there are issues that we haven't really discussed enough is in the early phase part, where it is truly exploratory, with the exception of maybe some pharmacokinetic-type variance, or in the post-approval stage, where the collection of the sample is more challenging than in the context of a phase 3 trial. And I don't know the answers there.

Certainly the phase 1/2 area is much easier to work with. But I do think that that's an area where there's -- especially on the safety side in the post-approval side, there's potential for a lot of added value.

But right now, with a few exceptions, abacavir being one of them, there haven't been a lot of examples where having the collection of samples has led to not only better development of the drug, but better use of the drug after development.

DR. VENITZ: Dr. Collins?

DR. COLLINS: So the discussion sort of confirms that I thought coming here, that if the wording of this question were, is it highly scientifically attractive? Is it conceptually appealing? Should we strongly encourage people to do this? You know, I think there'd be just spectacular support for it.

One of the issues is how do you build a case? If you really want to make it mandatory, how do you build the transition between what's conceptually attractive to what's really compelling? And I think

what's missing very strongly here, and some of the speakers have commented on it, is every single example we have is in the post-approval setting -- and not just the immediate post-approval setting, but in most cases the deep post-approval setting.

I'm fascinated by the cisplatin information. The cisplatin's been around for more than 20 years. And, you know, there's no way that that would have been -- you know, that's an example that's got -- you know, we're finding examples for a tiny fraction of the number of approved drugs and generalizing them.

I was very encouraged by the data that you showed that there's a tremendous amount of activity already in collecting it. And I disagree with the comment that 50 to 70 percent is a low number or -- I can't even imagine how it could be a highly biased number, given the fact that most of the value here is for rare events.

It's not that most patients get adverse reactions. It's that we're trying to protect the rare populations. And as long as you're collecting 50 to 70 on a voluntary basis, that's pretty impressive to

me. But if you want to make the case for it to be further, given all this incredible amount of activity in banking and analysis, then you ought to be able to have not just an example, not just a book, but a whole shelf full of books that are filed with case examples of where, in the prospective drug development plan, this made a difference, and we're glad that we did it, and it saved the patients. That would be my advice.

DR. VENITZ: Dr. Lesko?

DR. LESKO: So it might help frame or sort of bring this discussion back to say, okay. It's unlikely an agency anywhere is going to mandate DNA collection. But it could do other things -- strongly recommend, recommend, what have you. One practical reason is that DNA collection, if it were mandatory, could not actually be accomplished in many countries where global drug development is being implemented.

So put that aside and say, okay. So the recommendation for DNA collection is probably more feasible. It strikes me that one of the roles of early drug development, clinical pharmacology in particular, is to learn about the molecule. And we

oftentimes think we know more than we know.

I was thinking of the examples to bring this to bear. We just relabeled clopidogrel with 2C19. And when you look at the in vitro information on that drug, you would have never predicted the impact that polymorphism on 2C19 had. You would have looked at that and said, that's a 3A4 substrate, and forgot the 2C19. So in fact, it took the post-marketing studies to figure out what was going on with active metabolite levels and polymorphism because it wasn't looked at early on during the development phase.

So part of this thinking on this DNA collection is to not wait till events happen and then try to figure it out, but try to understand the events before they occur. I was thinking of a few examples because I think it helps to sort of frame our thinking in this.

Some of the things you can't do if you don't collect DNA. You can't explore an adverse event thoroughly during the pre-marketing period. And generally, a drug might be stopped in its tracks because of an adverse event. Think of something like

drug-induced liver disease. Then you enter into a rescue situation, which is somewhat later on.

I was thinking of the KRAS panitumumab situation, which in the early days of trying to develop an association between mutant KRAS and lack of benefit, the studies were hampered by an incomplete data collection. And if you look at statisticians trying to say, well, wait a minute. If you want to claim an association, whether it's to prevent risk or define a subset, you need a fairly high collection rate and you need a fairly high ascertainment rate, as it's called, because convenient samples don't work.

The other thing we've been sort of thinking about in this context is, what causes a PK outlier? And the issue is real when it comes to small studies but, you know, we're seeing studies in NDAs of early drug development with 30, 40 studies of phase 1, so that it isn't, you know, unthinkable to say, let's do a meta-analysis of these things if we had the data available to look at and explain outliers.

So this is kind of a backdrop for, can you learn new information about molecules that would

eventually bring value to benefit and risk, to better dosing? And, you know, if you don't collect the samples, our thinking is, you're not going to move from where we currently are, to where we might go with regard to improving the benefit/risk of drugs.

So if there's other ways to think about this, then I think it's good to hear that.

DR. VENITZ: Dr. Mager?

DR. MAGER: Yes. Just to follow on that, I completely agree. And I think although the cases are clear for confirmatory and post-approval stages, I think the case is also very clear for exploratory stages for collecting DNA data. It can be straightforward during that phase, in the learn phase, just to validate the causal pathway or the mechanism of action of the compound.

There's been a lot of focus, I think, on PK and adverse events, and rightly so. But I think we also need to remember that this is really the learn phase, where we're trying to understand the mechanism of action of the compound. And more information about that causal pathway lends a lot, not only to that

compound, but additional compounds that might come down the line for a particular disease.

DR. VENITZ: Dr. Zineh?

DR. ZINEH: I just want to build on both of those last comments in response to Dr. Collins.

So in terms of examples that we have, as you describe them, there are very few of those kinds of examples, sort of predictive examples, if you will. On the other hand, if pharmacogenetics is being done well in early development, you won't see -- the public won't see the value of pharmacogenetics because it's going to either kill a drug due to outliers, unacceptable outliers, or a margin that's unacceptable based on genetics; or in many ways, in many applications, it'll inform dose selection in later phase studies.

So at the end of the day, what you have is either a no-go decision, which no one will see, but that's still a valuable decision that was made based on pharmacogenetics; or you have a dose or a set of doses that were selected and informed by the genetics that the sponsor deems to be acceptable from a

risk/benefit standpoint in the larger population in the absence of genetics.

So you may not see genetics translate into a label even though it's been employed quite impactfully in the drug development space. So I would argue that there are actually a lot more examples than the public sees.

DR. VENITZ: Dr. Collins?

DR. COLLINS: Well, I agree. But for those of us around the table who don't work at the FDA, we'll never see it. But for those people who work at the FDA, you will see it. You will know it. And I would argue that you have an obligation to redact it fully, not disclose any commercial information, but inform the public about those cases.

If you can do just, in the last five years -- there were 250 NMEs, of which is the number one? Is the number five? Is it a hundred that were stopped because of this go/no-go decision based on prospective genetics? That would be extraordinary in terms of informing the public about the value of this.

DR. ZINEH: Just to be clear, in both of

those -- so we know the -- or we can get the numbers for the latter example. That's actually in the public domain in terms of the reviews that get posted. What I mean by that is if genetics was used to select dosing, that's part of the development program, and we have that information, and so does the public.

The decision not to pursue a drug, we have anecdotes. We never see them, so we don't have that information specifically.

DR. VENITZ: Okay. I think we covered Question No. 1 extensively. For the sake of time, let's just move to Question No. 2 and see whether there are any additional comments by any of the panelists. So this is comparing the genome-wide approach versus the hypothesis -- or exploratory versus hypothesis-driven approach. Any comments?

DR. BARRETT: Yes. I really applaud the proposal here. But I guess one of the things I was concerned about is, again, the clinical pharmacology. Early phase population seems to be at variance with the ability to identify signals. I'm not saying not to do it, but I think, you know, you're leaking into a

patient population eventually where you can take a look at the generalizability of the eventual marketplace.

But these are low frequency-occurring events. And to think that you can make those kinds of association during -- while you're accumulating that data, I think, is going to be challenging. I think the proposal, in terms of generating these kinds of mechanistic databases, is a good one. But I think you also need to have the complimentary patient-specific information.

In clinical pharmacology, we were very much focused on drug therapy, of course. And I think the example that Greg and others had given in pediatrics is a good one. But I liken it to the Etch-a-Sketch: When not a lot is written on it, it's easy to see who did it. But as we age, it becomes much more difficult to see what happened along the way. So things like environmental factors or other patient-specific co-variants are not part of the database where those kinds of associations would be established.

I think this is a situation where, if we did

have more of a retrospective view of certain highly public-knowledge areas, like the statins, like the COX-2 inhibitors, in terms of being able to drill down, would we have seen those events had we had focused this kind of a scope on the early phase development? That would be much more compelling in terms of building this case.

I think it's something that should happen just matter-of-factly because it's important that this kind of proposal move forward. But convincing people that it's rigorous and that it has the ability to identify these signals, and that the signals identified in a phase 1/2 population are going to be generalizable to a patient population, that's the story that I think has to be told as well.

Again, you've got small sample sizes. You've got differences in terms of the patient population. The exposures are not the same. It may be very helpful in terms of looking at acute toxicities or adverse drug reactions, et cetera. But in terms of predicting what's going to happen from long-term chronic administration, it may be less

clear.

Again, I think it's something that still should move forward, but understanding the complexities of the data and looking at the patient in a more holistic way, I think, has to be factored into this proposal.

You said here that the unifying theme is to identify variability and uncertainty at the individual level. But it seems that we're focused a little bit more on building the mechanisms, which again is an important building block here. I just think we have to keep in mind the patient-specific factors and how complex this is.

DR. VENITZ: Dr. Lesko?

DR. LESKO: I think there's another way of thinking about this question, and that is, it's not an all-or-none approach. So could one conceive of a risk-based approach to when I might decide to collect DNA in a drug development program, and what would that criteria look like?

Well, for example, would I rely on the mechanism of elimination of the drug, something

totally metabolized, something totally excreted through the kidneys? That might be one level of decision-making. Another might be: Do I know of a pathway that has a validated polymorphism, a 2D6 type of thing, as opposed to one that doesn't?

A third thing might be, you know, we've used the biopharmaceutic classification system of permeability and solubility to identify molecules that have an interplay between enzymes and transporters, you know. Would that be a sort of an attribute of a drug where you might want to look at a DMET chip, for example, to see what effect transporters have?

You know, begin to stratify the question into -- just like we do with populations. You know, here's a high-risk population. Well, here's a high-risk drug. And over here is a low-risk population, a low-risk drug.

So short of saying, let's just do this for everything, is it possible to identify molecule attributes that would lend itself to targeted DNA collection because we anticipate something?

We might even think about drugs in a class.

What have we learned from prior molecules with similar structures? You know, and think about it along those lines.

DR. VENITZ: Let me maybe follow up on that in favor of the candidate approach, where you have some mechanistic understanding how it might affect exposure or response. I think one of the benefits that you have, and I think that's implied in the question here, is that you can actually assess two things. You can assess the magnitude of exposure change/low response changes, and the potential clinical significance, which is something that you wouldn't get any other way.

So, for example, 2C9 poor metabolizers, we might know a lot about exposure changes based on phase 1 or drug interaction studies, but we have to translate that into clinical outcomes.

Then, obviously, a focused approach using that in phase 2 and phase 3 would help you to understand, does it lead to an increased incidence of adverse events or changes in efficacy as a palliative for clopidogrel?

So I think the candidate approach, to me, is very meaningful, not only to understand the mechanism, but actually to understand its clinical significance. And it goes beyond the drug/drug interaction. So I would actually be very much more in favor of a candidate type approach, where we understand the mechanism and can relate it to clinical outcomes, than hypothesis-generating that we still have to prove after the fact before we can make any dosing recommendations.

Dr. Giacomini?

DR. GIACOMINI: Yes. So I guess I'm in the middle of what Jurgen is saying and totally doing an exploratory GWAS without candidates. And that is, I feel like a lot of pre-clinical information, you know some transporters, some enzymes, that are interacting with the drugs. You're not sure quantitatively, clinically, which ones may play the more important role or not.

So in that case, I'm for including the pathway genes, including those in terms of your genetic analysis, but adding the other enzymes and

transporters that you may not know about as well in that first look. Because you may find that a variant, a polymorphic variant in one of those transporters or enzymes that you hadn't thought was that important in your pre-clinical study but was a minor role, may be playing a more major role.

So I like the idea of candidates. But explore the transporter ADME world in your pharmacokinetic determinations.

DR. VENITZ: Dr. Flockhart?

DR. FLOCKHART: Well, this may be stating the obvious, and I think I'm agreeing with a lot of what has been said. But I think the answer to these questions of whether to take a candidate pathway approach or genome-wide is very, very, very area-of-medicine-specific and it's very drug-specific.

But the simple things are, I mean, candidate genes are robust. They're cheap. They're fast. And genome-wide associations are not robust, they're not cheap, and they're not fast. I think in situations where you know a huge amount about it, actually sometimes it's very difficult to justify a genome-wide

association just on cost, simply on cost.

You need large, large, large numbers, and then you need to validate afterwards. And I think there are situations where let's be honest about this. We're trying to help people who are trying, in a very challenging environment, to not only present new drugs that will be useful to large numbers of people and safe, but be practical, be economically doable.

I think that in general, when you have a good handle on the basis of the pre-clinical work and what the genetics might be, it might be very hard to justify actually doing a genome-wide association study. It's not hard to justify collecting DNA. Never hard to do that, I think. Relatively easy to do that, building on the last question. But actually doing a genome-wide, when that is also itself evolving towards next generation sequencing and circulating microRNAs, it can be hard to justify.

DR. VENITZ: Any final questions or comments? Dr. Huang?

DR. HUANG: I just want to mention, just related to the candidate gene approach, and I want to

mention that with our draft drug interaction guidance, which we are revising to come out with another draft, which will be a revision of the 2006 draft guidance. And we really talk about pathways. If it's a metabolism pathway, we have certain basic enzymes that will suggest to study.

So they will have data in the submission, and based on the decision tree that we have proposed for metabolic enzymes. And later on you will hear a way to present for transporter, what kind of decision tree we have. You will have a pathway on how to evaluate the importance of certain pathways.

With that, we can have some information about genetics. And earlier on, we have heard that perhaps we need to know more about what we have done pre-marketing. And we do have a drug, tetrabenazine, which was approved several years for Huntington's chorea. All we know is a CYP2D6 substrate. And based on a prooxidase interaction study, we label it on 2D6.

So at that time, I mean, for this particular case, we do not have DNA samples, but we can extrapolate. But on the other hand, if we have

genetic data like the clopidogrel case, we can come back and ask CYP2C19 a question on genetics.

So I think it's very important to consider, if we want to talk about candidate gene approach, that it's very important to hear from the committee, if we are going to go through the candidate gene approach, what kind of -- which pathway that we should focus on.

I mean, I know there are commercially available gene chips with a lot of enzymes, more than we have recommended the sponsor to study, and also transporters. But it's important to get feedback on what are the ones that are mature enough that we need to evaluate at this point, or we would recommend the sponsors to do.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: Well, I think that we have a very pharmacokinetic-based discussion we've had so far. And certainly, the GWAS chips do a less -- or have poorer coverage of many of the pharmacokinetic candidate genes compared to some of the more custom chips now, the DMET plus, et cetera.

But it's pharmacodynamics that is the area

that we're kind of ignoring because it's so hard. And that's the area where there have been some nice insights. I mean, who would have ever thought we would have a validated marker for interferon response? The data that came out of there was -- those genes were not on anyone's list, would not have been on a custom chip.

Same with the more recent ribavirin. And, you know, even though Dave Goldstein's from another North Carolina-based university, he did some phenomenal work identifying things that were not obvious. And so I think where pharmacodynamics seems to be the key step, that we really have to go to a GWAS-type approach business because we're just not very smart.

DR. VENITZ: Unless there are main objections, I'd like to move us to topic 2 to stay within the timelines. Are there any objections? Any additional comments that anybody wants to make regarding pharmacogenomics, pharmacogenetics?

[No response.]

DR. VENITZ: Okay. Then let's move on to

topic 2, Question No. 1. I have a list of people that didn't get a chance to talk about it, and I think the first one is Dr. Caldwell. You had a comment to Dr. Abernethy.

DR. CALDWELL: Thank you. I just wanted to bring us back to the discussion we were having before, about looking at approaches to adverse events, and particularly in the post-marketing pharmacovigilance stage.

I think that databases are extant that can provide effective ways of being able to get at some of these adverse events in a non-biased way. And I think it addresses some of the questions of fuzzy phenotypes that we talked about earlier, and that is that most of the phenotypes that we work with for adverse drug events currently are biased by our own thoughts of what the adverse event should be, based on the class of drug, or what our experience has been.

But some of our recent experience using machine learning to interrogate electronic medical records has demonstrated to us things that -- you can pull out phenotypes quickly. You can pull out

phenotypes in an unbiased way that you would not necessarily have predicted before.

For instance, we can go -- we can look back at clinical data and could have predicted, within a year and a half after the COX-2 inhibitors were on the market, that myocardial infarction would be an adverse event from COX-2 inhibitors because with machine learning, as you interrogate it, the rules bubble up and you start seeing myocardial infarction associate with people who are on COX-2 inhibitors. It wasn't predictable at the time. It wasn't in our bias at the time. But it certainly comes true.

Similarly, with COX-2s, you can go in and predict with about 75 percent accuracy the people who are going to have an MI before they take the first pill, just based on clinical data.

Thirdly, you can go in and in a reverse way ask, of those people who are taking clopidogrel, for instance, what associates around the patients who are on clopidogrel. And one of the things that associates around them fairly early on is patients who are taking clopidogrel and also a metrazol and stroke.

So that these types of things, we have these databases extant. So I don't think we have to necessarily recreate these types of databases. I think we just need to organize and effectively validate and get much more experience with some of the very effective machine learning tools that are currently out there.

I think that this entire approach here is prescient, and is -- I applaud it because of the approach of beginning to take an organized way of doing discovery on adverse events in a nonbiased way.

DR. VENITZ: Dr. Barrett next.

DR. BARRETT: I think I actually gave my comments in the previous section, as you're looking at me confused. That's why.

DR. VENITZ: Dr. Lesko next.

DR. LESKO: Yes. The comment I want -- it sort of builds on what Dr. Caldwell just mentioned. We don't think you need to build a database. We have a contract which we've already announced publicly, so it's in the public domain, with a company called Biovista. And they make something called the Biolab

Experimental Assistant.

You're right in the context that this is extremely bio-informatic based. But one of the things we hope to do is connect databases in a way that's unique, i.e., can you take a smart system such as the Biovista, which connects, really, concepts and ideas based on information in the public domain. I think it sort of analyzes in a meta-analysis way as many as 23 different databases of pharmacology, toxicology, pathways, et cetera, and combine that with databases that are uniquely regulatory, i.e., the NDA database, or the post-marketing surveillance database, or even some of the strategic adverse event consortia data, which gets information on toxicity down to the patient level, and begin to interrogate that combined database.

That being said, what we find in the early going is kind of what Dr. Caldwell said. You know, you look at -- the user of the approach is very critical here because the bio-informatic piece is just a piece of computer software, if you will. But looking at it in an intelligent way and, I think, in a

clinical pharmacology/medical pharmacology way is really going to be key. And you need to be able to look in all domains of therapeutics, not just what you're used to, whether it be cardiovascular or neuro.

So the examples that have been published, acknowledging that these are not peer reviewed by people that have used this system include things like, can you predict with Tysabri before the event occurs, that this drug would activate the BK virus and cause PML? There's some evidence that that in fact was done. Can you predict adverse events of a class of drugs in oncology that were related to a five-year time period and accurately predict those events in a high percentage of cases? These are the kind of things, if you want to think about it in a more futuristic way, that we're trying to sort of explore the possibility of. And again, this has already been done and presented, at least in abstract form. So we find that kind of appealing.

So the twofold approach here, if you think about it, is to test prospectively hypotheses that might be done pre-marketing and then to explore

potential hypotheses post-marketing when events occur. And that gets back to this forward and reverse pharmacology/medicine approach that I was talking about.

DR. VENITZ: Dr. Kearns, I had you next.

DR. KEARNS: I don't think I have any other questions or comments that haven't already been said.

DR. VENITZ: Okay. Dr. Mager?

DR. MAGER: Thank you. This is a very exciting and timely approach. But I think we're also in the very early stages of being able to do some of these things. We talk a lot about bio-informatics, and although the systems biology tools are there, we really have no clue about linking this with clinical pharmacology and linking with macro-scale PK/PD.

About a year and a half ago, there was a meeting at the NIH to discuss this very topic. And they had to quickly close off the attendance because it was overrun very quickly. Everyone wants to know how to do this. And there's going to be another meeting this year to address this.

It was very interesting, though. We had a

very nice spectrum of tools that were provided, but I don't think anyone went home to do anything differently.

The point is, how do we begin to integrate some of these ideas? The very first question of that meeting was asked by an analytical chemist. And he stood up and said, what do I need to measure? And after a very long and awkward silence, they went on to the next question. And that is the point, I think, that Dr. McLeod was bringing up earlier as well, is what are the sponsors going to need to measure?

But I don't think that should be the focus. The point is, really, as you've nicely pointed out, Dr. Abernethy, is the focus on pathways. And the fact is that we already know quite a bit about molecular interactions that already exist in the literature.

If I could rephrase your question, it is not, what is the best way; it's what are the best ways? And we have to keep in mind that we really have to utilize an entire spectrum of approaches. And that can change quite a bit, depending on the goals and objectives of a particular analysis. It can also

change on the available data.

You may have very qualitative data up front for some very specific systems. And there are tools available to address those types of systems -- discrete dynamic, Boolean networks, et cetera. So there are a lot of machine learning and other approaches that were mentioned earlier that can be used in those qualitative stages.

But I applaud your focus on pathways because it lays down the platform, all right, the structure that these qualitative measures could be brought in at in the beginning. But it evolves, then, to add in sort of the ordinary differential equations, the kinetics that we eventually come to learn through collaborations with academic scientists, industry scientists, et cetera.

So I'll leave it at that.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes. I like this approach. I like the futuristic look into mechanisms and relating mechanistic clinical pharmacology to the epidemiologic surveillance that goes on at FDA. I

think it can be very powerful.

I also want to point out that, you know, you can -- there's a lot of information in the genome-wide association studies that can be used to inform the epidemiology and the biostatistics people as to what to look out for.

I mean, a good example is the GWAS hit on OATP1B1 for statin-induced myopathies. There you could predict -- you might not have genetic information, but you certainly would know people on drugs that inhibit OATP1B1. And therefore, those people would be at risk.

So mining the GWAS data along with the pathway data would be, I think, excellent for integrating the mechanistic clinical pharmacology with your post-marketing surveillance.

DR. ABERNETHY: Agreed completely. The kind of mining that Larry was mentioning essentially would include anything that's in the published literature. So that, we hope, will get us to those kinds of associations and then to formulate.

I'd react to that and then some earlier

comments. A huge piece, really, is to have sufficiently characterized phenotypic information so that one can then look at the associations that are made and test. When there was talk about, well, you didn't talk about proteomics or metabolomics, and others talked about the shifting phenotype, well, I think that's all part of the equation, and what I see as one of the big challenges.

Because when one goes to an electronic medical record, there is varying amounts of real characterization of that patient. And so we have to think and evolve how to best do that.

DR. VENITZ: Dr. Thummel?

DR. THUMMEL: Darrell, yes. Thinking about the pre-clinical domain and the idea of linking chemical systems biology with biological pathways, I obviously think that's a tremendous idea. But I wonder if you could elaborate on what your expectations are or envision that developing into.

Is it going to go beyond, you know, current structural alerts in terms of a chemical structure, or effector screening panels that are run, to something

more robust that involves a full structure/activity relationship between chemical structure and possible effect or interactions? And then, also, what do you envision the role of the sponsor is going to be in developing that database?

DR. ABERNETHY: I'll take the second part first. That's easier.

We're learning that a number of sponsors are very active in this area right now. And we look to collaborate with those sponsors, we hope, in the so-called pre-competitive arena so that we can really work together in a scientific collaboration to move that piece forward.

Now, how far can it go? Well, you know, I think there, you're tying in a time frame. If you'd say, what can we do in six months or what can we do in a year, I think that those will be probably fairly rudimentary sorts of linkages.

But thinking down further, really, you know, we're only limited by the science of linking those kinds of databases and those kinds of approaches together. And so I hesitate to give you a clearer

time frame, but, you know, I'm an optimist at heart. I think the sky is really the limit. But we just have to get the pieces of science in place.

I am very encouraged that within, as I say, particularly industry but some in academics as well, there are isolated nodes of really exciting activity. And I'm hoping one role we can play is bringing in a collaborative cross-talk to really move the area forward faster. That's a general optimistic comment.

DR. VENITZ: Dr. Flockhart?

DR. FLOCKHART: One tiny and very obvious point. But just to follow up on the last points about the quality of the data in the database, I think a message, really big message, that has to go out is the quality of the medication data is critical to this. In many of the epidemiologic studies that we have related to GWAS where we're looking for disease prognosis, you know, the actual importance of medication data, I think, has been underplayed a huge amount.

But actually finding ways that we can improve medication data in large databases I think is

really a critical thing to understanding toxicities, understanding the role of genomics, and all these other things as well. And it's a huge hole. We're not emphasizing it enough, and as a result, we're missing a lot.

DR. ABERNETHY: I think --

DR. VENITZ: Dr. Lertora?

DR. ABERNETHY: Oh, pardon me. I think our hope is that we'll be looking at specific databases that have the richest information possible. For example, we're encouraged by the kinds of databases that may exist in other countries that have different health care systems.

But within the United States, there are selected providers that really do have very comprehensive sorts of what I'd call phenotypic-including drug exposure information that we really want to hone in on. And we're hopeful that by selecting very carefully, that we can at least address that issue.

DR. VENITZ: Dr. Lertora?

DR. LERTORA: Again, I think this is a very

interesting and potentially very useful concept to pursue in terms of toxicity and adverse drug reactions.

I just want to comment in terms of opportunities for interactions and access to databases and other potentially useful information that, as you are probably well aware, there are initiatives at the National Institutes of Health, for example, in terms of quantitative and systems pharmacology.

Certainly toxicity of drugs is in that general paradigm, and also initiatives that link to the National Chemical Genomics Institute that also have implications along this type of conceptual approach.

So I think there are many opportunities, and we have great potential to advance the field in this area.

DR. VENITZ: Dr. Caldwell?

DR. CALDWELL: One of the other small points that I wanted to make is that the process of machine learning is it goes through a database, spits out rules, and then there needs to be some sort of an

interpreter, usually a physician, that takes a look at those and see if the rules make any sense.

But your pathway database is an excellent integration tool for that process. It's a very effective way of taking the rules that are coming out of a machine-learning approach to a database and then being able to come up with hypotheses as to what's actually going on in that situation. It's a wonderful mix.

DR. VENITZ: Any other comments before we move on to our next topic?

[No response.]

DR. VENITZ: Okay. Then I think we've finished topic No. 2, and we're getting ready to start our topic No. 3. And I think Dr. Huang will introduce that topic.

DR. HUANG: Thank you, Jurgen. As Dr. Lesko mentioned earlier, that in 2008 we did publish a concept paper on pharmacokinetic and dose adjustment in renal impairment where we talk about study design.

After that meeting, besides the comments that we received from the committee, we also received

some public comments. And so we worked on the comments and we have another guidance as a draft, which I was told by Mimi Phan it was just published and put online about 30 minutes ago.

[Laughter.]

DR. HUANG: So this is an update of our 1998 guidance. So I'll tell you what are the major recommendations as compared to '98 guidance. So everyone would have copies outside if you don't have it. We're waiting for it to be online before we can release the slides.

So the major changes are -- this is what you discussed:

Recommending renal impairment studies for drugs that are eliminated via non-renal route in addition to those via renal route, which we already recommended in the '98 guidance.

We have discuss the MDRD equation, and here we are recommend that GFR staging the categorized patients by both estimated GFR -- that's based on MDRD equation -- in addition to estimated creatinine clearance based on CG equation, Cockroft-Gault.

The third point is, we are highly recommending studies in dialysis patients both on and off dialysis. Based on our survey of newly approved NDAs from 2007 to 2009, we only have about 44 percent that have conducted hemodialysis studies, when they could have useful information in what does dialysis do to the new molecule.

So I will focus on the first point. We know that if drugs are cleared renally -- for example, we put out the first two compounds in the table, and the definition of drug that's cleared renally is 30 percent that is excreted of the drug excreting change in the urine. And you can see that there are some relationship between the area under the curve and the renal function. And this is based on our 1998 categorization. So we have creatinine clearance more than 80, 50 to 80, 30 to 50, and 10 to 30. And you can see there are both relationships between the GFR estimated by the CG equation and the area under the curve. And then accordingly, we have made recommendation on dose adjustment.

However, we also found, for drugs that are

not renally cleared -- here again, definition is percent excreted unchanged in the urine is less than 30 percent -- and you can see that we don't usually see a change in the area in the curve, or systemic exposure in renal impairment, unless the patients are under a severe category.

So based on that, in our current guidance that's just released, we recommended the study design. We could use a reduced study design. And what that meant is here there are five categories. So we have control, mild, moderate, severe, and end stage renal disease patients.

Under ESRD, we have patients less than 15 ml per minute. And I have listed eGFR and CLCR, so I have MDRD and a CG equation side by side. And I'll explain that more later. But we separate out our patients on dialysis and patients not yet on dialysis.

So our recommendation for reduced study is to compare two groups, the control group versus the severe group, ESRD. And we believe with the worst case scenario, it would apply to drugs that are eliminated via non-renal route because we usually do

not see changes in mild/moderate unless there's either severe or end stage on renal disease.

We also recommend full study design if this drug is eliminated via renal route, based on our definition. However, the sponsor can choose to do a reduced study because oftentimes we don't know all bioavailability, and we weren't sure whether this drug is -- when you cannot calculate the percent excreted and changed in the urine because you have to correct for bioavailability.

So they could do a reduced study, look at the worst case, the extreme cases of renal function. Then if it's positive, then you add the intermediate group, the mild, moderate and severe group.

So essentially, we have come up with a decision tree, which is a slight modification than what we have presented two years ago. So we say if the drug is for single use, it's volatile inhalation, it's not likely to be used in renal-impaired patients, then we will say you would not need to do a study. However, if there are chronical use, oral, or other parenteral route and it's very likely to be used in

the target population who have renal impairment, then we look further the route of elimination.

So again, if this is renally -- mainly renally eliminated, then we say, we recommend a full study. But the sponsor has a choice to do a reduced study first and then, depending on the outcome, they can do the intermediate.

For a drug that's non-renal -- that's on the left side of the screen -- then we recommend to go ahead and do a reduced study. If it's negative, then we label as such. If it's positive, which will be depending on the study outcome here, we say depending on the magnitude of the systemic is changed, exposure change, and also exposure/response relationship, then we may ask the sponsor to go back and do a full study. Then depending on if again, for certain groups, there is no change in systemic exposure, then we'll label as such. And if there's a need, then we label.

Look at the drugs that we have approved recently -- 13 drugs that are eliminated via renal route, based on our definition of 30 percent. All 30 percent has -- all these 13 drugs has changes in

systemic elimination, in concentration. And we have dose recommendation for them.

For the other drugs that are relabeled as non-renally eliminated, we found that more than 40 percent, they have a change in systemic exposure in the most severe group that the sponsor has studied.

Later on, the discussion with the committee will be what would constitute the worst group when we do the reduced study? Is it end-stage renal disease patients not yet on dialysis? Is it end-stage renal disease patients on dialysis? And our current recommendation in the guidance is end-stage renal disease patient not yet on dialysis.

So the second question -- and we did discuss two years ago, again, is about recommendation of GFR staging, either using estimated GFR -- that's the by MDRD equation -- in addition to estimated creatinine clearance by the CG equation.

Just to remind you, there are three ways that we have seen, methods in the submission, either direct measure of creatinine clearance, which we don't see as often. A CG equation is what we've seen have

the most in our recent submission. And this equation was derived from 249 men with 24-hour creatinine clearance that ranged from 30 to 130 ml per minute. And that's back in 1973.

We have seen increasingly use of MDRD equation, and we have received a lot of requests from the sponsor. Can we use MDRD to categorize our patient when we conduct renal impairment studies? Because the values are readily available, especially when you conduct large-scale study or when you do population studies, the MDRD is a common value that they receive. So they have asked us.

The MDRD equation, again, is derived from a large study where they're evaluating modification of diet in renal disease population. So it involved 628 patients with chronic kidney disease in 1999. And then it was re-expressed in 2005 because they have used -- the investigator has used a new method which does not have interference -- that the color, methodology that was used before, which overestimated the creatinine level.

So here, just a quick review of what the CG

equation look like and what the MDRD equation looks like. Both have age and gender in the equation. The MDRD equation has evolved from six to four parameters, and the latest one, which I cited here from the Kidney Foundation, it included not only age, gender, but also race.

Just note that the unit from CG equation is ml per minute. But for MDRD, it's 1.73 meters squared. So if you want to be very precise, it's not an average patient; with different body surface area, then you would need to correct for that number in order to get ml per minute when you do a dose adjustment.

This is just -- and we actually have the author in the audience -- I mean, on the committee. It's a comparison of the CG equation versus MDRD. On the left panel, it's a comparison of using MDRD equation compared to a gold standard. And this is using iothalamate to estimate GFR. The right is the CG equation.

Here, it shows 88 percent of MDRD variability can be explained by this correlation. On

the right, CG equation is 83 percent. When you look at the percent, the proportion of the data that's within 30 percent of the standard by iothalamate, 90 percent of the MDRD estimate has that. On the other hand, if you look at CG, the proportion of the data, based on CG and within 30 percent of the value by iothalamate, is 60 percent. So this is only one of the data that's been published recently.

So because in our '98 concept paper, and also we publish FDA's comments in November issue of Clinical Pharmacology and Therapeutics, we have received a lot of comments from individuals who support MDRD and individuals who support CG. And then we do have one expert on each on our panel today.

In addition, Dr. Shen Xiao has helped me collect all the information about who supported MDRD and who supported CG. So you can look at -- National Kidney Foundation indicated that among adults, the MDRD study equation may perform better than CG.

The American Society of Nephrology, American Association of Clinical Chemistry, American Diabetes Association, and College of American Pathologists,

National Kidney Disease Educational Program, they all support MDRD. In addition, the College of American Pathologists indicated, based on their survey, 70 percent of the clinical labs right now report out MDRD.

However, American Heart Association's recent publication, and also a lot of other publication, including pharmacy community, have indicated CG and MDRD may provide different dosing recommendations. So we need to be aware of this, especially for drug that's already approved and is labeled, and the dosing recommendation was based on CG equation. Even the GFR estimation based on creatinine clearance was based on the old method of creatinine assay.

We understand that there are major limitations of both equations. It would not work well with patient with low muscle mass; a low meat diet; patients with rapidly changing kidney function; patient with estimated GFR more than 60 -- you might be able to see some of the publications that show once the patients are more than 60, the estimation is not as accurate; patients with concomitant medication that

may modify creatinine production and elimination.

So there are other suggestions that we need a better equation -- not MDRD, not CG, not creatinine-based. Maybe we use iothalamate; there are some suggestion. And I look at the EMEA guidance which was finalized in 2004. They didn't mention use iohexol as the standard for doing the correlation between pharmacokinetics and GFR.

Although we did talk to our colleague at EMEA: Even it is in the guidance and so far they have not receive any that's used iohexol. Many of them are starting to use a combination of MDRD, which means they express ml per minute by 1.73 meters squared. But it's a mix of CG and MDRD. I don't want to speak for them, but I have seen some application which submitted both to the FDA and the EMEA.

Finally, the major recommendation from our current guidance is that we would like to recommend more studies be conducted in patients on dialysis. Based on our survey, there are drugs where we believe dialysis will affect its pharmacokinetics. But the studies were not done, and so we don't have any

information that we could put in the labeling.

Whether we have patients who are on hemodialysis, so Dr. Shen Xiao provided me this list, look at the recent survey. You can see that patients on hemodialysis, the upper blue curve, and the green curve is on peritoneal dialysis. So we have more than 300,000 patients here -- this is based on 2005 -- on hemodialysis. So it's very important that we understand whether we dose optimally for patients that are on hemodialysis.

In addition, with some manipulation of this data, Dr. Shen Xiao also indicated that for patients that are not yet on dialysis, the estimate is probably around 20,000 patients. And his communication was from VA hospitals. There are also patients that are not yet on dialysis, so which to indicate that if we recommend to study the worst case scenario, the patients may be available for study.

So our proposed recommendation, just to summarize, for what drugs are renal impairment studies needed? We indicated that renal studies need to be conducted for drugs that are not renally eliminated,

in addition to drugs that are renally eliminated, which is already in our 1998 guidance. And we have developed a decision tree to include a study design.

Renal function, we believe, could be evaluated by eGFR based on MDRD, and creatinine clearance based on Cockroft-Gault equation. We have told -- we actually have several cases already where we have told the sponsor that they can use either, although most of sponsor come in to say, can we use MDRD?

So we say, well, you could. But when you analyze the data and you're trying to find a relationship between the change in pharmacokinetic systemic exposure, you do both correlation so we can get an idea of how would they look like.

This is a table that we recommend, possibly to express if you use -- for example, you're looking on the left side. That's estimated GFR based on MDRD. So we put out five categories, although in ESRD, we did separate out patient not yet on dialysis and the patient on dialysis. Then the right side is estimated creatinine clearance based on CG. Here I listed --

the dosing recommendation is the same, but they may be different. It really depend on the data. And we have this draft guidance, and we hope the sponsor will do the analysis. So we have more data to tell us how different would these two be -- based on those two analysis, how different will be the dosing recommendation?

A lot of publications right now that's being published, and in addition FDA have quite a few research projects ongoing, is to look at marketed products while we have that in the labeling, and then recalculate. However, we know that those creatinine clearance was not as accurate because of the creatinine serum assay was -- and we really are not sure which assay was used. So we hope that, going forward, we will have data to help us estimate and come up with a better recommendation later.

So our third recommendation is, ESRD patients need to be studied. We would like to study patients, ESRD, not yet on dialysis to provide the worst case scenario. We also want to study patients ESRD on dialysis, but both on and off dialysis, so

that we have an idea how the dialysis affect the drug disposition. And we have provided a decision tree. Again, this is for patients not yet on dialysis so we can get an idea of how renal impairment affects drug exposure.

So I would like knowledge. This is a very difficult decision. We have a lot of different opinion on not only what populations should be used to find out the worst case scenario, but also whether to use MDRD and CG. And we have comments from both sides, and they're all very passionate so we have to discuss. And the same thing within our working group, that we all have very different opinion; and acknowledge Office of New Drugs, cardio-renal division.

We have two medical officers in our working group. On Office of Pharmaceutical Science, this is Dr. John Strong; before he passed away, he has contributed greatly on the mechanism of how renal impairment affects metabolism. We have various individuals who come to the FDA on sabbatical. Dr. Art Atkins has visited us several times, and Dr. Ken

Thummel, also here. Dr. Gil Burckart, who actually now is part of FDA; and other individual team leader, Mike Neely; Office of Medical Policy, although I have to mention that Dr. Temple now is not with that office. He's the deputy center director for clinical science. And Janet Norden helps us with the labeling language, and in particular, the table that we have proposed. So they have said, if this is useful, based on the public comments, then that's what we will go ahead.

I would like to acknowledge Shen Xiao from the cardio-renal division. Most of the slides on MDRD and CG were prepared by Shen.

Just very quickly, I want to talk about question for the panel. So the first question is for a reduced study. We have proposed to conduct a PA study comparing the exposure of drug or active metabolite between a control group with a renally compromised group -- and that's patients with end-stage renal disease not yet on dialysis, in order to provide a worst case scenario.

So our Question No. 1, which will need your

voting is, is it feasible or necessary -- or we can refine it to, is it feasible and necessary to recruit ESRD patients not yet on dialysis who may represent the worst case estimate and increase in exposure? If your answer is no, then we'll continue to ask, if it's not necessary or feasible to recruit the study ESRD patients not yet on dialysis, what other patients with compromised renal impairment should be enrolled to provide the best estimate of worst case scenario?

So Question No. 2. In 2008, many of committee members may remember, they voted MDRD as the preferred method for renal function classification. Now knowing that the MDRD equation has evolved and there are many other opinions from various communities -- from pharmacy community, clinical medical community -- we propose that since MDRD and CG are both being used to a great extent, so our proposal is that when sponsor conduct a study, both eGFR, using MDRD, and estimated creatinine clearance based on CG, be presented. And if there's necessary to change a dose, then present it such as this table.

So the question for the committee is, do you

agree that this type of table is the best way to present these data and would provide clear recommendation to providers? So that's a voting question. And if you say no, will this presentation of renal impairment group and associate dosing be confusing? So even if you say yes, this is going forward for drugs that we are reviewing right now. But for marketing drug, would that be confusing in terms of dosing adjustment for older drugs that's already on the market where most of the studies and recommendations are based on CG equation?

Thank you. That's my two questions.

DR. VENITZ: Okay. Thank you, Shiew Mei.

Any clarification questions? Please refrain from discussing the questions that we are going to discuss after the lunch break. So are there any comments or clarification questions that you may have for Dr. Huang? Oh, go ahead.

DR. CALDWELL: Shiew Mei, thank you. I just want to, for point of clarification -- these methods that you have told us about and are in your guidance are only for adults. So is there a reason to

stipulate that?

Secondly, with regard to children, when kids are beyond about 18 months of age, their renal function physiologically is normal unless they have some renal disease. But the use of estimated GFR in the context, especially of a phase 2 PK study in kids, can be very, very useful and informative.

So should the agency provide some specific guidance that would be applicable to companies who undertake studies in pediatric patients, but that would be accurate with respect to methods of obtaining the information?

DR. HUANG: Right. In our current guidance, we did discuss patients that are obese, pediatric patient. And we have recommended different formula to use for pediatrics, although we do not foresee that we will see renal impairment studies be conducted in pediatrics during the regular submission time.

So we did not discuss further on what equation. But we did say, if you want to do your dosing recommendation, there's certain equation that we use, and it is in our guidance. Thanks.

DR. VENITZ: Any other questions?

[No response.]

DR. VENITZ: Okay. Then let's proceed with our next speaker. And that's Dr. Richard Lalonde from Pfizer. And he's going to give us, I'm assuming, big pharma's perspective.

DR. LALONDE: Good morning, everyone. I'd like to thank Shiew Mei actually for the invitation to participate in the meeting here today. And thank you to the committee to indulge me here and to provide a perspective on pharmacokinetic studies in patients with renal impairment.

I just have about 15 minutes, so I'll go relatively quickly, a quick overview. I'll discuss the decision tree that was just discussed by Shiew Mei. I'll discuss also some practical aspects of studies in patients with renal impairment and dosage recommendations, focus a little bit on learning versus confirming approaches in these types of studies, and I will also touch on the modification of diet in renal disease study, or MDRD and the Cockroft and Gault equations, and especially how we want to use them for

the purpose of making dose adjustments.

So this was the decision tree that was just presented. I won't spend too much time on it, but just suffice it to say that in general, I guess in my humble opinion, it certainly would support the points that are being made here.

I'm not sure you can see my pointer, but the evidence is pretty compelling now on the changes in pharmacokinetics in renal impairment for drugs that are mainly cleared by non-renal route. So we've seen this in literature. We've seen this in some of our own recent studies. So I think this is actually quite compelling.

The question that I'll come back to later, exactly, is the study population for that reduced study because I think there are some practical issues that I want to bring up for the committee here. And I'll discuss a little bit about the other arm of that decision tree for the cases for drugs that are eliminated mainly by the renal route.

Just to give you an idea of the typical demographics in these studies, I just pulled this from

one of the studies we did a few years ago that's in the public -- that's published. So first thing to emphasize is the -- so this is a so-called full study across the different groups, and including hemodialysis patients.

So the first thing to emphasize is the fact that these sample sizes are typically small per group. So where that leads to, is that often you may see some inconsistent results when comparing means across groups. As you all can appreciate, these small groups, you'll have more extreme values that don't always line up perfectly well. You may see sometimes the moderate group that seems a little bit out of synch with either the severe or the mild.

One thing that we see once in a while is also the healthy group that will be out of synch with the historical data. We may have data on a hundred subjects, healthy subjects, from prior studies, and the six or eight or ten in the study may be a little bit unusual.

So as was recommended in the guideline, going back to 1998 actually, we are strongly

advocating the use of regression approaches, essentially a learning type of analysis, to look at this, where you can look at all the data as opposed to looking just pair-wise comparisons, and actually will even include population PK data from other studies to help provide more accurate estimates of the impact of renal function and to develop dosing guidelines.

One thing that I do want to emphasize is that patients with end-stage renal disease, or with eGFRs less than 15 mls per minute, are very likely to be on dialysis based on the typical standard of care. So in this study here, just to bring to your attention -- I don't know if you see the little highlight I have on the right there. For the patients in the less than 30 mls per minute, according to the '98 guidance, the average creatinine clearance -- that was done by Cockroft and Gault in this case -- was 23. We had one subject, one subject out of eight, that was actually less than 15. That was actually at 10, estimated creatinine clearance at 10.

So it's going to be a real challenge to try to find those kinds of patients. I also looked across

several of our studies recently, and the most recent one that we completed did ten subjects in that low creatinine clearance group. And that takes us about a year to conduct.

The real recruitment challenge is not to find the patients with relatively mild impairment or healthy people; the severe group took us a year, and again, the mean creatinine clearance in that group was about 20, and we had one individual again in less than 15. So you can do the math in terms of what are the practical implications of trying to find these relatively rare birds.

This is to come back to another point about how we often know quite a bit about our drugs before we do the renal study. So this is from a commentary that John Wagner and I wrote last year at, actually, Shiew Mei's invitation relating creatinine clearance to pregabalin clearance on the Y axis.

This is just to give you an idea that you sometimes have lots of data before you do this renal study. So we have a mixture there of healthy volunteers, patients. We actually very early on knew

that this drug was excreted unchanged in urine to a very significant extent.

So you can see that there's often very clear evidence that renal function would affect PK, and that the reduced study in those subjects in these cases would not be necessary and is very -- expected to be positive. Actually, it's about -- we can be as sure as anything we can be in science that this would be a positive study, if we were to do the reduced study. So what we typically do in this case is move directly to the full study, as Shiew Mei indicated. And this was actually the full study that was done, again relating creatinine clearance on the X axis, estimated by Cockroft and Gault, with the drug clearance on the Y axis, so showing again the typical type of relationship here.

Again, emphasizing the regression approach where we tried to use all of the data from that study to do a so-called learning analysis as opposed to emphasizing too much the pair-wise comparisons, where we can sometimes be fooled. And not to emphasize this too much, but we also in this study looked at patients

on dialysis. So this is where subjects were given the drug pregabalin, given a dose of pregabalin here, and eventually, about 24 hours later during their hemodialysis period, you see the very efficient drug removal of doing this particular hemodialysis.

So coming back to the decision tree, again this is not really rocket science here. But just to emphasize that it's great to have this option for the renally-eliminated drug to go both ways.

As Shiew Mei indicated, I think we will almost in every case go right to the full study because we typically have enough information -- even if we don't know the fraction excreted unchanged, we'll have enough scatter of our data from our early studies to look at the impact of renal function. So that will be the desired path for us to take because the other path would essentially be a little bit more time-consuming for us and less efficient.

So I'd like to discuss now an area that's going to be -- probably raise some passion in the audience or in the committee, to look at methods to estimate GFR. So as you all know, both these methods

are used to estimate renal function and glomerular filtration by using different markers. It's useful to remember that, you know, obviously Cockroft and Gault was designed to help predict creatinine clearance. In the case of the MDRD, it was iothalamate that was the marker of GFR. So both are essentially models to help predict the observed, if you wish, experimentally-determined clearance of these markers.

So as we all know, all models are wrong. Some are useful. So the debate essentially lies in, you know, how predictive are these different methods. And we have some experts here in the room that can comment on this.

A key difference that was mentioned by Shiew Mei is that the MDRD study equation, the eGFR is reported in mls per minute per 1.73 meters squared, whereas Cockroft and Gault is reporting mls per minute. That may sound like a very subtle difference, but I think it is quite important for the purpose that we want to use it for here.

The MDRD equation was originally developed to help stage renal disease, and eGFR is now commonly

reported by clinical labs, as we heard earlier. So there's no need for clinicians to know the complex exponential equation that was developed for this purpose. Standardization for body size is actually appropriate for this purpose. You -- it makes a lot of sense, actually, to standardize for body size. You don't want to start comparing people with vastly different body sizes for the purpose of staging renal disease.

However, what is needed for dosage recommendation is the patient-specific eGFR or index of renal function and not the standardized value to a typical body size of 1.73 meters squared. So just as a reminder in terms of -- I'll spend a couple minutes here talking about this potential confusion.

The MDRD study investigators used the Dubois and Dubois method to estimate body surface area. You all remember the 1916 paper, I'm sure. But it's actually very commonly quoted in the literature, a method of estimating body surface area, shown here on the slide, this exponential function. There are nomograms out there that have been developed based on

this.

So just as a reminder, the MDRD study equation was based with -- what was experimentally determined was the GFR, using iothalamate. Then this was multiplied times 1.73, divided by the Dubois and Dubois estimated body surface area, and the model was developed to then help predict this standardized GFR to 1.73 meters squared.

So clinicians using MDRD will therefore need to estimate the BSA using the above equation in order to calculate the eGFR for each patient for dose adjustments. So essentially what we need to do is to unstandardize, if you wish, the eGFR for each patient.

So, for example, what we'll need to do is take the eGFR that's reported by clinical laboratories and then multiply that times the BSA estimated by, for example, this equation, divided by 1.73 meters squared. Given that this unstandardization is not needed for Cockroft and Gault, there is the potential for confusion by clinicians who may not realize the difference.

So I've just pulled a couple of things from

the literature just to highlight some of this. The very nice paper by Dr. Stevens from last year that compared these dosing recommendations by these different methods, there was a nice, interesting exchange. But the comment there is just for your information.

It says essentially, "Calculating BSA in clinical settings is inconvenient and unlikely to occur. Without that correction, significant dosing errors might occur."

There was a very interesting and, I think, very appropriate, I felt, point/counterpoint in the November issue of CPT that Shiew Mei and, I think, Art Atkinson worked on together. And actually, this point/counterpoint I think illustrates or puts together very nicely the different arguments on this debate.

One of those comments from those papers -- again, it says, "If applied clinically" -- this is about the MDRD now -- "would require the clinician to calculate BSA using an exponential equation" -- sorry -- "an equation requiring weight and height

raised to an exponent, thus negating the applicability of the value that can be automatically reported by the laboratory." Again, keep in mind that we get this value from the laboratory. It's nice and simple. But this is the part that will be necessary to essentially use the patient-specific eGFR.

So again, in my humble opinion, I don't think we want to use the eGFR in terms of mls per minute per 1.73 meters squared as the basis for dose recommendations. Actually, I don't think there's any debate on this. When you look at the literature, when people have compared these methods, they do this unstandardization. So it's done correctly by the investigators.

So again, just to beat this point further, two patients could have very different actual GFRs and dosage requirements even though their MDRD-reported eGFRs from the laboratory will be identical.

Even if the discrepancy will be relevant only for patients with BSA significantly different from 1.73 meters squared, you still have to do this BSA calculation to know that. You can't just take a

guess at that.

Other potential areas of concern -- there's some limitations of MDRD that were mentioned by Shiew Mei. And in fairness, there's similar limitations to Cockroft and Gault, as I said. These are both models to try to estimate renal function. And as far as some of the limitations of MDRD, attempts have been made to try to correct them with the latest version that was published just this past year, the so-called CKD-EPI updated equation that I presume eventually could become the new standard and replace MDRD. Maybe we'll hear about this from the experts in the room.

So implications for renal impairment studies -- so the FDA, as we just heard, is proposing to use both Cockroft and Gault and MDRD in these studies. And actually, this is not a problem. So my comments that I'm making here are really -- have nothing to do with the conduct of the PK studies as we do them in renal impairment.

We can do this. People have done these types of studies. This will be generally manageable. And since we understand the science and the

mathematics involved, people can do the right determinations.

The categories of renal impairment should be based on patient-specific eGFRs, not standardized to 1.73 meters squared. We'll need to specify which method is the primary one. I'm talking about the two methods of renal function estimation here for the purpose of the renal function categories because of the expected discrepancies between MDRD and Cockroft and Gault. Again, that's not an advantage or disadvantage of either method. It's just that they won't give identical answers. There will be occasionally people that will fall in different categories. And we just want to specify this ahead of time. Again, that's not a real major issue.

What's probably more important is that an appropriate number of patients across the full range of renal function is more important than the cutoffs for mild, moderate, and severe because again, we're trying to estimate that relationship. We want to have a broad enough distribution of renal function with adequate sample size to characterize that

relationship.

So in summary, the proposed decision tree is a positive step. De facto renal impairment on the PK drugs, including drugs eliminated mostly by non-renal mechanisms, I think sounds very reasonable. The need to study end-stage renal disease patients defined by GFR is less than 15 mls per minute. Patients not yet on dialysis, will be challenging and given the typical standard of care.

I said "may" there and I think I can probably make that a little bit more definitive based on -- as I looked at our past experience with studies and spoken investigators that may be in the room who are at centers -- basically, centers that do these studies all the time. The question essentially is, you know, is there evidence with multiple drugs that these patients produce significantly different results from end-stage renal disease patients on dialysis, but studied in between dialysis periods, of course? And looking at this literature, in my humble opinion, I think it's actually very scant.

So I think we want to maybe take a look at

that evidence before we put a burden that could really mean that these studies could take multiple years to conduct.

The option to go directly to the full study will generally be more efficient for renally eliminated drugs instead of the sequential path, with the reduced study followed by the full study. I think I made that point earlier. There should be caution in interpretation of differences in means between renal function groups with small sample sizes, again using this learning-regression approach.

The MDRD eGFR needs to be unstandardized for BSA in order to get the patient-specific eGFR to be used in pharmacokinetic studies like we're talking about here, categories of renal impairment, and dosage recommendations. And I think there's a real potential for confusion and error in the clinical application of dosage recommendations based on MDRD versus Cockroft and Gault. Whichever method, if we're going to propose both, I think we need to pay very special attention with how we're going to handle this, especially these differences in units between the two.

That is, I believe, all I have.

DR. VENITZ: Thank you, Rich.

Any clarification questions? Dr. Harralson?

DR. HARRALSON: I would assume that we're talking about the effect of renal clearance on the clearance of the drug. But if you bring in the issue of transporters, I think the evidence would be, you may not see a big change in transporter function until you get down to the very low renal function. So you might miss that if you were simply looking at the regression that did not include end stage.

DR. LALONDE: Absolutely. I think that's a very good point. And I think for the so-called reduced study -- is what you're talking about -- then you're studying the two extremes. The question of -- all we're talking about exactly is what is that extreme for the patients with renal insufficiency? I agree.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: Rick, I think a very, very compelling presentation. I appreciate it. I think, in general, for a renally impaired drug, the

regression approach is right on.

But in Shiew Mei's data, she kind of showed the difference between -- okay. Other people might not. Anyway, with the renally impaired and non-renal impaired, she has more of a step function in terms of the end-stage renal disease as opposed to -- so, you know, the comments you make in terms of the small group size, I think, are right on.

But I'm curious, in your experience, when you look back at some of your historical data, have you seen that kind of relationship where you might make a case for the reduced study design, where you could make a better comparison between a control group and an end-stage renal disease, where that kind of continuity or the continuum doesn't exist?

DR. LALONDE: I think I understand your question. Let me try to take a shot at it.

So I agree with what Shiew Mei presented. I think we -- I mean, sometimes you don't have the luxury of both data sets. If you do the reduced study, all you have are the extremes.

DR. BARRETT: Right.

DR. LALONDE: When you do the full study, you will have, as Shiew Mei showed -- we do that most often for renally eliminated drugs and don't do that as much for drugs that are -- at least not in the past -- for drugs that are mainly eliminated by non-renal mechanisms.

You know, if you look at the slides Shiew Mei showed, there was -- you know, there's one there that showed a bit of a trend in the middle group. So again, I would just say that you might want to be careful looking just at means.

I agree that the regression approach -- the effect is only at the extreme -- would not be the desired approach. So that, in my case, was -- my point was mainly to be careful when we look at -- for drugs that are eliminated by renal mechanisms and to look at the totality of the information.

But non-renal mechanisms, I think the reduced study sounds reasonable. But I guess I'm kind of going on and on here. I don't think I have data to help address the other point that you made.

DR. BARRETT: Okay.

DR. VENITZ: Dr. Lesko.

DR. LESKO: Rick, in your analysis of your data from your database, did you see -- did you look at drugs that are cleared, let's say, mostly by filtration as opposed to those that are cleared by filtration plus other mechanisms? And whether or not estimates of clearance, for the purposes of dosing, differ between these two different equations?

If we had such drugs, would we have discrepancies? Could we pinpoint discrepancies that one's going to expect based on renal mechanisms by using both of these equations? And is it possible to think about where one might work better than the other?

DR. LALONDE: Right. I think the short answer to your question is I don't -- I have not looked at that. We definitely have looked at drugs that are actively secreted and, you know, those tend to track nicely with the overall index of GFR, the so-called intact-nephron hypothesis, you know, that as basically you're losing filtration, you're losing also the ability to secrete.

There's some discrepancies about this. Maybe there are experts in the room that can comment on this better than I can. But I don't have the data, again, to -- I've not seen the data to address the point as to whether one method would be preferred. For example, because creatinine is secreted, to say that would be a better marker for drugs that have some active secretion, I would be surprised if we find that kind of evidence. But maybe I can be surprised.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: In the context of comparing different equations, do you feel like we're trying to be too quantitative or too precise? It just strikes me that we're trying to have fancy equations, and then we bin people into four groups. Maybe we should look at being less precise for the purposes of the spectrum that we're trying to look at for drugs.

DR. LALONDE: Yes. Many of you know that I'm kind of a modeling type of person. I'm very quantitative. I'm very impressed with the nice work that's been done by the MDRD investigators. It is actually cool science.

I accept your point, though, I guess, is that as I said earlier, all models are wrong. Some are useful. We're trying to get a measure of renal function. When you really look at these two methods, they're a lot more similar than they are different in terms of what we're going to end up with in terms of categories.

There are some discrepancies, and I'm concerned, to be honest, more than anything else, with the point that I made about the -- say we're trying to fine tune certain things. People say, well, there may be a slight advantage of one versus the other in this setting or that setting.

I'm more concerned with people that will forget to do the BSA adjustment. That could be a very significant problem. If you have someone who is -- you know, with a BSA or 2.1 meters squared versus someone with a BSA of 1.4 meters squared, that will be a very significant potential problem.

DR. MCLEOD: And a BSA of 2.1 would be a small person in today's America.

DR. LALONDE: [Laughs.] No comments.

DR. VENITZ: Dr. Dowling?

DR. DOWLING: Dr. Lalonde, thanks very much for your excellent presentation. You showed some very nice relationships between drug clearance and creatinine clearance, that relationship when creatinine clearance is estimated by the Cockroft and Gault method, in your particular cases.

I was just curious on your perspective. Cockroft and Gault clearly has been used over the years. There's a lot of controversy in terms of which weight to use in that equation. I was just curious, in your perspective, how you address that issue generally?

Is there a cutoff in terms of using ideal body weight versus actual? Or is it generally -- you know, obviously the original equation was based on actual, and there's been many studies since to show that, you know, in obesity, there are some adjustments that probably should be made.

I was just curious on your perspective in terms of that, showing nice relationships.

DR. LALONDE: Right, right. Okay. Good

question. As you can imagine, when we select subjects for these studies, we probably are not selecting the extremes of the distribution of body weight. So that doesn't really pose much of a problem for most of us in these studies, at least in my experience.

When we've done the correction you're talking about, it doesn't really make that much of a difference because we're not dealing with people who are, you know, 150 kilos or, for example, where there would be, you know, a real issue with using total body weight for, let's say, Cockroft and Gault.

DR. DOWLING: Thanks.

DR. VENITZ: Dr. Kearns?

DR. KEARNS: Rick, I'd look at you but I can't talk into this thing and look at you at the same time.

DR. LALONDE: I'm seeing your best side here, actually.

[Laughter.]

DR. KEARNS: I know. I know. Other people have said that.

It probably goes without saying,. But since

I do pediatrics, I'm going to say it again. This is all really good unless you're small. And the reason I bring it up is you brought out the point of confusion, and that's very, very important in the context of a clinical trial.

I can't tell you how many times we receive a protocol from a company. Of course, none of the companies that may be here today are guilty of this. But we receive a protocol from a company that, in essence, the word "adult" has been taken out and "child" has been put in it.

So all of the methods that, you know, the FDA puts in the guidance that says, these are our standard approaches, they wind up in the protocol. And it really causes some of the sponsors a great deal of confusion when we come back to them and say, well, I know this works for adults, but for kids, we have to normalize this. You have to use this equation.

So, you know, I would implore this group and the agency as decisions are made about refining what these documents say, to make sure those distinctions are crystal clear. That will improve doing these

studies in children.

DR. LALONDE: Good point.

DR. VENITZ: Any other clarification questions? Last one, Ed.

DR. CAPPARELLI: Yes. I think one of the differences that's implied, but I think we need to explicitly think about, is the assumption there that size is critical. It's critical for us in pediatrics because, as Greg points out, in the dosing for one method versus the other. Because if you're saying that we need to normalize, if we have a drug that we do feel that we do need to normalize based on size in an adult population, then doing that normalization step is necessary.

But if we're talking about a situation where, for the standard population with normal renal function, we aren't adjusting for size, then I think really looking at sort of the grade of renal function might be the approach. So we really do need to make that distinction. Where is the variability coming from? Do we need to make these distinctions at that point for the sake of simplicity?

DR. LALONDE: Yes. That's a very good point. Indeed, I've thought about this a great deal, and when you think about it, the purpose of these tables that were shown is to individualize drug doses. We're trying to use a covariant renal function to adjust doses based on that patient.

So it seems a bit counterintuitive to me to say I'm going to use a standardized measure of renal function when I'm trying to individualize doses based on index of renal function. So just to me -- I agree with you that, you know, for the -- obviously, if somebody is close to the average, this is not going to be a problem.

You want to be careful. And I'm just concerned. We get reports at times that people find our dosing guidelines like this confusing, a relatively simple table. So I just want to make sure that whatever we decide here, whatever you decide, whatever the agency, we can comply. This is not the issue.

All I'm trying to do is to make sure, remembering my clinical pharmacy days, of the types of

errors that exist or occur quite commonly.

DR. CAPPARELLI: Just one follow-up point for the group. We also then need to be very careful on how we dose-reduce because the issue of -- you know, as you go down, if we say that size is important when incorporating into that component, then changing -- extending the dose, which is a common approach to reducing the dose in renal function, may not be the same approach that we would use in a smaller patient.

DR. LALONDE: Good point.

DR. VENITZ: Mr. Goozner?

MR. GOOZNER: Forgive me if this sounds a little ignorant because as the consumer representative on this committee, sometimes I always wonder what I do or don't know.

But I get the point that it's very difficult to find people who have very low renal function and, you know, sort of difficult to recruit, and people who are on dialysis are much easier to recruit.

But also, I thought I read in the background documents that the average patient on dialysis is

taking something like ten drugs. So I'm curious if there's a real difference in the number of people -- the number of drugs being taken by people who are not yet on dialysis and on dialysis, and if that might have some impact on the results.

DR. LALONDE: Well, you raise a good point. These patients are not, you know, clean the way we -- when we do healthy volunteer studies. And that's just -- what we try to do essentially is try to avoid drugs that are -- you know, mechanistically we would see as would impact the PK of the drug that we're trying to evaluate. And that's just the nature of these kinds of studies. We just have to deal with that.

But to your point, maybe there's -- I'm sure there's better experts than I am in the room. By the time someone's GFR gets down to 15, these people have significant renal impairment. When people get on dialysis, they may get some other treatments. But they're not going to be clean patients one way or the other.

DR. VENITZ: Any other clarification

questions?

[No response.]

DR. VENITZ: If not, then let's take an early break, and let's reconvene at 12:25. Again, just a reminder for the committee members: Please do not discuss any of those topics outside the realm of our panel discussions.

[Whereupon, at 11:24 a.m., a lunch recess was taken.]

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

DR. VENITZ: Okay. Welcome back.

What I'd like to do is, before we start the panel discussion and the voting on the specific questions that we are asked to vote on, I'd like to finish the presentations. And we are now moving into a new topic, topic 4, the drug transporters. And our first presentation is Dr. Zhang, who's going to give us the intro.

DR. ZHANG: Thank you, Dr. Jurgen, and good afternoon. We have heard a lot of presentations this morning, and we kind of consistently heard a message. That is, it's very key to understand the inter-individual variability during the drug development, as early as possible, in order to manage those inter-subject variability in the clinical setting.

We know many factors could affect the inter-individual variability, both intrinsic and extrinsic factors. And this afternoon, we are going to focus on one of the very important extrinsic factors, that is, the drug/drug interaction that could affect a drug's exposure as well as response, both favorably or

unfavorably.

In the past, a lot of focus has been on the cytochrome P450 mediated drug interactions. We have learned a lot in the past, and also in the 2006 draft FDA interaction guidance has talked about a decision tree or some thought process on how to focus on the major cytochrome P450s in order to evaluate the drug interaction early in the drug development phase and learn how to manage them. And we all know, and we also heard, transporters many time today because transporters has also been found to be very important in determining a drug's pharmacokinetics through the absorption, distribution, metabolism, as well as excretion process.

These transporters are mainly memory-bound proteins that could either facilitate a drug's access to the cell, that is, uptake transporters, or limit the access to some certain tissue, such as efflux transporters may do.

So they are very important in not only determining the pharmacokinetics of a drug, but also in many cases, they are also determining a

pharmacodynamic reaction, such as by governing the delivery of the drug to the site of action, and also control the tissue concentration. In some cases, transporters themselves could be a drug target, delivery target.

So we know transporters, along with metabolite enzyme, could contribute to the variability in drug concentration and the response. For some drug, transporters could be a very important component for that determination, and by not considering drug transporters during drug development, may lead to unexpected toxicities or drug/drug interactions later on.

So this diagram just shows you the selected key transporters that express in the important absorption as well as elimination organs in the body, mainly the gut wall, liver and the kidney. As we all know, the liver and kidney -- or liver and intestine are the major organs that express various metabolism enzymes. And now we also know that these tissues also express various transporters, both on the apical side of membrane as well as basolateral side of membrane.

Here, I just show you the major efflux transporters that take the drug outside of cell, namely multi-drug resistance protein 1, also known as P-glycoprotein, and also breast cancer-resistant proteins. Both of these efflux transporters have been shown to be very important in limiting a drug's absorption when the drug encounter them in the intestine cells.

Also, we have found that there are many important uptake transporters, which located on the basolateral side or the cells that could help or facilitate drug uptake into important organs such as liver. That is a major site for metabolism to be happen, and also that could be a drug target site for certain drugs such as statin drugs.

The main uptake transporters in the liver are organic anion transporter, protein polypeptide OATPs. And in the kidneys, similarly, we also have a lot of transporters expressed on the basolateral side which function in the taking the drug from the blood into the cell and later get excreted into the urine. And the main ones are organic cation transporters as

well as organic anion transporters.

Also, we have seen in the literature or during the post-marketing drug approval phases, there's many reported drug interactions that cannot be explained by cytochrome P450 needed drug interactions such as are listed in this table. We know many of these affected drugs or those substrate drugs are not metabolized, mainly metabolized by cytochrome P450s.

So the interaction we saw here by the interacting drugs cannot be explained by the P450 needed interactions. And then later, based on in vitro studies, they were found to be likely needed by transporters such as P-glycoprotein as well as organic anion, OATP, or organic cation transporter, OCTs. And the consequence of this interaction could be ranged from twofold to sevenfold.

So by looking at those drug interactions, we are thinking whether we can use similar strategies we use for cytochrome P450 needed drug interaction evaluation, that is, to incorporate the in vitro tools early on to help us either identify or prioritize the drug interaction we need to be considered later on

during the drug development phase, or prior to the drug get approval to the market.

As Larry mentioned this morning, transporter, although it's emerging and a new area, but we have been discuss about it and being watched for its development since 2003. We have been discussing at the AC meeting since 2003. And in the past seven and eight years, there has been a lot of new development in the area.

So we today, we just want to see whether there are enough clinical evidence or enough tools which will allow us to put into a systemic way to study the transporters more systemically during the drug development. And also, we know from the literature that many transporters are there, and maybe not all of them are important in terms of drug disposition and drug interaction.

So the key question is which transporters we should be focused on that are clinically important and should be considered for evaluation during drug development. And today, I will post two questions to the committee, mainly focused on for drug -- new

molecular drug entity as a substrate or as an inhibitor for transporters.

As we all know, there could be two separate considerations here because for drug that is a substrate, they may not necessarily be an inhibitor for certain transporters, and vice versa. So we do need to consider them separately and may develop different decision tree or thought process for these two kind of -- these two parts of the drug interaction evaluation.

Since the 2006 AC, in that AC we mainly focus on -- because we just published a draft drug interaction guidance which we mainly focus on the P-glycoprotein. But we also want to see what other transporters we should also be considered based on the available literature, data, and the reported drug interactions and adverse event cases.

So in 2007, the International Transporter Consortium was formed, mainly from experts in both academia, industry as well as FDA. Actually, today we have at least four members in the audience. We have Kathy Giacomini and Shiew Mei Huang. They are both

co-chairs for International Transporter Consortium. And we have myself, and also Dr. Joe Polli as a member for the consortium. We have had very many discussions since 2007. And the ITC held a FDA critical path, and Drug Association Information Society sponsored a transporter workshop. And following the workshop, the ITC group developed a transporter white paper, which was just published in March of this year in Nature Reviews Drug Discovery, March issue.

We pose very similar question to the ITC, such as, what are the major transporters that we should be considered, and also, what tools we can be use to study them, and what are the decision tree we should be made during the drug development process.

Since many rigorous discussions, the group reach a consensus to focus on the seven major transporters, which are the P-gp, BCRP, two of the OAT, OCT2, and OATP 1B1 and 1B3. The group thought that these seven transporters represent the -- based on current data, maybe represent the most important ones we should be considered.

Subsequently, the group discussed what are

the drug development issues by considering those transporters could help to address, and also what other decision trees should be used in order to decide. Based on in vitro tools and other totality of the data, we may conduct specified drug interaction studies to understand those drug interaction potential.

Now I'm just going to focus on how those seven transporters may play a role in drug absorption, distribution and the excretion. First is the intestine, which is an important organ for drug absorption. In intestine, we mainly focus on the efflux transporters, as I mentioned early, P-glycoprotein and the BCRP.

They are very important in limiting the oral absorption of the oral drugs, and by inhibiting those efflux transporters, can cause increase in drug blood levels. And we already see in the literature ,the particular examples that are thought through P-gp or BCRP inhibition. Digoxin, that drug is very well known, and for BCRP, the clinical evidence is the GF120918 inhibit topotecan PK. And also there's a

2.44 increase in topotecan exposure.

Now we move to the drug elimination organ such as liver. The focus is on both the uptake and also the efflux transporters. The uptake transporters mainly are the OATP 1B1 and the 1B3. They found it to be very important for determining the PK of the one particular -- especially the statin drugs. They are found to be substrate for those transporters. By blocking those transporters, you will see not only the increase in the PK, and because the site of action is the liver, you may also affect their efficacy. In terms of efflux transporters, those MDR1 and BCRP are very important in the liver.

So in terms of the OATP interaction, the magnitude could be very large, such as I mentioned early. The cyclosporine could increase rosuvastatin exposure by sevenfold. And more recently, we found that HIV protease inhibitors are also inhibitor for OATP and causing twofold increase in rosuvastatin exposure.

In the kidney, the main uptake transporters are the organic cation transporter as well as organic

anion transporter, mainly OCT2, OAT1, and OAT3. And again, the efflux transporter, P-gp, are thought to be important in the renal clearance of drugs.

By blocking those uptake transporters, again you will see the increase in blood levels. And this organic anion and organic cation transporter inhibition has long been observed and reported in the literature. And until more recently, when the in vitro assay is available, then we tease out which OCT and which OAT are responsible for those reactions.

So now we moving from learning from the CYP experience. That is, there are many drug interactions. However, if you understand the CYP, you may be able to help you predict the drug interactions.

So now we add the transporter into the picture by understanding both enzyme and transporters that may be involved in the ADME process. And the potential for a drug to be either a substrate inhibitor or inducer for those process, we might be able to help predict the potential for drug interactions. And I envision this as an iterate process. So you will use in vitro models and tools to

help predict in vivo DDI studies. But many times, you may observe the in vivo DDI studies first. So you will use the in vitro tool to help you understand or explain what you have observed in vivo.

Then, later on, you may apply this knowledge into another drug on the board which were found in vitro to be either substrate or inhibitor. And that knowledge can help you predict what maybe happen.

Using rosuvastatin and cyclosporine interaction as example, so we already know cyclosporine could increase rosuvastatin exposure by sevenfold. And along the years, the possible mechanism of inhibition by cyclosporine were studied in vitro.

Initially it was found it could be OATP1B1 mediated because cyclosporine is an inhibitor for OATP1B1 and rosuvastatin is a substrate for that particular transporter. And more recently, it was found also 1B3 may be responsible based on in vitro results. Then, later on, BCRP, which is the efflux transporter, also found to be play a role because both rosuvastatin and cyclosporine interact with this

transporter. So in order to understand the in vivo interaction we observe, we know probably all of these transporters may play a role. By blocking them, that's how maybe you can explain the sevenfold exposure of rosuvastatin.

So learning from that example, we can use that knowledge to project the OATP and BCRP-based interaction. For example, cyclosporine as an inhibitor, they could inhibit other OATP or BCRP substrate. And this knowledge was used in a new developing statin drug, that is, pitavastatin.

It is found to be an in vitro substrate of OATP1B1, 1B3, and BCRP. And the sponsor conduct a drug interaction study during the drug development and found that cyclosporine increased pitavastatin exposure by 4.6-fold. So this information was obtained before the drug is on the market, and based on that particular drug, the recommendation is to counterindicate the use of cyclosporine with pitavastatin.

From the rosuvastatin data, we know rosuvastatin is going to be inhibit because it's a

substrate for OATP and BCRP. So for new drug that's going to inhibit OATP or BCRP, we probably would anticipate a drug interaction. This is a newly data we just obtained in the literature, that is lopinavir/ritonavir, was observed to increase rosuvastatin exposure by twofold. And the in vitro data indeed found that lopinavir is a very potent inhibitor for OATP 1B1 and 1B3.

Many times we know in order to understand the in vivo clinical significance of drug transporters, you would need in vivo data to study the role of transporter in the disposition of a drug. And typically that can be determined by either genetic studies, as we heard this morning, or specific inhibitors.

But many times, specific inhibitors may not be available. So the in vivo significance of transporters maybe rely on the polymorphism of the genes, if that exists, and to conduct comparative PK studies in people with gene of normal function versus the reduced absent functions.

So for OATP and BCRP and the P-gp, their

polymorphism has been described in the literature. In this recent review by a Finland group published in the Clinical Pharmacology and Therapeutics in the January issue of this year, they summarize what's in the literature and very nicely show -- because we know, even studying drug, they are all OATP substrate -- the relative contribution of OATP and possible other transporters could be different.

So by using those comparative PK data, we can estimate what the relative contribution of either OATP1B1, BCRP, which is the red bar here, and blue bar, which is P-gp on a disposition of a particular statin drug.

From this graph, we do recognize there's a different effect -- the statin drug. For example, for rosuvastatin, both BCRP and OATP are seems to be important in the disposition of rosuvastatin. But for pitavastatin, OATP1B1 seems to be more important. And for simvastatin, P-gp -- all of three transporters play a role, and P-gp and OATP1B1 have a bigger effect.

So this knowledge, coupled with what we

know, those statin drugs also are differently metabolized by various cytochrome P450, including CYP3A4, CYP2C8, and CYP2C19. So we know the relative contribution of each transporter or enzyme on the disposition of statin drug, as an example, is different.

It's going to be dependent on the inhibitor specificity for those transporters. And the enzymes' interaction with different statin may be different. And this information will be very useful for the practitioner. When they look at those data, they might decide what co-med they can give to a particular patient, or when they select which statin drug to be given to a particular patient who is already on other medications.

So with that, I would like to present to you our current proposal on how to evaluate new molecular entity, either as a substrate or inhibitor for transporters, and how to use that knowledge to direct the further drug interaction studies.

So for new molecular entity, we would like to put them into three different categories. For all

NME, we would like to propose to determine whether they are either P-gp or BCRP substrate. The reason is because the BCRP and the P-gp are express in various tissues and could affect a drug admin process.

Based on the in vitro data to show whether they are a substrate or not, then there will be further decision tree to decide whether there's a need for in vivo studies. And I'm not going to go through those, the blue box here. And it was expressed. The proposed decision tree was published in the transporter white paper, which was just published in March of this year.

For OATP transporters, the decision will be mainly depend on the drug characteristics, what it is going to be eliminated through the body. If it is hepatic or biliary secretion is the major route, then it will be very reasonable to consider determining whether this new molecular entity is OATP1B1 or OATP1B3 substrate. And then there will be a separate guideline on what in vitro data will prompt you to study the in vivo drug interaction studies.

Also, in order to study a drug as a

substrate for OAT or OCT, the renal -- whether the renal active secretion is major is a consideration; need to be considered before we conduct a study to determine whether new molecular entity is OAT1, OAT3, or OCT2 substrate. And based on the in vitro results, further decision could be made in determining whether in vivo studies are needed.

So for substrate, it will all depend on the characteristics, both physical, chemical, as well as pharmacokinetic characteristics of a substrate in determining which transporters you need to consider during drug development.

The next is the decision tree for evaluating of NME as an inhibitor for those seven major transporters. That is mainly to understanding the potential effect of those new molecular entity on other drugs.

So for a new molecular entity, the decision is mainly going to be decided by the therapeutic area and the likely co-medications. And for P-gp, BCRP, and OATP and OATP1B3, we would recommend to study all new molecular entities as an inhibition potential for

those four transporters because these four transporters will transport a vast majority of the medication going to be given by a patient population.

Also again, the blue box will represent the further decision tree, based on the in vitro data, in order to determine the need to conduct in vivo studies.

And for OAT and OCT, we use similar strategy just in order to determine whether -- for OAT mainly is also to determine whether NME is likely to be co-administered [inaudible] with the known anionic drugs that are known to be substrates for either OAT1 or OAT3; and the example given here, methotrexate, tenofovir and acyclovir.

If the answer is yes, we would recommend to determine in vitro whether the new molecular entity is an inhibitor for either OAT1 or OAT3. And for organic cation transporter, it was found that metformin is a substrate for OCT2, so if your drug is likely to be co-meds with those known cationic drugs -- the one example given here is metformin -- then there's a reason to determine whether an NME is an inhibitor for

OCT2.

There's a further decision tree based on the in vitro data to determine the need to conduct in vivo studies. Also, since the emerging research in the transporter area, this table just lists you the examples of the drugs that are known to be transporter substrates based on the literature search, both in vivo data, as well as sometimes when the substrate is not specific for that particular transporter, the in vitro data used to confirm those drug substrate for that particular transporter.

As we can see, there is overlapping in terms of a transporter, that they can interact with different transporters. Methotrexate is one of the example. They found it to be a substrate for BCRP, OAT1, and OAT3. And similarly, those tyrosine kinase inhibitors such as lapatinib was found to be a substrate for both P-gp as well as BCRP.

The statin drugs, as I mentioned earlier, some of them are substrate for all three transporters, including BCRP, OATP1B1, and OATP1B3. And some statin drug is also a substrate for P-glycoprotein.

In terms of the drugs as transporter inhibitors or inducers, we also see a lot of examples, in particular for P-glycoprotein, that has been studied the most. And we found there's overlapping inhibitor selectivity for transporters as well. And cyclosporine has been found to be a multi-inhibitors, inhibitors for multiple transporters, including P-glycoprotein, BCRP, OATP1B1, and OATP1B3. In terms of inducers for transporters, many examples exist in the P-glycoprotein area. And it was found that those inducers have a lot of overlapping with cytochrome P450 3A inducers because they act on a similar mechanism in activation of the PXR receptor. As an inducer, I didn't -- inducer for other transporters, currently the knowledge is lacking in human.

So how we translate the information into the labeling that the physician or the patients can use that information to manage the transporters needed by -- or drug interaction needed by transporters? This is just a quick survey on the currently approved drug that has transporter information in the labeling.

They are not expressed in a very consistent way. Some of them state that they are substrate. Some of them state they are inhibitor. Some labeling did state they are known substrate or known inhibitor. And again, we see P-glycoprotein is the one probably studied the most. That's why we have the most information on the drugs that have been looked at. And we also see other transporters, six transporters we mention earlier, including another one, MRP, also has been mentioned in the labeling.

For example, recently we have an update on the labeling for atorvastatin, one of the statin drug that was found to be a substrate for OATB1B1. And I will show you the example later. And cyclosporine, as I mentioned earlier, is found to be an inhibitor for multiple transporters. However, in its own label, there's no such information. But it was mentioned in other products' labeling, such as in the atorvastatin label.

There's one recently approved drug, eltrombopag. This drug was found to be an inhibitor for OATP, and it was put in the "Highlights" session.

And I also will show you the labeling examples.

So clearly we need consistency in how to express the transporter information in the label. And also, another survey we did internally is by looking at the new molecular entity approved from 2004 to 2009, and we found that about 38 percent of the oral route drug contained transporter information. So we know those transporter has been studied, either based on the literature information or during the drug development.

So this is just to quickly show you the label example of atorvastatin, and that the information was contained in the drug interaction section by saying that atorvastatin and atorvastatin metabolite are substrates of the OATP1B1 transporter, then further saying that inhibitors of OATP1B1, for example cyclosporine, can increase the bioavailability of atorvastatin.

That later section also describe how big that interaction is, which is by increasing. And also there is a significant increase with Lipitor. And also, there's a labeling recommendation in terms of

those adjustment. Atorvastatin should not exceed 10 milligram.

This is the substrate example. So the next one is the example on OATP1B1 inhibitor. Eltrombopag is found to be an OATP1B1 inhibitor. And the labeling says that it can increase the systemic exposure of other drugs that are substrate of this transporter. And the label also give a few example of a known OATP1B1 substrate.

Furthermore, the sponsor conduct a clinical drug interaction study with rosuvastatin, and found that rosuvastatin AUC was increased by 55 percent, and that the language was also in the highlight section to say that they need to be use caution when concomitant administer this drug with drugs that are substrate of OATP1B1, and the patient should be monitored closely for signs and symptoms of excessive exposure of the drug that are substrates of OATP1B1, and also consider reduction of the dose, if needed, based on the drug, therapeutic index of the drug.

So in conclusion, based on the current data, we believe understanding transporters and their

interaction will provide a mechanistic approach to explain variability in pharmacokinetics, pharmacodynamics, and safety in clinical trials. Also, if we study them early, by knowing them early we can identify patients at risk of developing adverse events associated with the drug in question, or sometimes at-risk drug combinations. And this can also lead to actionable steps to manage those interactions.

So just to echo what Larry has presented to you this morning, we need to think about the tipping point for special studies we need to ask for, for transporters during drug development, with focus on, what are the clinical questions and what are the data generated can help us address those questions? And what transporters are mature enough to be studied?

How to evaluate new molecular entity as either substrate or inhibitor of transporters? And not to forget, transporter can also interplay with metabolite enzyme that may not be completely understandable from the in vitro system. And more importantly, how we translate those information into

the label that could be useful to the prescribers.

So here comes the question for the Advisory Committee.

DR. VENITZ: Can you hold off with those questions since we are going to discuss them in great detail later, if you don't mind?

DR. ZHANG: Sure. Yes. I won't go through detail, just -- so this is the decision tree we propose here. It's not something new we just created. This is just simply based on our discussion with the experts in the field, and we try to put it into a more systemic way. And this kind of approach has already been used in some companies and drive the development program.

So the question mainly -- although it's two questions, but they are very similar -- mainly just ask whether we should study -- consider those as major transporters and to be evaluate them routinely during the drug development process, and what transporters should be included in the flow chart if they are not a major one; and whether there's alternative criteria we can stratify the use of this decision tree based on

maybe therapeutic area, whether there's certain therapeutic area, you would think may be more appropriate to use this decision tree versus the other.

Because we do not want to increase the burden for the drug development. But in the meantime, we do want to obtain those information early on and have an idea about how to manage those drug interactions. And this is the decision tree for the inhibitors, and we pose the similar question to the committee.

So finally, I would like to acknowledge many peoples who have been play a major role in the development of not just the drug interaction guidance, and also this presentation, as well as the peoples from outside of the FDA, the International Transporter Consortium, and also the FDA critical path funding. Thank you.

DR. VENITZ: Thank you, Lei. Any clarification questions?

[No response.]

DR. VENITZ: Then let me ask you -- I notice

that MRP, in particular MRP2, is not included in the ITC report. Can you explain the reasoning behind that?

DR. ZHANG: Just I think this is mainly focus on -- the MRP2 can play a very important role in some of the endogenous compound as well as in toxicity. However, when you look at the drug interaction, we haven't found many drug to be interact with this transporters.

Therefore, they are on the emerging list, although they don't make the seven in this list. But they are on our radar screen and we will collect more data to determine how to evaluate them. And they could be very important for a particular drug.

DR. VENITZ: Okay. Thank you.

Dr. Thummel?

DR. THUMMEL: Yes, Lei. You mentioned in your discussion about labeling recent data suggesting 30 percent of NDAs, was it, that have some type of information about transporters in it?

DR. ZHANG: Yes, 38 percent for oral drugs. But if you look at totality of all route, there's 23

percent.

DR. THUMMEL: Yes. My question was, what fraction of that consists of basically negative information versus information that would affect dosing?

DR. ZHANG: If there's a particular drug interaction has been conducted, then we have more specific dosing recommendation. But a lot of time, I think we only have in vitro data, just say they are substrate or they are inhibitor.

Then we have the labeling language, as I show you here, just say caution should be exercise when you dose with another drug that is a substrate or inhibitor. So not very actionable, I would say.

So we hope we can gather more data so we can have better recommendation in the future.

DR. VENITZ: Any other? Dr. Lesko?

DR. LESKO: To clarify a clarifying question, so Dr. Thummel asked the question. Is the point of that question that when negative results are available from these studies, they should go in the label, as should positive results? And can you

extrapolate from a negative finding on a 2-by-2 study, basically, one drug and one drug, to say the world of drugs don't need to worry about it?

DR. THUMMEL: That's sort of what I was getting to, but I was more specific. It's just how often is the report simply, it's not a substrate, not an inhibitor? And you're counting that as information about transporters, versus something that's more clinically compelling.

DR. LESKO: Yes. Okay.

DR. VENITZ: Dr. Huang?

DR. HUANG: Yes. In the labeling there, it's not consistent. And it's also depends on which section you have. Most of the information are in the clinical pharmacology section. You may indicate that this drug is a substrate of this transporter, or it is an inhibitor of this transporter, but there are no actionable items.

When there are cases where there are actions -- I'm also talking except eltrombopag -- it's not specific because we would say, if you're giving with cyclosporine, reduce the dose by one-eighth. But

we didn't say because it is OATP1B1, although now the theory is OATP1B1 could be very specific for some of the statins.

BCRP and OATP1B1 could be important for cyclosporine interaction, for rosuvastatin. But our labeling currently not that specific, but we know the mechanism is possibly because of transporters. So we don't have that detailed information like we have with cytochrome P450.

DR. VENITZ: Any additional clarification questions?

[No response.]

DR. VENITZ: Okay. Thank you, Dr. Zhang.

DR. ZHANG: Okay.

DR. VENITZ: Then our next and our last presenter for the day is Dr. Polli, who's going to give us the Glaxo perspective on drug transporters.

DR. POLLI: Thanks very much for the invitation to come and share some perspectives on transporter mediated drug interactions in drug development. I'd like to thank Dr. Zhang for a nice overview of the transporter area and the white paper,

and for highlighting some of the FDA's position.

What I'd like to do in the next ten, twelve minutes is talk a little bit about how we prioritize and think about doing these transport studies from early discovery all the way through post-marketing.

So you've heard that this is a rapidly growing area, with many in vitro, pre-clinical, and clinical publications, and there are a number of challenges for us right now. There are more than 30 drug transporters involved in ADME. We have few agreed clinical translation approaches in the area.

Our tools and reagents are much more limited in the CYP enzymes. However, this issue is resolving. There are now a number of commercial vendors that supply some of these reagents, and so they're becoming more accessible to most companies.

One of the challenges still here is, unlike CYP enzymes where you can purchase a single vial and do seven or eight enzymes in from one stock, you need to buy individual transporters or have assays for individual transporters. There's no way to combine these yet. So that's certainly a challenge.

To me, one of the biggest challenges of measuring drug exposure in plasma may not actually reflect the impact on the drug's disposition, so we're going to have to be more creative to understand where the impact is in tissues, and try and understand the PD effect.

Then finally, as you can imagine, in any emerging area, especially with this number of transporters and acronyms, we are creating some conflicting message to our prescribers, our patients and the regulatory bodies. So we need to be careful that we're clearer of what we're talking about.

This is just a general strategy one could use to think about transporters during drug development, all the way from discovery, all the way through your NDA application. If we start on the far left from discovery to first time in human, really what we do is we think about the clinical strategy.

The things we consider at this time are, what's the therapeutic area? What are the co-meds we expect this compound to be given with? What's our product profile? What kind of development plan do we

want to have? And what are the physical chemical properties of either the molecule we're thinking about or the series we're in? And we take all that information, we integrate it, and we begin to hypothesize potential transporters that might be involved in the disposition of the molecule.

As we get to our first time in human study in our series of clinical work to proof of concept, this is where we really want to focus on building understanding of that molecule and the role the transporters could have.

We do a lot of nonclinical studies, both with in vitro and in vivo at this time, and we also have an opportunity to do a number of clinical studies, in particular understanding the pharmacokinetics of the molecule in both healthy volunteers and in our patient population. And of course, we're gathering safety all along the way.

Then finally, as we hit our proof of concept to our new drug application phase, we really need to think about how to translate this information into drug labeling. And what type of mechanistic or

investigative studies do we want to consider at this time or even post-marketing? And then, of course, we have our clinical program still ongoing, and we can use that as leverage to learn more about the molecule.

The message I want to leave with you from my view is that the central tenet is the clinical plan, which considers the therapeutic area, the co-meds and the patient population. And we revisit this on a constant basis.

As you've heard that there are about 450 transporters in human genome, there are about 30 involved in ADME. And if I counted correctly, there are 27 transporters highlighted in the white paper. That's a lot of information. There are a lot of acronyms there. It's hard to understand; which transporter and when do you study it?

So this is just an illustration of one example of how somebody could, in theory, prioritize the transporter. And it's really just for illustration. Again, we start on the far left and think about discovery to first time in human.

Let's say you're in the area of neurology,

and you know you have to get that molecule across the blood-brain barrier. You might want to consider about the efflux transporter, such as P-gp, both clinically as well as pre-clinically in your models to predict your clinical efficacy.

If you happen to be in the cardiovascular area and you're going to be dosing with digoxin, that could be an important co-med early in your program. You might want to consider about P-gp inhibition.

However, if neither of these are important to your program -- you might be in diabetes -- you may not need to do this work this early in discovery, and you might want to place it later in the development program.

As mentioned, statins are a very large prescribed population of drugs. So this could in fact impact your clinical enrollment no matter what your therapeutic area, so it's a consideration that we think about. As well, it could impact your commercial view, depending on what area you're in. And then, of course, knowing something about the molecule and the area, there may be other transporters to consider very

early in your discovery to first time in human work.

Again, as we do our first time in human work and a proof of concept, we really focus on safety and enrollment. As Lei mentioned, topotecan is an interesting molecule, but it's only oral topotecan where you need to worry about BCRP interactions. And that can be quite marked with a BCRP inhibitor.

For metformin in diabetes, do you think about OCT1 around efficacy? And what about OCT2 for renal drug clearance? And then finally, OAT renal clearance for some other co-meds like sitagliptin or now a therapeutic drug like methotrexate. So again, it's taking all this information together, integrating it, and building your understanding and prioritizing your transporters.

Then again, as I mentioned earlier, the translation of this information to your drug label, your mechanistic studies, and these other transporters, which I'm sorry we couldn't address in the white paper, but we do think about mates and MRPs as well along the way.

Again, the message here is that there is no

agreed timing for these studies, and that the objective should be driven by the clinical plan, and to understand the key transporters by phase 3. And the definition of key transporters here are the ones you think are important in the drug's disposition, its efficacy, and/or the co-meds that you're going to be giving it with. You don't need to cover all of these by this time. There's plenty of time in development to go back and do more work.

So I'm just going to show you a real-world example of lapatinib, which is Tykerb. It's a breast cancer drug. We actually studied 13 drug transporters in this program over about seven or eight years. And if we were going to go back and work on lapatinib or, let's say, a backup program today, what are some of the things we'd think about?

Well, we know it's a tyrosine kinase inhibitor. Lots of interactions with transporters, and we already know what those are. We know it's a very special patient population of breast cancer patients. We know CNS disease is important in treating these people. And we know these molecules

tend to be large and lipophilic. That drives us immediately down a certain route of transporters that we would think about right out of the gate.

Again, as we go into our initial clinical work, we're worried about safety. P-gp, BCRP, and OATP would be things we'd be paying attention because again, it's a big, large lipophilic molecule. Tyrosine kinase inhibitors tend to interact with these. And this is what we'd be driving our strategy around.

Then again, as we get to our translation and patient response and drug interactions, we'll pull in the second level transporters, OCTs and OATs and MRPs, which historically have not been that big of an issue in the tyrosine kinase area. The reason you study these is because of the other drugs -- cisplatin, pemetrexed, digoxin. The tumors, what are they doing there? And so it's again to gain our understanding and translation to the clinical situation.

It's a very customized approach based on the target product profile and the clinical plan. And again, like any drug, we're going to do post-marketing

work on drug/drug interactions, on toxicity in CNS metastases in this area around breast cancer patients.

Lapatinib has a lot of drug transport in the label. This is the 2010 label. You can find information, again in the drug interaction section as well as in the clinical pharmacology section. And I think it's important that as we go, we continue to ask ourselves, what is the value of this information in the label? Are we linking it back to the clinical data so that patients, payors and providers understand what we're talking about? And this does require diligent education on our part.

Again, there are a lot of these transporters. The acronyms are quite complicated, and we have to make sure that when we talk about these transporters, it's very clear. Just to highlight, we have OCT1 and we have OCTN1. And people are going to get those transporters confused. So we're going to have to make sure that we're clear when we make dose adjustments.

The future is pretty exciting, actually, from my view. I love studying drug transporters. I

like working in drug development. When I see papers like this from Alfred Schinkel, it's very inspiring for me to go back and design studies to support our programs.

In a nutshell, what this paper is about is investigating hepatotoxicity. And what this group showed was that you could knock out one transporter and you might get a little bit of hepatotoxicity. But if you knock out two transporters, you get quite severe hepatotoxicity.

What was really interesting about the paper was you could do this in two separate combinations of transporters, again, highlighting the redundancy that the transporters can have; as well as the other interesting thing about this paper is the TK -- or the PK of the molecule doesn't really change, the parent molecule. But the kinetics of the metabolites are very different in these knockout animals. So again, measuring parent PK may not tell us the whole story.

Then finally, I think the other important aspect of this paper, it's one of the first ones that I know of where transporters are probably the bio-

deactivation pathway. They're handling these potentially hepatic metabolites. And you can give this drug quite safely to a normal animal. And it's only in the deficiency of the transporters that you actually get the hepatotoxicity.

Modeling has been mentioned a number of times, certainly in the transport area. This is a very active area of research, and I assume it's going to -- it will continue to grow. It will allow us to test our hypotheses, and most importantly, to identify where the most important determining step. Is it uptake, is it efflux, or is it some interface between metabolism and transport?

Ideally, in the future, it's going to be great if you could come to me with a list of co-meds. I can sit down with my clin pharm colleagues, and we can basically do a paper exercise and try to make some risk assessment. And then maybe we would go do the in vitro study. I think that will be very exciting in the future, and I think it's going to be possible, hopefully in the next decade.

So I just want to leave you sort of with the

puzzle where we are. It's not just about drug transporters. We've talked a lot about drug-metabolizing enzymes today, as well as this committee has over the years. It is an interplay between both of these. Very important to understand how transport and metabolism work together.

Both of these processes are subject to inhibition as well as induction, and these can be different, depending on the compound. We know this from the HIV franchise, where we can see induction or inhibition on day one, but we actually get induction over time. And we see changes in drug interactions.

Protein-binding species differences. Age. Our patient population. Pediatrics. Geriatrics. All very important to take into consideration on the effect of PK and toxicity.

So it's a very complex system. We'll have to always integrate the data and be prepared to do the next experiment to understand where to take the information.

Again, with that, I hope this has been informative to the committee as well as to the

audience. I thank you again for the opportunity to share some of my thoughts on this topic, and I'd be happy to answer any questions.

DR. VENITZ: Thank you, Joe.

Any questions for Dr. Polli? Dr. Lesko?

DR. LESKO: Joe, thanks. So thinking of your flow chart in general and with Tykerb specifically, it's sort of like a graded approach to transporters. And the question I had was: How often does the information coming from these studies in each phase -- how often has that changed the drug development program for the drug, or what you envisioned in the beginning as your targeted product profile?

Or the third option would be, has this been simply information that you'd gather and hopefully would use in, say, a post-marketing situation where maybe an adverse event occurred or an unexpected drug interaction? I'm trying to get an insight into how important this information is in the context of the development program.

DR. POLLI: I'll try to give you two

examples. The first will be sort of the more general one from a global drug development perspective. Again, statins, I think one of the biggest classes out there. You're always going to run into this as a question about drug interaction strategy.

So in our company, we actually do look at OATP inhibition quite early in discovery because that could, in fact, be a differentiator on a molecule. That's not unlike 3A4, so that we study very early. Do we study the other transporters that early? No, we don't, because it's hard to differentiate molecules and to know that clinical impact on the end.

In the case of lapatinib, you're probably wondering why did we study 13 transporters. Right? And the reason is the clinical program was quite big. I mean, we have something like 140 clinical studies for this project. And it covers everything from cisplatin dosing to taxanes, which have transporter aspects as well as metabolism to all kinds of other co-meds. And we really were trying to get a handle on where that risk is.

Again, the problem we're struggling with is

that we don't see a lot of PK changes, but we definitely see changes in toxicity and the dose-limiting endpoints. And that's what we tend to focus on right now.

DR. VENITZ: Dr. Collins?

DR. COLLINS: You were clear in noting that you were just representing your own views. But I was wondering if there was any, you know, industry/scientific groups within pharma or other trade associations who've sort of grappled with this question on whether there was any consensus about the need for guidance and how specific it should be and things like that.

DR. POLLI: Yes. I think the ITC committee is pretty well represented from industry. In fact, there's a small subcommittee that has rolled off from that group that will continue to sort of monitor from a big pharma perspective where we take the information in the future, and where are the gaps? How do we feed back to this ITC group where we think research has to be done both at the academic level as well as sort of the industrial level?

APS has had a very big program in transporters over the last ten years. They have a sort of biannual workshop on drug transporters where a lot of this information is actually vetted.

DR. VENITZ: Any other questions?

[No response.]

DR. VENITZ: Okay. Thank you again, Dr. Polli.

As you can guess by now, we don't have any open hearing, which means we have a little more time for our discussion. And what I would propose -- we have two topics to cover; both of them have voting questions involved -- that we go back now to our topic 3, the renal guidance, and maybe spend up to or not more than 20 minutes discussing whatever panelists would like to discuss, and then move into the voting mode, and then change over to topic No. 4 and do the same.

Any violent objections?

[No response.]

DR. VENITZ: Okay. Then we are back to topic No. 3. Any discussion on the renal guidance?

[No response.]

DR. VENITZ: Okay. Then let me go ahead and get -- okay. Dr. Giacomini. Dr. Stevens. Go ahead.

DR. GIACOMINI: I'm sorry. So we're going to argue, meaning that questions like -- are we taking them one by one, I mean, in the renal --

DR. VENITZ: Well, ultimately. Right now I just want for everybody to have a chance to provide whatever informal feedback --

DR. GIACOMINI: Just anything?

DR. VENITZ: -- or discuss anything related to the renal guidance. And then we start the voting in about 20 minutes. But then we go question by question. So right now it could be anything related or unrelated to any of the questions.

DR. GIACOMINI: But if it's related to one of the questions, should we hold it for that question or just go ahead?

DR. VENITZ: I would ask it now, but that's up to you.

DR. GIACOMINI: Okay. So yes, I do want to second what I heard from Rick Lalonde and from some --

I guess from him in particular, and that is the MDRD and that 1.75 meters squared BSA. I feel it's very confusing if you put that in the label together with the Cockroft and Gault, which isn't at -- which is expressed per individual patient.

So although I like the MDRD and we've used it in some of our own studies, we know, of course, that that just gives it per the meters squared, and then we need to make that adjustment.

But I would be very concerned that clinicians would not do that, and they would make a mistake. And that mistake is just a devastating mistake, you know. If you express it in terms of 1.75 meters squared, and somebody is smaller, a lot smaller, you change their dosing category immediately.

And, you know, so I guess I want to just add that.

DR. VENITZ: Dr. Stevens.

DR. STEVENS: Well, thank you for inviting me. I have several comments to make.

First of all, I agree with the introduction of MDRD into the drug dosing. I think, as has been

explained by clinicians and by sponsors, this is something that can't be ignored. So I think that's very good. And basically, I would agree to anything that includes the MDRD. I do, though, have some specific comments and some concerns that I think this may not be as clear as it could be.

So, first of all to start back, I think that the goal should be that the best kidney function assessment for the population to whom the drug will be applied, and I don't think that concept is necessarily understood in the drug dosing guidance as it is stated.

From a clinical perspective, we look at the patient and we understand if creatinine, as a marker, is appropriate to be used, and regardless of the equation, for many patients it's not appropriate. And I think similarly, for the sponsors doing the studies, they may say, in this population such as very sick patients in intensive care unit, very sick patients for cancer drugs, or in the very obese, of which neither equation has been well-validated, this may not be appropriate. And I think this has to be very

clearly stated.

So then the table, and then even the discussion from both talks, don't seem to actually, I think, get at some of this -- not just a nuance, but actually really the fundamental part of how we assess kidney function. And then so let's talk about the equations. Shiew Mei showed you my slide with the comparison of the MDRD and Cockroft-Gault. And I think there's a distinct -- the conversation since then, I think, has missed a very important point there, which is the P30 of 60, which is the percentage of estimates for the Cockroft-Gault equation are 60 percent. That means 40 percent of people have an estimate that is 30 percent greater than the measured GFR.

Now, in this study we actually corrected the measured GFR to make it more like a creatinine clearance, and we looked at the difference between the creatinine clearance and MDRD. So this is greater than 30 percent from their measured creatinine clearance at Cockroft-Gault.

So the problem with the Cockroft-Gault, the

equation -- and let's not talk about the units yet. The problem with Cockroft-Gault is that it's very imprecise. And that means that in those people, those six people you concluded in your category for the drug dosing, the pharmacokinetic studies, they'll be very different from the patient you see in front of you. They may have the same value for their Cockroft and Gault, but will have a very different creatinine clearance or measured GFR, whatever you want to use or consider as a gold standard. And I think this is my problem with the Cockroft-Gault, and I really think it should be discarded. Now, I understand it may not be able to in a practical sense. But from a scientific sense, there's really no advantage.

There's a completely separate question from the issue of body surface area adjustment. And they get confused, and I really think we need to unconfuse them. I would agree that for drug dosing purposes, we need to put it for an individual patient, not what is the appropriate kidney size for a particular person to look at CKD or not CKD.

It is difficult to unadjust the MDRD study

equation as it stands now. But I don't think that necessarily -- because of my concern about the imprecision of the Cockroft-Gault, I don't think necessarily the answer is to use the Cockroft-Gault.

In most people, because it's in for 1.73, for most people it's around 1, and so there's not a lot of differences. And I think that in the very small people or very big people, creatinine itself is not going to be a great marker. So I think that what the education for clinicians has to be is to become more understanding of that we need to really think about GFR, and we can't just look at the value in front of us.

So I think, and going back to the specific question about the table, I think the table should be mls per minute because I think that's the science of drug dosing. And I think that does put some onus on clinicians, and that's okay because that's unfortunately, or fortunately, where the science is now.

Where the conversation I think we could all have here is, you could say to me as a developer of

equations, say, why don't you develop one not adjusted for body surface area? And I think that may be something that potentially, you know, we could think about. And that's maybe where this conversation should go rather just focusing on the specific equations.

What are my other comments? And again, I come back to those limitations of creatinine because I really when you're -- particularly for as a clinician, which I am, you know, looking at a patient, this is fundamental. And I understand it's harder from a sponsor level to look at that equation, look at that concept. But I think that could be incorporated into the guidance.

Then finally, I think that there could be some flexibility for the new equations. I think coming back to my overall concept of the best kidney function estimate, that should be how best it's done.

I know the European Medicines Association Agency, EMA, they talk about having cystatin. Now, I think that's far away from use in clinical practice, but the concept of having different markers, I think

the guidance should allow that flexibility, or at least understand that this is really an interim solution for where I hope we're going to really go, which is have much better estimates that are going to be available clinically.

DR. VENITZ: Dr. Thummel?

DR. THUMMEL: Yes. I just would like to follow up on one point made, that if you make the decision that an individualized estimated GFR is the way to go, then the separate question of how to implement it should be, you know, kept separately; that from my perspective, you know, if it needs to be done in the most efficient way to assure that -- you know, that normalization is going to occur, you know, why couldn't it be incorporated in the lab analysis?

The report out is always individualized. And the lab's not reported out unless the data that's needed to provide that individualized estimate is provided. So there's an assurance there. The lab -- basically leave it in their hands rather than in the clinician's hand.

DR. VENITZ: Dr. Dowling?

DR. DOWLING: Thanks for the opportunity here. I just wanted to comment.

The discussion of imprecision in the Cockroft and Gault equation, certainly that's relative to a measured GFR. So we know that the creatinine clearance is going to be different than the measured GFR. We know that because creatinine clearance results are the result of some tubular secretion of creatinine. We know that.

Certainly many drugs undergo that same renal elimination mechanism. Tubular secretion is extensively involved in the clearance of many drugs, in the renal clearance of many drugs.

So what it comes down to is how precise does the Cockroft and Gault equation predict the drug clearance? And Dr. Lalonde presented some data that shows a very nice correlation, very tight relationship between the Cockroft and Gault equation and the drug, the clearance of the drug.

So I think that's the fundamental question that we need to be asking; how well does the MDRD or any of the GFR equations -- how well do they predict

the drug clearance using regression-type approaches? So I think that really needs to be done.

We can talk about ways to maybe do some due diligence here in terms of the data that the FDA might have at this point to be able to do some projections, some risk/benefit models in terms of, if that equation was substituted in a case where we have a drug label that clearly specifies use of the Cockroft and Gault equation -- and which we know many labels actually specifically indicate Cockroft and Gault equation -- that if we were to substitute in MDRD or some eGFR, whichever equation of the week is popping up here, whether that substitution would result in significant dose changes.

We know that some of the data from many of our clinicians, Bill Spruill, Keith Wargo [ph], Gil and colleagues, especially in the elderly population -- when the MDRD equation was substituted for the Cockroft and Gault, it resulted in significant dose discrepancies, and in most cases higher doses being given to patients. And in the elderly, this could be a significant risk. I think we need to really assess

that approach and what potential risk could be imparted by that approach.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: I think this is a key point you're bringing up regarding the potential difference in terms of how a patient presents and how they're evaluated clinically as far as their renal function.

So, you know, I don't know that we have enough data from the MDRD. But it just appears to have superior performance as far as predicting kidney function, at least based on what I've seen so far.

I guess the other issue or question that I had -- this is more of a question. I'm guessing this is available, but the MDRD already also has race as a part of this equation as well. And I haven't heard a lot of discussion about this.

But what do you do as in a mixed-race individual? How does that factor in here? So I think it has some interesting properties. But I think, as well, I'd like to see exactly how this would translate into a label because as you're saying, if the issue is in terms of making dose adjustments, maybe its value

lies in terms of a clinical prognostic factor for renal function and not so much in terms of adjusting dose.

I don't know. I don't think we -- I know I haven't seen enough data yet. But I think it's probably a reasonable exercise to think about what would the label look like with this kind of information from the MDRD in it.

DR. VENITZ: Dr. Collins?

DR. COLLINS: Regardless of which nomogram you use, I'm a little concerned about the cutoff points for what's normal and so forth. I know these have been around for a long time.

But to say that 90 or above is normal, you know, that may be healthy. It may be what's desirable. But I don't think it reflects the real world. At NCI, we studied 11,000 patients entered into our phase 1 studies, and they were outliers. They weren't the dominant group at all.

In Dr. Stevens' paper in the New England Journal of Medicine, if you look at the nomogram, the graph that Shiew Mei Huang showed, it's hard to find

the little dots greater than 90. In our studies, it's -- you know, we think of fairly healthy patients are in the 60 to 90 rate. That's the dominant category for patients who don't have a specific disease but have cancer that are entered.

So, you know, in terms of what the reference group is for being normal, I don't want to be semantic. I just want to say that we normally choose our reference dose for labeling based on what will help the majority of the patients. And it looks like, even though these are maybe really better, in better shape from a kidney standpoint, they don't really represent the majority of patients, at least in the studies, that 11,000 that we looked at.

DR. VENITZ: Dr. Kearns?

DR. KEARNS: I have a question for Dr. Stevens or anybody in the room. And I'm listening to all this, and I'm getting progressively concerned and confused because I just don't believe it's this hard.

The Schwartz formula, which is used in children, and it's now been validated in a huge study

funded by NIDDK, is bang-on pretty good. And they've kind of revised it and some iterations to it in terms of is it .55 or is it another factor. But when you look at it, how it lines up with inulin clearance, it's really very, very excellent.

Has anybody ever evaluated the validity of the Schwartz formula in adults?

DR. CAPPARELLI: They have not. The equation, though, uses height, and we have looked at both -- by the way, both height and weight in development of our new equation, CKD-EP equation. They don't add any information from what's there. So we've basically looked at the parameters in combination, which are in the Schwartz equation. So I don't think so.

DR. KEARNS: Okay. So it looks like we have some work that can be done.

But in terms of what's -- I'm thinking about the prescriber thing. You know, what's important to a prescriber? So the physician wants to know, do I give it at the regular dose interval? Do I give it whatever? And to make that determination, you have to

turn the estimate of GFR into some factor that allows you to correct the clearance of the drug.

You know, we've got a lot of people in the world doing programs and very good things and trying to estimate clearance. And renal function is probably the easiest thing in the world to do that with as opposed to the liver. I'm looking at Dr. Rostami out there, and I know he's one of them who does this stuff.

But are we making it too -- are we trying to make it exact and reductionist and neat when it may be wrong? I mean, I'm thinking about kids. I mean, if I open prescribing information and I see that handy-dandy little table in there and it tells me, well, cut the interval to every 12 hours, and I've got a child who's maybe, you know, less than 2, do I just apply that? Is it good for everybody? Or do we just need a one-size-fits-all and get on with it?

DR. VENITZ: Dr. Mayer?

DR. MAYER: I guess I worry about having a decision tree with two different pathways where one patient could have this different dose depending on

which way you go. So I think you really only need one, either the left- or right-hand side of the table. I would vote for ml per minute because that's the real patient, his or her GFR or renal function.

I think, much like Ken said, a lab ought to be able, if you've input the stuff that goes into a BSA determination, get that for you and get you actually back to what your ml per minute for that individual patient would be.

So I'd go for one side of the table, not two, because I think it makes an inconsistent dose in some patients and just leads to a decision tree where that dosage and administration section is typically very straightforward.

Secondly, a different topic completely: Just the end-stage renal function group, I think it's going to be nearly impossible to find those patients not on dialysis when they're at a very low ESRD. And in addition to finding those patients, which are going to be impossible, you won't be able to find normal matched controls for those people, either. So you'd be boxing yourself into a study that really could not

even be performed.

DR. VENITZ: Dr. Lertora?

DR. LERTORA: Again, I want to emphasize and echo some of the comments that were made already. I mean, we're talking about information that is going to go in the drug label in terms of dosing adjustments in patients with impaired renal function.

I think the message has to be very clear for the practitioner. And I think -- I also agree that the units ought to be milliliters per minute in terms of a reflection of creatinine clearance or GFR. Otherwise, we have to introduce the body surface area corrections that Dr. Giacomini mentioned earlier.

So that is a concern in terms of the clarity of the message to the practitioner. And I think that is a very important consideration.

DR. VENITZ: Dr. Flockhart?

DR. FLOCKHART: This is a side point. But since you'd asked for all comments, I'm not -- just as a clinician, I'm a little concerned about the metrics, and the metrics that we're using, the arithmetic, the math that we're using because the general approach our

residents have to creatinine clearance is that the equations that we have work well when we're within normal range. But if you go without the normal range of renal function, they don't work particularly well.

So I just wonder -- and this is really a question to Dr. Stevens and other nephrologists -- whether that is really the case. Simply drawing a line through all the data, which I'm sure is my instinctive approach, doesn't tell you actually whether the predictive value, the P60, is good at the low range where the people you're scared about work and where most of the adjustment is done; or for that matter, at the high range, at the other end. Are we simply biasing our mathematical assessment by focusing on the points in the middle that are the normal range?

Let me just emphasize it one other way. If you have a bunch of normal people where it collates really, really well and you're missing the fact that it's way off low and high, you're not providing something that's very clinically useful.

DR. STEVENS: It's a good question. It's,

you know, how do you -- it is hard to use one number to describe the performance of equations. And in our work and when we've evaluated things, we look at a lot. When we try and summarize it, we have to pare down. We literally look at 50 numbers for every equation because it's both overall and within all the subgroups.

One subgroup in particular we pay a lot of attention to is by level of estimated GFR. And so when we put up a slide like this and we summarize the data, it really tries to incorporate the overall message of all of these different metrics. One of the differences, by the way, is looking at things in a percent scale versus the raw scale because a different of 4 mls will be 50 percent if your GFR is 8. And so you really have to consider that. And so that's a good overall metric. But the problem is really seen across the range of GFR for the Cockroft and Gault.

DR. VENITZ: Okay. Let me use the prerogative of the chair and invite somebody from the outside who wants to respond to one of the questions that was raised.

DR. SWAN: Thank you very much. My name is Dr. Suzanne Swan. I represent DaVita Clinical Research in Minneapolis, Minnesota, and I'm also on the faculty of University of Minnesota Medical School, and I work at Hennepin County Medical Center. I am joined by two colleagues in the room as well, Dr. William Smith from New Orleans Clinical Research and Tom Marbury, Dr. Tom Marbury from Orlando Clinical Research.

Our three sites do the lion's share of phase 1/2 renal PK work with new compounds. In my hand, in our hands, we have data from nearly 500 subjects who are just the normal matches for renally-impaired subjects in these studies. And by MDRD, none of them -- none of them -- have clearances greater than 90.

So if I could go back to the earlier comments, we just have three points here that kind of get to the nitty-gritty, tire-meeting-the-road issues.

One, your brief or reduced PK approach, we think, is a good one. But it needs to be people with GFR determinations. Let's just say kidney function

since we're all debating Cockroft-Gault versus MDRD, and we don't have the answer for you, either. Your abbreviated renal PK approach should be all comers less than 30 mls per minute regardless of body surface. Let's just say 30 percent kidney function.

It's below 30 percent at which point drug accumulation occurs. People with kidney function less than 15 percent do not exist if they are not on -- those that are not on dialysis and are less than 15 don't exist. Medicare pays people, pays physicians, to dialyze people once their clearance is under 20. So that population is really just not clinically relevant. They aren't out there.

So where you want to do your abbreviated renal PK is less than 30, including dialysis patients. So people less than 30 not on dialysis, people less than 30 on dialysis, and they should -- and the dialysis subjects should be studied both inter- and intra-dialytically.

The second point is, we need to figure out which equation or which approach we're going to use to stratify these people. By all means, collect

Cockroft-Gault and MDRD from this point on moving forward, and we can all decide, hopefully, a year or two from now after everybody crunches all the numbers, what's best. But at this point, Cockroft-Gault has the track record, and for all the reasons that have been stated, probably cannot simply be tossed out the window.

Regardless of which one you approach -- or which one you use as your approach, the third point is, normal is not greater than 90. We don't have 11,000 data points, as one of the speakers just commented. We have 500. But none of these so-called normal matches, when we plugged them into MDRD -- they were all done by Cockroft-Gault -- when we plugged them into MDRD, none of the normal matches, people over 40, had a clearance greater than 90.

So in our opinion, those of us who do these studies, it takes us three to four months to do a renal impairment study at best, and this is between three sites. If we're going to now study all the drugs or lots of drugs that are not renally cleared because of the data showed earlier and written and

published in CP&T last spring --

DR. VENITZ: Dr. Swan, can you come to a conclusion, please?

DR. SWAN: -- we would ask that we'd streamline these studies, and the three points that we mentioned will help do that. Thank you.

DR. VENITZ: Thank you. Let me raise maybe two points that I don't think we've talked about yet, and get away a little bit from the MDRD/Cockroft-Gault.

The first has to do with this abbreviated or reduced PK study that you're talking about. And I think I would concur with Dr. Lalonde wholeheartedly for drugs that are mainly eliminated by renal excretion. I'm not sure what that contributes because you end up doing a full study anyways. I think the potential benefit that it might have might be for drugs that are primarily eliminated by non-renal pathways.

Having said that, and this is something that I pointed out before, the proper way to look at those drugs is not just looking at the areas under the curve

or the CMAXs, but it's the unbound areas and the unbound CMAXs since the changes that you might have in plasma protein binding could offset any changes in total plasma concentrations that are typically measured.

So I would add, or at least modify, the diagram or the decision tree that you have to make sure that in order for you to decide whether there's a significant change that needs to be followed up by a full study. For example, that you're looking at the changes in unbound concentrations and the unbound drug, not just the total area under the curve.

Otherwise, you might conclude the total area under the curve in normal renal function and end-stage renal or close to end-stage renal patients are the same. But if you graph for plasma protein binding, you might find that those end-stage renal patients have areas that are three- or fourfold higher. And that is what obviously should drive the ultimate outcome.

Second point related to that, the guidance right now focuses primarily, as far as I can tell, on

the drug. And obviously, we have to look at active metabolites as well, with the same caveat, if there's any plasma protein binding issues to consider, that is run in an integrated fashion.

So I just throw that out to either revise the guidance or at least incorporate in the next version.

Now, are there any other comments before we get to the official voting for each of the questions? Dr. Collins?

DR. COLLINS: Just because there's no other place to get on the record, the thing that we've overlooked in all these questions is, FDA has done a major change from its previous guidance, and I think they should be congratulated.

When the original guidance came out, there was complete consensus everywhere that you did not have to study drugs that were not primarily renal excreted. There was no need to have that. And that's in writing. Many of the people in this room, including myself, thought that was just a terrific idea, and we were saving the world from a bunch of

studies that didn't need to be done.

You've paid attention to what's gone on scientifically. You've done your homework. The industry has done their homework, as Rick pointed out. And it's very helpful I think to have made that change in the guidance. We're not voting on that today, but I think that's -- FDA should be applauded for that.

DR. VENITZ: So with kudos to the FDA, can we now proceed to Question No. 1?

[Laughter.]

DR. VENITZ: And I second that, by the way.

Shiew Mei?

DR. HUANG: One of the points well taken about the normal group, there's some fine print -- not exactly fine print; it's still found at 12 in our guidance that was published this morning. And we did mention if a drug, if we know that it has a wide therapeutic range and the subject was 60 to 90 ml per minute GFR without kidney damage, then they can be lumped together with the control group. So a modification that I did not include in our -- in my presentation about the control group. We do have that

provision in the guidance.

DR. VENITZ: Okay. Dr. Lesko?

DR. LESKO: Yes. I kind of relate it to the same thing. The Table 1 that Shiew Mei showed listing five stages with the eGFR and the creatinine clearance, at least with the online calculators for the eGFR, there is no value reported over 60.

In other words, it's over 60. Everybody gets lumped together so that, that table's somewhat confusing in that the so-called control and the mild decrease in GFR would be one category, using eGFR. But on the other side, it would be two categories.

Now, the question is: Is that clinically important? That is to say, how many times have we had to reduce dose from "the normal" to the mild decrease, and would that get lost in the shuffle? I don't know. I'm just guessing that's probably not often. But it could be a source of confusion, if not a clinical important thing.

So I don't know if anyone has experience of how you deal with those estimates over 60 in terms of the validity of the equation, given the calculators

report them out as "normal."

DR. VENITZ: Okay. We should have on the screen Question No. 1. Question 1(a) is a voting question, and Question (b) would be a follow-up depending on how you vote. Let me read you the instructions.

We will be using the new electronic voting system -- uh-oh -- for this meeting. Each voting member has three voting buttons on your microphone, yes, no, and abstain. Once we begin the vote, please press the button that corresponds to your vote. You will have approximately 20 seconds to vote.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The chair will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and vote into the record, as well as the reason why they voted the way they did.

Are there any questions about the process or procedures?

[No response.]

DR. VENITZ: Are there any questions about what we're voting on?

[No response.]

DR. VENITZ: Okay. Then I would propose that we all vote on Question 1(a): Is it feasible or necessary to recruit ESRD patients not yet on dialysis that may represent the worst case estimate in increase in exposure in order to conduct reduced PK studies? And you have three options, yes, no, or abstain.

So I think the 20 seconds are ticking. And I think within the 20 seconds you can change your mind, but after 20 seconds you can't.

[Vote taken.]

DR. VENITZ: Okay. It looks we have a final tally of the votes. And I think we're going to start to my right with Dr. Giacomini to go on the record with your name, your vote, and the reason of why you voted the way you did.

DR. GIACOMINI: I'm Kathy Giacomini. I voted no. The reason was that I felt that the hemodialysis patients on a day off dialysis might be

appropriate for this kind of worst case scenario, and the end-stage renal disease patients who have not yet gone on hemodialysis might be very difficult to collect.

DR. VENITZ: Thank you. Dr. Thummel?

DR. THUMMEL: Ken Thummel. I voted no, primarily because one of the major reasons for doing this abbreviated study is the issue of hepatic dysfunction. And the data that were presented, actually the group that was studied were those less than 30. So I didn't see a compelling reason why to make it more restricted to end-stage renal disease.

DR. VENITZ: Dr. Lertora?

DR. LERTORA: I voted no. And again, I considered, rather, the difficulties in terms of recruiting this special population, and felt that the guideline would otherwise be appropriate.

DR. VENITZ: Dr. Dowling?

DR. DOWLING: Tom Dowling. I voted no. Again, I think in the category of patients with GFRs or creatinine clearance less than 30, I think that's sufficient to detect a significant change in PK in

those studies.

DR. VENITZ: Dr. Harralson?

DR. HARRALSON: I voted no, I think mostly because of the difficulty in getting patients in that category, and they're difficult to interpret; although I have concerns about the effect of end-stage renal disease on the transporters. And so I think we're kind of dodging that issue. But my vote is still no.

DR. VENITZ: Dr. Flockhart?

DR. FLOCKHART: I voted yes.

DR. VENITZ: State your name.

DR. FLOCKHART: This is Dave Flockhart. And I voted yes because I think while it's expensive, it is feasible. It can be done if enough effort gets put in to recruit those patients. And I think it's valuable information.

DR. VENITZ: Mr. Goozner?

MR. GOOZNER: Merrill Goozner. I abstained. I think I was almost prepared to say yes, but the information that it would be so hard to recruit these patients seemed to be fairly compelling. So I decided to abstain.

DR. MCLEOD: I'm Howard McLeod. I voted no because the data that could be obtained in the dialysis and peridialysis setting would, I believe, tell us enough information to help with this category of patient without having to go out and do a straight study.

DR. MAGER: Don Mager. I voted no. I agreed with the comments before, that I suspect a serious problem with feasibility. And I haven't seen data to justify a strict criteria.

DR. VENITZ: Well, I'm Jurgen Venitz. I voted no for the reasons that you heard about.

DR. COLLINS: Jerry Collins. I voted no for similar reasons. I just think that you get the most information for the cost and the resource of the study if you match the groups that are studied with the real world of what the patients are like there.

DR. KEARNS: Greg Kearns. I voted no for the feasibility issue and also agreeing that carefully studied patients between periods of dialysis give you the physiologic information that you need to answer the pharmacologic issue.

DR. CALDWELL: Michael Caldwell and I voted no because I believe this is a vanishingly small population of patients. And I believe you can get the data that you need from dialysis patients.

DR. STEVENS: Lesley Stevens. I voted yes because I take care of these patients. I know they exist, although understand my perspective may be skewed. I also think that for people with low levels of GFR, if they have to be on dialysis, they're probably sicker and have other medications, so it may have more interactions. And so this may provide some valuable information.

In a practical sense, I may say less than 20 versus less than 15. But I think between 20 and 30, there's a -- it's quite different from when the very low levels of GFR, and it's worth, in these limited PK studies, to identify such a group.

DR. BARRETT: Jeff Barrett. I voted no for similar reasons, the feasibility predominately. And then most of the emphasis on the single group comparison with low sample size.

DR. CAPPARELLI: Edmund Capparelli. I voted

no for the feasibility as well as the lack of a demonstration that there really was a worst case scenario in that group not on dialysis, compared to dialysis patients in between dialysis.

DR. VENITZ: Okay. Let's switch back. I think we have a Question 1(b), if anybody wants to take a shot at that. I think you heard some of our comments, that dialysis patients would be appropriate, or maybe using less than 30 as a cutoff. Is there any other comments that anybody wants to make?

[No response.]

DR. VENITZ: All right. Let's now move to our religious war of the day, the MDRD versus Cockroft-Gault. Question 2. We'll get it on the screen in a minute.

Okay. I think the question that we are asked to answer -- you all saw the table that Dr. Huang presented. And the question that -- that's the table that has both the Cockroft-Gault and the MDRD with the different dosing recommendations. The question we are supposed to vote on: Do you agree that this type of table is the best way to present

these data and would provide recommendations to prescribers?

Are there any questions to the question, or do we all know what we're voting on? And I would slightly, in my mind, modify "best way." I would say it's an acceptable way. That's what I say in my mind. How much -- there might be better ways.

Dr. Dowling?

DR. DOWLING: I guess just a question on the table itself. With eGFR, there's a superscript b there that says, "Estimate of GFR based on the MDRD equation."

Now, with the other equations that are on the horizon, you know, are we voting on this as in its present form or with the modification potentially of whatever eGFR equation is relevant for the time frame?

DR. VENITZ: Dr. Huang?

DR. HUANG: In our guidance, we gave as an example the most recent four equation -- four parameter MDRD equation. But it would be what's being reported out at that time, and at the National Kidney Foundation's recommendation. And currently, it's the

four-parameter equation.

So that is what we're recommending at this point, eGFR, estimated GFR.

DR. DOWLING: So I guess the final question, then, is we're going based on whatever the National Kidney Foundation is guiding us?

DR. HUANG: No. Right now we just say we are basing on the MDRD equation. And we gave an example in our guidance as a four-parameter equation. So I guess for today's voting, I would use that.

DR. DOWLING: The MDRD specifically? Okay.

DR. HUANG: Yes.

DR. VENITZ: And the units would be mls per minute per 1.73 meters squared. Would you add a footnote to point out that you need BSA to calculate the individual clearance, as a friendly amendment?

DR. HUANG: You would need a BSA in order to convert it to ml per minute.

DR. VENITZ: But I'm saying would you put that as part of the table so the prescriber can actually be reminded of that?

DR. HUANG: Yes.

DR. VENITZ: Okay. Dr. Collins?

DR. COLLINS: Does that mean that FDA wants us to vote on whether to have side-by-side comparison of different units in the table?

DR. HUANG: That was our original intent, but we did hear a lot of feedback today about --

DR. COLLINS: Yes. I mean, I think there's sentiment for having both approaches available. But some people who would ordinarily vote yes would vote no if there's different units in the table. And I don't even see any heads nodding around the table now. I mean, maybe you could just caucus for a minute before we vote?

DR. VENITZ: That's what we're doing right now.

DR. COLLINS: Okay.

DR. FLOCKHART: Well, a way structurally to do with it would be to propose an amendment to the question.

DR. VENITZ: Want to propose one?

DR. FLOCKHART: It's not my position. I mean, I --

DR. VENITZ: Okay. Well, I think I've already amended the table to reflect that at least it's pointed out in a footnote that the units are different, and in order for you to take, for the prescriber to take advantage of the MDRD approach, they will need the BSA and they would have to calculate it.

Dr. Lesko?

DR. LESKO: Just to be clear on that, so the Table 1 in the -- under Question 2, if the eGFR was mls per minute with the understanding that there would be a conversion using BSA on an individual basis and a column 2 with clearance creatinine, is that the amendment or is that what would be acceptable or -- I'm trying to be clear on how to change that because I think the question on the table is the units are confusing.

DR. VENITZ: Without knowing what the BSA is, you have to then base it on the assumption that's the average. It's 1.73. You cannot individualize it into mls per minute unless you know what the BSA of the patient is.

DR. LESKO: So the best to do is some sort of note in the table --

DR. VENITZ: Right.

DR. LESKO: -- to make the calculation or conversion.

DR. VENITZ: Dr. Stevens?

DR. STEVENS: I would make a further amendment to yours to actually change the table based on mls per minute for both equations because the sponsor who's going to do the pharmacokinetic study and make the drug label can actually do that calculation. And then it's the clear message to the clinician that they have to make that.

So I will go further and make a friendly amendment to your amendment.

DR. VENITZ: Everybody understand the amendment and the amendment to the amendment?

DR. FLOCKHART: I think we might ought to restate what the whole thing we're voting on is.

DR. VENITZ: Yes. Can you go back to the table? Okay. If you look right, now on the right-hand side, that's the -- I'm sorry, the left-hand

side. That's the eGFR. That is right now listed in mls per minute per 1.73 meters squared.

So there will be a footnote that says, in order for you to individualize it, you need to know the patient's BSA. Right?

Your amendment, Dr. Stevens?

DR. STEVENS: So my amendment is that the sponsors use the MDRD making the adjustments because -- and the PK studies are based on that. Therefore, really what you could just have is a column, eGFR or e-creatinine clearance, and then mls per minute.

DR. LERTORA: Again, for the sake of clarity, now, the question says, do you agree that this type of table is the best way to present this data, and would provide clear recommendations to prescribers?

So while, you know, that may be a valid thought as far as what the drug development companies, you know, would do in terms of presenting the data, the question here is that would this kind of table provide clear recommendations to the prescriber. And that's what I'm considering.

DR. VENITZ: Shiew Mei?

DR. HUANG: Well, the original intent is in the next couple years, hopefully we will have information using both methods, and we will be able to see whether there are large differences. And if there are -- only if there are differences, then we will want to display.

If we ignore the BSA, then we are essentially -- I don't know how we display it because you would have two different outcome, but you have the same ml per minute. And that would be very difficult to have.

DR. COLLINS: Let's be clear that the column on the left is originally calculated as mls per minute. And then it's divided by the BSA and then printed there, and then you have to take the BSA and re-multiply it.

So the original calculation on the left is in mls per minute, and then you're moving it back to per surface area, and then moving it back to milliliters -- let's say that in oncology we want -- oncology and infectious diseases are the two main

culprits for why "per 1.73" -- you know, they're the only disciplines where doses are given -- and with pediatrics, it's just a first approximation.

But in oncology, there's still a lot of doses that are given in milliliters per minute per meters squared, or dose is milligrams per meters squared. None of the new drugs that are being developed use that, and many of the old ones are trying to be converted back. We learned the hard way from dosing errors.

The dosing areas of oncology -- errors in oncology are frequently fatalities or severe morbidity. We don't need to export those mistakes to other therapeutic disciplines, I don't think.

DR. HUANG: The only reason I say that, because when we construct this dosing recommendation, it was based on MDRD. MDRD is -- I mean, on the left side, is with the 1.7 meters squared.

But when you want to apply it to a patient, then you need to know their ml per minute. Once you have MDRD -- well, you actually have the 1.73 meters squared in the equation already. If you use MDRD,

that is the number that you have.

So I don't see why you need to convert. Once you've fit into MDRD equation, you come up with that number.

DR. VENITZ: Okay. Then let me propose we have no amendments. We're voting on this table. Because I don't think we're going to solve it today, at least not within the next 35 minutes.

So we're voting on the table as it is right now, and being asked the question whether we think that's the best way of presenting the data.

DR. KEARNS: Just a proviso that may prevent me from voting no, then having to explain. And I apologize; this sounds like a broken record. But people who treat children read the drug labels occasionally, and when they're looking for guidance for renal dosing, they take right out of the table.

Every formula that estimates GFR in children estimates it as mls per minute per 1.73 meters squared. So if you put this table in and you maintain the two different units, even though the data may not be intended for use in children, like 70 percent of

all the data that's published in a drug label, at least people will have some direction that they can make physiologic sense out of.

If you reduce those units back to Cockroft and Gault units, then people will make mistakes.

DR. FLOCKHART: So, Greg, you would be for purely per-meters-squared data?

DR. KEARNS: I can deal with -- it's easy for me to look on the left hand of that column or the right hand of that column. So I know if I got a kid, and I've estimated the GFR, and it's mls per minute per 1.73 meters squared, and I want some guidance from adult studies, I'm going to look at the left side of that table. I'm going to ignore the right side.

DR. VENITZ: Okay. Any further discussion?

[No response.]

DR. VENITZ: Okay. Then I'll call for the vote. I think you know the instructions, and I think we've got 20 seconds to push a button.

[Vote taken.]

DR. VENITZ: We have our final tally. We've got 5 yes, 11 no, and no abstentions.

Let's start on the left-hand side with Dr. Capparelli.

DR. CAPPARELLI: Yes. I voted no. I think that the idea of incorporating eGFR from the MDRD equation is going to be important. But as it's currently structured here, it's confusing. And so I think some of the suggestions that went around in terms of potential amendments, I think would rectify that. I think that -- but this, as the best way of presenting the data to prescribers, I just think it's not quite there.

DR. BARRETT: Jeff Barrett. I voted no as well. Similarly, I mean, I just don't think this -- we can't even decide its clear representation around the table. So I think in the prescribing community it would be doubly hard.

One other point, though, that wasn't brought up. There are -- this example just so happens to have the information be the same in each of the stages. But, you know, as we talked about, there could be certainly scenarios where they're not going to agree.

I think there, any time you have, you know,

the left-hand side stage description the same and then the guidance being different, again, understanding that the units are different, it just requires another level of interpretation for the caregiver. And it's 2:00 in the morning. You got to make a quick decision. It's another bit of uncertainty they don't need.

DR. STEVENS: Lesley Stevens. I voted yes. I just think that this is not necessarily optimal, but I think any introduction of eGFR will help the clinicians. And I think the table will be easy to follow, and they will figure it out.

DR. CALDWELL: Michael Caldwell. I voted no. I agree that that may be what happens in the future, but I think this is not ready for prime time, and most physicians would just look at the right-hand side and completely ignore the left-hand side at this point.

DR. KEARNS: Greg Kearns. I voted yes because I believe that the agency can clean this thing up and add all the appropriate stuff to it that we discussed about. So it's a little bit of a vote on

faith, and that's it.

DR. COLLINS: I voted no because I think the agency can clean this up.

[Laughter.]

DR. VENITZ: My name is Jurgen Venitz. I voted no, and I'm seconding both of my preceding panel members.

DR. MAGER: Don Mager. I voted no. I think it just needs some work to be cleaned up for prime time.

DR. MCLEOD: Howard McLeod. I voted no for the lack of consensus.

MR. GOOZNER: Merrill Goozner. I'm the consumer representative. And I voted yes because, you know, it struck me, from a completely different field, that more information is better than less information.

Based on the idea that there's a religious war going on out there -- I like that -- therefore, you know, you're going to have practitioners who are going to be using one or the other and thinking in those terms. And so it's probably good to have both.

DR. FLOCKHART: I'm Dave Flockhart and I

voted yes because I believe we were in the process of amending this to something that was acceptable, which should be a word that's in the language. And again, I trust the agency to clean it up and make it acceptable and communicatable.

DR. HARRALSON: Art Harralson. I voted yes. I edited it myself to "acceptable."

[Laughter.]

DR. HARRALSON: And I think at the stage we're at, people can use both sides of it, depending on your particular bent. And I guess for me, the underlying question is, which better relates to drug clearance? Even though we have good evidence relating to GFR, we don't have good evidence relating specifically to drug clearance, and it may be different for different drugs.

DR. DOWLING: I'm Tom Dowling. I voted no. I do agree that it's important to start to look at the relationship between eGFR and drug pharmacokinetics. But at this point, it just seems to me for practitioners, it's too easy to go to this table and use the automated, reported eGFR and plug that in, and

end up with dosing, significant dosing errors.

DR. LERTORA: Juan Lertora. I voted no, basically for the reasons I stated earlier, that I think this, as currently constructed, it would be confusing to the prescribers.

DR. THUMMEL: Ken Thummel. I voted no. If you're going to make a change, get it right the first time.

DR. GIACOMINI: Kathy Giacomini. I voted no. I like the idea of the two, but I like it all in mls per minute, one unit.

DR. VENITZ: Okay. Thank you, and I think you have enough comments to deal with part (b). Right?

Then, with the last 35 minutes looming around the corner, let's move to our final topic, which is a whopper, the drug transporter topic. And again, we have at least one, I think two voting questions. But I would like for us to have an opportunity to maybe spend ten or not more than fifteen minutes to talk in general about this topic before we go to the votes.

Let me go first. I have a whole bunch of issues that I'd like to bring up in the record, regardless of the vote.

I think part of what concerns me in making this a general rule is the ability to actually translate in vitro information to in vivo.

A couple of things that I took note while I was listening and as I was reviewing especially the ITC paper, the first one, I think, was mentioned briefly by Dr. Polli, and that is: Are those inhibitors that are supposed to be used in vitro and/or the cell lines, are they available so companies can use it, or are they only available if you're in big pharma?

The second is a more scientific question. Are those selective inhibitors, in particular, if you don't have cell lines, as selective as we think they are? And I'll note that cyclosporine is listed as a selective P-gp inhibitor even though it also inhibits MRP2. So I also note that in your decision tree, you put in at least one or more inhibitors.

So how selective can we really conclude, or

how conclusive can we really conclude based on presumably selective inhibition studies whether an NME is a substrate or not?

The next item has to do with extrapolating that to in vivo potential for interaction, where you're using different concentrations. And I noticed that you're using unbound concentration as it relates to portal vein or systemic concentrations.

If my memory serves me right, for drug interaction at the metabolic levels, we're using total concentrations to look at the CP over IC50 ratio. So again, what's the difference if you're talking about systemic inhibition, not necessarily pre-systemic inhibition?

A general question that I think I have on this whole method that you have those decision trees: Has anybody ever looked at whether they work? I mean, or is it just something that we take based on mechanistic evidence, we take that for face value?

Two more things. The last thing, or the second-to-last thing, we always have a box that tells us there's going to be in vivo follow-up. What does

that mean? What kind of studies? And the same questions. How selective are whatever in vivo inhibitors are? How selective are the substrates that we're proposing, or that you're proposing to do clinically?

Then in one of the diagrams, where you're going to assess whether a drug is likely biliary excreted or not, you have a 25 percent cutoff on biliary excretion. What study would be required in order for you to conclude that? It's pretty easy to conclude whether something is 25 percent renally limited or not, assuming that you have it IV.

But what about the 25 percent biliary excretions? You would need ADME studies. You would need IV ADME study as far as I can tell. That's the only way you can truly conclude that.

So those are the kind of issues that I'm just throwing out for you all as you consider the comments from the panel in general.

Any other comments, questions, before we proceed with the votes? Dr. Huang?

DR. HUANG: Just a quick comment. We would

like the committee to vote on the importance of those transporters, and the criteria we put out are based on -- mostly on in vivo.

What we know about in vivo under these conditions, then we study this as a substrate. Under this condition, we study. But we didn't say you must study in vitro. So you could go directly to in vivo or you could do in vitro and then follow by in vivo. I just want to make it clear in case. Otherwise, we will need to spend time in talking about how in vitro would project in vivo.

So the vote is more of the initial step, as you have mentioned. How do we determine 25 percent hepatic involvement or 25 percent of the active secretion? That's the key. So these are what we want to get the committee to vote, on the importance of these transporters and the criteria that put out.

Just a very quick question because I have to leave. On cyclosporine or the non-specific inhibitors, if you use those to study and the results are negative, then we could say you don't have to do all these other inhibitors study.

DR. VENITZ: But I'm worried about the opposite, that you have a cyclosporine catechol-2 [inaudible] interaction and you conclude it's a P-gp substrate, and it's not.

DR. ZHANG: Yes. We noticed there is a lot of overlapping, either substrate or inhibitor. But sometimes we were able to use those nonspecific inhibitor if we know from in vitro data the substrate is specific for one of the transporter. Then we still can use them because we know only that transporter will be involved, or that drug only have the potential to interact with that transporter.

So it's all relative. Yes, if you have multiple selectivity for both substrate and inhibitor, yes, it is hard to explain. You just have to say all these transporter may be involved, especially if you have a positive in vivo data.

DR. VENITZ: Any other questions or comments? Dr. Thummel?

DR. THUMMEL: My question was what happens to those drugs for which you don't have IV data? You'd have no regress assessment of fraction renally

cleared. What's the intent then?

DR. ZHANG: Yes. We just putting the -- it's just like ask the sponsor to collect all the data they possibly could collect. Could be either from in vivo animal data or other sources. Just like to think -- prompt them to think how they get a sense of how important renal is and how important hepatic is.

But they will ask that question during the ADME studies, and also to determine whether they need to do a hepatic impairment study or renal impairment study. So these all could be connected.

DR. VENITZ: Dr. Polli?

DR. POLLI: Thank you very much. I'll do my best to try to go quickly through a few of the answers.

Inhibitors in substrate assays, certainly a challenge. Some of these reagents are commercially available. Some are not. Most are not selective at all. I would say that we don't have any selective agents.

However, from a drug interaction point of view, clinically we want to know what the dose

adjustment is, and then we can backtrack potentially the mechanism. I think that's, to me, the first thing in my mind, is do we need to make an adjustment? And then we can sort of backtrack mechanism if we have to.

DR. VENITZ: But those decision trees read differently. They say you have an NME, and you now have a selective inhibitor, and then you conclude it's a substrate or not. Right?

DR. POLLI: I understand. In vitro, you know, obviously if you over-express a certain transporter, you can get at this first. But again, I think Dr. Zhang really sort of hit it. It's an integration of all your preclinical data.

What do we understand on the disposition in preclinical species, and does it sort of fit what we understand clinically at that point? So we're always going to be reassessing the information to try to predict where we need to go.

You asked about the decision trees have been vetted. I wouldn't say they all have been vetted. I think the OETP1, the ITC, we spent quite a bit of time sort of validating that as an approach. We actually

had several approaches that both worked equally.

We ended up on this portal vein decision because we felt it was the most straightforward for the average person to calculate. So you didn't have to be an expert. And I think we ran 14 or 15 compounds through it, and we were quite good at predicting an interaction clinically.

I think the other question around free fraction versus total, I think you'll see in the next year a number of papers, even around CYP enzymology, where free fraction actually is quite a good estimation of the drug interaction over total. I think modeling and simulation has really pushed us to do a better job than we have, you know, since the previous guidance, which was a good place to start. Thank you.

DR. VENITZ: Thank you. Dr. Zhang?

DR. ZHANG: I just want to add to that is the P-glycoprotein. We propose like .1 cutoff at the last AC meeting. Then subsequently we did a further study just to collate in vitro to in vivo, and we found unbound actually is less predictive than total

concentration. But if you add a drug dose, the intestinal concentration, into the picture, have it like cutoff of 10, that can capture a lot of false negative.

So a lot of research is still ongoing, even in the P-gp area. We are sure we can learn from that and to apply to some other transporters. Thank you.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes. I guess we're going to be voting, I guess, on the important transporters that were up there and presented in the white paper, and whether we agree they're important. I just want to go through what the ITC had a lot of deliberations on deciding which transporters were important.

We really looked for overwhelming clinical data that the transporters played a role. And sometimes that was in the form of genetic polymorphisms of these transporters, where you had individuals with a polymorphism. You gave them a drug. You clearly showed it.

So it wasn't based on these so-called dirty inhibitors that might be inhibiting a lot of other

things. So I want to say that those transporters on the list were highly vetted, and there are more transporters that are sort of in the pipeline. But at least on the first question, that was very strongly looked at for clinical evidence.

DR. MAGER: Just a quick question on the criteria. It said clearly in the white paper that there was not a complete consensus from the ITC group to some of the criteria, full changes in some of the parameters. And I'm wondering, will those continue to be updated, or has this consensus been reached?

DR. ZHANG: Yes. You raise a good point. These are be continues to be looking at. We propose those decisions as a starting point to prompt the sponsor to think around that direction more and collect more data. Based on the data we generated, maybe we will -- it will be continuous monitoring those decision tree and will be modified based on the data.

DR. VENITZ: Dr. Lesko?

DR. LESKO: One of the questions that's come up as we discussed this issue was that we have at this

point, unlike CYPs, a limited number of, let's call them inhibitors of NMEs via the transport process. So, for example, one of the model drugs that appears in the tables that were shown quite a bit is cyclosporine. It's not your average, everyday drug that is going to be given to people.

The other area is the HIV/AIDS drugs. So again, drugs that are used in very specific, relatively small subsets are those that we know now to be the offenders, if you will.

So one of the questions we've sort of tossed around is, how generalizable is that kind of information? That is, how big is the problem when you're only looking at offending drugs that are limited to a subset of the population, let's say transplant patients?

So what can we get from a cyclosporine interaction in terms of other, let's say potentially more common drug interactions that may occur in the general population?

DR. FLOCKHART: If I could draw the analogy with the CYP world. I mean, for many, many years,

what we've done with drug interactions with cytochromes is, in the drug approval process -- and I can hear Bob Temple saying this now many, many times -- because of the concern for safety, you look for the worst possible thing.

So we've used ketoconazole for years and years. And if I went around this room and asked for a highly specific drug that hits one -- that's not ketoconazole, you know. We use that because it's the worst case scenario.

Now, the difference between that scenario and this one, though, is that ketoconazole is not cyclosporine. And it's okay, I mean, it's relatively easy to do a one-, two-, even three-week study with ketoconazole with a little possibility of liver dysfunction as a concern.

Cyclosporine, that's different. For me to take a normal volunteer, or even someone who's sick, and give them a toxic thing like cyclosporine is really a different question. So I guess this just emphasizes the point that we don't have the tools yet.

DR. VENITZ: Okay. Are we ready for the

vote, given the time that we have? Okay. Then you have the question right in front of you. We are voting on Question 1(a):

Do you agree that P-gp, BCRP, OATP1B1/1B3, OAT1 and 3, and OCT2 are the major transporters that should be routinely evaluated based on the proposed flow chart during drug development? You've only got 20 minutes to -- 20 seconds.

[Laughter.]

DR. VENITZ: Twenty seconds to press one of three buttons.

[Vote taken.]

DR. VENITZ: Let's start with Dr. Capparelli this time.

DR. CAPPARELLI: I voted yes. And while I think this is a much more difficult clinical question from the standpoint of coming up with dosing and understanding the interactions, I think this is a very good start.

So we may not have the tools. We may have different issues in the sense that we're not just looking at systemic PK but tissue issues. But I think

that this breaks down some of the major components that -- when we get drugs in pediatrics, we're always asking, what is the adult information here so we can extrapolate? So I voted yes.

DR. BARRETT: Jeff Barrett. I voted yes as well. I wanted to commend the committee on the transparent process. And I think one of the important things in saying yes was that I had the confidence that this was going to evolve over time, and that when new information was available, this would get updated.

DR. STEVENS: Lesley Stevens. I voted yes also. It just seems like a very good start for a complex area.

DR. CALDWELL: Michael Caldwell. I voted yes because I think that the data as they were presented were compelling. And I think the tools are coming kind of quickly in this area.

DR. KEARNS: Greg Kearns. I voted no. I do agree that those transporters are reasonable. I have an issue with the flow chart, and the issue of the availability of tools. It's really easy to make hard and fast discrimination points, and I agree this is a

great start. But throwing this out there to the pharmaceutical industry, it's just not ready for prime time yet and we need more tools.

DR. COLLINS: Jerry Collins. I voted no. I think it's a great start, not only within FDA but within industry and within the consortium. But I just can't vote for routinely recommending in vivo studies of four -- for four transporters both as substrates and inhibitors.

Before Shiew Mei left, she agreed that the in vitro tools can't be used as a pre-screen. So that means for every new molecular entity, the routine expectation will be to do eight in vivo studies. And that, to me -- you know, it'll get better.

But until we have some pre-screen for that, the magnitude of the efforts, even with cyclosporine, Larry, don't come anywhere near what it was for metabolism-based drug interactions. At the time the first guidance went out, 10 was considered sort of the minimum value, and we had cases of 20, 50, and 100 at that point.

So it'll get better, but it's not urgent.

It would be better if we invested our resources in improving the tools rather than buying a lot of needless clinical studies.

DR. VENITZ: I'm Jurgen Venitz. I voted no on the third in a row of the no bloc. And I think I couldn't have said it any better than Jerry Collins did.

DR. MAGER: Don Mager. I voted yes. I think this is a great start. I share concerns about availability of in vitro assays and some of the components. But I like the white paper. I like the clinical focus. And I think this is a great way to move forward.

I would also like to see, though, in terms of criteria a move to include modeling and simulation as well as a component of that.

DR. MCLEOD: Howard McLeod. I voted no. I think it is also an exciting area. Jerry summarized most of my reason for voting no.

I would ask that, in the future, every time we want to add something, we should also identify something we want to take away because I think the

burden currently on industry is at the point where we need to stop adding and keep it as a net same number.

MR. GOOZNER: I'm Merrill Goozner. I voted yes because I think the tests seem to pan out, and more information is better than less.

DR. FLOCKHART: I'm Dave Flockhart. I voted yes for two reasons. One is I assumed that this is not something that will stand forever in time, just because of the small number of transporters. I mean, tomorrow or next week there may be more data that suggests more important things. So this can't be something that will stand forever. I also voted yes because, to directly address Jerry Collins' point, I don't view this as legislative. It's a guidance.

DR. HARRALSON: Art Harralson. I voted yes, but I also have issues, or not issues, but I'm concerned about the flow charts and I think they need to evolve a little bit on those. And I guess I would be shocked if there were many drug companies that were not actually looking at this already. It's, I think, the tip of an iceberg and we're going to see a lot more action. So I'm voting yes primarily on the fact

that if they were thinking of not doing it, that they should.

DR. DOWLING: Tom Dowling. I voted yes. I think the transporters listed there, as Dr. Giacomini had mentioned, that those had been vetted fairly rigorously through the ITC. And I think there's good clinical evidence to show drug PK related to changes in those transporters.

DR. LERTORA: Juan Lertora. I voted yes. And again, I was persuaded that there is sufficient information in terms of the role these transporters play or may play in terms of drug interactions and perhaps drug toxicity, that again, I felt comfortable with the available information.

DR. THUMMEL: Ken Thummel. I voted yes. I think the pre-clinical tools are there available. And the white paper makes a compelling case for the inclusion of these transporters.

DR. GIACOMINI: Kathy Giacomini. I voted yes. As part of the International Transporter Consortium, I felt like, that those transporters had been well vetted.

DR. VENITZ: Okay. Thank you. Just one thing: I failed to officially, for the record, read the final count. We had 12 in favor, 4 against, and no abstention.

Now, getting back to our Question 1, we still have subsection (b) and (c). Are there any additional comments that any member wishes to make? Again, I believe that the comments that you got when we went around the table pretty much address it. Right?

DR. ZHANG: Yes.

DR. VENITZ: Thank you. Any additional comments?

[No response.]

DR. VENITZ: All right. Moving right along, Question No. 2, which I think has again a subpart that requires us to vote. So the way I see the difference, here we are voting on whether the proposed flow charts allow to study the inhibitory potential as opposed to the potential as a substrate for an NME. I think that's the only difference. And the question, I think, is worded basically the same way -- I mean, the

question (a) is worded the same way.

Any questions about Question 2(a)?

[No response.]

DR. VENITZ: Everybody knows what we are voting on?

[No response.]

DR. VENITZ: Then you've got the Jeopardy music for 20 seconds.

[Vote taken.]

DR. VENITZ: So our final tally is similar to the previous one. We've got 11 yes votes, 5 no votes, and no abstention. Let me start with Dr. Giacomini.

DR. GIACOMINI: Yes. So this is about inhibitors, so I voted -- I'm Kathy Giacomini. I voted yes. I feel like we know a lot about inhibitors, and there are a lot of tools to address whether an NME is an inhibitor. And I also liked using the unbound concentrations for the clinical go/no-go decision.

DR. THUMMEL: Ken Thummel. I voted yes for the same reasons stated.

DR. LERTORA: Juan Lertora. I voted yes, again persuaded by the information available about the potential value of these studies.

DR. DOWLING: Tom Dowling. I also voted yes. Again, I think these are important transporters to be evaluated in drug interaction studies.

DR. HARRALSON: Art Harralson, and I voted yes again for consistency. And I think the flow chart I'm not so sure about. But definitely, we should be looking at it.

DR. FLOCKHART: Dave Flockhart. I voted no because I do have problems with the flow chart, and because of the lack of specificity of the clinical inhibitors.

MR. GOOZNER: Mel Goozner. I voted yes for the same reasons before. And I would just make the additional comment that, addressing something that Dr. McLeod said earlier, potentially, I think, doesn't this make the potential for drug development to be more efficient rather than less efficient if it identifies things early. So just a thought.

DR. MCLEOD: Howard McLeod. I voted no for

all the reasons that Jerry Collins is going to eloquently tell us about in a second. No, I voted no for the same reasons that we discussed during the last vote.

DR. MAGER: Don Mager. I voted yes, pretty much for the same reasons as before. I also share concerns with the flow chart, but I understand that this is a guidance, and that this is going to be continually updated. And again, I'd like to see modeling and simulation criteria considered in the future.

DR. VENITZ: This is Jurgen Venitz. I voted no for the same reasons that I did before. But in this particular case, I would also add again my discomfort with using unbound versus bound concentrations and those ratios that you're using right now. What is the relevant inhibitor concentration either in the gut or in the systemic circulation? And until I've seen peer review to actually show that it works, I'm not convinced that it will.

DR. COLLINS: Jerry Collins. I voted no for

the same reasons as before, and also because I'm aware of the thin line between what a guidance is and what rapidly becomes a requirement.

DR. KEARNS: Greg Kearns. I voted no, and Jerry just summed up the reasons, including the guidance versus requirement.

DR. CALDWELL: Michael Caldwell, and I voted yes for the reasons I gave earlier.

DR. STEVENS: Lesley Stevens. I voted yes for the same reasons I gave earlier.

DR. BARRETT: Jeff Barrett. I voted yes because I didn't want to be a flip-flopper.

DR. CAPPARELLI: Edmund Capparelli. I voted yes for the same reasons as before.

DR. VENITZ: Okay. Thank you. Any additional comments that anybody wishes to make about (b) or (c)?

Hold the horses, we've got a request to go back to Topic 1, Question 1, and actually at least show a show of hands to see how we agree or disagree with some of the genomics. So if you don't mind, we still have a few minutes left. I'd like for us to do

that.

Topic 1, the pharmacogenomic question, Question 1. And we are asked to basically answer for each of the subparts (a), (b), and (c). So the question is: Should it be mandatory to collect samples? And then we go down (a), (b), and (c). and just if you agree with it, just raise your hands.

So the question is, should it be mandatory to collect DNA samples in any of the following drug development contexts? So first to vote on exploratory clinical studies in the preapproval phase of drug development. If you're in favor, please raise your hand. If not, please don't. Okay. So I -- yes, we are going to go (a), (b), and (c). Each is a different voting question.

DR. ZINEH: And they're not intended to be mutually exclusive categories.

DR. VENITZ: All right. So we're voting on (a). Anybody that thinks that it should be mandatory to collect samples for exploratory clinical samples in the preapproval --

DR. CAPPARELLI: Just for clarification, we

had a discussion earlier about the ethics of being able to -- within the scope of this, there's the allowance of subjects to decline to participate. Is that correct?

DR. VENITZ: I don't see any reason why not. But I'm not trying to put words in the -- is that correct?

DR. ZINEH: Yes. You know, with all the caveats that we -- where allowed by ethics and IRB committees, if you will.

DR. FLOCKHART: So the word "mandatory" is actually “acceptable”? Is that amendment --

DR. VENITZ: Strongly encouraged. It's your wording. It's not mine. What would you like to reword it to make it palatable?

DR. ZINEH: We know what the vote is going to be if we say "strongly encouraged."

[Laughter.]

DR. ZINEH: So, yes. Mandatory is pretty close. So I guess we can go to "strongly encouraged" to facilitate voting.

DR. VENITZ: So the question is modified.

The word "mandatory" is replaced by "strongly encouraged." And what we're voting by raising our hands is sub-question (a), exploratory clinical studies in the pre-approval.

[Unanimous by show of hands.]

DR. VENITZ: Okay. Now we're moving to --

DR. ZHANG: Hold on one second, everybody.

DR. VENITZ: Oh, okay. So they actually do want to count.

DR. ZINEH: This was intended to be a voting question.

DR. VENITZ: Okay? All right. Now we're moving to the second, confirmatory clinical studies in the preapproval phase of drug development. And maybe I'll make it easier. Just the no votes, please raise your hands.

[Unanimous by show of hands.]

DR. VENITZ: Okay. Moving to Question 3, post-approval studies required by the FDA to assess a safety issue or question. Just the no, raise your hand.

[One no vote by show of hands.]

DR. VENITZ: Okay? Does that help you?

DR. ZINEH: Can we get some commentary on the no vote for the last question?

DR. VENITZ: Dr. Harralson, it's all yours.

DR. HARRALSON: I guess I was thinking that in the post-approval process, it's in an entirely different setting. And this may be people who've experienced the reaction.

I think the idea that you would then go to them and ask them for a DNA sample, I don't think that's going to work. I totally see the utility earlier, but in terms of mandating it afterwards, I think that can't really be done. Am I misunderstanding the question?

DR. ZINEH: That's fine. Thank you.

DR. VENITZ: Okay. Any additional comments about any of the topics that we discussed?

[No response.]

DR. VENITZ: If not, I'd ask Larry to get us on the road.

DR. LESKO: A couple of brief remarks and we can hit the road, as they say.

In the beginning of the day, and I'll kind of address this to the audience, we thought it would be of use to bring the Advisory Committee down here to Atlanta to the annual meeting. And we thought it was an informative educational offering as well. And I hope the audience that sat through our day began to see the conundrums of regulatory science.

Science is information. Regulatory science is science we can use in making decisions. And there's a big gap between the two. And you can see the fun that we have at FDA when we're not approving drugs.

Secondly, to the Advisory Committee members, I want to thank you very much. And you can tell from the complexity of these issues, we don't have all the answers. We don't know -- you know, I mean, it would be naive to say we can go this without the expertise and input and wisdom that you've all provided us. And certainly on all of these topics, you've given us enough to think about to go back to the bench, think about what was said today, and incorporate that into our thinking. We can't take everybody's comments into

account and, you know, follow that advice. But I think what we got today is certainly enough for us to go back and revisit some of the things that we talked about.

Thirdly, I just wanted to thank the guest speakers that we had from industry, and also the FDA speakers, for their presentations. Behind the scenes, we do these little dry runs, believe it or not. It may not always come across as that slick. But we do have to be very careful what we present at these meetings, and people do take a lot of time to put their thoughts together in a coherent way so that you can understand the nuances of it all.

Lastly, as I started in the beginning, I want to thank the support staff for pulling off this meeting here in Atlanta. And without them, we'd be back in Silver Spring doing this.

So I hope everyone enjoyed the science, the discussion. And, you know, we look forward to maybe doing something like this again in the future.

[Applause.]

DR. VENITZ: Thank you, everyone, and the

meeting is officially adjourned.

[Whereupon, at 2:48 p.m., the meeting was adjourned.]