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ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY (ACPS-CP)

Tuesday, March 18, 2008

8:30 a.m.

Advisory and Consultant Staff Conference Room
Room 1066
5630 Fishers Lane
Rockville, MD 20857

PAPER MILL REPORTING
(301) 495-5831

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P R O C E E D I N G S

Call to Order

DR. VENITZ: Welcome to the Advisory Committee meeting for Pharmaceutical Science and Clinical Pharmacology. My name is Jürgen Venitz and I am the acting chair of this august committee. I would like to call the meeting to order and go around the table for everybody to introduce themselves, starting maybe with Dr. Kearns, please. So, please state your name and your affiliation for the record.

DR. KEARNS: Good morning. I am Greg Kearns. I am the Director of Medical Research at the Children=s Mercy Hospital in Kansas City, and also Chief of the Division of Pediatric Pharmacology there.

DR. RELLING: Mary Relling. I am the Chair of the Pharmaceutical Department at St. Jude Children=s Research Hospital in Memphis.

MR. GOOZNER: I am Merrill Goozner. I direct the Integrity and Science Project at the Center for Science in the Public Interest, and I am new to this committee and thank you for having me.

DR. MAGER: Donald Mager, assistant professor at

the University at Buffalo.

DR. GIACOMINI: Kathy Giacomini, Chair of the Department of Biopharmaceutical Sciences at the University of California, San Francisco.

DR. VENITZ: Jürgen Venitz, clinical pharmacologist, Virginia Commonwealth University.

DR. PHAN: Mimi Phan, designated federal official, FDA.

DR. MORRIS: Marilyn Morris, professor in the Department of Pharmaceutical Sciences, University at Buffalo.

DR. McLEOD: Howard McLeod, Director of the Institute for Pharmacogenomics and Individualized Therapy at the University of North Carolina, Chapel Hill.

DR. BARRETT: Jeff Barrett, Director of the Laboratory for Applied PK/PD at Children=s Hospital in Philadelphia, associate professor of pediatrics, University of Pennsylvania.

DR. CAPPARELLI: Edmund Capparelli, Director of the Pediatric Pharmacology Research Unit at UC, San Diego.

DR. LESKO: I am Larry Lesko, Director of the Office of Clinical Pharmacology, Center for Drugs at FDA.

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

DR. FRUEH: Felix Frueh, Associate Director, Pharmacogenomics in Clinical Pharmacology.

DR. LEE: Ike Lee, clinical reviewer at the Office of Clinical Pharmacology, CDER, FDA.

DR. YASUDA: Sally Yasuda. I am a safety team leader in the Division of Neurology Drug Products in CDER, FDA.

DR. AGRAWAL: Mukul Agrawal, Associate Director, Medical Affairs at Roxane Laboratories, Columbus, Ohio.

DR. MAYER: I am Phil Payer, Assistant Vice President of Clinical Pharmacology at Wyeth.

DR. VENITZ: Thank you, everyone, for volunteering to come to attend this meeting. Before we begin with the scientific proceedings Dr. Mimi Phan is going to review the conflict of interest statement with us.

Conflict of Interest Statement

DR. PHAN: Thank you. Good morning and welcome to the Advisory Committee for Pharmaceutical Science and th
agenda topic includes, one, the New Clinical

Pharmacogenomics Concept Paper. The key issues to be discussed include, one, an industry survey on collection of pharmacogenomic samples and, two, application of pharmacogenomic and clinical development.

The second topic will be the Quantitative Clinical Pharmacology Critical Path Opportunities. An example of a disease model and its application will be presented. The key issues to be discussed include the regulatory experience, designs and implications of pediatric studies.

The Food and Drug Administration is convening today's meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology of the Center for Drug Evaluation and Research under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representatives, all members and consultants of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflicts-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 U.S.C. Section 208 and Section 712 of the Federal Food, Drugs and Cosmetic Act are being provided to participants in today's meeting and to the public.

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

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

Related to discussion of today's meeting, members and consultants of this committee who are SGEs 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 the purposes of 18 U.S.C. Section 208, their employers.

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

For today's agenda, the committee will discuss and make recommendations regarding the New Clinical Pharmacogenomic Concept Paper and the Quantitative Clinical Pharmacology Critical Path Opportunities. This is a particular-matters meeting during which general issues will be discussed.

Based on the agenda and all financial interests reported by the committee members and consultants, conflict-of-interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) and Section 712 of the FD&C Act to Dr. Mary Relling. Dr. Relling=s waivers involve her employer=s and her spouse=s patent royalties for which between $10,001 and $50,000 is received per year. The waivers allow this individual to participate fully in today=s deliberations concerning topic one, the New Clinical Pharmacogenomics Concept Paper.

FDA=s reason for issuing the waiver is described in the waiver documents which are posted on the FDA=s

website at www.fda.gov/ohrms/dockets/default.htm . Copies of the waiver can also be obtained by submitting a Written Request to the agency=s Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting, and will be included as part of the official transcript.

Further, we would like to disclose that Dr. Howard McLeod has an interest related to an issue to be discussed in topic one concerning the New Clinical Pharmacogenomic Concept Paper. Dr. McLeod has been recused from this portion of the meeting.

Dr. Mukul Agrawal and Dr. Philip Mayer are serving as acting industry representatives, acting on behalf of all regulated industry. Dr. Agrawal is employed by Boehringer Ingelheim and Dr. Mayer is employed by Wyeth.

With respect to FDA's invited guest speakers, we would like to disclose the following: Dr. Rene Bruno is employed by Pharsight and owns stock at that firm. Dr. Eric Lai has a relative who is employed by LabCorp. Dr. Lai is employed by GlaxoSmithKline. He owns stock in GlaxoSmithKline and LabCorp.

We would like to remind members and consultants 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 any firms at issue. Thank you.

DR. VENITZ: Thank you, Mimi. Before we proceed I would like for Dr. Lertora who just joined us to officially announce his affiliation for the record, please.

DR. LERTORA: Thank you very much, and my apologies for being delayed. Juan Lertora. I am the Director of the Clinical Pharmacology Program at the NIH Clinical Center, in Bethesda, Maryland.

DR. VENITZ: Thank you and welcome. Since we have a full program for the next day and a half I would like our first speaker, Dr. Larry Lesko who is the Director of the Office of Clinical Pharmacology, to set the stage for the three topics we are going to discuss.

Introduction to the Meeting Topics

DR. LESKO: I would like to add my welcome to everyone on the committee. I was just doing some mental calculations, and it has been some 16 or 17 months since we last met and a lot has changed in that time interval.

[Slide]

You can tell from the title slide that we have a new name, and that is because the charter was rewritten for the subcommittee, Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Sciences, and I want to thank Helen Winkle, Igor Czerny and a couple of other people that helped make that happen. It was not an easy thing to do but I am very pleased that it did happen because what that means for this committee is that it is recognized officially as a full committee and has full voting privileges. So, this is a timely event.

We also have, as a result of the charter, new members on the committee, and as people introduced themselves around the table you could recognize who they are, and I want to extend a welcome to them as well. It only makes the strong committee that we have, I believe, stronger.

I also notice we have a new setup today with a

little more elegant breakfast so that may be part of our new committee, the coffee and the donuts. So, thank you very much for that.

As I mentioned, it has been 16 months since we met and, besides redoing the charter for our committee, we have been busy with a number of the topics that we talked about 16 months ago. If people remember, we talked about the relabeling of tamoxifen with 2D6 information, and the committee at that time recommended that we, in fact, move forward on that.

We have moved forward on that but, as a result of new studies being done, we continue to evaluate new data and continue to look at the issue of relabeling and what we are going to do about it.

The second topic that we had 16 months ago, again, I think relates to what we are talking about today. We discussed drug-drug interactions and transporters in particular, and where the evolving science was going and what might be pertinent to drug development. Today we are going to hear a little more about transporters in the context of something else, namely, the effect of renal disease on drugs that are both metabolized and handled by

transporters in the body.

Finally, 16 months ago we introduced the topic of disease models and using disease models in prior information to make decisions in drug development and regulation. I am happy to say that one of those models that we discussed, the Parkinson disease model, is going to be discussed publicly in April at an FDA and, I think, DIA co-sponsored meeting. So, that has matured as we moved forward from our last committee meting.

So, I guess, in short, the point I am making is that the deliberations of the committee are extremely important and we continue to utilize this input in the development of our program in clinical pharmacology at FDA.

Setting up this meeting is always a challenge under the new rules of advisory committees and I want to thank Mimi Phan, whom you have met here, Peter Lee and a couple of other people that worked really hard, the speakers that are presenting today, to pull together the program that I think and I hope you find exciting.

The topics are important to us. Typical of our advisory committee, we don=t have any drug-specific topics

to talk about. We are not talking about approvals today. We are talking about some general topics that are important to clinical pharmacology; that are important to drug development; that are important to regulatory decision-making, and as the day unfolds you will see what that importance is.

[Slide]

What I am going to do now is try to set the stage for the topics and let you know what we were thinking about in putting the advisory committee together. The first topic that we will talk about today is clinical pharmacogenetics. Clinical pharmacogenetics, in my mind at least, is really looking at inherited gene variants and their influence on pharmacokinetics, pharmacodynamics, drug response, dose response and things of that sort.

The differencesB-and these are just some general principles that I think are pretty straightforward, but differences, as we know, in PK and systemic exposure are related to genetic variation in one or more CYP enzymes and transporters. By and large, these relationships are causal in nature. They are mechanistic based.

There are usually no surprises when we are dealing

with known gene variants, and we have a fair amount of history with this. This committee has discussed some of these genes in the context of our relabeling of coumadin that we finally settled on in August of 2007.

Differences in systemic exposure as a result of changes in PK and PD can potentially lead to significant changes in relevant biomarkers and clinical endpoints. I highlighted the word Apotentially@ because we recognize that genes aren=t everything, that when it comes to pharmacokinetics, dynamics and clinical endpoints other factors besides genes can play a role and interact with genes in some interesting ways. So, things like environment, demographics, other drugs that a patient is taking are also part of the picture.

Genetic polymorphisms in drug targets may potentially cause important differences in PD, an emerging area when talking about polymorphism and drug targets. And, we have seen this come to life in our prior discussions of coumadin and the VCore C1 and how polymorphisms in VCore C1 influence anticoagulation response.

The fourth point is that there are various options available to evaluate differences in PK and PD with genetic

variants. As we thought about the topic, as we think about the future with regard to, let=s say a draft guidance, we want to really develop a guidance that recognizes the emerging aspects of the field and not get too hung up on being descriptive or definitive.

Finally, genotyping may potentially be needed to stratify dosing in subsequent clinical trials. I think this principle really is dependent on the data so it is a very data-driven thing.

Now, if you had the background paper which we call the concept paper you probably would have read about these principles, but as you probably search through your packet you are wondering what happened to the concept paper we were talking about.

What happened to the concept paper is that these kind of documents need to be cleared as part of the background package for the advisory committee and we underestimated the time that that would take. Therefore, you did not get the concept paper so we really revised our slides, and the way Felix will present this will sort of take into account what you might have read about in the concept paper but didn=t. So, I apologize for that but we

are all dealing with some new rules with the advisory committee.

[Slide]

So, here is the objective of the proposed draft clinical pharmacogenetics guidance. As all guidances are intended to do, it is intended to assist the pharmaceutical industry who are conducting new drug development. But more recently we thought it would also help companies that are involved with relabeling of previously approved drugs as new information becomes available on pharmacogenetics.

Basically, we are focusing on early drug development PK and PD. On my previous slide I talked about exploratory pharmacogenetics, and the reason I did that is because many of the studies in the early part of drug development are not powered to generate hypothesis testing, although we are certainly interested, as we have been, in drug interactions or renal impairment studies to look at confidence intervals when comparing two different groups.

We are further focusing on genes that generally are well characterized, well known, related to the ADME and target, and these studies have implications for preparing informative drug labels. We surveyed drug labels. We find

that roughly 25-30 percent of labels have pharmacogenetic information in them. Oftentimes the information is not as informative as it should be in terms of regulatory decisions or in terms of clinical decisions, and I think we probably need to change that as the field emerges.

I should point out that all the regulatory agencies, EMEA and Japan, are looking at this topic in terms of guidances. It has been talked about within the ICH in a preliminary way, and I think this just reflects the fact that everybody thinks it is important.

The methodologies have far outrun I think the science that we see, and I think it is important that we think about this topic in terms of striking a balance between being practical about what is necessary in drug development and a focus on what really matters.

[Slide]

So, why now? Why are we talking about the topic now? Well, numerous genomic biomarkers affecting PK and PD have been well characterized. There aren=t a lot of them. This is an emerging field, but certainly you are well familiar with 2C9, 2D6 and that kind of stuff that we have worked with over the years. Cost-effective technology

exists. The chips that are out there can explore lesser known gene variants as well as the common gene variants in a relatively cost-effective way.

Other FDA clinical pharmacology guidances refer to PK/PD without being specific in regard to pharmacogenetics. So, if you look at exposure response as a guidance or you look at drug interactions as a guidance, and so on, the labeling guidance that we have in draft form now indicates pharmacogenetics as a section of labeling.

So, again, these are some of the changes. I mentioned that the European and Japanese regulatory authorities have published preliminary guidances. They don=t call them that. They call them reflection papers in Europe and something else in Japan.

Further, the ICH genomics working group has finished their work for the most part. The document on harmonization of definitions is at a step 5. It is called E15. And, we are going to continue, I hope, focusing on pharmacogenetics in terms of harmonization.

[Slide]

One of the topics we are going to, hopefully, get into a discussion of is the rationale for collection of DNA

for exploratory analysis in early drug development. The rationale for thinking about this is that it is not always known why we have inter-individual variability whether we are talking about patients or whether we are talking about volunteers.

As a result, there are surprises sometimes in terms of serious adverse events or the absence of a benefit of a particular drug when one expects it. And, the question usually is can we identify a predictive marker that may have benefit in the future for dealing with that. The current thinking on idiosyncratic responses is that there is a genetic basis for these differences, and without DNA collection looking at these differences is going to be impossible.

Clinical studies, and in particular early clinical studies, provide a really good opportunity to begin collecting and storing biological samples for DNA. Then it enables us to investigate those differences when, in fact, they occur. So, the question there again is going to be when should those samples be collected; in what studies; how might they be used; and when.

[Slide]

Now, this second topic is, again, a continuation of our discussion on quantitative clinical pharmacology. Sometimes we refer to this as pharmacometrics. We see drug disease models as a critical path research opportunity. Companies are not being expected to use these. They are not required to use them. They are not going to be the basis for drug approval.

But we think they are an excellent basis for decision-making in clinical drug development and in regulatory decisions. We do now use them in making regulatory decisions, and we have talked about them extensively in the meetings we have had with industry at the end of Phase 2A.

So, FDA is working through its critical path initiative with public-private partnerships, industry and academia. I might also add that we have had significant interest from foundations, such as the Huntington Foundation and Parkinson Foundation, to collaborate and put together a drug disease model that could represent perhaps a package of Ahow-to@ in terms of drug development and provide that to these foundations to contract with their own systems in terms of doing drug development.

So, the long-term goal is to develop models that can potentially be used to do a couple of things: Design better trials, and we all know what the current failure rate is in clinical trials in different therapeutic areas. It is unacceptably high. We know about the productivity of drug development. We think this is one way to address those kind of problems.

The other benefit of a drug disease model is that it allows one to look at biomarkers and clinical endpoints, and perhaps develop some predictive biomarkers that would relate to predicting adverse events or optimizing dosing.

A third goal of models is the potential to identify which subset of patients are most likely to receive benefit or be harmed. These could be explored in many different clinical trial options using disease models and simulation. I would see some benefit in doing that before embarking on an actual clinical study.

Improving the productivity in drug development is a priority under our clinical path and we think this is one of the realistic approaches to solving that problem. Today we are going to discuss one such model, and the model was selected very carefully because of the background

information we had on non-small cell lung cancer.

Unfortunately, we don=t have a long selection list of drug disease models because of gaps in information, and what-have-you, but as the information becomes available through the literature and through the database FDA has through consortia we select those areas for disease models and that is how we ended up with non-small cell, as we did with Parkinson=s, actually, the last time we met. It was the same sort of basis for picking that as a disease.

[Slide]

The next topic we will talk about is still under the umbrella of quantitative clinical pharmacology, and it is pediatrics. One of the goals that our office has in collaboration with the Office of New Drugs and the pediatric group within the Office of New Drugs is a pilot project for doing a better job leveraging prior information and using the quantitative tools that we have in clinical pharmacology to improve the quality of requests and informativeness of data.

When we say leveraging prior information, you will hear people talk about using the data that we know about from prior pediatric submissions, the data we might know

about from the adult population, taking into account the age-related differences in clinical pharmacology, and so on. But our goals in this initiativeB-and we are going to pilot it and today we are going to hear from both Dr. Mathis and Dr. Stockbridge who are collaborators on thisB-we are going to pilot this new approach to pediatrics in the area of cardiovascular medicine and probably a few others.

But, basically, what we are trying to accomplish is to find better ways to use this knowledge and improve the following, dose selection for pivotal pediatric clinical trials. We think a lot of the outcomes of studies, both successful studies and, quote, failed studies are related to the dose that is selected and inadequate work-up of the drug, and that is PK/PD; other design features for pediatric clinical studies, such as selection of endpoints and selection of biomarkers that would be informative; putting a little more time into the pediatric Written Requests when we work collaboratively with companies, so improving the quality of those requests.

Finally, what I think it is really all about is getting better information in the labels of drug products that would help prescribers and patients and parents to know

how to use these drugs appropriately, or at least most appropriately in pediatric populations.

[Slide]

The final topic for our meeting has to do with renal impairment, and you do have, I think, a concept paper and the background. The rationale for this is basically that we have a guidance on renal impairment that is approaching ten years old. It is a 1998 guidance and we have learned a lot over the past ten years about renal impairment and its effects on clinical pharmacology.

Our premarketing observations, which are first-hand, have indicated that renal impairment can cause significant changes in exposure, beyond what you might expect. In other words, drugs that are not highly cleared by the kidneys are influenced by renal impairment. So, for drugs that we normally thought about as metabolized or transported we are finding interesting results that could not be explained by drug-drug interactions.

Quantitative assessment of drug metabolism or transport in renal impairment may avoid some of the potential adverse events related to these observations that I just mentioned, these, in turn, being related to changes

in the PK and PD profiles.

Third, if you looked at the >98 guidance you would see that it was silent on premarketing studies on how to assess hemodialysis in terms of drug exposure. What this has done, it has really led to some uncertainty in how to deal with patients on drugs who are being dialyzed. The concept paper gets into this area and talks about some of the potential studies that might be done during the course of drug development if it is anticipated that this drug will be used in such patients.

Finally, in line with all of our guidances, we want to update this guidance to assist the industry. We want to bring in the most recent evidence that we have; share that; get the expert input that we have arranged for today and, hopefully, at the end of the day our goal will be that we have going forward some informative premarketing renal impairment studies.

So, I hope that sets the stage for today, why we brought the topics forward and what we hope to accomplish. And, I am going to pause and turn it over to Felix Frueh. Felix and I chair the pharmacokinetics working group. We have a fairly large working group of all disciplines and

people have come from all the centers except Food Safety and Veterinary Medicine. He is going to be presenting next on the work of the group and some of the things that we would like to discuss with you.

DR. VENITZ: Felix, before you start your presentation I would like to recognize that we have two members join us, Drs. Topp and Caldwell, and I would like for each of you to introduce yourselves and state your name and affiliation for the record, please.

DR. TOPP: I am Elizabeth Topp, professor of pharmaceutical chemistry, University of Kansas.

DR. CALDWELL: I am Michael Caldwell. I am a vascular surgeon from the Marshfield Clinic.

DR. VENITZ: Thank you. Felix, please? So, our next presenter is Dr. Felix Frueh. He is Associate Director of Pharmacogenomics in the Office of Clinical Pharmacology, and he is going to review the key issues in the elusive concept paper on pharmacogenomics.

Topic 1: New Clinical PGx Concept Paper
Key Issues in the Concept Paper

DR. FRUEH: Thank you, and good morning.

[Slide]

As Larry already pointed out, it is a concept paper that is yet to be. He pointed out also the reasons why we weren=t able to put it out into the public at this point in time.

What I am trying to do though over the next 20 or so minutes is to summarize the highlights that we have so far from writing this concept paper and go into some detail about the aspects that I think would be of interest to discuss here at this advisory committee.

[Slide]

Larry already pointed to the background and the rationale for the concept paper so I would like to just briefly touch on some of the issues that really I think are relevant for the discussion to understand the highlights that we will then discuss in more detail.

We think that the increase in our understanding about the role of genetic variations and the focus here on human germline DNA has helped us to understand a lot more about drugs and the way drugs work, meaning PK/PD, for the last few years.

So, studying well characterized allelic variations I think is something that we can recommend to do in a more

general sense. But then, also, we have new technologies that allow us to learn a lot more about the PK and PD in a much more general context, so enabling the exploration of these phenomenons is something that we would like to recommend in this concept paper as well.

[Slide]

As you may remember, we issued a guidance for industry pharmacogenomic data submissions in 2005. This guidance provides a general, pretty broadly applicable framework concerning the use of genomic and genetic biomarkers in drug development.

It clarifies the type of genetic and genomic information that we expected to be submitted, and when. Importantly also, it introduces a novel pathway that we call voluntary genomic data submissions for submitting early stage exploratory data that is not yet ready for making regulatory decisions.

[Slide]

The 2005 guidance does not discuss in detail the decision-making process itself. It also does not talk about design of studies for using pharmacogenetic information, and it does not touch on the implications of that information in

drug label, depending on the conduct of these pharmacogenetic studies.

[Slide]

So, the scope, therefore, for this new concept paper is to clarify our current view on whether or not clinical pharmacogenetic studies should be performed. It should talk about the scientific basis and rationale for conduct of these studies, which is obviously based on the amount of data that we have available; outline some general strategies to do that, and the design of these clinical studies. It also should discuss the implications of doing these studies on the drug label.

[Slide]

So, this is a brief overview of the outline of the content that we envision for this concept paper. It talks about, as I just mentioned, the general strategies and then provides a decision tree that should help to decide where to indicate pharmacogenetic studies in the drug development process; talk about in vitro studies that help to evaluate the drug as a substrate for polymorphic genes and what to do with that information; and then go into some aspects of design of clinical pharmacogenetic studies; and talk about

the labeling indications.

[Slide]

What I want to discuss here in a bit more detail are the three sections on general strategies, decision tree and the design of these studies.

[Slide]

As for general strategies, I think exploration of the feasibility of using pharmacogenetic information to adjust the dose, or to identify who responds or does not respond with specific treatment really is based on the availability and study of the DNA information. Therefore, having access to that DNA is obviously critical. Hence, we recommend to collect and bank DNA samples from all participants in clinical trials. That would need to be verified in more detail, and this is going to be part of the discussion that we hope to have at the end of the presentations this morning.

The information, we believe, should be used as early as possible in drug development, and should then be carried forward into the later stages as appropriate. Therefore, we recommend to conduct pharmacogenetic studies in early drug development because, obviously, you need that

information if you want to use it in later stage development.

[Slide]

The considerations for conduct of pharmacogenetic studies in early drug development are, for example, that this information can be used as entry criteria as early as Phase 1. For example, when you have preclinical studies that suggest that a molecule is metabolized by a polymorphic pathway you might want to use that information in your early, first-in-man studies.

So, Phase 1 and 2A studies are often exploratory. We realize that and the information that you derive from those type of studies obviously should be treated as such. But, nevertheless, it can be important for the hypothesis generation and for defining subsets of dosing or for identifying responders that you want to use in your later Phase 2 or Phase 3 studies.

Associations between a marker of interest and outcome can be found in such studies but, again, they usually require confirmation through study replication in larger, later stage Phase 2/3 studies.

Banked samples can also be important for exploring

unexpected safety results or safety signals. Larry alluded to that in his introduction. Obviously, having access to those samples is key in order to study these events.

[Slide]

I want to go over the decision tree. That should help to decide when and what to do with the pharmacogenetic information. So, the goal of this tree, as we look at it, is to assist the integration of this information in early drug development processes.

[Slide]

If you start out with a new molecular entity and you conduct preclinical in vitro studies with candidate genes that are well characterized, and these results point to a new molecular entity that is a known substrate of a polymorphic enzyme and the metabolism is more than 25 percent affected by this, we think that you have a very good reason to collect DNA in your Phase 1 and Phase 2 studies and see whether there, in fact, is a difference between the genotype or, in other words, the full metabolizers or the extensive metabolizers that could help explain differences that you may observe in PK or PD.

So, I think this really is the pathway, that is

probably undisputed, that genetics really will have an impact, and it might be a good idea to study this in more detail. Depending on the results of the studies, if there is no effect then there is nothing to do, and we feel that it would be appropriate to move this information into the label in such a way that it states that these studies have been done and that this enzyme does not have an effect or that the variation cannot be explained by that.

If it can be explained though, we think that it might be prudent to use that information to select the genotype-driven dose, or patient stratification or enrichment based on that genotype for later stage clinical trials.

If the new molecular entity is a known substrate but it affects less or has influence on less than 25 percent of the total metabolism or clearance, we don=t think that this information is relevant enough to move forward into larger Phase 2 studies. Yet, we think that, nevertheless, the information should appear in the drug label.

In situations where we don=t know whether the new molecular entity is a known substrate or in cases where we know that it is a substrate of a less well characterized

enzyme, we again feel that it would be important to collect DNA in Phase 1 and Phase 2 studies and then use that for the exploration of the PK or PD variability that was observed. So, for example, screening of DNA for a panel of gene variations in one of these newer available technologies might be an interesting way to study these effects.

Again, if nothing is seen, then there is not much that you can do about it. But if something is seen, you can move that information back into the area where you want to perhaps use that information in later stage clinical trials. In any case, however, it is important to collect and bank the DNA for future studies because of the potential for use of it to explore safety signals that might come up in later development stages.

If you are using something that is not known or not well characterized, we further recommend to consider a voluntary genomic data submission. Again, this is information that will not be used for decision-making but it could be fairly important for us to learn about so that this information really could be used in further development and enhance our understanding of PK and PD variabilities based on genetics.

[Slide]

Moving to the design of clinical pharmacogenetic studies, the purpose of these studies, obviously, is to understand the importance of genetic factors that may help to explain inter-individual differences in drug exposure and in drug response. We feel that this usually requires well-designed prospective studies, and we want to move into a discussion of some of the general considerations for conducting these studies.

[Slide]

Clinical pharmacogenetic studies can be performed as an independent study or as an add-on to larger clinical trials. I think that is an important consideration. We really feel that this field is important enough to be considered for independent study if we have evidence that genetics, indeed, plays a role in PK/PD variability.

The sample size of these studies will depend on the purpose of the study and the acceptability of error rates attuned to the phase in which the study is being conducted. Obviously, if you are doing it in a Phase 4 or early Phase 2 you have to accept a higher error rate but you need to make sure that you are appropriately powered in

later stage trials to assess the variability that is due to the amount of understanding of genetic information that is available at this time.

A specific clinical pharmacogenetic study may be warranted based on preclinical data. This goes back to the decision tree that I was just mentioning. So, if you have information from preclinical studies you may want to use that in your early phases of clinical development.

These studies can be conducted sequentially during drug development or in parallel with the other studies. In order for these studies to be meaningful, you need to be confident that you know what you measure. In other words, the analytical validity of the test and of the methods that you are using should be well established.

[Slide]

Talking about study populations that can be enrolled in these type of studies, we usually have Phase 1 studies being conducted in healthy volunteers. However, we realize that there are situations in which this would not be appropriate, such as for example study of anti-cancer drugs.

The exclusion of subjects from clinical trials might also be important when it is known that subjects with

certain genotypes would not respond favorably, or if there is a safety concern. Obviously, all this pertains to the fact that if we know something about the genetics we might want to consider that information in the design of the studies themselves and not unknowingly cause harm.

Ethnicity may be an important factor, for example, as a covariate for consideration in these cases. We, of course, know that allele frequencies vary, or may vary, significantly between different ethnic groups.

[Slide]

I apologize, this might be a little difficult to read but you have the next few slides in your handouts. They go over the study types that we see fit for use and conduct of clinical pharmacogenetic studies.

The first study type is a volunteer study, a Phase 1 study, that helps to explore the genotypes that affect the PK or the safety of the investigational drug. These studies pertain to the early learning stage when valid biomarkers or clinical endpoints may or may not have been defined yet.

[Slide]

The next study type is what we call a panel study. That, again, is conducted in healthy volunteers or, now, in

patients. It is a study that helps to compare the PK and PD in subgroups or panels that were preselected. Again, this pertains to a situation where you already have some information about the use of this genetic information that you want to test. It still is at the learning stage when the biomarkers or the clinical endpoints may already have been defined based on the genetics that you study.

[Slide]

The third study type is a dose-response study. This helps to determine the impact of a genotype on the dose response or the exposure response of the investigational drug. These studies can happen at the interface or in both type of stages between a learning and a confirming stage of drug development. At the learning stage it would help to find the doses and study the doses that would then be confirmed in a later stage at which acceptability of safety, genotype-guided doses, etc. are being explored further.

[Slide]

Obviously, a critically important type of study is the randomized, controlled trial. These studies are being conducted at the confirming stages of clinical development in order to support regulatory decisions and labeling, and

they need to be powered appropriately to include that information in a solid fashion in the drug label.

Obviously, these studies compare clinical outcomes between the test drug and the control or the placebo, and what you want to study here is the genotype of interest in randomly assigned subjects.

[Slide]

Lastly, cohort studies. They are also being conducted at confirming stages or the label stage of drug development. They are envisioned to observe phenomenons that have been looked at in a prospective observation for all subjects that received the drug and compare the therapeutic outcome with the differences in genotypes.

[Slide]

This is my last slide and I just want to go briefly over it. These are the questions that we hope to discuss at the end of this series of presentations.

First, as you now know, we propose to collect DNA samples from all participants in clinical trials. We would like to discuss what issues or barriers should be addressed to facilitate routine collection of DNA samples. We would further like to discuss when, and under what circumstances,

to what degree DNA should be collected ruing drug development for use in exploratory analyses.

We created a decision tree depicting the integration of pharmacogenetic studies in the drug development process. We would like to hear from you comments or recommendations on that decision tree pertaining to the scientific rationale and thought process that is embodied in this tree.

We outlined some different types of studies for clinical pharmacogenetics and we hope to hear from you comments on the design of these studies and their proposed impact on subsequent clinical trials.

I end here and give it back to Dr. Venitz.

DR. VENITZ: Thank you, Dr. Frueh. Let=s defer discussion of those questions until we have listened to all three presentations. So, right now I open the floor to any questions or comments regarding Dr. Frueh=s presentation.

Let me get started. Looking at the decision tree, you have this 25 percent cutoff.

DR. FRUEH: Yes.

DR. VENITZ: Two questions. How confident do you think we are at the early development stage on the

contribution of any pathway? How did you come up with the 25 percent?

DR. FRUEH: The 25 percent number is a number that is described in the drug-drug interaction guidance, and we felt that is a good starting point at least for having a discussion about where the cutoff should be. So, it is not a number that is written in stone. I think it is a number that is up for discussion but it has some bearing on prior information and prior guidances that we have out there.

DR. VENITZ: But how confident are you based on in vitro data? I mean, this is preclinical. You haven=t done anything in healthy volunteers yet--

DR. FRUEH: Right.

DR. VENITZ: B-that you know 25 percent or less, or 25 percent or more is metabolized by a certain pathway?

DR. FRUEH: Yes. Maybe, Shiew-Mei, you want to comment on that?

DR. VENITZ: Dr. Huang?

DR. HUANG: Sure. The decision tree is a modification of the decision tree that we have for the draft guidance on drug interaction that was published in September, 2006 and it is very similar. We did put in 25 or

30 percent of the metabolic pathway. So, if you look at major CYP enzymes or UGT, then you need to do a drug interaction study. But we did specify.

What was not specified here is either if it is more than 25 or 30 percent, or if the contribution to the pathway is unknown, then you need to do a study. If we know for sure it is less than 25 percent, then you do not need to do a study. Oftentimes we don=t have the absolute bioavailability so it is very difficult to know exactly what so we use a more conservative approach. If it is unknown, then it is timely you do a drug interaction study.

So, oftentimes we will get some information from the drug interaction study to see whether the pathway is important or not and will be useful for this type of study.

DR. VENITZ: So, you default position is the very right-hand arm of that decision tree. Is that right? It is unknown until you have drug interaction.

DR. HUANG: No, for the well-defined genes. For drug interaction we specifically tell about 1A2, 2C9, 2C19, 2D6, 3A and 2CA and 2B6. For these enzymes, if you don=t know the pathway then you need to do a study. So, based on drug interaction you will also have the information to know

whether that pathway is important. So, you are complementing the information from the drug interaction study to here.

So, this is an adaptation. But in the drug interaction guidance we did say that instead of conducting a drug interaction study you could study a poor metabolizer versus an extensive metabolizer to define the contribution of that pathway. Similarly, here you could do a drug interaction study to define whether this genotype is going to have an effect. So, they are complementing each other.

DR. VENITZ: But you won=t have a drug interaction study in Phase 1 yet. My fundamental point is that I think you are putting a little too much confidence in us predicting the contribution of a single pathway before we have any human data, be it Phase 1 studies or drug interaction studies. So, personally, I think the right-hand arm would be the default position. It is unknown, or at least it is not known with enough certainty to say that it is more than 25 percent.

A follow up to that, what about transporter genotypes, PP1? B1?

DR. FRUEH: Right, we were talking about this, and

I would say that we haven=t felt comfortable enough to say that we already know enough about the impact of these enzymes or transporters, according to the nomenclature in the pharmacogenomics guidance, to call them known valid markers. In other words, we would like to study them in more detail regardless.

DR. RELLING: I just want a clarification. Are you stating that if you fall in the less than 25 percent category you are not recommending that DNA be collected? Why is there only a path to collect DNA under certain of these things? It seems to be in conflict with your goal that DNA always be collected.

DR. FRUEH: I would have to agree with this.

DR. RELLING: Okay, because I think that is important. That makes me less worried about whether you are 25 percent, 30 percent or 50 percent, but the idea is that you get DNA for everybody.

DR. FRUEH: I agree.

DR. VENITZ: Dr. Huang?

DR. HUANG: I just want to clarify. On the left-hand side, when you say less than 25 percent it is for a specific well-characterized gene. So, if we didn=t see more

than 25 percent for, say, 2D6, then we can label that 2D6 as no effect for either inhibitors or poor metabolizers. However, on the right-hand side, this will be Aother@ because there are many, many genes that we will be talking about. For well-characterized genes if there is not you can go ahead and label. So, you will not continue to do the studies for that particular gene but you will continue to do other genes, and that is in the right panel. We could just draw a line--

DR. FRUEH: Right, you could draw a line through here basically to here.

DR. HUANG: Yes.

DR. VENITZ? Dr. Lesko?

DR. LESKO: So, when we thought about the 25 percent, as Shiew-Mei mentioned, it was based on the drug interaction guidance and that is based on in vitro data. Now, would you have a sense from the in vitro data what fraction goes down what pathway? You can rely on that information I think in human studies if you have a sense of what the bioavailability of the drug is. You can estimate whether that pathway is going to be important in affecting drug exposure or not.

So, that is sort of the thinking on that. But I want to get to the part about stopping on the left-hand side. If you are in that category where you know an NMe is not a substrate for a polymorphic enzyme in terms of metabolism or clearance, you would then sort of lead to a conclusion that the clearance of a drug between individuals is not likely to be affected by genes. So, the collection of DNA at that point would be for the purpose not of pharmacokinetics or pharmacodynamics per se, but the collection would be for the possibility that in later phase clinical trials, if an event occurs, one would be able to go back and access the DNA.

So, I want to get some clarity on that point that people are asking about. What would be the right rationale for not stopping but continuing to collect DNA in that situation?

DR. RELLING: I think you need to leave the door open, that we certainly don=t know about all the important polymorphic gene products that affect pharmacokinetics and pharmacodynamics. If that is what is being suggested, then that is the wrong message. So, yes, you are leaving the door open for collection of DNA for potential

pharmacokinetic and pharmacodynamic genes that aren=t yet on the list, as well as other gene products that might be involved in rare adverse events or as yet unknown causes of therapeutic failure.

DR. VENITZ: I would want to second that. I would add that when I looked at this decision tree I thought this was a decision tree that helps me to figure out whether I should collect samples or not. And, in my personal opinion you should always collect samples.

DR. FRUEH: Okay.

DR. VENITZ: That is why I kept talking about the default position, meaning the right-hand side. If we don=t know, well, maybe we will learn something. But I think we are now talking about what to do with that information once we collected it.

DR. FRUEH: Okay.

DR. VENITZ: Then I can see that there would be a stop and label appropriately.

DR. FRUEH: I agree and I think that was an oversight here. I mean, that should be stated here as well.

DR. VENITZ: But I mean fundamentally I agree that we should continue to take those samples, collect them, put

them away and use them if necessary. I am pretty sure we are going to talk more about what hurdles are associated with doing that, but just the potential benefit of having that I think, to me, is worthwhile.

DR. FRUEH: I agree.

DR. BARRETT: I had two questions. One, in your position paper I know the emphasis has been so far on focusing on early drug development, but it would seem that there would be tremendous value in looking at this across studies and across agents as well. Is that covered at all in this position paper or in the guidance proposal that you laid out? Because probably many of us are thinking about the potential value in looking across compounds this way. If so, has there been thought to the nature of the data analysis that would fall from that kind of data collection?

DR. FRUEH: Well, first of all, the emphasis that we want to put forward in this concept paper or draft guidance is on early development. So, that was the stated goal. We have a series of guidances that are coming out for later stage developments, not necessarily for genetics per se but for the more statistical design approaches in these trials for enrichment and stratification purposes etc. that

are directly relevant to the use of genetic information. So, we were trying to strike a balance between that.

SecondlyB-I lost my train of thought. What was your second question? Oh, the analysis, yes.

DR. BARRETT: Right.

DR. FRUEH: Yes, I am sorry. Absolutely yes. We are going back and forth between how much information we should include in this particular document. We have several other documents that are in development, one of which has been issued, I believe, late last year on recommendation for the analysis of genetic data, genomic data. It is a companion guidance to the 2005 guidance. This goes into much more technical detail about all of this.

Much of the analysis of the more complex types of technologies is still in development, and I don=t think it would be prudent at this time to actually issue a guidance on that. We have several fairly large collaborative efforts that are going on, such as the Microarray Quality Control consortium where we are looking into exactly what you are referring to.

DR. BARRETT: I guess tied into that question, and consistent with what Dr. Venitz is saying, the certainty of

the information you collect at early stages is I think one of the questions. In particular, with the first Phase 1 studies, healthy volunteer studies, you have a design piece where you mentioned that this allows you to determine the population frequency of genotype and phenotype if unknown.

But I wonder if there is really adequate information in that population to give you a good estimate, and do you know from historical data what the overlap is? How informative is that Phase 1 study relative to the ultimate population you will treat?

DR. FRUEH: Right. Yes, I think that is a very important question and a very important consideration for the design of these studies. Obviously, if you are dealing with low frequencies you may not be able to recruit into your Phase 1 studies as you would like.

Nevertheless, I think that the information that you gain from these studies will help you to answer some of these questions that so far you just have not been addressing at all. There is no doubt there are limitations due to the size of the trial that we cannot circumvent at this early stage of development. So, I agree.

DR. VENITZ: Dr. Topp?

DR. TOPP: I will pass.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes, Felix, on the issue of collecting DNA I think I also agree with what is being said, that that is an important thing just to have. It also brings up issues immediately related to ethnicity and race, etc. Is that being conceived of as part of this guidance? Is it already required that you collect that kind of information on subjects?

DR. FRUEH: Yes, there is a guidance on race and ethnicity out there and we are, of course, encouraging that the clinical studies should be conducted in an ethnically diverse background. I would think that this guidance actually just strengthens the notion of doing so and that genetics probably could help to do it more appropriately and get more information about this particular issue.

DR. GIACOMINI: Thank you.

DR. VENITZ: Dr. Morris?

DR. MORRIS: In looking at the decision tree, it just came to my mind, the possibility of active metabolites and how they fit in here. They could be formed by a polymorphic pathway or eliminated by a polymorphic pathway.

I think that again sort of emphasizes the importance of collecting samples, you know, even if there is less than 25 percent cleared by a polymorphic pathway.

DR. FRUEH: I agree.

DR. VENITZ: Dr. Lertora?

DR. LERTORA: Basically, I do agree with the recommendation that we should collect samples, even if you are in that category of less than 25 percent for a given metabolic pathway. I think it would be important in your own design here where you later have the dose-response study, you know, where you propose to study the impact of a genotype on the dose response or exposure response relationship. If you don=t have the sample up front I think it would not have the necessary information to analyze this trial later.

DR. FRUEH: Yes.

DR. VENITZ: Dr. Mager, last question?

DR. MAGER: I was interested in that the entry into the decision tree is largely driven by pharmacokinetic information and you really don=t get to pharmacodynamic variability until much later in the tree. Have you considered an additional line and column looking at

pharmacodynamic variability? I think that would largely be much more informative for exposure response information.

DR. FRUEH: I agree with you, although I believe that the current information and knowledge that we have is probably very limited in terms of PD. We certainly know a lot more about the PK variability if you are looking at drug metabolizing enzymes which today are the ones that we feel confident to actually use for that early decision.

So, I think we are a little bit at an impasse in terms of scientific knowledge here for using PD information that early. You are not going to get it from in vitro or early ADME studies but you do get it probably later in the development process when you are going into clinical studies. So, obviously, at that point absolutely yes, one should use that information. But we didn=t feel as confident in the state of designs at this point, I guess.

DR. VENITZ: Let=s defer any further questions. We have a whole section to discuss later on. We need to stay within the time schedule. Thank you, Dr. Frueh.

Our next speaker is Dr. Lisa Shipley. She is the Vice President for Drug Disposition and PK/PD at Eli Lilly, and she is going to present to us the results of an industry

survey on the use of PGx.

An Industry Survey on Collection of PGx Samples

DR. SHIPLEY: Good morning.

[Slide]

I would like to thank the coordinators of this meeting for having this opportunity to present basically the industry=s perspective or PhRMA=s perspective on the use of pharmacogenomic genetics information.

[Slide]

We actually set about, about two years ago, to put a white paper together because we recognized the emerging importance and the continued importance of this field in drug development. So, what we will be looking at is this white paper, look at some of the specifics of the survey and not the entire white paper, to present the pharmaceutical industry=s perspective on the recent and future utility of pharmacogenomics related to the ADME properties of drugs and drug development utilization.

We wanted to offer perspectives on the current state of practice, not best practice but the current state. We recognize that we didn=t even understand ourselves kind of what the baseline was for the industry. We knew what our

own companies were doing but we didn=t know what the baseline really looked like. As we said, it was not intended to provide a best practice but baseline, and the second half of the paper actually discusses our current understanding of some of the clinically significant polymorphisms of both drug metabolism and transporters.

[Slide]

So, our approach was to establish a cross-industry perspective on how we were using ADME pharmacogenomic data, and we conducted a survey of recent studies that had been conducted between the years of 2003 to 2005.

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For the survey itself we assembled a series of questions to elicit broad information about the current practices in this area at the different pharmaceutical companies. The survey respondents were instructed to base all their answers, as I said, on studies from the years 2003 to 2005. We actually began this effort in 2006 so that kind of gives you the dating on that.

Companies were also asked to provide citations for peer-reviewed original research papers in this area, and examples of how ADME information has been used for internal

decision-making and in our regulatory interactions.

To maintain the anonymity of each company and to allow people to feel free to answer, we actually had this done through PhRMA. They collected the data anonymously from each one of the companies and then they aggregated it and provided it back to us just in the aggregated form except, of course, for the published papers. It is pretty hard to hide your affiliation when you have an author on a paper.

As you will see as we go through this, not every company answered every question. And, I have reordered some of these. There are 21 questions in the survey for some ease of presentation.

[Slide]

Who were the participating companies? We thought it was important to put this data in so you can see the magnitude of the players that responded. I won=t read through all of these; you have them in your packet. But you can see that it is most of the large pharmaceutical companies that are represented in this. Others were invited to respond. If they chose not to respond to the survey in the time allotted, then we just moved on.

[Slide]

So, let=s get into the meat of the survey. How often has your company collected DNA data with consent for ADME-related genotyping? You see the listings down beside each type of study. As you can see and, you know, perhaps you are more comfortable with what you are seeing here given Felix=s presentation, in many of the very early studies, the first-in-human and the multiple rising dose, the prevalence of the companies do collect DNA data at this point. Also, in the drug-drug interaction studies it is quite prevalent, with most companies responding. So, it does seem to be a basic practice of the industry at this point.

As you get into some of the other types of study, proof of concept and some of the pivotal studies, you see that there is a little bit more heterogeneity in the data, and this may also reflect the number of PK samples that are collected during this phase. Obviously, with the early studies there is PK-rich sample collection at that time.

[Slide]

Now, while we collect those, we don=t always analyze them, as you can see. Looking again, the column sometimes is quite populated as you come down through here.

So, we collect those samples but we are not always using them.

This may reflect a couple of things. You don=t know what you don=t know at the beginning of this and we are in a very exploratory phase so it is better to have collected those samples and then perhaps find that you don=t need them when the results of those studies are seen and further analysis won=t add to the interpretation of the study. So, we do have a lot of samples that are collected and, as you will see later, we keep them for quite a while.

[Slide]

Has your company used ADME-related phenotypes in study design? We obviously use them both in the selection or in our inclusion criteria, with ten of the companies saying yes, or in screening with, again, ten of the companies saying they use it in their exclusion criteria.

As you look at some of the genes listed below, you will see that the most prevalent ones that are being used are those that are generally considered the validated biomarkers by the FDA, specifically 2D6, UGT1A1, the CYPC19 and C9.

[Slide]

Again speaking to the analysis and plans, as you can see, how often has your company specified PG-PK analysis in study protocols? Then the following question, how often does your company have a written plan or strategy for a compound in development? Predominantly it is in the Asometimes@ category. So, there is more of a prevalence for this to be happening but it is not a predominant practice in the industry, with only really three companies out of the 14 saying that they always or usually have either a plan, a strategy or analysis planned in at the beginning.

How often has your company used phenotyping to ensure genotype assigned phenotypes are correct? Again, more are saying never than saying that they do, and only some are saying that they sometimes do this. This may very well reflect the fact that exclusion criteria should take individuals out that might perhaps be, you know, extensive metabolizers that are on an inhibitor, becoming poor metabolizers. They really should have been sorted out in the exclusion criteria of the studies that you are running. But, in fact, most companies do not.

Moving to statistical power, how often has the

statistical power of the analysis entered into study design criteria at your company? Again, only sometimes. Again, as these studies are largely exploratory in nature and often piggyback on the back of other studies and we also tend to combine multiple studies, statistical power often isn=t taken into consideration in these types of studies.

Kind of a question that was organized just for ease is how often has your company used any FDA-approved in vitro diagnostic for clinical trial applications? Again, only in the Asometimes@ category as this is not a requirement.

[Slide]

So, the breadth of genotyping, this is a pretty busy slide but you will see again a predominant number of responses is yes, or in the usual suspects, the ones that are the well-known, validated biomarkers. So, the CYPs are 2D6 and, I guess, with the exception of 3A4 and 3A5 which are not validated, there is a pretty high incidence there as well; 2C9, 2C8 and the UGT1A1. Also, you will note that there is a fair number of yes responses with regard to the transporters, specifically around the OATP1B1, the BCRP and the MDR1 categories. Other transporters are measured but I

guess that will also reflect the different compounds that are under development.

[Slide]

So, has your company only genotyped when preclinical data indicate a role for a gene in a compound=s PK, or do you genotype a broader range of genes? It is almost a 50-50 split there. Many go with the preclinical supporting data only, and that is the in vitro type data. If you look across the industry, generally it is at that 30 percent cutoff. If you see 30 percent of the drug being metabolized or the clearance being down that pathway of a polymorphic enzyme, then generally there is a targeted effort around that particular enzyme in the study designs. Again, the other half uses a more broad range that is using the broader platforms. Some get the multi-chip formats.

Has genotyping been done within your company or outsourced? As you can see, the answer is both basically. Every company seems to have some internal aspect or laboratories doing this type of work but there is a fair amount that also gets outsourced. We will talk a little bit about some of the quality aspects around that in a moment.

Has your company coded samples collected for PG-PK

research? And, it was okay, as you can see, to check more than one response. The single coded would be similar to any other kind of data that would be gathered during a clinical trial. Many have chosen to double code this, which gives an added layer of security. Then, three companies said they have anonymized or made it anonymous. There could be some issues with this obviously if you wanted to go back and audit this data so we need to think about that as well.

[Slide]

So, has your company kept/banked DNA beyond the initial period of the clinical trial? The answer was an overwhelming yes, we do keep these samples. Again, as I said, we don=t know what we don=t know at some points and it is often useful to be able to go back and look at that data when you see something else come up later on in development.

I kind of mentioned this before when we were talking about statistical power, has your company combined samples across studies of a single compound to enhance statistical power? The answer, again, is an overwhelming yes.

Has your company used large-scale, multi-chip based exploratory analysis? This seems to reflect equally,

or I guess supports the data we saw with the single approach or broad approach in how we look at which genes we include.

Does your company apply the following standards for human DNA sample collection and generation of human genotype data that might be useful in regulatory submissions? Overwhelmingly, everybody does good clinical practices and many are claiming good laboratory practices. Again, there are some limitations to GLP in this setting. There are pieces of it that could be very useful around sample management, as well as, you know, the instrumentation. But those were developed for animal studies and not for human studies so it does have its limitations.

A few actually claimed GMP, which may reflect the fact that some companies may be wanting to move into an in vitro diagnostic with some of the work that they are doing.

[Slide]

So, as we said, again, samples in the Phase 1 and the drug interaction studies, but there seems to be some heterogeneity with regard to whether we think they are actually required or optional. So, the answer in the early stages seems to be both. That may, again, be dependent upon

the particular study that a company is responding to.

But, again, as we fall into the Phase 2 and Phase 3 studies we really seem to see that as pretty optional and, again, it may reflect the fact that we don=t often collect as many pharmacokinetic samples in these types of studies, or there is a limited number of samples collected in that phase.

[Slide]

How important has replication of a PG-PK finding been in your company? Please check only one box. As you can see, we do think it is very important with regard to replication when we are using it in regulatory submissions unless it is a validated biomarker. But really the place where we are using it the most frequently and most companies responded is that we use unreplicated results for our internal decision-making. So, we find that it is very important to feel that we can replicate it if it is coming into a submission. If we are using it internally we are less likely to do that replication.

[Slide]

Lastly, I think we have all benefitted, all the industry has benefitted from the research in this area.

About eight of the companies responded and provided some of the publications that their scientists have published in peer-reviewed journals around the work that they have done in this area. Eleven of the companies said yes, they have used it internally in decision-making.

Has your company interacted with the FDA or other regulators regarding this area? Ten of the 14 responded in the affirmative.

[Slide]

So, to summarize, we have seen that the pharmacogenomics has already had a significant impact on drug development and is beginning to utilize more and more the utilization of these drugs.

It allows the identification, confirmation or exclusion of clearance pathways. It can help us explain the variability; ensure the trial population is appropriately balanced; ensure the safety of volunteers and of patients; and provide mechanistic information.

These studies may support labeling claims concerning PK dosing, ethnic variability and safety. Not covered really by the survey but, you know, a significant effort still remains in the education of the public,

prescribers and ethics committees and investigators on the appropriate use of this type of data.

With that, that was the survey and if there is time I will take any questions or comments.

DR. VENITZ: Thank you, Dr. Shipley. Before we go to comments, we have another member of the committee join us. Dr. Flockhart, would you please introduce yourself for the record with your name and affiliation?

DR. FLOCKHART: I am Dave Flockhart, and I apologize I am late. I am from Indiana University.

DR. VENITZ: Thank you. Any questions? We have about five minutes for questions for Dr. Shipley, plus whatever time we have later on in our general discussion. Dr. Giacomini?

DR. GIACOMINI: That was a nice overview. I guess the question that comes to my mind isB-I don=t know what slide it is, but the one in which you show that although many companies are collecting DNA, there has been very little use of the DNA for, you know, any kind of association with ADME. Can you express, is that becauseB-I guess you didn=t find that kind of information out, but I would like to know is that because of a fear of regulations and nobody

wants to do that? Or, is that just because it is not a good hypothesis? Is it a cost issue? What is the reason?

DR. SHIPLEY: So, I will be speculating because the survey was meant to be, for ease of collection of this data, just what are we doing at the most general times. What we have speculated in the white paper is that some of that is, as I said, kind of that you don=t know what you don=t know so we collect. Then, if we are moving on and seeing results, let=s say actually doing this analysis is not going to aid in the interpretation of the data that you have seen, why would you incur the additional cost and time to do that?

So, that is what we are speculating with regard to across all the companies. I don=t know that anybody is, you know, kind of afraid of the regulation.

DR. GIACOMINI: Then a second question, and that is your companies are fairly large companies. It is not a spectrum of large to small. Do you imagine, I guess, that the same kind of data would be obtained in smaller companies?

DR. SHIPLEY: So, there are a few small companies that chose to respond. I mean, any PhRMA company was invited to participate. Some just chose not to, which may

reflect that they are not really doing this. It may reflect that it didn=t get to the right person within that particular company to respond, but we left it open for a six-week period for response and did make sure that it got to the different companies. So, I can=t speak to it.

DR. VENITZ: A somewhat related question, did you ask how long they actually keep this information? Is it like a registry that they keep for 10, 20 years?

DR. SHIPLEY: We didn=t ask that question. Often when you see a survey you realize some of the questions you should have asked.

DR. BARRETT: I didn=t see it in the survey but I am just curious, in your discussions with various PhRMA members was there any discussion about any difficulties in terms of getting patients or volunteers to participate, you know, through the informed consent process? Was there any liability associated with that, but for the most part this has been very well received by the population you are studying?

DR. SHIPLEY: Relatively well received. There was no discussion of it being problematic.

DR. VENITZ: Dr. Topp?

DR. TOPP: Yes, I noticed the DNA is not always collected, that most of your companies fall in the category of Ausually collected.@ Can you say something about the cases in which DNA is not collected? Does that come through from the survey, are there circumstances when companies say, no, it is not worth it in this case?

DR. SHIPLEY: One of the things that we speculated is that perhaps in some of the biomolecules they make they may choose not to collect the ADME enzymes because it is not relevant. That is about the best we can speculate with regard to the survey. Amgen was on there and other companies are involved in large molecule development.

DR. VENITZ: Dr. Huang?

DR. HUANG: Lisa, in one of the slides you mentioned about the participation being optional or required. When it is optional, do you have a sense of the percent of participation either in the early clinical trials or in late clinical trials?

DR. SHIPLEY: I don=t have a feel for that, Shiew-Mei. This looked at, you know, kind of the mix of studies that were being run between 2003 and 2005. Perhaps there were places where they felt-BI mean, you know, one company

who usually does felt that it was an option in particular studies because of what they knew. Again, it is just hard numbers at this point.

DR. HUANG: Oh, I meant when it is optional what is the patient participation rate.

DR. SHIPLEY: I don=t know.

DR. HUANG: You don=t?

DR. SHIPLEY: I don=t know.

DR. VENITZ: Dr. Lesko?

DR. LESKO: Thanks, Lisa. Two questions. One, the survey was conducted between 2003 and 2005. Do you have a general sense, given how rapidly this field evolves, what would be different if you did the survey today, in 2008, versus 2003 to 2005? Then I have a second question.

DR. SHIPLEY: I would be speculating obviously--

DR. LESKO: Yes, obviously.

DR. SHIPLEY: It has been growing. I think we would see some more moving into doing this, you know, more on a regular basis or doing it always.

DR. LESKO: The other question is I know the survey was related to ADME-related genotyping, but it just struck me that one of the important studies that would have sort of

a bearing on genetics would be a proof of concept study. That is to say, if a proof of concept didn=t succeed as expected there may be a reason to go back and look at subset analyses for efficacy or perhaps safety. Do you feel there is any DNA being collected for disease-related genotyping?

DR. SHIPLEY: I think the answer to that is yes, but it was out of scope for this particular survey.

DR. LESKO: Yes, right.

DR. VENITZ: Dr. Yasuda?

DR. YASUDA: I was just wondering what people would do with the anonymized samples that wouldn=t be traceable.

DR. SHIPLEY: Again, I can=t answer the particulars on that.

DR. VENITZ: Thank you, Dr. Shipley.

DR. SHIPLEY: Thank you.

DR. VENITZ: Our next presenter is Dr. Eric Lai. He is Vice President for Pharmacogenomics Experimental Project Coordination and Analysis at GlaxoSmithKline.

Use of Pharmacogenetics Information in Clinical Settings: Are we Ready for Prime Time?

[Slide]

DR. LAI: Good morning. I would like to thank the

organizers for inviting me.

[Slide]

First of all a disclaimer, this presentation represents my personal views and does not necessarily reflect the policies or endorsement of GSK.

[Slide]

I guess at this point all of you have the handouts so I am going to go through some of these slides very quickly because you can always go back to them.

First of all, I don=t think I need to say anything about what is PGx. It really deals with the effect of individual genes on the action of a specific drug. But I do want to spend a minute or so on the misconception about PGx, in that there is really no such thing as a personalized medicine, and people keep saying the right medicine for the right patient at the right dosage or right time.

[Slide]

This is really a perfect example of marketing talk in that drugs are not like cars or computers where you can look up on a computer and say I want certain options for my car or computer. That is not the case. Clinical trials are really done on populations and effects are observed in a

group of patients. You just happen to be in that specific group.

So, PGx really increases the probability whether a drug is going to work for you or work against you. And, the drug is not specifically designed for you. It is not a personal thing, but for a group of targeted individuals so really the better term would be a targeted medicine, or informed medicine. So, it is more like clothing size. Okay? Whether you are size zero or size 14, you go into a department store and you pick the size that fits your group.

The reason I want to spend any time on this is because to set up expectations for PGx is very, very important. I think that when we go out to educate patients we have to really understand what we are trying to tell them. Later on, I have a little survey that we did which is really revealing about what a patient thinks about medication.

The final thing is that not all clinical trials or drugs have PGx components. At GSK about 30 percent of trials actually have a PGx component, not all of them.

[Slide]

At GSK PGx results are used mainly for these four

major groups of experiments. They are used to support the post-marketing risk management, meaning, to increase the safety profile, what we call the safety PGx, and they are mainly Phase3/Phase 4 post-marketing management. We also use them for supporting progression of a molecule in Phase 2 and Phase 3 to either improve the efficacy profile, or what we call the efficacy PGx, or improve the safety profile.

We also use PGx in Phase 1. We have had discussion on the PK and PD already, and I will come back to this at the end of the talk. We also try, if possible, to understand a little bit better about disease-understanding but that is not a main focus of the PGx.

[Slide]

So, in the next 10-15 minutes of my talk I am going to go through these six different bullet points and basically try to address is PGx ready for prime time for routine clinical applications? I am going to divide up the topic into safety PGx and then efficacy PGx because they are very different as far as application, as far approach, and as far as the timing of the application of the PGx.

[Slide]

So, I am going to talk about the safety of PGx

first and I am going to use the abacavir hypersensitivity project, for which I was the project leader for three years, between 2000 and 2003.

[Slide]

So, what is abacavir hypersensitivity? Abacavir is a commonly used drug in the treatment of HIV infection. It is in three products. It is well tolerated, but it has a hypersensitivity reaction associated with the drug in about five percent of the clinical patients. They have a hypersensitivity reaction. It is a multi-organ syndrome. Usually 90 percent of the patients have fever; they have a rash; they have some GI problems. Most of the patients have this hypersensitivity reaction within the first six weeks of the therapy. The symptoms will get worse if you continue abacavir, and it would be life-threatening if they are re-challenged. So, that is not indicated in the usage of the drug.

[Slide]

In 1999 when GSK got the approval from EMEA and FDA, we made the commitment to the regulatory agencies to conduct research to understand abacavir hypersensitivity reaction and potentially develop tests to confirm the

hypersensitivity reaction.

Before the genetic work was done there were a lot of pooled analyses done to look at some risk factors for HSR as far as race, sex, prior drug treatment, and so forth, and all of this has been published and I am not going to go through them.

[Slide]

This shows the cumulative patient-year exposure to abacavir products and the reported HSR-association as far as mortality is concerned. We can see that since the approval over a million patient-years of exposure have been accumulated.

And, because of the clinical management program that we actively put out and manage, you can see that the number of patients that die from abacavir actually has been very low. But still, that is a clinical management program, meaning that the patient will have to take the drug and then we manage the side effects. But what we really want to do is to be able to predict which patient will get the hypersensitivity reaction.

[Slide]

So, in 1999, after we got the approval for

abacavir, there was an internal team set up to understand the abacavir hypersensitivity reaction at the genetic level.

For two years we did retrospective studies and candidate gene study at the time and found, in 2001, that HLA-B57 was highly associated with the abacavir hypersensitivity reaction, and that in the Caucasian male, depending on the study, in that the GSK study was a large retrospective study, it gave about 50 percent sensitivity, where a group of researchers in Australia have done a very small, single-center study and their sensitivity was over 90 percent sensitivity. But both studies showed a very high selectivity of 98 percent.

In 2003 the result was extended to Caucasian females by increasing the retrospective study at GSK. In 2004 to 2005, LabCorp started offering 5701 screening assays in response to the requests by the U.S. HIV clinicians. The first prospective study you a research group was reported in 2006 and GSK conducted a large prospective trial to understand the clinical utility of 5701 in the management of abacavir hypersensitivity, and in 2007 that trial was published.

The reason I show this slide is that I just want

to show how long it has been from the initial association that we found in 2001 to the actual clinical utility demonstrated by a prospective trial. This is one project that I have seen through from the market discovery phase all the way, at this point, to a really clear result.

[Slide]

So, is the science robust enough for routine application to drug development for safety? I think it is, in that what we have done is we have gone through and looked at what is in the literature on all the PGx experiments that have demonstrated that they have been able to find genetic factors or markers associated with an adverse reaction on a drug.

What we found is that in all the cases that have been reported so far the effects are pretty large, in that in some of them, like abacavir, there is a 36 odds ratio. So, you would be able to find, if you look hard enough, major genetic factors associated with these adverse reactions, and you don=t require too many cases.

A lot of people, when you start thinking about safety of PGx always say, well, you will never be able to collect enough cases. The thing is that you don=t need to

collect a whole lot of cases. We are not talking about looking for disease genes. Okay?

Granted, we are only looking for major genetic factors. On the other hand, only the major genetic factors are the ones that will provide clinical utility. You are not going to be able to find markers with an odds ratio of 1.2, 1.3 and you would think that they would be of clinical utility.

So, the second question is, is the pharmaceutical industry ready to incorporate PGx in post-marketing safety and management and improve the probability of success in drug development? The answer is yes, if they are forced to, in this case abacavir. That was in agreement with the regulatory agency and we did it.

[Slide]

Now, the other major factor about safety for PGx that is very different from all the other studies is that when talk about safety for PGx, that means that your molecule is already on the market a lot of times, in this case abacavir. What that means is that any physician, any PI would be able to do the study, not just a drug company.

So, I just want to show in this case that the

first prospective study on the use of B5701 in screening to reduce the patients with HSR was actually done by a research group in western Australia. They started screening patients in 2002/2003. As you can see, they have decreased the HSR cases tremendously. Actually, the two cases that turned out to be 5701 were either not screened because they were not aware of it, or they were screened after administration.

[Slide]

So, in 2005/2006 GSK decided to do a large prospective trial, multi-center study, double blind, to determine whether prospective screening for 5701 will result in a significantly lower incidence of clinically suspected HSR or, to go one step further, to use skin patch testing to confirm the immunologically confirmed HSR.

[Slide]

This is the study that was published in The New England Journal of Medicine this year, just about a month ago. As you can see, the clinically suspected HSR cases had gone down from 7.8 percent to 3.4 percent, and in the skin patch test positive patients had gone down to absolutely none. Every single case was screened out by screening with 5701.

[Slide]

So, the conclusion is that prospective B5701 screening can really eliminate patients that have very high chances of development abacavir HSR.

[Slide]

So, are physicians ready to order PGx testing? Are the payers ready to pay for PGx testing?

[Slide]

Well, if you just look at the situation in one clinical lab, in this case LabCorp, this shows the growth of the B5701 testing that was requested of LabCorp.

As you can see, when they started offering the test in 2005/2006 there was a very low volume. With the presentation of the PREDICT-1 study at the AIDS conference last year, in July, it starts to pick up. Now, as you know, the HIV clinicians are very aware of the latest information in the literature, and it had gone up from about six months, and then in January and February because of the holidays it kind of plateau=d a little bit, and then in February, because of the publication of the paper, it went up again and it is still going up.

So, as you can see, physicians are ready to order

the test. And, since I assume LabCorp is a for-profit organization, I assume that they are getting paid for this. They are not doing this for free. So, they must be able to get reimbursement for these tests.

[Slide]

Are the patients ready for PGx testing? This is a very interesting phenomenon. I did some surveys in a lot of the countries that I have gone to and common sense is a very interesting thing and you can=t really predict people.

So, what am I saying? If I ask people about odds of winning in a casino or ask them will you pay for a test if the results can tell you whether you can improve your odds of winning from five percent to 50 percent, 80 percent of the people will say, yes, they would definitely pay for the test in order to know whether they have a better chance of winning when they walk into a casino. No problem.

Now, you ask exactly the same question and I asked them, okay, what are the odds of getting an adverse drug reaction from taking the drug? Will you let your physician order a test for you if the test will tell you whether you have a higher chance of getting an adverse reaction, from five percent to 50 percent?

In this case only about 50 percent of the people will say yes, even though they don=t have to pay for it. And you will have all kinds of interesting answers when you ask them why they don=t want to be tested, even though it is exactly the same odds and you increase their probability. Those of you who want to understand all the reasons behind it, I can talk to you later. So, it is really interesting in that you really have to educate people on what the use of the test is going to be.

[Slide]

Now, is PGx ready for prime time from the regulatory agencies? We will come back to that later.

[Slide]

Efficacy of PGx.

[Slide]

I am going to go through this very quickly here. I don=t need to say anything about this because everybody knows that not all drugs work in all patients. This is the data from a 2001 paper. The first author is actually in the audience so you can ask him if you have any question about this.

[Slide]

Here I just want to show some of the examples that are currently on the market and have FDA guidelines as far as a requirement for tests. So, this are efficacy PGx on the market already. So, FDA is indeed doing it. The science is there. There is no question about it.

[Slide]

I want to come back to this. Is the pharmaceutical industry ready to incorporate PGx in the efficacy to increase the probability of success in drug development? And, are the regulatory agencies up to the task of implementing PGx?

[Slide]

I just want to take this one quick slide about the co-development and I just want to make two points. The first point is it is very unrealistic for anybody to look at this and think that you will be able to identify markers pre-Phase 1 or even Phase 2 from animal studies or from any kind of study that drug companies have done.

Let=s be realistic, if we know so well about the drug, if we know so well about biomarkers, and so forth, don=t you think that we would design a better molecule and have a higher success in the pipeline instead of five, ten

percent? Most of the time we don=t really know that much about the target. Okay? So, most of the time you don=t even get into efficacy PGx until you are in Phase 2 or end of Phase 2. What that means is that there is absolutely no way that you can incorporate co-development of a diagnostic in this same time frame.

The second thing is that it is almost impossible not to extend currently to Phase 1, Phase 2 and Phase 3 if you put PGx onto your project because no project leaders will want to put in PGx if you tell them that it is going to increase the time because of the NDA collection, because of the analysis, and so forth, and so forth. So, those are just realistic expectations. So, you have to change the guideline in order to incorporate that into the drug development process.

[Slide]

Last thought, what is the most important thing out of all those six bullet points that I mentioned? I think the regulatory agency is the most important.

I am going to digress for 30 seconds and talk about something that is not science. You know, you have to have fun sometimes. So, I just want to pick the history of

mobile phone development.

[Slide]

You don=t have to read all of this; you can read it later. But the most important thing is that the FCC regulates the radio frequency that anybody can use in the United States. In 1947 the frequency that cell phones could use was limited to only 23 phone conversations possible at any one time, in any one cell. Okay? So, just imagine, cell phones would not work if you only allowed 23 people in this room to use them at any one time.

[Slide]

In 1968 the regulatory landscape changes in that they basically open up and say, okay, you guys can have a different frequency and now cell phones can be used in a much wider radius and cover a lot more people.

[Slide]

With that, in 1983 Motorola was the first to develop the first phone. I am sure some of you have used it. It was $4,000 and it weighed almost 2 lbs.

[Slide]

Then, in 1995 they started mass production and now it is only $300, with better coverage and more reliable, and

then it takes off.

[Slide]

The same thing is happening in PGx in that regulatory decisions are critical. Okay? You need a common standard, cellular transmission. You need a reasonable cost. In order for it to be a reasonable cost you have to apply this to not just the top one percent of patients. You have to make sure that it is available for the general public. Then you have to have reliable service or coverage, and it is not so good in the United States in some areas still.

[Slide]

Lastly, I just want to touch back on the PGx and PK/PD application. P450 testing has been around for a long time. The enzymes have been described in the 1950s. Most of the genes, the polymorphisms have been known since the 1980s. So, why hasn=t it been taken up in clinical practice?

Well, the problem is that it is a very complicated gene family and some of the assays are very difficult. Then, there is lack of a standard and agreed panel that anybody can use. And, up until now there was very little

regulatory input and guidelines to use it, and there is very little interpretation of the test.

[Slide]

About 18 months ago Ray Cochrane and myselfB-Ray Cochrane from Eli Lilly and myself basically started an ad hoc group with nine pharmaceutical companies and three genotyping platform companies to basically look at all the ADME genes to see whether we could come up with some consensus. We have had three meetings so far and quite a bit of work, and we have basically come down with what we call three lists of genes, the core list, the extended list and the investigative list.

The core list is the genes that we all felt we must have. They are FDA validated. There is significant scientific burden of proof. We should use them for all of our studies, and there are about 33 genes in there and about 213 markers.

The reason that we want to do that is because we want to have a standard panel that everybody can use, talk the same language and know exactly what we are talking about, and the interpretation. You will be surprised, it took us a long, long time, over a year, to agree to all

these genes on this list. Then it took us quite a lot of time. Once you say, well, 2D6, whatever, you would think that everyone would know exactly what that is. No. Everybody has to come up with the same sequences, come up with the same nomenclature, and it takes a while.

[Slide]

I just want to show you some of the companies that have contributed to this and the different Phase 1/Phase 2 genes in the different companies= lists.

[Slide]

This is the core list that we have come up with, and we are in the process of writing up a publication for review on this.

[Slide]

At the end I just want to say that pharmacogenetics is a core component of drug development and drug safety, but it requires many different stakeholders and we all share responsibility and I think regulatory agencies and committees like this should play a major role in guiding PGx. Thank you.

DR. VENITZ: Thank you, Dr. Lai. Any questions or comments? We have about five minutes before our break. Dr.

Flockhart?

DR. FLOCKHART: This is really a very nice overview. Thank you. One of the things that is most interesting to me about the abacavir story is the relationship between the science and the publications and the FDA approval. If you put your slide up that showed the use within LabCorp, where are the FDA approvals within that, and are they related? Because the hypothesis I would really like to test is whether or not use is actually only subliminally related to FDA approval and, actually, when you have a big publication, like here, that really drives use.

DR. LAI: Well, I have to make sure that I limit myself to what I am good at. I am a scientist; I am not a regulatory person; I am not a lab person; I am certainly not in PR.

What I can tell you is that the original application came out in 2001, both our paper and Simon Mallal=s paper. They came out back to back in 2001. With the publication of that paper, it was pretty, clear because it was such an independent study, replicated and so forth, that people understood the importance of the marker but they couldn=t quite understand how to use it. So, the clinical

utility wasn=t there.

But as we published more and more papers, in 2003 we published the replication in Caucasian females, a much bigger study, physicians are starting to notice. LabCorp, in 2005, realized that there were actually physicians ordering the HLA panel, the whole panel, and then only using the 57 data, because they were actually writing down test 5701, even though there was no 5701 test on the panel.

I have to say that in the HIV community publication I think is very important and guidelines are very important. And, I cannot tell you whether that is the most important thing. All I can tell you is that these are the numbers that LabCorp has shown and really before this year they were really the major lab that was doing this. And, I really don=t know whether publication or regulatory or guidelines really drives it or not. My understanding is that FDA has not decided what to do about the drug labels yet. We are still in negotiation with abacavir. So, it is not in the drug label yet at this point.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes, I was curious about your presentation on common sense and predictably irrational

behavior. I mean, it seems like my bias is that the public is more concerned with adverse drug reactions, yet, this slide said that they were more concerned with efficacy than adverse drug reactions. Where did this come from, and what kind of a study was done to assess where the concerns are in the public?

DR. LAI: I do that every time I go to a meeting like this and then I will go to the wine and cheese and ask people. Okay? You ask them after one or two glasses of wine and it works really, really well.

So, what I can tell you is that it is very interesting. You ask people why is this the case, and it turns out to be that people identify themselves as the winner. So, nobody goes into a casino and thinks that they are going to lose. Nobody. Everybody thinks that they are going to win when they go into a casino. All right? So, even if you tell them that only five percent of the people win in a casino when you go in, they identify themselves as the five percent, not the 95 percent. Okay?

So, if you tell them that you will increase their chance of winning they will do that. So, this is the same thing as efficacy. Okay? If you only tell somebody that

this drug has a 20 percent chance of being effective for you, they will attach to that 20 percent, thinking that it will work for me.

Whereas, with the adverse reaction, they automatically associate themselves with oh, I=m not going to get an adverse reaction. The other 95 percent of people are going to get the adverse reaction so I don=t need to test it because I am not going to get it. It is very interesting. It is a very interesting phenomenon. Now, if you asked them before the two glasses of wine it might be different.

DR. VENITZ: Let me just take time out because we are supposed to have an open hearing at 10:30. We have nobody signed up for it. Is anybody in the audience planning to give a presentation for the open hearing? I don=t see anybody scream, yell or raise their hands so it looks like we can continue for maybe five minutes before we take our break. I think Dr. Frueh is the next one on my list.

DR. FRUEH: I have one very brief question. It is a follow-up question to what Dr. Flockhart was asking regarding the testing for 5701. What is the percentage or an estimate of the percentage of overall testing to date

that you think has been done? It is not clear from your chart.

DR. LAI: Yes, that is hard to say for a number of reasons. One is that I have no idea what those actual numbers are because that is from LabCorp. Those are their commercial numbers. So, they only gave us the growth of the numbers. So, that is one.

Two, when we first modeled how many patients would test this, we based our models on abacavir-naive patients, meaning people that have never had abacavir; that people will only test this if they are considering using abacavir, and so forth. And, we were wrong in that assumption.

It turns out that a lot of physicians actually order the testing when a patient comes in and have this in their chart, even though they might not be thinking that they are going to prescribe abacavir to this patient. So, it is very similar I guess to the Herceptin test. The doctor would just order the test and have it in the record. So, it is kind of a skewed model, quite a bit. So the estimate could be as many as 25 percent, depending on who you talk to, and so forth, and so forth. We don=t really have a good number.

DR. FRUEH: Okay. The second question I have is regarding the number of cases required to achieve 80 percent statistical power, slide number 13. The examples that you list are, in essence, single gene effects with a fairly high penetrance, and I was wondering whether you were running the same numbers for situations where you have two or more genes contributing to the identification of the risk, and how these numbers would be growing because, obviously, I believe that this is a situation that we will encounter fairly often.

DR. LAI: Yes. Well, first of all, not all of them are single genes. There is one case here with two. In abacavir we actually looked very hard for multi-marker combinations to increase the sensitivity and specificity and we didn=t find any. So, I am not saying that there will not be any situation where you have multi-markers. I am sure that there will be.

The message that I am trying to go through is that you are not going to find ten markers, each one with ten percent of contribution. You are most likely going to find one or maybe two or three. There will be cases where you are not going to find it. All I am saying is that if there

is a single major or maybe two major contributions, you will be able to find it using a small number--

DR. FRUEH: I was thinking of cases such as Warfarin, and what I would be interested in is sort of the cases required to identify the size of a potential trial that would tell you that type of information.

DR. LAI: We haven=t done that one. We could do that.

DR. VENITZ: Dr. Kearns?

DR. KEARNS: Thank you. It was a great talk. It was interesting, you started your presentation suggesting that personalized medicine was not ready for prime time, and part of that was, well, the insurance companies will pay for this and I just want to make a point about that.

If I send-BI don=t send it personally but if my hospital sends a specimen to LabCorp my hospital pays them to do that test. Then we have to file the insurance claim, and I will tell you it is not completely recoverable.

DR. LAI: Yes.

DR. KEARNS: And that is an issue because if it is carbamazepine, which a lot of children receive for years and years and years, if you look at the frequency of Stevens-

Johnson syndrome, provided that you could plot carbamazepine out by itself, it is really quite low. But if we did an HLA B1502 and it cost $500 to do that test, then if I genotype a thousand patients it costs half a million dollars to do that test in those patients.

So, I am not a health economist by any stretch, but I think the people who are trying to weigh whether or not payment for these things is reasonable are looking at these numbers and, at least today, they are not uniformly convinced. And, Dr. Lesko, even a wonderful guidance from the FDA I think is maybe not going to be sufficient to move people along.

DR. LAI: I am not suggesting that you get 100 percent reimbursement. It never happens and that is never the case. You always have non-payments.

What I am trying to say is that from the discussion that we have had so far with a lot of the testing companies, with the insurance companies, with some of the large payers, the bottom line is if you can demonstrate clinical utility--by whatever means, maybe in the drug label or may it be well established, and so forth--you are not going to have a problem getting reimbursement but you still

have the normal reimbursement issues that you always have, no matter what you do.

DR. VENITZ: Dr. Relling?

DR. RELLING: Well, I guess just a follow up on that table, I don=t know what you mean by number of cases required for 80 percent power. These numbers seem misleading.

DR. LAI: It is a power calculation. It means how many cases do you require before you are sure that you have the association with that phenotype, with that marker.

DR. RELLING: Cases? You mean cases that express the phenotype of interest?

DR. LAI: Yes. So, in this case for abacavir hypersensitivity reaction you need 15 cases to find the 5701 marker highly associated with the phenotype.

DR. RELLING: And a lot more controls, as Dr. Kearns was just pointing out.

DR. LAI: No, not necessarily.

DR. RELLING: How do you do a comparison?

DR. LAI: Well, what do you mean, a lot more controls? In abacavir the control was 200 controls, and they are normal controls.

DR. RELLING: I don=t really understand what point you are trying to make with this slide, but I think, as it stands, it is very confusing because the number of individuals you would have to use genetic tests in, in order to show that you had power, 80 percent power--

DR. LAI: Just for the detection of the marker. This table shows you how many cases of patients you need to have to screen in order to identify the marker associated with the adverse reaction.

DR. RELLING: Well, I think those numbers are very misleading, and the effect sizes are also incredibly high. For things like irinotecan I don=t think there is an effect size of 28-fold.

DR. LAI: That is the odds ratio size.

DR. RELLING: Well, then those are based on the smallest studies with the highest odds ratios. It is not going to serve us well if we think that we can study so few cases and have those large effect sizes. I don=t think that is representative of most of those genotype phenotype associations that are listed there.

DR. LAI: No, these are the odds ratios and the power calculation of this genotype phenotype association.

DR. RELLING: There are many examples that would contradict those effect sizes.

DR. LAI: There are examples that will require a lot more cases. If your genetic risk factor is much lower you will require a lot more cases. But in these examples, in the calculations in the literature that is what they are.

DR. VENITZ: Dr. Topp?

DR. TOPP: Yes, you mentioned at one point the effect of this testing on the drug development timeline. Can you say a little bit more about that in terms of the additional time and/or resources required to fully implement this?

DR. LAI: Right now for PGx, to incorporate into Phase 1, Phase 2 and Phase 3 it is not routinely incorporated into the protocol. So, most of the time it is an additional protocol that you add on so at a minimum you are talking about a few weeks to easily a few months additional work because you are going to have samples. You are going to have to do genotyping. You are going to have to do additional analyses, and so forth. So, it is one of those things that if you want to make it efficient you have to incorporate it on day one.

DR. TOPP: What I am hearing you say is that the weeks to months timeline doesn=t sound that resource intensive. If I heard you correctly during your presentation, you recommended extending the drug development timeline in response to a requirement for Pgx.

DR. LAI: No, I didn=t say that.

DR. TOPP: Okay.

DR. LAI: What I am saying is that if you don=t consider it right from day one, it is an additional timeline on itB-right now, if you look at that diagram on Phase 1, Phase 2 and Phase 3, it is the standard, traditional drug development process. And, for most people that means that they would do exactly what they do now, and then if they require PGx they will add on to it. Okay? What you really want to do is to incorporate PGx on day one to run it in a parallel fashion.

DR. VENITZ: Last question, Dr. Lesko.

DR. LESKO: Thanks. Eric, while we have this slide up here, the abacavir, let=s take the cases required there. Fifteen cases are required to detect the association. I was looking at the timeline on this and, in a sense, we are talking about recommending collection of DNA in clinical

trials as part of this future guidance.

There are two parts to the question. One is if we roll back the clock to 1994 when clinical development was initiated did you have enough cases in the clinical development program that, at the time of approval, you would have had the abacavir sort of ready to go without waiting for the post-marketing studies to have occurred? Maybe they would have occurred more efficiently or most cost effectively at the time. That would sort of lead to the value, or at least one case of the value of having DNA available at the time you have these hypersensitive reactions during clinical trials premarketing.

DR. LAI: That is a very good question and I don=t know the answer to it because I started the project in 1999 and we did not have any DNA samples at the time, and I have never gone back and looked at potentially if we started collecting samples, as you suggested, in 1994 would we have enough. So, I don=t know the answer to that.

The other thing that I can tell this committee about the collection of DNA is that it doesn=t happen overnight. GSK started collection of all trials, all Phase 1, Phase 2 and Phase 3, and all of U.S.-funded Phase 4

trials starting in 2003. And, last year our collection rate was about 65-70 percent after, you know, all these years of hard work. And, this year we are aiming for 80 percent. You have to have the infrastructure to do this even with the commitment.

DR. LESKO: A quick second question, very quick, when you enter into a study like PREDICT, do you have a predetermined threshold level for sensitivity and specificity of the test that would be considered success in the trial, as opposed to an outcome that simply says here it is? Or, do you design a study to have a certain sensitivity and specificity of the test for safety genetics?

DR. LAI: The PREDICT trial was powered to address the sensitivity and specificity as we saw in the retrospective trials. So, you know, with the assumption of at least 50 percent. It could be as high as 94 percent. So, the trial was powered to detect if it is even 50 percent it would be able to confirm it.

DR. VENITZ: Thank you, Dr. Lai. We are finally going to take our break. It is now 10:45 so let=s reconvene at 11:15 for our discussion of our topic 1. I apologize, we only have a 15-minute break so 11:05 is what I really meant

to say.

[Brief recess]

Committee Discussion and Questions

DR. VENITZ: To get started on our discussion, I have asked Dr. Frueh to review the questions that we are supposed to discuss.

DR. FRUEH: Yes, thank you. We have three questions, the first one pertaining to the collection of samples from participants in clinical trials, what issues or barriers should be addressed to facilitate routine collection of DNA samples?

Secondly, under the same question, when, and under what circumstances, or to what degree, should DNA be collected during drug development for use in exploratory analyses?

Secondly, we would like to discuss the decision tree that depicts the integration of the pharmacogenetic studies into drug development processes, and hear from the committee the comments and recommendations on the scientific rationale and the thought process that went into the decision tree.

Lastly, question number three pertains to the

study types for clinical pharmacogenetic studies that are being proposed, and we would like to hear the committee=s comments and recommendations on the design of these clinical studies, and also their proposed impact on subsequent clinical trials.

DR. VENITZ: Let=s start by tackling question number one. Any comments? Dr. Yasuda?

DR. YASUDA: I just wanted to give a couple of clarifying comments on our thinking when we were thinking about this concept paper, and having to do with the collection of DNA and also getting back to the safety that Mary and others were talking about.

We think it is important to collect the DNA from everybody in the trials, including the people who are controls, not just the treated group. That would help a lot with understanding the safety implications.

Then, secondly, about the anonymized versus traceable samples, that it is really important to collect traceable samples so that we can link it back to a medical record.

DR. VENITZ: Dr. Kearns?

DR. KEARNS: With regard to question number one, I

know at our place there is a pediatric angle with this, and we have some members of our IRB who are very uncomfortable with the prospect of DNA from a child in a trial who cannot consent to have that DNA put in a biobank or repository for an unlimited period of time.

I am not an ethicist, I don=t know totally what the ethics are around that, but I know that every time I go in front of my IRB, which is frequent, and I talk to them about doing a study that combines PK and PG I am forced to answer the question, and they have been 100 percent faithful to say that if the sample is collected they want time-limited wording in the consent document. So, that is point number one.

Point number two, the question of de-identified versus identified samples, I think we all probably agree that the ultimate utility of a sample is greatest when you can trace it back to a medical record, which is full of patient identifiers and, as long as we have the bumbling and stumbling of HIPAA around, there are institutions that will be challenged by having samples that are identifiable to a patient. So, I would just offer that as things to think about, not necessarily action.

DR. FRUEH: May I just briefly comment on your last statement? I think what is important is to keep the samples in the context of the clinic, not necessarily to the individual patient. But you want to be able to generate genotype phenotype associations. I think that is what we are referring to. You can de-link it from Social Security numbers or from other personal identifiers.

DR. KEARNS: I agree with you almost. Okay? Because let=s use the carbamazepine as an example so let=s say that we do have an association between HLA-whatever and carbamazepine and another drug that maybe isn=t as used as often, and you are trying to go backwards to tease that outB-was it really that drug, or I have this purported association? Was it another drug? What are the other aspects of therapy? And, really to get that coal out of that mine you have to work through all the dirt, so to speak. So, IRBs with kids have trouble with that.

DR. VENITZ: Dr. Topp?

DR. TOPP: Yes, this is an unrelated point, but based on the way this is worded, it is proposed to collect DNA samples from all participants in clinical trials. It is not clear to me whether there would be drugs or drug classes

that would routinely be excluded from this. Dr. Shipley earlier said, of course, we wouldn=t do that for biologics. So, is there a sense that the paper will provide information, or that what the FDA is providing will say these are the types of drugs that we are going to suggest this for, and that there are types of drugs that this will not be required for?

DR. LESKO: So, I think that is a good question. One of the things we tried to think about is how you would stratify collection. For example, you just mentioned a couple of maybe exclusions. The other might be, well, what about a non-absorbable drug? Would you collect DNA in a clinical trial for something like that? What about a topical drug? So, I think we have to think about the balance between pragmatism and cost, and what-have-you, and the benefit of the sample being available.

The other part of this is sort of the two-step process. You collect in the clinical trial and then you analyze in the clinical trial. One of the things we have sort of talked about and maybe we will discuss in the committee today is if you collect in all clinical trials, exclusions aside, what would be the circumstances that would

prompt a recommendation that these samples actually ought to be analyzed? That could range from the appearance of an adverse event in late-phase trials, late Phase 2 or 3, or it could arise from significant variability in pharmacokinetics, or it could arise from trying to understand whether the dose response is affected.

So, I think we have to sort of think through, in recommending collection, how the benefit would accrue from that collection. So, yes, we have to think about these exclusions.

DR. TOPP: I don=t think those things are right now captured in the decision tree, as I read it.

DR. LESKO: Yes. The other question that one could ask because we focus primarily, because we know about them, on metabolism, genes and transporters at least in the early phase of drug development, so, for example, what if a drug was cleared renally and we know a lot less about that? Would you then say, well, we had better collect DNA in all those clinical trials where we don=t have any sort of hypothesis about what might happen as a function of gene variance?

I guess one answer would be, well, if you have the

sample and you had something totally unrelated to renal clearance, like you had an adverse event you didn=t expect, having that sample collected in that trial would allow you to go back and try to understand the genetic basis of that adverse event. So, it is a little bit of a maze as to how that is eventually going to play out but, you know, we are looking for comments along those lines.

DR. VENITZ: Dr. Flockhart?

DR. FLOCKHART: Just two points I guess. The first is that I really don=t agree with the biologic point. I think there are lots of situations, in fact, in biologics where we understand the target very well. AGF is an example or EGF is an example where we would want genetics. I think the point that was being made was that for biologics we don=t need to worry so much about cytochrome p450 as transporters. That is for sure. But there are genetic things we need to be concerned about.

I guess the second point is that where we have a good basic pharmacologic mechanistic understanding of what is going on we have obvious target candidates that we can go after, and that is easy. But the value of DNA collection might be greater almost in situations where we don=t because

you have to go and look in genome-wide ways that you don=t have otherwise if you don=t do that.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: In light of Dr. Lai=s presentation and the proposal, I am not sure that the time that this information becomes available where we start to feel certain about it is actually able to be integrated into a drug development plan so that you can actually learn things early on, as the proposal kind of indicates. So, there may be a little disconnect there that may be something for consideration.

The other fallout of that comment is that I would worry that perhaps we don=t get too aggressive with the inclusion/exclusion criteria by perhaps limiting individuals in early stages of development where we may end up learning less because they are not included in the actual trials. So, I think overall more clarity on the place in drug development where this would be valuable in the timeline should be revisited.

DR VENITZ: Dr. Relling?

DR. RELLING: Just to address what is up in front of us, I mean, it is being proposed to collect DNA samples

from all participants in clinical trials, and I completely agree with the wording of that statement and without having any exclusions for biological agents, or agents which we think we know how they work, or agents that we think are renally cleared and so we don=t understand the genetics. I mean, I like the extremely broad wording of that. It doesn=t even limit it to drug studies whatsoever, which I think is correct.

Also, in terms of the point that Dr. Kearns raised about barriers to address, I agree with you that there are some consent issues to address. I suggest that there are a lot of people that are collecting DNA even from children, even for very long-term use, and there are IRBs, including central IRBs, that are associated with the NIH that have come up with wording that always allows patients to retrieve their DNA and to stop participating at any point in the future, be that because they mature and become adults or because they decide they don=t want to participate. So, I think that there are ways around that.

And, I guess I don=t really understand the second bullet point because you are asking us to address when should DNA be collected during drug development for use in

exploratory analysis. Always. I mean, the main point addresses that doesn=t it? So, I don=t understand why we have to even address this second bullet point.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes, I agree with Mary that DNA should be collected in all clinical trials, and for the reason that I think it will be informative to both adverse drug events as well as drug response.

But in the decision tree you focused a lot on pharmacokinetics, right, on the ADME piece. There, I want to ask the question whether you considered narrow therapeutic window because sometimes understanding the genetic determinants of pharmacokinetics is irrelevant if you have a huge therapeutic window.

So, are you considering, at least for that part, narrow versus wide therapeutic index drugs, or are you just saying, well, let=s collect the DNA because you never know when we are going to use it anyway for an adverse drug event or something later on?

DR. LESKO: You know, in a simplistic way we think about the genetic factors as covariates, like we think about other things, whether it be a drug interaction; whether it

be hepatic impairment; whether it be elderly studies. And, one of the questions that comes about at some point in time is does the difference matter?

So, when we think about the genetics, the question that sort of comes up is if I have differences related to genetic factors and exposure of the drug, what is known about the dose response of the drug? So, I don=t think of it in terms of the therapeutic range, although obviously from the dose-response curve you have an idea of that, or from a PK/PD relationship.

But I think the differences in exposure that may drive somebody to analyze DNA to sort of segregate or stratify patients, you would then have to interpret it on the basis of some relationship between the exposure and the response, and then go on to what you might do next.

DR. GIACOMINI: So, you are saying just collect it as a piece of information--

DR. LESKO: Yes.

DR. GIACOMINI: -Bas a covariate and then later on interpret that. So, I would agree with that.

DR. LESKO: And I think the other part of this, a nuance of all of this is whether you collect and then it

sits in the freezer until you have a reason to analyze, or you collect with a study design that would give you the answer right off the bat.

So, if I had a drug that had a very well-known, characterized polymorphism, and let=s just take 2D6 because everyone is familiar with it, and you know right off the bat you are going to see probably, if that is a major clearance pathway, maybe a ten-fold difference in exposure, would I treat that differently than a drug where there may be a two-fold difference in exposure?

In the first case I might say let me design a study that would be enriched by genotype, look at the difference of exposure in the same context and look at what that difference would mean as opposed to let me see the variability and see what happens, then I will go back and answer the question.

So, I think we are not going to be, I would say, prescriptive in this thing, but there are going to be nuances that companies will use to get the answer to the questions I think, and there will be different approaches to doing that. And, I think that is okay.

DR. VENITZ: A couple of comments from yours truly.

I am one of the proponents of collecting everywhere, always as well. So, I think your decision tree, which is what the next question refers to, shouldn=t refer to whether you should collect or not, but maybe when you measure what you are going to do with that information. A part of it is related to the fact that you learn most by looking across studies, not individual studies, at least early on in the exploratory stage.

Second comment, barriers. I think you have heard about IRB issues. Our IRB requires you to set up a registry if you keep samples beyond four or five years. So, how long you want to keep it and what you want to do with it, allowing opting out, those are major issues that I think you should discuss in the guidance as well.

The logistics of actually de-identifying information and still allowing them to link to individual studies, not necessarily individual patients, of if you have to allow them to opt out you actually have to be able to ultimately get to a patient=s social security address and, so, keeping that up to date is a potential obstacle.

I noticed when Dr. Shipley presented her very interesting results that I think it is a selected or biased

sample, if you like. It is large PhRMA and small PhRMA that does this kind of stuff. All the other companies didn=t respond because they don=t do it. Okay?

So, I don=t think we should look at thisB-and I think you pointed that outB-as what we should be doing as what is being currently done, not necessarily state of the art but state of the practice.

So, keep in mind that, in my mind, the majority of companies, especially small to mid-size companies, don=t do any of this stuff at all. So, the guidance should be helpful not only by telling them the potential benefits but also how to do this kind of stuff. Dr. Flockhart?

DR. FLOCKHART: I am just trying to think about the resistance to this, which I think is going to be real. One of the legitimate arguments is that it might be seen as an unfunded mandate. And, there is an argument that goes something like this, the cost of storage is not benign, partly because the cost of cataloging and accessing can be considerable. That has always seemed to me kind of a digital question. If you have a good database why is it such a problem? But I think the cost of fridges containing large quantities of well catalogued DNA, one could argue, is

real.

I think if the guidance confers flexibility on the situation by making it clear that there would be multiple ways of effectively storing DNAB-DNA can be stored dry cheaply. There are all kinds of different ways. And, if the boogeyman of the big, expensive freezer is brought up consistently, I think that is not fair.

I think there will be small companies where storage will be really costly in the percentage of their total picture and something that they would have to think about really hard. But I think the guidance could help by making it clear that there is more than one way of storing DNA. The stuff is incredibly stable and amplifiable off all kinds of things.

DR. VENITZ: Any other comments regarding question one? Yes, go ahead.

MR. GOOZNER: I just want to return to the issue of privacy and underscore that I don=t think you want to set up roadblocks to people participating in clinical trials. In the context of this guidance, I would think that you would want to spell out with some specificity something around the whole issue, not just for pediatric privacy but patient

privacy in general.

Whether it is valid or not, there is a lot of public concern around that issue and Congress is thinking about acting on that issue, which suggests that, you know, perhaps there is some perception, whether it is reality or not, that there is some threat out there. Therefore, if you are going to demand this of all clinical trials or give guidance on that, you ought to really somehow address that issue, which I guess gets to the first bullet point.

DR. VENITZ: Dr. Lesko?

DR. LESKO: I just want to get some clarity. As the committee talks about all clinical trials, what we are speaking about exactly? If we think of clinical trials, they obviously range from Phase 1 through Phase 3, and the question I have is are we talking about all clinical trials throughout all phases of drug development, or are we talking about all clinical trials in early drug development?

Let=s say, for example, that I collect samples in early drug development and I never see any kind of signal of interest; I don=t see wide variability in pharmacokinetics; I don=t see variability in PK/PD relationships, is there any point where I would sort of stop and say, well, I have sort

of addressed the question of does genotype matter, at least in the usual things?

The alternative view to that is I should collect samples in all clinical trials because I don=t know what to expect beyond the dose-response PK/PD issues. I think as Eric=s presentation showed, abacavir would not have seemingly been predicted in early clinical trials based on exposure since that wasn=t an exposure issue but a hypersensitive reaction. So, I just want to be clear on what we are talking about with regard to this question, and what the committee is recommending.

DR. VENITZ: Well, if I speak for myself, I mean all clinical trials until you have actually assayed those samples and come up with conclusions that allow you to conclude that there is no need to do it and I find it hard to believe that you can actually do that early on.

So, to me, the issue I think is not collecting samples as much as what do you do with that information, and how does that impact on further collection. Kathleen?

DR. GIACOMINI: Yes, so I agree, all clinical trials because of the adverse drug events or things that may occur later and you may want to go back. Whereas, if you

determine in an early trial that there is no association with things that you know, it is not until a later trial done in larger numbers of people that you will see that kind of an association.

Can I go back? When you say collect DNA samples, so we sometimes collect a DNA sample, which really means collecting blood samples and storing the blood. We haven=t yet extracted the DNA for periods of time. So, are you going to specify what you mean by a collected DNA sample, and just have a hair in the freezer?

DR. LESKO: Yes, so does it have to be blood or could it be a saliva sample? We haven=t actually thought much about that, but it is a good point that we have to address. The question is do you store the biological material that you collect or do you store some extract of that, or whatever? We have to think more about that.

DR. GIACOMINI: And that will go back to Dave=s point of cost.

DR. LESKO: Yes, definitely.

DR. GIACOMINI: If you have a blood sample, that is one thing but if you are extracting the DNA and bar coding it and doing all thatB-

DR. LESKO: Yes. I mean, it would seem that you would want an event to drive the analyses as opposed to having all of that analysis with, you know, questionable value to it.

DR. CAPPARELLI: I think that there has been a lot of discussion about collecting across studies, and I agree with that in terms of getting to some of the pharmacodynamic and toxicity issues. But with that in mind, really this guidance is getting to some of the PK issues and we really have to be very specific from a temporal standpoint, that it is clear, you know, the pathways and getting this information early so that we can get that exposure information would be extremely helpful.

The other question we are going to have, you know, is that it is going to take those larger studies to actually see the signals, to see the dynamics. But I think that is one thing we do have to differentiate in here if we come out with that broad statement that it isn=t currently being listed.

DR. VENITZ: Dr. Caldwell?

DR. CALDWELL: I just want to address a couple of questions. One is the privacy issues and the issues

regarding people=s interactions when you collect their DNA. We have been through that experiment. We collected 20,000 patients= DNA with access to their electronic medical records. We went through focus groups; went through analysis of why people contribute their DNA and don=t contribute their DNA, and how much they really are concerned about privacy, and the like, in the process. And, it is actually considerably less than you would think.

The people who don=t participate because they are concerned about privacy issues is less than two percent. Most of them who don=t contribute DNA don=t contribute DNA because they are too busy, or don=t think it is worth it, or are not interested in the study. It is not a big deal from a privacy standpoint.

It is a big deal from the standpoint, in my opinion, of potential discrimination by insurance companies or employers based on genetic information, and to that extent, I think it is the reason Congress is addressing this issue and trying to have national non-discriminatory laws that prohibit that type of action occurring. We have that in our state, but we certainly don=t have that nationally.

I also favor collecting DNA through clinical

trials, and I would suppose that that could be done and stored relatively inexpensively and I would assume that you are talking about collections through Phase 3, not necessarily in Phase 4 trials. But I don=t know, we haven=t yet talked about that.

The other thing that seems reasonable to me that pharmaceutical companies might consider is that genotyping and understanding the metabolism of new drug entities that they have may actually help them be able to be proactive instead of reactive to the pharmacogenetics of the compound. That is, if they understand where it is being metabolized and if that is going to have an appreciable effect on their medication, they may very well be able to modify their medication to somehow get around that approach.

So, I think that there is a lot of utility in this process and, as people start having the samples available and start thinking about it in a little more imaginative way, they may find that there is some utility they hadn=t thought of ahead of time.

DR. VENITZ: Dr. Topp?

DR. TOPP: Yes, I just want to echo the question that Mike raised about Phase 4. When we say all clinical

trials, is that included in that?

DR. LESKO: We have not included that in our discussion. We just haven=t had any discussion internally and in FDA there are a lot more people we would have to talk to, to get into that area.

DR. TOPP: So, you are really talking pre-approval.

DR. LESKO: Yes, we are talking about premarketing.

DR. VENITZ: Are we ready to move to the second question now? Felix, do you want to introduce the second question?

DR. FRUEH: The second question pertains to the decision tree, and we would like to hear comments from the committee on the scientific rationale and the thought process that is proposed in the decision tree. Can we put that slide back up?

DR. VENITZ: Are there any comments about this? Dr. Kearns?

DR. KEARNS: Thank you. As in all things pediatric, the decision tree is going to need a little bit of thought with regard to studies that are enrolling children around the time of birth. The reason I say that is that, you know, the sense that we can accurately predict

phenotype from genotype is a little bit fuzzy for some months in the development of a child. And, even when you have genotype phenotype concordance, the activity of the drug metabolizing enzyme or the transporter may change over a period of time.

So, what that DNA sample tells you at age 30 days is a lot different than if it is put away somewhere and analyzed when that patient who was in that trial is three years old or 13 years old. So, I don=t know how to make a box there but I think in some of the wording that goes around how to interpret that there have to be some caveats nested in there for pediatric patients.

As well, as a corollary to discussion on point number one, the situation I have just described could limit the relevance of DNA that is in a bank if it is not interpreted in the context of development, either early in life or at a point when senescence plays a role and changes the phenotypic expression of what you might expect.

I think the last comment I would offer is that we always tend to try to be reductionist and neat with these things. Of course, it is never that way. And, as our group, Andre Gedik and other folks have shown with 2D6, it

is not so much what the phenotype is as the relationship between the activity and how that associates with the genotype.

So, in a limited kinetics study that we might do in pediatrics where there are only 24 kids, you know, we could use genotype data maybe to explain a spotted ten-fold difference in AUC. But over timeB-and I forgot who mentioned itB-the longitudinal value of this over time is seeing if we can build those associations, which makes that genotype information far more rich in terms of what we can predict from it. I think there would be an opportunity to do that five years down the road if this stuff were done right.

DR. BARRETT: I am not so sure we need a decision tree at this point. When I think of the discussion we had this morning, we seem to have made a decision in the previous discussion that if you want to collect this data in all studies, then the value of the tree at this point, and also given that it is very PK-centric, is limited, especially given that we have probably a default pathway.

I think the issue, back to Dr. Lesko=s earlier comments when he introduced this topic, is to improve the

guidance provided in the labels and to be more specific and more relevant to actual dosing modifications. So, that I think is an issue in terms of how you interpret this data and actually incorporate it into the label. Because the end of the road in every one of those elements or branches of the tree is to stop and label appropriately, and I think there is where real guidance needs to be provided.

DR. VENITZ: Dr. Mager?

DR. MAGER: I completely agree. Again, I think the focus on pharmacokinetics here really sends the wrong signal. As I mentioned earlier, I think that we really need to have a pharmacodynamics or an adverse reaction component to it if we don=t get rid of the tree--if you do keep the tree. I think having the focus on metabolism and transporters, while a very important component to it, I think sends the wrong message, particularly for the increasing amount of biologics that are being developed now.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes, when I looked at this tree I just thought it was a tree for drugs which are metabolized by known polymorphic enzymes, and you were trying to provide some guidance to the industry for those because I do agree

with everything that was said, you know, collect the DNA and there will be things that will come up later on. Was that what the intention was, just for known polymorphic enzymes that we already know good allele frequencies? That is what you meant?

DR. LESKO: Well, my point of view was that, yes, in fact while these are well-known metabolic enzymes with gene determinants of activity, it is probably safe to say these drugs haven=t been worked up as well as they should. And, I think it is evident from the survey. It just struck me that a lot of DNA is collected but very little of it is used. And, when we go back and look at labels of drugs that are candidates for re-labeling, and most of them have been old let=s admit that, but when you go back and look at drugs that have been studied in recent past, we don=t know a lot about the determinants of exposure and the exposure-response relationship.

I think the thing I said was that the first step is let=s deal with what we know to be true and give some instruction, through a guidance, to industry on how to appropriately consider the questions that need to be asked for those drugs. I would say that was that center path we

went down the decision tree, and it may seem obvious to everybody but it isn=t, in my opinion.

The right-hand side was more the exploratory. It was more the things that Eric pointed out with the extended list of genes that he referred to when we don=t see variability in anything--efficacy, safety of dosing--with regard to the core list. So, I almost substitute core list for the central thing. What happens next? Well, I collect that DNA. I may want to look at that extended list, which is a combination of metabolism genes, transporter genes, there are some pharmacodynamic genes in there, and that would give me some insight to that variability when, in fact, it does make a difference.

You know, beyond that we sort of got down the tree and sort of said collect DNA for future clinical trials to evaluate outliers, adverse events or efficacy failures in whatever phase we are talking about. It could be a proof of concept; it could be a Phase 3. But you can=t understand those things if you don=t have DNA. That was sort of the thinking as we went through the tree.

DR. GIACOMINI: Yes, I mean, I agree with that kind of thinking. I don=t think it was clear to us at first. I

mean, there is collect the DNA for, you know, what may happen in the future and all of the adverse drug events, and then there is collect the DNA for these known polymorphic genes that people, as you point out, have not been studying and then provide guidance to industry for what to do when you do have a known polymorphic gene and how to handle that.

DR. LESKO: Yes, we thought about it in sort of a stepping stone way. You have to lay the first paver down before you begin to go off into some other areas, and if you are not clear on that very first step the rest of it gets very muddled very quickly. I think that was our thinking on this, let=s get the first step clear when we know these enzymes are important, and we know that because we are going back, looking at old drugs where this makes a difference, the coumadin, the irinotecan. You know, you could argue if those were drugs in today=s pipeline, how would you work those up? That is what we are trying to achieve in that middle path.

DR. VENITZ: Dr. Relling?

DR. RELLING: Yes, I guess I don=t have any trouble with having this algorithm but, as we have said before, just to move up at the very first step is to collect DNA and then

say, yes, you want to go ahead and give specific guidance on those polymorphisms where there are clear applications for disposition and effects of a lot of drugs.

DR. VENITZ: Dr. Capparelli?

DR. CAPPARELLI: Yes, the break very early on I think is very helpful in terms of if you focus on the middle column and move the others out where we collect the samples; we will do exploratory analysis. Not to think that it is going to loop in very early on but it is probably going to be towards the end.

The one aspect of not sort of ignoring this that really hasn=t been done is the box that is in the yellow on the left, just above Aselect genotypic-driven doses for phase 2B and 3 or dose adjustment in label based on genotype.@ This is I think an important component that really hasn=t been done.

So, you know, if you get into that small category of drugs in the sense that, you know, you know that it is being acted on by a polymorphic pathway, rather than just to collect the DNA, you already have it there, you analyze the DNA very early on so that you do get a feeling for what the exposure issues are and answer the question of is the

importance different than actually addressing in the development pathway how do we dose, rather than a generalized statement about we know that there are more adverse events when we give this drug in this genotype, or we know that there may be a higher exposure, but to really give some more practical information in the label will come from that particular box that really isn=t, I think, in the paradigm right now.

DR. MORRIS: Yes, I basically agree with this discussion. You know, I think it is important to generally address the use of the DNA for efficacy, for toxicity. But this is a specific manner in which the samples can be used, and I think it is useful to have some sort of guidance like this to address exactly how it can be used, at least with regards to ADME.

I mentioned before the specific issue of active metabolites, and maybe that is something that should be addressed as a comment with regards to this guidance, and for information or elimination of active metabolites by polymorphic pathways may be important and should be examined.

DR. VENITZ: Dr. Huang?

DR. HUANG: The decision tree, as I said, we have this for drug interaction and you will see it tomorrow for the renal guidance as well. Usually the first one, when we say molecule, new molecular entity, will apply to critical metabolizers as well. Again, this is an iterative process. For every well-characterized gene you want to think about it this way.

The one issue that I think is important to put in the guidance is as we have more genetic studies that we receive in the submissions, the more review issues we will encounter. For example, everybody knows 2D6 is well characterized. But then you would see in a submission, when you try to combine data across studies, that each study may have different genotypes. This study only evaluated *4 as a poor metabolizer. All the others have more alleles.

So, I think we do want to provide some guidance and also get expert input on what are the essential alleles, genotype or haplotype, that need to be studied in order to get certain labeling that this 2D6 will have no effect, for sure. Because sometimes you get counter results from different studies. It really depends on how you characterize your genotype.

Again, for some of these, say MDR1, we really do not know what to recommend to study, what haplotype, what alleles to study. So, we have this part, the VGDS part, voluntary submission. I think it is very important to address this in the guidance not only for industry but also for our reviewers when we review these data as we are expecting to see more of them.

DR. VENITZ: Any other comments on the decision tree? Dr. Barrett?

DR. BARRETT: I don=t want to keep the role of the tree surgeon, but I do want to have one more point on this. In the center pathway, the yellow pathway, presumably you have identified that there is a difference between PMs versus EMs. So, there was some study outcome data that let you do that.

If this is the yes that is going to the left here, you have this section where you select genotype-driven doses for Phase 2B and 3. So, assuming that is part of your trial design scenario and sample size calculation, etc., you will have a situation where you could most likely have more patients exposed and, you know, this would be a good thing because you would see the connection between a genotype and

safety/efficacy outcomes. So, I think that would be nice confirmatory data.

However, presumably, if you have identified this difference at earlier stages one could use in silico techniques to actually simulate that. I mean, this gets to the next point as well on the trial design issues. You know, you have an excellent group here in pharmacometrics. One of the things in terms of your proposal on study designs I would like to see is a lot more simulation work considering the design piece relative to these frequencies.

One of the nice things in Dr. Lai=s talk is that he showed you the impact on sample size relative to these various odds ratios. So, it would be nice, looking at different attributes and the impact of design considerations as a part of that.

So, back to my point here, that box to the left there probably needs more branches on that part of the tree in terms of other acceptable feedback to industrial sponsors.

DR. LESKO: So, the box is limited to an 8 X 11 page. But the point is well taken. In the text of what we say we would advocate-Band we do this actually not just in

gene-determined dosing but in dosing that is determined by any covariate where there is a question by use of modeling simulation, these types of things to design your clinical trial, and ask in that context is this going to make a difference in terms of the probability of an outcome, whether it be efficacy or safety.

I would agree with that and I think you will see it in the text part of this, that those kind of tools ought to be exploited in the way you described.

DR. VENITZ: I think we just had a nice seque to question number three, right, because he talked about study design. So, let=s tackle the last question.

DR. FRUEH: So, the last question pertains to the five different study types that we have been proposing, and we would like to hear comments and recommendations from the committee on the impact on subsequent clinical trials, as well as on the overall proposals for these types of studies.

DR. VENITZ: I would propose that what you refer to as Phase 1 would not just be specific to a single study but it could be a multitude of studies because a single study may not tell you as much as looking at a single dose escalation. Multiple dose escalation might be a food effect

study, whatever, and all of a sudden you end up with 50 healthy volunteers.

DR. BARRETT: I just wanted to follow up on a couple of points on in silico options. I am sure you are familiar with some of the newer tools that are being developed, such as the SimCIP application and PK-SIM where they are trying integrate in vitro metabolism data as part of the database on the trial simulation aspect of it.

So, I would think these would be very valuable because you could actually start preclinically and, you know, before you actually do your first time in man study, do some simulation work to maybe assess the importance of integrating this into even the first Phase 1 study designs.

The other part that kind of falls out of this, and it is a follow up to Dr. Venitz= question, is perhaps more guidance on these kinds of meta-analyses should be provided in this as well because I think any one individual study, particularly that first time in man study, you are alternating panel-rising dose design. If you do envision scenarios where perhaps you stop early or maybe the paradigm is shifted based on unanticipated toxicity, you may want to be able to pool that with additional data in your meta-

analyses to be more useful.

I think the other thing, just to add here, is with respect to, you know, the individual study designs. I think you have laid this out relatively in detail but, again, I would think that with the document itself it would be nice to have some actual simulations as part of that piece. I think it would be much more clear to the readers.

DR. FRUEH: Just to clarify, by simulations do you mean actual in silico simulations for this or are you referring to, like, case examples to illustrate what such a study could look like?

DR. BARRETT: No, I think actual in silico simulations where you could kind of consider the design elements of this, and I think you have some, you know, general features of the study designs laid out here. But I think in order to be completely illustrative if you looked at different attributes, different ratios of PMs and EMs, and gave some examples with simulation I think it would be very clear to the sponsor what you are talking about.

DR. VENITZ: Dr. Lesko?

DR. LESKO: So, there is a little bit of a philosophic view to this question that we have sort of

kicked around. Let=s say it is a given that DNA is collected. Then let=s say that we have some preclinical evidence that a well-known, well characterized metabolic gene has some influence on exposure. So, the question then is what do I do to show that it matters or not?

I could, for example, do a prospective study that says I am going to enrich my Phase 1 trial, let=s say, with EMs and PMs and answer the question I would call definitively because I am very clear on whom I am enrolling and what I am looking at. I could approach it a different way, that is, I am going to collect my DNA and not really do anything with it until I do, let=s say a PK study.

Then, based on the extent of variability which may have a soft thresholdB-I don=t know how you would define thatB-I would go back and say let=s see, the people that are high I am going to hypothesize are PMs and those that are low are EMs. So, I am going to go back retrospectively and analyze it.

There is still a third way to think about this. What if I did a drug interaction study where the NME was a substrate and I did an inhibitor study with a strong inhibitor and I found no, quote, significant difference.

Would that indirectly answer the genotype question?

I put this out there because later on you are going to have to label the product in a way that says, yes, this is a substrate for a polymorphic gene but it doesn=t matter, or it is a substrate and does matter. You have to adjust the dose like you might in elderly patients, or what-have-you. So, I think the question revolves around how definitive you want to be in the early phases of this drug development paradigm.

DR. VENITZ: Kathleen?

DR. GIACOMINI: Yes, so I think one of the helpful things in all your guidances are the drug-drug interaction studies where you don=t just simply take a whole group of people and enrich for peopleB-I mean, you just say whatever drug they are on you actually test the drug interaction specifically. The same here when you have a CYP that you know is being metabolized by CYP2D6, I feel like your panel design where you have enriched people will give a pretty definitive answer to does that genotype affect the disposition of the drug.

Whereas, if you do it as you have in your volunteer study Phase 1, where you just bring people in and

you haven=t enriched, I don=t think you will get an answer in a small study like that as to whether that genotype did affect the PK. So, I would like some panel discussion to get an explicit answer on a known drug metabolizing enzyme polymorphism.

DR. VENITZ: Dr. Relling?

DR. RELLING: So, I guess this clarifies again that you are really talking about drug development studies, Phase 1, 2, 3. Because I think it is important to not have such stringent requirements for proving whether, let=s say, a polymorphic enzyme was important in an enriched cohort design but to include all the information. Because I don=t expect a manufacturer to have to do a drug study in every possible clinical situation, which might be that there is a 2D6 poor metabolizer, that also has low 3A, that is also on four different 3A drugs, which is not unusual at all in, let=s say, cancer patients.

They don=t have to deal with every eventuality where CYP2D6 might be important, but knowing that it is a substrate itself is important information to potentially go in the label so that informed clinicians and pharmacologists can make recommendations about dosing in those more

complicated situations, which are not fair to require the developer to study prospectively but the information should be included in the label as to whether or not the enriched cohort design showed that it was unimportant.

And, that is the problem I have with drug interaction studies. We make a lot of requirements for people to perform these studies. They do it in healthy volunteers where there aren=t concurrent drugs; where there aren=t problems of age; where there aren=t problems of reduced liver or kidney function and, therefore, the results aren=t extrapolatable to treating patients anyway.

So, I think it is just important that they indicate what studies have been done and that that information goes into the label, without necessarily making specific dosing recommendations based on the outcome of that normal volunteer study which is not useful clinically.

DR. LESKO: But along the lines of that, I mean, one of the things we are trying to do with labels is put information in that is useful in decision-making, and what you just described, to me, sounds a little bit like descriptive information to leave somebody, either a doctor or a patient, hanging on what to do with the information.

We run into this now with re-labeling, as you well know from other advisory committees. You know, the 2C9 and VCOR is important in Warfarin, and what we hear is, okay, what would you recommend then we do about that if we, in fact tested a patient? Would you recommend 2 mg, 3 mg, 5 mg? I think that is sort of where we are trying to head here.

If you get to that middle part of that box and it is, in fact, important, then obviously there have to be some criteria on, I would think, dose response, for example. Then you might want to make a recommendation that you need to reduce the dose. It is no different than a patient with renal impairment. I am trying to understand the comment.

DR. RELLING: Yes, so, you may have to put in more detailed information about how to act on that. However, I do think that it is not up to the FDA to come up with dosing recommendations in every possible clinical situation that is required to be in the label. I mean, it is not going to be possible to get to that level of granularity.

So, all I am saying is I would not put so much emphasis on conducting, you know, the cohort study that is enriched for poor metabolizers. Because there are going to

be so many downstream effects that are important to consider also that that shouldn=t be considered the definitive study that allows the label to say this drug is a substrate for CYP2D6 but we don=t think it is important.

If that is the conclusion of the study, that we don=t think it is important, it has to be really clear how they got to that conclusion because if it was by studying ten poor metabolizers that are normal healthy volunteers on no drugs, and ten extensive metabolizers that are normal healthy volunteers on no drugs, that needs to get out there into the label so that clinicians can evaluate that data which is not terribly useful for clinical practice.

DR .VENITZ: Dr. Lertora?

DR. LERTORA: First of all, I want to say that I would be in favor of the early collection of a DNA sample so that that information is available at some point in time later in the context of adverse drug reaction and response analysis.

But when we look at the decision tree, if I could go back to that for just a moment, and we look at the right-hand side of the graph where we do not have a well characterized polymorphic enzymeB-and I think we have all

been trying to address this issue to some extent, but one of the critical issues in the context of drug development is to define the right dose or dose range for a confirmatory Phase 3 trial.

So, if we are on the right-hand side of this decision tree, to what extent then do we expect the manufacturer to explore every possible source of variation, and that would, of course, include non-responders in a Phase 2 clinical trial, before launching a confirmatory trial and actually having to come up with the appropriate dose or dose range for the confirmatory Phase 3 trial? That is, of course, a premise that we want to go into a Phase 3 trial with a good level of assurance that we are selecting the proper dose for a confirmatory trial.

So, in the context of that right-hand side algorithm then, to what extent do we require or expect that pharmacogenetic information be, in fact, obtained at that level if it could potentially explain a great deal of the variability in a Phase 2 study?

DR. VENITZ: Dr. Huang?

DR. HUANG: Just to get back to Dr. Relling=s point. Your points are well taken. There are so many drug

interactions. Sometimes they are really crowding out our labeling. For example, Warfarin, there are 400-600 interactions in different sources, including FDA labeling, and at times people just override-Bpharmacists will just override the interaction and not do anything.

So, I think it is a very important point and we did try to address that in our draft guidance that we published in September, 2006. It really depends on the significance of the drug interaction. Not everything put in the labeling has the same weight. It is dependent upon which section. Is it in the highlights? Is it dose administration? That is how we differentiate the significance of drug interactions.

But I think, based on what you said, if we say 2D6, if we are sure that with proper haplotype alleles that were done and we know it is not interacting, we do put that in the labeling. I think for corvalol we did say 2D6 has no effect. This is the specific studies conducted plus a population kinetic study in patients. So, it is in the labeling.

I think we should be able to get a feel for which pathway is important. For example, a lot of HIV drugs,

miraval as an example--recently we put in the labeling, depending on whether you are giving it with protease inhibitors or 3A inhibitors, then you say, okay, I will give 150 mg. If you don=t have those modulators, 300, you have inducers, 600. But there are very specific instructions and I think they are very important.

The issue that we still continue to have to address is that now we have these combinations. You have other drugs, some of them are inducing, some of them are inhibiting one of the transporters. So, what do we have to do? And, we are now trying to develop, as Dr. Barrett mentioned, SimCIP or other type of model to see how those enzymes and transporters interplay. And, I think the interaction exercise will apply to genetic exercise, and I think this is really an issue that is important to address, and we are addressing it.

DR. VENITZ: Dr. Mager?

DR. MAGER: Just to echo those comments, I think modeling and simulation could go a very long way to addressing the significance issue that you are raising and at all levels of this tree I think could be included to address this issue directly. It would give ideas about

probability and the importance of certain reactions, and could lend guidance for future Phase 2, Phase 3 studies. So, perhaps a role of modeling and simulation could directly be put into this as part of the paradigm.

DR. VENITZ: Dr. Kearns?

DR. KEARNS: Larry, I am first going to say I agree with Dr. Relling in principle, but I can=t say everything she said because she already said it.

Back to the decision tree, Phase 1 and Phase 2, does it help to understand the outliers? Absolutely, absolutely. I mean, we and others and Dr. Flockhart have uncovered new allelic variants of genes because we dealt first with an outlier in a clinical trialB-very, very important.

For drugs that have a narrow therapeutic index, is it reasonable to cohort based upon genotype? It may be. It may be because that gives you some adaptive control, if I could use that phrase, that you might not otherwise have if you are just doing it in the wild. If you do it in the wild looking for associations, that is clearly important in trying to unravel them and it makes for knowledge that is potentially useful. I don=t completely understand how I

would advise a pharmaceutical company with regard to their making knowledge that may be ultimately useful some day.

The next point is the issue of constitutive expression. I think to Mary=s comments and drug interaction studies, if you look at the proton pump inhibitors, right away, you know, the multiple choice answer would be 2C19. Well, let me tell you it depends upon the molecule as to whether or not that is really, really important.

I think lastly, a lot of this is very good discussion but I get back to the ADA medicine, atamoxitine, and the fact that 2D6 is very important for that drug, to the point where we have actually had patients who came in and said I need this test on my child because I need this information before I give the drug. The fact is that I think the way this works out is it was interesting but in terms of really affecting the safety profile of that drug, I am not aware that there was anything, there was no signal there.

So, I offer that not in criticism. I think I am stating the obvious, Larry, to you and Shiew-Mei, but these things have to be considered in the context of a guidance where the purpose of this document is to give direction to

the pharmaceutical companies so that they might get information that could give direction to prescribers, realizing it may not be directive information.

DR. VENITZ: Dr. Capparelli?

DR. CAPPARELLI: In focusing again on this being a guidance, the concept of focusing on the S pathway, if you do test for a signal where there is going to be important exposure difference I think it is important to incorporate that in the design.

What I think might be lacking here is that it goes right to label appropriately after that, and I think there is a multiple staged approach. You know, you do get that healthy volunteer. Even if that turns out negative you are going to have those situations where in real patients it may be a big issue. So, rather than just going straight to label appropriately, really it becomes more the exploratory analysis as well and that really, you know, feeds into the overall structure.

So, you know, it helps you in designing your study, designing your development pathway, but you still need to come back to look at it and not think that, well, I have answered in healthy volunteers. I have that Phase 3

data. But if you have the genotype across the group you actually can=t do those analyses looking for issues.

DR. VENITZ: I think that concludes our morning session. It is 12:05 and we will reconvene at 1:00 o=clock for the topic 2 discussion in the afternoon.

[Whereupon, at 12:05 p.m., the proceedings were recessed for lunch, to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. VENITZ: We have a few FDA folks join us. If you would, please, introduce yourselves? Joga?

DR. GOBBURU: Joga Gobburu, Pharmacometrics, Office of Clinical Pharmacology.

DR. O=NEILL: Bob O=Neill, Director, Office of Biostatistics.

DR. WANG: Yaning Wang, team leader in the Pharmacometric Team within the Office of Clinical Pharmacology.

DR. VENITZ: Thank you. The second topic that we want to discuss today is quantitative clinical pharmacology and Dr. Gobburu is going to give us some introductory remarks. He is the director of the pharmacometrics group.

Topic 2: Quantitative Clinical Pharmacology:
Critical Path Opportunities
Leveraging Prior Knowledge
to Guide Drug Development Decisions

DR. GOBBURU: I would first like to thank the committee for taking time to come visit us, and we look forward to the comments that you are going to provide on the topic of leveraging prior quantitative knowledge.

[Slide]

The theme of this afternoon=s session is going to be the topic you see here, how do we best utilize the prior knowledge that we have from the plethora of clinical trials here to have more efficient development and regulatory decisions in the future?

[Slide]

The agenda you all have in front of you. I will be very brief. I will not take my 20 minutes. Then we are going to talk about an example of the disease model, focusing on the non-small cell lung cancer model where you will see Dr. Yaning Wang present his work, in collaboration with the clinical and statistics groups at the FDA and outside the FDA, on relating tumor size changes and other risk factors to survival from about 3,500 patient data.

That talk is followed by Dr. Rene Bruno, as a guest speaker from Pharsight Corporation. He will be talking about the utilization of the FDA model and other expertise within their organization to employ prior knowledge to make drug development decisions, such as dose selection, molecule screening, which molecule, should we take this particular molecule to the Phase 3 trial, and so

on.

We then hope to have discussions on the three questions we posed for this part. From the FDA side, Dr. Lesko and myself will be the constant panel members for this afternoon session. Specific for the non-small cell lung cancer, the membership will include Dr. Yaning Wang and Dr. Bob O=Neill.

Then after the break we are going to get into a different aspect of this theme, which is how can we better design pediatric studies? So, Dr. Lisa Mathis, who is the head of the pediatrics and maternal health staff, will update us on the latest legislative amendments for the FDA Act as pertaining to the pediatric studies, followed by Dr. Stockbridge, who will share his experience and, in his opinion, the opportunities for leveraging prior knowledge in terms of designing pediatric hypertension trials.

Then the last presentation will be a case study of how this was specifically done for a particular drug. That will be by Dr. Pravin Jadhav, followed by a discussion on that specific topic. We will also have about three questions for that.

[Slide]

So, just to be clear, pharmacometrics is a science that deals with quantifying disease and pharmacology to influence drug development and regulatory decisions. The focus is more on learning as much as we can from the data to maximize the knowledge we can derive from clinical trials, rather than on confirmation of a prespecified hypothesis.

As you might realize, there is diverse expertise that is needed. It needs clinical pharmacology, quantitative clinical pharmacology, clinicians who have the domain expertise, statisticians and bioengineers to make this happen.

[Slide]

Briefly, what are the disease, drug and trial models? So, if we can agree that prior quantitative knowledge can be synthesized into three different pockets that are specific to the disease, drug and the trial model, the input to such models would encompass the FDA data, of which we have a lot, and the public literature available to everybody, and diverse expertise from the prior experience, and the underlying science of a given disease.

When we say this model, it means that it is the quantitative representation of the underlying biology. So,

if you have an HIV dynamic model, that captures the HIV dynamics. Then another constituent of the disease model is natural progression. Parkinson=s disease. This committee, I am sure, is aware of the previous topic we discussed last year which was on Parkinson=s disease. There we dealt with natural progression in terms of how patients get worse in terms of symptoms over time and placebo effects. What happens when these patients take a placebo, and how do we quantify that? And biomarker outcome relationships.

So, again, the preamble is that if we have these disease models we can use them early on in the development to make decisions. So, the example today that we are going to present falls under this category of biomarker outcome relationship, which is relating tumor size change over time to the outcome, which is death, in the non-small cell lung cancer patients.

The next component will be the drug model which is the pharmacology aspects all the way from preclinical in vitro studies, animal studies, healthy volunteers and into patient studies.

So, we believe that the disease model is independent of the drug and anybody should be able to use

it. Particularly, sponsors can overlay their drug model which is specific to that molecule on top of the disease model.

Equally important is the trial model, meaning what are the inclusion/exclusion criteria, and what are the covariates between each of these inclusion/exclusion criteria, or the baseline tumor size, cancer diagnosis, smoking status, the disease status, the ECOG performance status, are all of them independent, or are they all mutually related somehow? So, that is one part of the trial model.

Then you have dropout. Why do patients drop out of the trials? Is it because they have excessive toxicity, or they are cured, or they are not cured at all and they want to move on to some other treatment? So, that is about understanding and quantifying the dropout patterns.

And compliance, especially in areas like HIV where missing a dose might turn out to be costly. So, what is the pattern of the compliance and the consequence of that in terms of therapeutics?

So, in a nutshell that is what we really mean by prior quantitative knowledge. And, since the main focus,

which is to share with everybody, is about the disease model--I am not trying to diminish the roles of the other--we try to collectively call these three as disease models. So, when somebody else says disease models I don=t think they really mean only this part, but they do imply that they are an integral part of that definition.

[Slide]

So, we have talked about the input and what they are. Now, how do we see them to be used? One of the areas is for molecule screening and I think this is going to be one of the aspects that Dr. Bruno is going to talk about.

Then, patient selection maybe. If we look at all the 8,600 trials from the depression area, maybe we can come up with some criteria of why or which kind of patients are more suitable to recruit into the next depression trial. So, that is the idea when we talk about patient selection and dose selection and trial design.

[Slide]

Briefly, I will highlight the status of the disease modeling initiative within the FDA. There are basically two main initiatives. There are other, I would say, acute applications of disease models we have performed

on a Aneed to@ basis when reviewing protocols. We have summarized those experiences in a recent article in the Journal of Clinical Pharmacology, and we are today focusing on the other major efforts which took us three to four years to come to this stage.

So, for Parkinson=s disease, which was discussed at the last advisory committee meeting, the objective was to derive endpoints to discern disease-modifying and symptomatic drug effects. We are familiar with approving drugs for symptomatic drugs but we have not had any experience in the new area of approving drugs for modifying the disease. So, we compiled all the data within FDA and came up with a disease model and explored different trials and disease endpoints for Parkinson=s disease.

It is completed in our opinion, and we have already started providing input in sponsors= protocols. There is a public meeting which is jointly sponsored by the FDA and American Association of Pharmaceutical Scientists, Michael J. Fox Foundation and Parkinson Study Group, which

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share the scientific aspects of the model and trial design there. There is a draft publication that is ready.

For the non-small cell lung cancer, which is the topic for today, the object is to quantify the tumor size change and other risk factors, as you will see, and the survival relationship to guide future drug development decisions.

Again, we have achieved the major milestone there. We are ready to share that model with the public. I will draw particular attention to the background package. We have a 20-page technical report about the non-small cell lung cancer model that you can use really to design and employ that to make your decisions. Today is the AC meeting to discuss that and, again, a draft publication is ready and it is going through the clearance process.

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It is not that we have done this alone. We needed support from scientists and experts within the agency, as well as outside the agency. In particular, I have to mention that the Office of Clinical Pharmacology partnered with other disciplines within the FDA, such as the Office of Biostatistics and the Office of New Drugs for these projects. That is why Dr. O=Neill is also here.

As far as the data, we procured the data from

mostly within FDA sources, but the NIH and Parkinson Study Group were generous enough to share their data from a big trial with us. Again, we received scientific input from this committee last year and several academic experts outside and, as I said, there is a public meeting to discuss that.

For non-small cell lung cancer mostly the data is from the FDA and we have received input from several academic experts and, again, this meeting and we are planning on another meeting to have a much more detailed technical discussion which perhaps is not likely to occur here.

[Slide]

So, those are the three questions about the disease model. So, as you go through these presentations I encourage you to pay reference to what comments or solutions do you think you have to improve the different aspects of the disease model, and how do you think we can best utilize such a model, industry or the FDA, to improve drug development in general, And, any other general recommendations you have on this broad topic of disease models.

[Slide]

The second half of this afternoon will be on a related topic, which is a pediatric initiative to come up with more efficient trials. Experience dictates that pediatric trials could be designed better to render more useful information. And, the goal is to employ, again, the prior knowledgeB-you have seen that slideB-from adults and pediatrics and general disease for that particular indication to design future pediatric trials.

It is important for us to realize that FDA is in a unique position as far as the pediatric Written Requests are concerned. That is, the Written Request is a contract between the FDA and the sponsor, so we see this as a very fruitful and efficient investment in employing prior knowledge to design pediatric trials because we are in a position to tell the sponsor exactly what designs and endpoints to use for us to maximize the success.

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So, briefly, you have the decision drug trial model. You have an interdisciplinary team which will apply the disease model to develop the Written Request which will be sent to the industry, and they will conduct the trial,

and then there will be data, either through the FDA or directly through the industry, and there will be a library of disease models and generalizable models for everybody to use. Also, that knowledge will go back.

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So, the three questions we have are, do you think such an approach will render pediatric trials more informative? Given limited resources, which I really wanted to put in bold and underlined, please advise us on how to prioritize pediatric programs for applying this model-based trial design. Do you have any solutions on how to improve the approach with respect to closing our knowledge gaps in pediatric pharmacotherapy?

With that, I would like to invite Dr. Yaning Wang to walk us through the non-small cell lung cancer disease model.

An Example of Disease Model:
Non-Small Cell Lung Cancer (NSCLC)

DR. WANG: Good afternoon, everyone. In the next 20 minutes or so I would like to present an example of a disease model in the area of non-small cell lung cancer.

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We started this project about three years ago and there have been a lot of people working on this project. Dr. Cynthia Sung and Celine Dartois were two former fellows in the Office of Clinical Pharmacology, and Dr. Roshni Ramchandani used to be a clin. pharm. reviewer on the oncology team, and Dr. Brian Booth is the current deputy director for oncology, and Dr. Ed Rock used to be a medical reviewer in oncology, and Dr. Joga Gobburu is the pharmacometrics division director.

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I would like to start with some numbers to show you why we are doing all this. This is the cancer death rate in the U.S. As you can see, for both males and females lung-related cancer is the top killer among all the cancer deaths.

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Unfortunately, the success rate for oncology overall is very low. It is one of the areas that has the lowest success rate, which is only about five percent.

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When you look at the failure rate across different stages, you can see at very late stages, which is phase III,

the failure rate in oncology is more than 50 percent.

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Given this situation and the urgent need for the oncology field to improve the drug development process, we decided to look into the large database within FDA and try to generate some useful information that can eventually be shared across industry to increase the chance of oncology drug products.

Specifically, we started with screening risk factors for survival in non-small cell lung cancer. Then we developed a disease model to quantify how the tumor size changes over time. Finally, we linked the tumor size-related matrix with the final survival.

The goal is to look for some early biomarkers, such as this tumor size change, to predict survival. Here I want to point out that maybe this note is too low and maybe I should have put it at the top because it looks like it is blocked, but we are not using this as a surrogate endpoint and it is exploratory too. So, that is why I underlined this in red just to make sure of the purpose of this product.

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The perceived utility of these models are the following, and I am sure Dr. Rene Bruno will show some real cases in the next talk. We think the models can be used to decrease the attrition rate or have better screening in the early phase, and can also be used to optimize dose selection by targeting meaningful tumor size reduction and balancing toxicity, and can also be used to increase the success chance of the survival trial by, say, targeting meaningful, or having objective evaluation of the survival benefit of the new compound relative to a comparator. Also, you can decide based on the predicted survival whether you should go for a non-inferiority trial or superiority trial.

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The database we used included four large registration trials, A, B, C, D, for non-small cell lung cancer. These four trials include eight active treatment arms and one best supportive care. Trials A and B are used for first-line treatment and trials C and D were for second-line treatment. They were both for the locally advanced or metastatic non-small cell lung cancer. The sample size ranged from 243 to about 500 per arm.

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There are 11 risk factors we evaluated as potential predictors for survival or prognostic factors for survival. These are based on what is reported in the literature and also based on stratification factors that have already been used in those four trials. We used a Cox regression method with a stepwise selection, using inclusion significance of 0.1 and exclusion criteria of 0.05.

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So, among the 11 risk factors we found that the baseline ECOG performance score and the baseline tumor size are consistent significant factors for overall survival. The other potential risk factors or stratification factors are not consistent, at least across the nine arms within the four trials. One factor is an exception, that is the LDH, which is the lactate dehyrdogenase greater than the upper limit of normal.

As you can see, as long as a trial or arm collected this information it is significant. But we decided not to include it because the other two trials did not have the information. But, as you can see, within the first line we may also add a third risk factor to improve to the prediction.

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The second step is that in order to systematically evaluate whether some early tumor size change, for example at week four or six or eight, can be used to predict survival we need a model to describe the tumor profile. Not every patient in these four trials has the week four or week six or week eight tumor data.

There are other tumor models, more complicated, more mechanistic models reported in the literature and we first tried those models but, given the Phase 3 data nature we could not apply those more complicated models to this data set. Therefore, we came up with a relatively simpler model that includes two components.

The first component is mainly describing the shrinkage of tumor and the second component is describing a linear growth process. As you can see, we are quantifying or modeling the tumor size, which is the sum of the longest dimensions at certain time points and the primary A is basically the tumor size at baseline. The K is the decay rate, which is treatment dependent, and the B is tumor growth rate which is also treatment dependent.

The main reason is that in the four registration

trials, they all use one dose level. Therefore, we can only treat it as one treatment effect, but you can easily see that if you have multiple dose data or multiple exposure data in, let=s say, a Phase 2 database, you can easily include the dose or exposure effect on these risk parameters to reflect the drug effect at different dose levels of different exposure levels. We used between subject variability to allow every individual to have a unique tumor profile.

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This is the data set for the tumor model. As you can see, there are about 20-30 percent patients without any post-baseline tumor measurements. So, we cannot use those patients. This is line of treatment, first-line or second-line, and the total sample size is listed here. But we end up with about 70-80 percent of the total data set for the tumor model.

This is basically the distribution of the tumor data across different weeks. Of course, when time goes too late you are losing patients because some patients may die or drop out. So, eventually we won=t have some early biomarkers but we also have to say the biomarker has to be

predictive of survival so it will be a balance of timing and also the predictive power and how many patients will be left for model building.

[Slide]

This is just to show how the model fits data. The blue solid line is the mean patient population. As you can see, the overall trend is that the tumor will be suppressed for a certain period of time before it goes into the progression phase. But at the individual level, which is the red dotted line, you will see all kinds of profiles. The black dots are the observed data.

Some individuals can go into progression right away, and some individuals will be suppressed immediately, and some individuals can stay stable at the baseline level and then go to progression, and some individuals pretty much follow the average profile, and some individuals can be suppressed and then stay suppressed for a long period of time. So the model fits the data reasonably well.

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The next step is now we have significant baseline factors to predict survival, and we also figured out a way to quantify the tumor size at, let=s say, different time

points, at four, six or eight, and we are trying to figure out which one will be the tumor size-related predictor for survival. So, basically, you know, based on the balance between how many patients are left and whether it is early enough, we picked weeks four, six and eight, and we call this tumor percentage reduction at week X relative to baseline.

In terms of the model building process, we started with the data from drug A1. That is one arm within trial A. We built the model based on the data using a parametric survival model. Put in simple terms, basically it says the survival time will depend on the patient=s baseline ECOG performance, and it also will depend on the baseline tumor size, and also will depend on how much tumor shrinkage or reduction the patient will have at a certain week.

We went through all the typical distributions for survival modeling, which includes, you know, the gamma distribution, survival distribution and exponential distribution and a lot more. They are all in ,the background package, and you can see eventually log-normal and it came out as the best distribution for all the nine arms.

In terms of model evaluation, we basically used the model that is divided based on treatment A1 to predict what is going to happen to the other eight arms in terms of survival time, and which could come, from you know, different trials and have different mechanisms of action for the tumor treatment.

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First I want to say that eventually we picked week eight, instead of week four or six, as the tumor reduction predictor for survival. These are just showing if I use the model based on A1 and if I predict A2 or all the other arms how the prediction looks relative to the observed data.

The red lines are the median and the 95 confidence interval for observed survival data. The blue line and yellow shaded areas are the predicted median and 95 confidence interval. As you can see, overall the model predicted the data reasonably well. But you also see that for trial B there is a consistent positive bias. But if, let=s say, the goal is to predict relative difference you see that the impact will be minimal.

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Similarly, for predicting the other four arms in

trials C and D, again the model did a reasonably good job.

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When I say week eight is the best tumor reduction predictor, it is mainly based on its consistent significant factor for all the nine arms.

But if you want to see how much this tumor size contributes to the survival prediction, I just want to pick one to show you that if, on the left side, you include all the three predictors what it would look like in terms of prediction, and if you only include the two baseline covariates what would the prediction look like. This is how much tumor shrinkage at week eight contributed to the survival prediction. The magnitude of variation varies across all the other eight arms but they are all consistently showing that tumor reduction at week eight is significantly contributing to the survival.

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After all this model checking we eventually pooled all the nine arms and analyzed them together. We found that the relationship between the expected survival time and the tumor reduction at week eight is different between the first-line treatment and the second-line treatment.

As you can see, the blue lines represent the median and the 95 confidence interval for the first-line treatment and the red line represents the second-line treatment. Overall, you can see that the sensitivity of the survival time is less for the second-line treatment. In other words, even with the same level of tumor shrinkage the benefit for the second-line treatment is less than the first-line treatment.

These shaded areas are the observed median shrinkage, tumor shrinkage at week eight. As you can see, for the first-line treatment almost all the treatments will have significant shrinkage at week eight, which is about 25-30 percent. But for the second-line treatment--these are all the observed data from the four trialsB-for the second-line treatment at week eight the tumor size on average remains the same and some patients got progression and some got some reduction. But overall the first-line treatment is shrinking the tumor more than the second-line treatment.

[Slide]

So, what about those excluded patients? What should we do about those, 20-30 percent of the overall population? When I compare he excluded patients versus the

included patients, across all the nine arms they are showing consistently shorter survival time. It is almost like these patients represent some less responders to all the nine arms.

Since we don=t have any post-baseline tumor data, the only information I have is those baseline prognostic factors. So, by looking at those things I found that only the ECOG is a significant predictor for survival within this limited population. Therefore, a very simple parametric survival model was used to quantify the excluded 20-30 percent of the patients. It is used as a categorical variable. So, for first-line treatment there are only two levels, zero or one. But for the second-line treatment there are four levels.

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Similarly, we followed the same model evaluation. If I use the model based on drug A1 to predict all the other four first-line treatments, this is how it looks. As you can see, now the prediction is more variable because the band is wider and in some cases the bias is a little bit more than the included population because we only have one baseline predictor. Therefore, this is not surprising.

[Slide]

Now I cannot use A1 anymore because A1 doesn=t have the ECOG level of II and III. So, in order to evaluate the second-line treatment I basically used the data from drug C1 to develop a model for the excluded population and to predict the other three arms. I put C1 here just to show you if you use the model from C1 to predict back the data it will be very nice.

So, this type of diagnostic plot is not sensitive if you use the data to develop the model and then predict back. It is only sensitive if you predict other arms or other trials. There is a bias for the C2, but overall the median survival did not, you know, deviate too much.

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In summary, we found that the baseline ECOG performance score and the tumor size data are significant or consistently significant risk factors for the non-small cell lung cancer. The simple tumor model can be used to describe the tumor profile reasonably well within the Phase 3 trial.

Finally, the tumor survival model shows reasonable consistency across all the nine arms and the sensitivity is

less for the second-line treatment. And, in order to simulate the full patient population two different patient populations should be included because they have very different survival median times.

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Again, I want to emphasize the utility of these models. I am sure the example presented by Dr. Rene Bruno will further give you a concrete idea about what this means.

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Finally, you know, as I said earlier, this is a group effort and we got help from the Office of New Drugs and also from our biostatistician group. Mark Rothmann gave us a lot of helpful suggestions. And, we had two former OCP fellows. They actually started this whole project. And, within the Office of Clinical Pharmacology we had many people to help us, and we also got help from external experts in this area. Finally, when I took over this project, this whole project was funded by the Office of Women=s Health. That is all. Thank you.

DR. VENITZ: Thank you, Dr. Wang. I suggest that we hold off any questions until we hear the second presentation. Let me invite Dr. Rene Bruno. He is with

Pharsight, in Marseille, France, and he will follow up on the same disease model.

Application of FDA=s NSCLC Model

DR. BRUNO: Thank you.

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Good afternoon. First I would like to thank Dr. Gobburu for inviting me and giving me the opportunity to present some of the work we have been doing to illustrate the use and value of drug independent survival models to support clinical drug development in oncology.

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First I will give some consideration to drug development in oncology, not much because we have already heard something about that. Then I will present to you a drug disease model and framework that we are developing to support drug development in oncology. This framework, as you have seen, comprises a tumor growth model and a survival model.

I will show you a couple of cases to illustrate the use and value of those models. The first one is a project that we did with Roche. It was a retrospective project to show how we could use those approaches to support

end of Phase 2 development decisions. The second case will be how we can make use of the model that you have just heard about, developed by the FDA, to help companies to make decisions at the end of Phase 2 and even Phase 1B drug development.

I will conclude with a few considerations about the value of those and what we are missing maybe to do more of those, particularly in terms of the drug independent models that could be developed.

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Here I am not going to go into the details but I think we have already heard about the high failure rate in Phase 3, and we believe that a lot of that is due to the fact that companies are not learning enough from their early trials. One important problem here is that the analysis of the clinical trial data which is performed is generally poorly informative.

In terms of the primary endpoint for the end of Phase 2, it is often response rate, and response rate is not very useful in predicting what is going to be the future benefit of the drug. It is the same for safety with the grade of toxicity being the end, and so on. So, I think a

way to increase the learning ability that we can have from those data is to use a drug disease model, as you have seen illustrated in the first talk.

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So, this is the model framework that we are developing where actually the dose intensity and the exposure to the drug is driving the main effect, which is on the dynamics of tumor size. We are using this kind of longitudinal model that you are seeing to quantify this effect.

Then, this change in tumor size is used as a biomarker, as you heard, to predict survival, and it is interesting because we came kind of independently to very similar models that you have just seen in different tumor types. So, we think that the concept is working pretty well.

Also, we are developing a model to predict dosing reductions that may be due to dose-limiting toxicities because we are interested in simulating the expected dose response for a given treatment so you have to account for dose-limiting toxicities.

So, with those three models, actually a model to

drive the dosing reductions, a model to quantify the change in tumor size, and a model to relate change in tumor size to survival, we are able to simulate all the endpoints of interest in clinical oncology studies. Of course, the change in tumor size is driving survival, but with the longitudinal tumor size model you can also predict time to progressive disease, and with survival data we can predict progression-free survival, which is time up to progression of the disease or to death. We can also predict response rate, which is a categorization of tumor shrinkage that is seen during drug treatment.

So, using this model actually with this model we can predict all the clinical endpoints of interest in oncology. Also, of course, we take into account covariate and prognostic factors. Here, I believe, is where you would factor in the pharmacogenomic information that you may have, as we discussed this morning, that could easily influence pharmacokinetics, pharmacodynamics or clinical endpoints. Then you could use such a model and framework to simulate a clinical trial to assess the effect of pharmacogenomic differences.

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Let=s focus on the efficacy part and tumor size dynamic survival relationship that we are particularly interested in today. Here the interest is that you already heard about this model, linking tumor size dynamics to survival. As I said, we independently came to a very similar kind of a model where the tumor shrinkage at an early time during treatment, week eight, week six, is used as a predictor of survival for a given treatment. And, this is disease specific.

Then, here is a drug-specific part of the model where you quantify the drug effect on the dynamics of tumor size. Of interest, in this model there are drug-specific parameters-Bthe potency of the drug for example, but also disease-specific parametersB-for example the tumor growth rate, and you will see a little bit more about that. The interest of this framework is that we can use things that are measured in Phase 2 in early studies, even Phase 1B study in tumor-specific studies, to predict the endpoint of interest in Phase 3.

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This is a little bit about the tumor size model that we are using, which is a little bit different from the

one you have seen. The main difference I believe is that we are using exposure to drug and drug effect. So, this allows us to perform dose-response simulations. Also, we are estimating the tumor growth rate that is a disease-specific parameter that we can use to scale early data observed in, let=s say, Phase 2 patients and simulate expected change in tumor size in a Phase 3 patient population that may have different characteristics of tumor growth rate.

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So, this is a project that we conducted with Roche. The idea here was to evaluate the model and framework to support early drug development decisions. By early drug development decisions, I mean go/no-go decisions and that is very important because there are so many new compounds in development in oncology that it is pretty important to have quantitative methods to select the promising drugs and, if the drug is promising, then help in the design of Phase 3 studies.

The idea here is to simulate expected survival difference in Phase 3 based on Phase 2 data of a new drug and historical data of a reference drug because you need to have a larger database to develop the survival model. At

this time we didn=t have any model from the FDA. Now we have one and that is very interesting and that is what I am going to illustrate next.

This actually was a retrospective project that we did with Roche. The pharmacometric guys in Roche wanted to convince their colleagues from clinical development and biostatistics that they could use this approach with confidence. So, we did the project where the company provided us with the Phase 2 data of capecitabine and historical data of the reference drug, and the reference drug was docetaxel in metastatic breast cancer or 5-FU in colorectal cancer.

They asked us to simulate Phase 3 studies that they had already run, but they didn=t give us the results of the Phase 3 studies. We performed the simulations and then we compared the outcome. This has been published at ASCO a few years ago.

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So the capecitabine data, as I said, was from Phase 2 studies. Here we have two studies, pretty rich studies with 170 patients. I am only going to show you the metastatic breast cancer simulations here. We did the same

thing in colorectal cancer and in colorectal cancer we had Phase 2 data which was a much smaller study. They also provided us some docetaxel data from a Phase 3 study that they had in their clinical database.

Roche is a big company. They have been developing drugs in oncology for ages so that they have this kind of data that allowed us to develop the survival model, because you cannot develop a survival model using small Phase 2 data sets. But a lot of the companies involved in oncology don=t have this database. That is the reason why the model that we have seen is very useful.

So, we simulated based on the single agent data Phase 2 capecitabine and docetaxel, a Phase 3 study comparing the combination of capecitabine and docetaxel versus docetaxel. Here we assume the additive effect for the combination and this was based on preclinical data. Also, we scaled the capecitabine drug effect from Phase 2 to Phase 3 using the specific estimate of tumor growth rate that we could estimate using the Phase 3 data for docetaxel.

This project focused on efficacy so we didn=t do models for dose-limiting side effects. We have done that now. But the simulations in that case were conditioned on

observed dose intensity and the drug effect was driven by dose.

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So using the model we developed, as I said, we simulated a combination study, and what you can see here is first the performance of the simulations in simulating the reduction of tumor size at week six. This was a combination of docetaxel and capecitabine.

What you see here, in blue, is the predictive distribution of the model and, in orange, the observed data for the median and for the quantiles. Here you have numerical data where you can see that the model predicted a 27 percent decrease in tumor size at week six compared to 21 percent observed for the combination of the two drugs.

Then, using the simulated change in tumor size, we used that to drive the survival and we simulated survival for this treatment and also for the reference docetaxel arm.

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And, this is what we obtained. This is the combination arm and what you see in the blue envelope is the predictive distribution of the survival following administration of the combination. In black you see the

observed data and, similarly, for the reference arm. So, you can see that we were able to simulate data for this Phase 3 trial.

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Now let=s assume that you are in an early stage of drug development. Then, you could have a comparison of the expected survival of your new treatment which in this case is a combination, compared to the reference, in blue here, and you could have an estimate of the expected difference in survival as quantitative support for decision-making.

Here, for example, as we have the results you can see that we predicted a 57-day difference in survival when th

those numbers, but just to show you that we were able to simulate a Phase 3 trial based on an early Phase 2 trial of an investigational agent.

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So, we have done that with Roche for three cytotoxic drugs. We also had similar models for 5-FU in two tumor types, breast cancer and colorectal cancer. Change in tumor size was a good predictor of survival. So, modeling of longitudinal tumor size is much more informative than

response rate determination because, using response rate, response rate is a very poor predictor of survival. This is mainly because you are losing information when you categorize the change in tumor size to assess response rate, but also when you are looking at response rate to survival correlations you have to do study-level correlations because for each study you only have one response rate and for a given treatment you have survival outcome.

But here what we are doing is patient-level correlations so we are relating the change of tumor size in one patient to the survival in this particular patient. So, that is also one of the reasons why it is much more powerful.

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Let=s now go to the use of the model you have seen. I mean, a lot of companies are very much interested in doing this kind of simulation at an early stage, but the thing is that they have only data for their drug, Phase 1B combination study, Phase 2 data, but they don=t have a survival model because they don=t have a big enough data set to develop this kind of model.

So, if we can use this model, the model you have

seen, and you combine that with change in tumor size that you can predict from Phase 1B or Phase 2 studies, then you can make inferences about the expected survival. This is what we did for the company and we issued a press release to announce that. The company was interested in getting expectation of survival for a new chemical entity in combination, and this was to support the decision to start a large Phase 3 study.

They had a Phase 1B combination study in non-small cell lung cancer. They had less than 30 patients. We used the model you have seen and we simulated expected survival based on observed tumor shrinkage in this study and patient prognostic factors. So, you may not even need the tumor size model if you don=t necessarily want to make inferences about dose response. You can even use the observed change in tumor size in those early studies.

We got in contact with the pharmacometry team because we needed a little bit more information. At this time we only had the presentations they made early last year at the DIA meeting. They provided us the information we needed, power estimates and also some information about what they excluded from the studies which have to be taken into

consideration. So, now I am glad to see that they have developed a model for those patients.

So, we used that model but the company didn=t want to disclose anything about that and I am not able to present that. So, I used the case using the literature data. The problem is that in the literature you don=t have any tumor shrinkage data.

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Fortunately, just recently I came across a paper by the team of Mark Ratain, from the University of Chicago, where actually they are proposing to use change in tumor size as a primary endpoint in Phase 2 studies. I think that is a very good idea, and they are making the point hereB-this is a paper in JNCB-they are making the point that you can get much more power in the research endpoint as opposed to using response rate. The interest for us here is that they report data on change in tumor size in this paper from four trials, and we used data to perform the simulations that you are going to see.

[Slide]

They are proposing to use week eight change in tumor size in their paper as a primary endpoint of Phase 2

studies. So, that is a good thing because this is the endpoint that is used in the FDA model. So, we used those data and, more specifically, the algorithm of the ratio of week eight size to baseline which is normally distributed, and based on those data in the paper and some assumptions on the distribution of baseline tumor size, and also some assumptions about the ratio among ECOG 1 and 2 patients, we were able to simulate a thousand replicates of a virtual treatment arm of 300 patients in second-line non-small cell lung cancer, treating ECOG 0 or 1 patients because those are the patients included in the FDA model.

Here we used C and D models, models that you have seen C and D because now we know, but at the time we inferred, that they were a model for second-line treatment because of the proportion of ECOG 2 and 3 patients that were in those trials. At this time we didn=t have the second-line model that is very useful. We used actually C1, C2 and D1 and D1 models to simulate the expected outcome by sampling 25 percent of the replicates in the different models. We adjusted the simulations with the early dropouts.

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This is what you can obtain with this kind of simulation. This is expected survival for the treatment that we chose to simulate. In this case it was 7.2 months with a 95 prediction interval. This is actually slightly longer than what they observed in the particular paper that we used for the change in tumor size. But those simulations only concerned ECOG 0/1 patients, whereas, in this paper they had a proportion of ECOG 2 and 3 patients.

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So, to conclude on the value, I think it is pretty easy with this model to predict the survival probability distribution of an investigational treatment based on early tumor shrinkage and basically based on early clinical data, like you can have in Phase 1B or Phase 2, and this can be a new chemical entity. It can be a new combination treatment.

Then, you can simulate an arm of the investigational treatment, conditional on the sample size, to mimic a clinical trial. Those simulations can, of course, be compared to the survival distribution from a reference treatment and the expected treatment difference can support decisions.

You can also simulate Phase 3 clinical trials to

assess the probability of success, but this is a bit of a stretch because the FDA didn=t provide us for now the distribution of change in tumor size that you see with a reference treatment. That would be very useful.

[Slide]

So, as a conclusion, I have already said change in tumor size as a good predictor of survival is a useful endpoint. The drug independent survival model allow to predict survival expectations or simulate Phase 3 trials based on early data, but the problem is that the availability of these models is limited, and FDA is in a unique position to develop such models.

We currently have a very useful model in non-small cell cancer for survival but we need much more of those models. Companies are very interested to use those models in order to mount breast cancer, renal cell carcinoma and so on, and it would be of interest also to have models for other endpoints, like progression-free survival, which tends to be more and more often used as primary endpoints in clinical trials. Thank you.

Committee Discussion

DR. VENITZ: Thank you, Dr. Bruno. Any questions

for the two presenters before we start tackling the three questions?

Dr. Bruno, let me ask you what model did you use to link your tumor shrinkage to survival?

DR. BRUNO: Very similar model to the one you have seen presented by the FDA. It is a parametric survival model assuming parametric distribution of survival. I mean, you can choose the best distribution to use here. Log-normal distribution can be valuable. I mean, based on the data you select the distribution and then you assess change in tumor size and other prognostic factors as predictors in this model.

DR. VENITZ: Did you end up with the eight-week tumor shrinkage as the best predictor as well?

DR. BRUNO: Yes.

DR. VENITZ: So, you used basically the same.

DR. BRUNO: Yes, we came independently to very similar models.

DR. VENITZ: Dr. Lesko?

DR. LESKO: Yes, I probably should know our own data, but before registration trials A, B, C and D and then I guess the trial that you discussed, were these clinical

trials that had a targeted patient population based on, for example, EGFR being positive or negative, or something along those lines? Or, were these studies that were conducted in all-comers irrespective of their tumor genetics?

DR. WANG: I think they used all-comers. That is true? Right? We have a statistician from oncology to confirm that. I think I haven=t seen any genetic, let=s say, measurement in these four trials.

DR. LESKO: The reason I am leading with that question is that the association between survival and tumor shrinkage in all-comers obviously includes some non-responders. I mean, the responder rate in these four trials, and I don=t remember what it was but it was probably relatively low. And, the question kind of would be how would the relationship between tumor shrinkage and survival have been if I only looked at the stratified population based on some genetic characteristics of the tumor?

DR. WANG: Actually, that is a very good question. See, the part that is missing in the modeling process is would you now try to look for what the patient characteristics would make those patients be more a responder, or like a good responder versus a bad responder.

As you can see, there were at least 20-30 percent of patients who are, like, poor responders and we did not look for, let=s say, what baseline characteristics or prognostic factors can be used to screen out those patients so that you only, let=s say, recruit the patients that would belong to the 70-80 percent of the patient population.

I believe, yes, if you can further, let=s say, refine the patient population the predictive power of the model should be even better. But right now without that factor we just have to include everyone, but including that 20-30 percent is almost like a non-responder but they will contribute to the noise to make the signal more variable.

DR. O=NEILL: I have a question for both of you with regard to this magic eight weeks, which is surprising given that the model is really a time-dependent tumor change and then you essentially use that at the end of the day to condition on eight weeks and then that is predictive, which is surprising because response rate is not very predictive which, again, is sort of a categorization, yes or no.

I guess I would be interested in how much moreB-I think you suggested this but other than the baseline

covariates, how much more is that predictive and it is not the slope of how fast you get there. In other words, if you are an aggressive progressor versus a not so aggressive progressor to what extent that is predictable.

The other question to both of you is how do you think this would work in a cancer situation which didn=t have such a high mortality rate? I mean, there is a huge mortality rate here, and you can only model time to death if you have a lot of deaths. So, if you have a situation where you don=t have a very high mortality rate for five years it is very difficult to get that model.

I was curious with regard to the Roche example, which was surprisingly on the money. I forgot what that survival rate was, but it would be interesting if that was very high.

DR. BRUNO: Yes, the median survival was something like one year, I believe, or a bit more. I don=t have the numbers. But to your two questions, I believe with respect to the use of an early time in tumor shrinkage, I think that is because it is powerful because you have most of the patients still at this time. I mean, then you are losing a lot of patients.

But I think that one option also would be to use change in tumor size as dynamically linked to the hazard of death over time. So, you could have maybe something more predictive, particularly in case of the new targeted therapy not producing a lot of shrinkage but maybe long durations of stable disease for example.

Now, maybe regarding your question concerning long survival, I believe that in such a case survival might not be the primary endpoint in a clinical trial. I don=t know but maybe you may be more interested in progression-free survival and then you can use the model also to predict this endpoint.

DR. VENITZ: Dr. Mager?

DR. MAGER: I just had a quick question. Were concentration data not available? I think both models ignored inter-individual variability in drug exposure and I was wondering if that was done on purpose or if such information was not available, and what implications this has then in pharmacokinetic-dynamic relationships.

DR. WANG: In our case, as I mentioned, those are Phase 3 trials. There is only one dose, you know, for each arm. You can see that actually you really don=t need a

disease model when you have the observed tumor size data, say, at week eight, like Dr. Rene Bruno showed. You really don=t need a tumor model. You use the observed week eight tumor shrinkage to directly pug into the tumor survival model.

In my case, I was merely using it, let=s say, if someone is missing week-four tumor data, or week-six, week-eight. I can use that model to generate that because not everyone has tumor measurement at those specific time points. Actually, yes, there is no PK data. There is no PK data in those trials. That is the simple answer.

DR. BRUNO: Yes, in the Roche case that I showed here we didn=t have PK data either. But we have used PK data in a number of projects since. I think it is very useful to have PK data. Then you can have an exposure response model because this will allow you to make inferences about dose response because often in Phase 2 studies you only have one dose, or maybe a couple of doses. If you take advantage of the PK variability, then you can make inferences about the dose response. It is very interesting for that.

I had another point. There is another thing that

you can do. Here what we have developed is an exposure response model. So, the effect is driven, let=s say, by the Randall=s curve, things like that. So, you can also develop a PK/PD model where you account for the time course of the PK and this could be useful if you want to sort out schedule differences. So, this is one thing that you can do also with PK data.

DR. GOBBURU: Yes, I had a similar point. Unfortunately, we didn=t have the concentration data for these decision trials until oncology. Perhaps if the pharmaceutical industry sees this as an advancement and these models are prospectively used, I would say that as part of a commitment they should probably collect more PK data.

I think steadily we see more and more trials with PK data, specifically early on. Tagging on the concentration-dependent, exposure-dependent model to the tumor progression has to be done if we want to hone in on the dosing regimen. That is inevitable. We have to do that.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: I was interested in the LDH data

that you presented in your talk because that was, to me, surprising. Baseline tumor size, that didn=t surprise me and ECOG score, that wasn=t surprising but the LDH was a little bit surprising. So, were you able to model that in some way against tumor size, and is that predicting tumor size?

DR. WANG: We did not try to use that to predict tumor size. That is actually one of the baseline characteristics. We are trying to see whether they are linked to survival or not, just to control, you know, patient to patient difference. Yes, we put those data into the Cox model and they always turn out to be significant.

DR. GIACOMINI: And you put it in quantitatively?

DR. WANG: In the Cox model it is quantitative but without including the tumor size shrinkage yet. We just say which baseline can contribute to survival. Actually, probably we should have, let=s say, developed an independent model just for first-line where they all have the LDH data as the third baseline predictors. I think that will further improve the predictive power of this overall model.

You know, during the early stage it was mainly because I was trying to see whether I could use one model to

predict either first-line or second-line irrespective of the treatment. That is why I excluded but, you know, in a retrospective way probably I can just model first-line but including, say, the LDH as a third predictor.

DR. GIACOMINI: Then, I was also curious about the disease model for tumor size in which you model tumor growth in a linear way. It seemed like it would grow in a little more exponential way.

DR. WANG: As I said, it is more empirical because if I apply a more mechanistic model not every arm will give me some reasonable results. So, I came up with the simple model and, given the Phase 3 tumor data they collected, it described the observed data reasonably well. Yes, it is linear growth but, see, if you look at the combined curve it is a mixture of growth versus shrinkage. So, if you look at the individual primary estimate, some of the growth rate could be very low, almost close to zero and some individuals could have a larger linear slope but it is the combination of these two processes that overall describes the overall profile reasonably well

DR. GOBBURU: Just to add on that comment, if you think about the real-life situation there will be no

physician who will leave the patient, you know, progressing just so that we can estimate the model parameters. So, we are constrained by the practicality of data collection and that is one of the main reasons for us to see that linear is reasonable.

DR. VENITZ: Dr. Mager?

DR. MAGER: I was wondering if either group looked at the use of preclinical data where you have, say, model-fitted parameters of efficacy and whether or not those preclinical parameters could be used as covariates in this model with, for example, the kill rate in the more mechanistic model or the empirical kill rates, moving the whole scheme back a bit to discovery and development stages.

DR. WANT: So far we haven=t looked at that area yet.

DR. BRUNO: Yes, we are working on that, but this is pretty challenging because the tumor xenograph model that you have in preclinical studies is very different to what you are going to find in the patient population. So, extrapolating drug effect from those models to a clinical situation, I think that is a real stretch.

But what you can probably do is if you have a lead

compound and backup compounds, for example, you can estimate relative potencies in those models and then maybe plug that in a clinical model for the lead compound. Then you may be able to get good simulations for the backup compounds.

DR. VENITZ: Are there any more questions for Dr. Bruno? If not, then I would ask you to please sit down.

DR. LESKO: I have one question I could ask. The use of the model by both Yaning and Rene seemed to be in registration trials, and I take that to assume registration trials that succeeded in achieving a primary endpoint that led to an approval. Is that true?

DR. WANG: Actually, in the four trials some failed. Not every arm was a successful arm.

DR. LESKO: Well, it is sort of getting to the question because of the reason we invest in these kind of models, the perceived utility. One of the questions is optimal dose selection and to take any of the, quote, failed trials and sort of reverse engineer using the models and say, oh, this trial failed because the dose was wrong based on this hypothesis of a model being a better predictor of dose. In other words, could you understand the failure?

DR. WANG: In my case, those so-called failed arms,

it is mainly because of the comparator. They did not achieve, you know, the preset goal of, let=s say, beating the comparator. Maybe they are as good as the comparator, they just did not surpass, you know, whatever rule they set up earlier.

That is why I say when you use this model you can see what is the expected survival, let=s say, for a treatment. Then if you are using a reference that is almost as good as the new compound you can probably only aim for, let=s say, non-inferiority with a realistic sample size. But, you know, failure or success is mainly relative to what you are using as a comparator and what kind of goal you are trying to achieve.

So, I think in those four trials those failed arms, they are not necessarily not working; they are just not working as well as the sponsor expected or, you know, planned.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: Yaning, in your objective slide you have a note at the bottom that says it is an exploratory tool, not intended for a surrogate endpoint. However, it looks like Dr. Ratain is a little bit projecting that this

could, in fact, be used as the basis for an approval. And, based on what I have seen here, that seems to be the biggest value in all of this because what I think you have shown is that if I have patients who are further, who have a certain disease burden I can actually pool data across mechanism and then I will be able to forecast survival based on tumor size. I mean, that is what it looks like here.

And, in terms of your question there, it would be very helpful to see this be able to make these kinds of predictions across varied mechanisms and incorporating this kind of, you know, broad guidance so that you could, in fact, consider this as a surrogate and be part of the basis for approval as opposed to just a covariate.

Having said that, what I think is not there, however, is really the disease progression piece. I have no idea when a patient comes into the trial who is at an early stage of disease how they are likely to perform because we are getting further into treatments so that you can normalize out the drug effect. So, the real value I think would be, as Don and others have pointed out, you know, could we in fact have the drug specific piece of this where you have the attributes of the drug, the mechanistic piece,

that part of this where you could make predictions earlier on. Then, you know, the generalizability would come in much later as you got further stages of that.

But do you feel, based on, you know, where you are at now-Bwhat do you think the potential is for this becoming a surrogate based on what you have done? I guess that is also a question for Dr. O=Neill.

DR. WANG: I think based on what I have seen from those four trials and also the predictive value, I think it is too much of a stretch to say it can be converted to a surrogate because when I simulate I do see a lot of uncertainty. You know, in oncology, if you look at the difference it is like one month, two months between the two arms. And, with that kind of predicted uncertainty you almost always predict that the two drugs will overlap with the predicted uncertainty. Basically, you don=t know because you are trying to detect a very small time range and the uncertainty is still large.

That is why, you know, if you say, given this tumor size, I am very sure that the survival will be this much, that is still too much of a stretch I think.

DR. O=NEILL: Yes, I think if you wanted to go down

that road there is a lot that has to be put in a foundation here, which we haven=t heard about. The whole sort of validation of a surrogate is that essentially you would have to have superiority show a difference in the trial to essentially establish a surrogate as working because the question you ask is how much of a treatment effect on survival is explained by the treatment effect on the tumor change.

And, we haven=t seen any analysis of that, nor is the simulation directed towards that. And, that is a real hard problem, and you need to look at that over multiple studies and there is a whole field that has been thinking about that for 20 years in the oncology area.

But I was surprised when Yaning=s predictions were so tight as things go. There may be a lot of reasons why that is the case. There is some censoring going on here. Yaning was talking about not having tumor data on some folks, and those folks are generally sicker than the rest of the folks. So, if you really did have data on them and you threw it in, how would that sort of re-jigger your predictions?

But, nonetheless, I think the other point I had

made earlier, and I think it is correct, is that you almost had 90 percent mortality data on everybody. Is that correct?

DR. WANG: In this area the death rate is very high. Without this type of data you cannot develop this model basically.

DR. O=NEILL: Right, it is very unusual here. But you are right. I mean, I suggested the same thing to Yaning. With such tight sort of predictions people will ask why can=t I use this for something else? I think what we were talking about earlier, and it is unfortunate because the dose data and exposure data is not here, you would actually want to be able to say when you are moving along is what anticipated tumor change should I see at eight weeks if I have an effective agent because wouldn=t want to drop that.

If this was a design where you essentially were adapting to three doses and you were clueless about which dose you wanted so you would use the decision at eight weeks to drop those two doses if you didn=t get any change in your tumor shrinkage, or whatever. Then you would keep the dose that actually was going. And, you would hope that this

would be predictable of something. But that data is not here for that sort of use, which would be very useful.

DR. VENITZ: Dr. Relling?

DR. RELLING: Did you confirm that the deaths were always due to tumor?

DR. WANG: That is a very good question. Actually, in the background I summarize the reason for deaths because, as you can see, in this type of model we tried to focus on the efficacy part, you know, that we believe that was the main reason for deaths. Actually, during the paper review one author raised this question, what about those safety caused deaths? I went back to see. Most of the deaths are caused by the disease itself. A very small percentage is due to whatever toxicity. That is why I think overall the model should be very robust.

DR. RELLING: But that might not be true for all drugs.

DR. WANG: Yes, that could be true, but especially in this disease area I think most of the deaths are due to disease, not other toxicity. But, yes, for other minor tumors the death rate may be significantly due to toxicity. That could be true. That is why I think for those disease

areas you probably should also have a toxicity-linked deaths model to, you know, integrate the deaths.

DR. CALDWELL: Could someone help me understand how you got your rate constant of resistance appearance? It is the lambda in your tumor size model. How do you get that?

DR. VENITZ: Dr. Bruno?

DR. BRUNO: Yes, you see that some patients respond to the treatment and then progress after a while so this allows you to estimate that rate constant. But you need to have a pretty large data set to be able to do that.

DR. CALDWELL: So, after exposure what I am trying to figure out is if this is circular reasoning here. The rate constant of resistance appearance actually is looking at change in tumor size over time and response to exposure.

DR. BRUNO: Yes. Let=s say that for a given exposure you get a drug effect, but after some time you lose the drug effect. So, you maintain the exposure but the tumor is no longer shrinking but is progressing again. Using those data, you can estimate the rate constant for resistance assuming that the drug effect is decreasing over time.

DR. CALDWELL: Okay, so it is lack of growth after exposure. It is both shrinkage and lack of growth after exposure

DR. BRUNO: Yes. Yes, using the longitudinal tumor size data, whatever it is. But what is very informative is to see progression after drug effect. After some time you see the disease progressing again because the drug effect is gone actually due to the resistance.

DR. CALDWELL: It almost seems like that would be something that would be a gold standard for pharmaceutical trials. I mean, if you could solve for that and put the other parameters into the equation that would give information to pharmaceutical companies and it would be extremely useful.

DR. BRUNO: Yes, this is actually what is used when progression-free survival is used as an endpoint. So, this is data mining time to progressive disease actually.

DR. CALDWELL: Thanks.

DR. VENITZ: Mr. Goozner?

MR. GOOZNER: I don=t know the four arms that were put in there but I am curious. I am not an oncologist. But there have been a number of drugs that have been approved

based on surrogate endpoints and I believe tumor shrinkage may well have been some of those endpoints. Then later data came in where there wasn=t survival data.

So, I am curious just if you could explain how this model might compare to what happened in some of those drugs. I am thinking for instance of Irissa. I don=t remember what the original approval was based on. I was just trying to look it up. But I do know that eventually it came in that there was no real survival data so the FDA had to go back on its original surrogate endpoint. So, how does that fit into the model? Maybe that was one of your trials because I think it was also in non-small cell lung cancer.

DR. WANG: The four trials were selected mainly based on whether the electronic data were available or not so we can look at data. Actually, I did try to include Irissa because it was the case that it was approved based on response rate but it turned out that survival was not significant, but the data was not there.

Having said that, for most of non-small cell lung cancer when you approve some drug based on, let=s say, tumor shrinkage or response rate you still have to do the survival trial. You are approving the drug based on accelerated

approval and you still do the survival trial. I don=t know the history of Irissa and why the survival trial failed and we still have the drug on the market based on the original response rate. But people always bring that up. I was trying to include that as D-E, you know the fifth arm, but we just don=t have the electronic data.

MR. GOOZNER: You mean on tumor size?

DR. WANG: On tumor size, that is right.

DR. VENITZ: Go ahead.

MR. GOOZNER: I just want to make sure I am very clear that this is being proposed as a tool for, like, going from Phase 2 to maybe Phase 3 because there has been a question raised that this might be a model and the answer seemed to suggest this couldn=t be really a model for a surrogate endpoint. And, I just want to underscore that that is exactly what you are saying, that you don=t see this as a model for that.

DR. WANG: No, it is for an exploratory tool, not for a surrogate. Even though those predictions look tight on the plot, that is because they are small. If you put it on a one-month, two-month kind of delta scale they are wide. If you overlay any two of those predictions they are highly

overlapped. Therefore, there is still tremendous uncertainty in the survival prediction. That is why you cannot say, you know, if I achieve this tumor shrinkage I am very sure I will have, let=s say, one- or two-month survival benefit. The uncertainty is too huge.

DR. VENITZ: Dr. McLeod?

DR. McLEOD: I would encourage you to do some prospective work with this within the NCI cooperative group setting for the very simple reason that you need some real data that can allow you to push this a little bit further. Right now I have a hard time seeing a company making a no-go decision based on this model, partly because so much of that decision is non-science.

So, you do have at any one time somewhere between three and eight non-small cell lung cancer trials in advanced disease going on in the United States from another federal agency, but one that I think you can talk to, that also has three letters. So, I think there is some opportunity to really push this forward because it has to be more than it is now.

This modeling is really needed, not only because of the desperation of this disease but because of the dismal

success rate that we are having across oncology.

DR. GOBBURU: I have a question. Why do you think the pharmaceutical industry will not use this at this point?

DR. McLEOD: Well, I think that a lot of the go/no-go decision with folks that I interact with is based on a lot of other things, other than the science, such as what else is in the pipeline; how much they believe the preclinical data; whether Phase 2 looked good enough to make it worthwhile.

In this model the error bars around the survival data are wide enough, and the link between response and survival is poor enough that I think most folks would take a chance. Because the models have been so wrong before, so why should this model be right? That is maybe a little negative way of looking at things but, you know, it is two-plus o=clock in the afternoon.

DR. VENITZ: And that brings us back to question number one. Go ahead.

DR. MAGER: I guess my question too is whether there is really enough power here for a company to decide after Phase 2 data, with a limited number of subjects, whether they would really drop a compound or not because I

think at the moment it would be hard to make that assessment.

DR. GOBBURU: You are from industry. How would you make a decision today?

DR. MAGER: All right, you are extrapolating from Phase 2 to Phase 3 and hoping that the relative response rate that you saw there would be better than what you saw in Phase 2.

DR. WANG: So, basically you just wish for it. See, that is how the current decision is made.

DR. MAGER: No, you have some data to make that choice but, you are right, it is a small sample size and, like the previous question, there are other things that you considerB-what else is in your pipeline; how big the need is; now much the sales are, potential sales.

DR. VENITZ: We are already running late. Can I just get us back to the three questions that we want to provide formal feedback on to the OCP folks?

I think we have already talked a little bit about all this. Are there any additional comments that the committee members might want to make?

I would just add my opinion to what Jeff already

mentioned before, that I think what is missing in the model, from my perspective being a clinical pharmacologist, is exposure response. Right now exposure response is dose, and I think you mentioned that as well, Don.

So, either you take advantage of measured concentrations, areas, Cmax or what-have-you, or PK estimated ones. I think you also want to look at schedule dependence. If you can demonstrate schedule dependence in your model and can verify that in a clinical trial, I think that would be a major improvement in terms of acceptance of this model. Dr. Mager?

DR. MAGER: Just to underscore that, I would encourage the group to not only include exposure response but to do it in as a mechanistic way as possible as to whether the drug is inhibiting growth or enhancing cell kill, those relationships could be put in there. So, that is sort of the structural component.

But you alluded to the sparseness of the data causing difficulties in convergence and model structure. Have you considered more recent robust approaches to establishing those relationships, for example an CPen algorithm or using a Matt Bayesian approach to constrain the

parameter space in your model, using Phase 1/Phase 2 information to inform on what those parameters might be so that you can begin to make the models more mechanistic and robust?

DR. VENITZ: Dr. Lertora?

DR. LERTORA: Yes, I will echo the comments related to exposure-response relationship. What I was going to mention, as a non-oncologist, is, I mean, the number of studies that you described that only had a single dose level in terms of the efficacy trials, and I think that is something that needs to be addressed.

DR. GOBBURU: I really want to make a statement about that. Why is it so hard for the pharmaceutical industry, when they have a new compound in Phase 1 or Phase 2, to develop their exposure response for the tumor model and head onto this tumor survival model? I want to hear why can=t it be done. It is not a big deal in my opinion. We do it all the time and the pharmaceutical industry can do that for every compound.

DR. MAGER: I think in that area we probably pick a first dose too early and there is not as much dose response, but you are usually titrating up to a certain point and that

is your dose going forward without much exposure response.

DR. GOBBURU: So, you do generate that data and you can develop that piece of the model and tag on. I would hate to see that the whole responsibility is on one group for FDA to come up with every model. It is not going to happen and there are other issues. When you are talking about drug models, then you are talking about proprietary information about that drug model versus the disease model which is more generalizable and publicly shareable.

So, I think I would encourage the public and the committee to consider that the add-on model for pharmacological effect is not that foreign to what we do in drug development and can be added relatively easily by different drug sponsors.

DR. VENITZ: Dr. McLeod?

DR. McLEOD: Well, that is part of what is behind my comment about interacting more with the NCI cooperative groups, partly because of the large Phase 3 studies, but partly because this has to be a special approach. Currently, in Phase 1 where the dose escalation is occurring it is in very small groups of patients per dose level and in heterogeneous tumor types. First time in human Phase 1 is

rarely in one tumor type. It is in folks who don=t have other options and are, therefore, willing to go onto these new drugs.

So, tumor response or tumor measurements are usually worthless because there is a very low incidence of tumor response in that context, and also what does a tumor response in a sarcoma mean compared to a tumor response in a breast cancer or gastric cancer?

So, I think it is what Dr. Mager mentioned. The doses are picked so early, before they go into tumor-specific trials and, therefore, you don=t have that data. But those trials could be done but have to be in the context of the cooperative groups because right now I can=t see any reason why a for-profit entity would do those trials because I don=t think it is in their advantage.

DR. MAGER: Just to follow up on the tumor measurements, the recent study showing large inter-individual variability in observer determinations of what the tumor size actually is, less so within an individual but considerable inter-observer variability, are the data robust enough that that type of information can also be included in the model?

DR. WANG: See, you have to understand that the key is to show or to share this tumor against survival relationship. In terms of how you get the, let=s say, week-eight tumor data, you can pretty much observe them. You don=t need any model to predict. In the Phase 2 scenario, like what is published in the paper, they already observed. And in this observed week-eight tumor shrinkage they already included the between subject variability on PK and also the between subject variability on PD, the response on the tumor side.

That is probably the best source and the simplest source you can summarize. If it has a large variability, that could mean that the PK is variable and also, let=s say, the PD is variable but it is combined variability and that will be what you have for that drug. You just summarize the distribution and plug that observed into the tumor versus survival model. That should be sufficient. You don=t have to predict, let=s say, based on preclinical or Phase 1. You observe them from your Phase 2 data.

So, in that model I was mainly using it because, you know, some people are missing certain time points, and you can pretty much just use observed data. Yes.

DR. BARRETT: I want to provide some input into your question, Joga. You were asking more or less why this isn=t a more collaborative effort and why these kinds of exposure response relationships are not generated earlier on.

I think there are two parts to this answer. One is that the nature of the patients that are available to participate in these Phase 1 studies is very different from your eventual target population. That just is a consequence of not being able to provide them an opportunity to continue on in those trials. So, you really don=t have the continuity of the patient populations.

The other part of it that is still an issue is that safety or toxicity is still a surrogate for efficacy with the early phase development of an oncology agent, except for a couple of classes in which you have targeted mechanisms where perhaps we have better biomarker data. I think that will be the interesting thing in the future, to marry up the cytotoxic agents with some of these other targeted therapies in which you don=t have that kind of a signal.

But all the more reason I think to expand these

kinds of models where you are not so much looking so far downstream where you have this obvious correlation between tumor burden and then survival. So, I think they need to kind of come forward and, you know, get these kinds of exposure response relationships early on, and then I think they have a better dosing rationale because you have, I think, really understood the therapeutic window better than just really buying up against the safety side of things.

DR. VENITZ: I should move us on to question number two because I think we have exhausted question number one. How does the committee envision how such a model can be best utilized in drug development? Does anybody want to comment on that?

The only comment that I would make is that one of the potential utilities that you mentioned is dose selection. Obviously, without exposure responseB-not to belabor the point, I am not sure how it can contribute to dose selection. What might be of interest though is comparing different mechanisms of action. Again, maybe not the existing model but in a future version of it I think that would be of significant benefit because then you would do in silico simulations to see whether a particular

mechanism is potentially useful or not.

DR. O=NEILL: I would just like to put in my two cents in there with regard to this thinking being used as increasing the planning sophistication of these trials.

The modeling part has been going on for 30 years in the cancer literature if you look at the statistical literature, the Cox model, logistic regression model, different kinds of models to look at what are the risk factors associated with longer or shorter progression.

But I think the value here is to marry it with the dose issue and essentially get to better planning at the design stage even to size the trial, and not to kid yourself in terms of the effect size that you think you are going to see. A lot of this is let=s pick what I would like to see as opposed to a reality check of what you are likely to see.

And, I think the value to some of these models is to do better planning so you have a realistic expectation of the expected size, the duration, how you ought to choose the mix of the population, how much the staging counts in terms of your ability to be able to see a change at six months versus 12 months. Those are basic planning issues and we look at that when somebody comes in with sort of a sample

size and says I have chosen 400 subjects. I am going to do my study in these five countries. I am going to use this particular mix of patients.

And, I think these models actually put some meat on the bones in terms of saying empirically this is our best shot at what your hazard rate is likely to look like over a two-year horizon. This is likely to be how many folks are going to have to get switched off this treatment and withdraw from treatment for cytotoxic effects. This is likely the response you are going to get from what you know at this point in time in terms of the dose that you have chosen.

So, in my mind, these are sophisticated planning tools in the spirit of the critical path to increase planning the success rate of clinical trials, which is really where Yaning was coming from in the beginning in terms of what tools are available to increase a priori, before you even start the trial, the potential planning for the success rate of the trial.

I think that is where some of this has value. Rather than thinking of it in terms of surrogate markers or anything like that, it is very useful in terms of forcing

people to think through the trial that you are going to design and the simulations as a modern tool for protocol planning.

DR. VENITZ: Any other comments to question number two? Last but not least, any general recommendations? Mr. Goozner?

MR. GOOZNER: You know, I have been thinking a lot because I was actually involved in helping to create the recently enacted law that is going to require registering of clinical trials and posting results, and I am intrigued by your comments that you couldn=t get access to certain parts of the data in certain trials.

I am just curious, in terms of future modeling for early stage drug development, if it doesn=t make sense when the FDA sits down to write the rules on what has to get posted on clinical trial results, then it really begins to look carefully at some of these data sets and say, you know, we really need this kind of data, and this kind of data, and this kind of data. Because I have heard comments that a lot of the data that will eventually get posted will be in very general terms, whereas if it were much more specific it might be much more useful for model development.

DR. GOBBURU: I would like to make two comments. One is that there are two types of data we talked about. One is the concentration data which were not there. We do have a guidance and we try to encourage sponsors to collect that in registration trials in all subjects, as much as we can, and we are seeing an increase in the number of trials with such data collected. You have to also understand that these are older trials. As you see newer trials perhaps this will not be the case.

The second one is about specific data that we talked about and lack of access. To be fair, if we picked up the phone and asked the sponsor they might have shared the data with us, but we didn=t do that. The reason for that is that this work has taken us four years to complete and to come to a stage where we can respectably present to the public. So, it is an evolving process and we do take your comments to heart and we will try to improve that in the future. But I just wanted to be fair to the other side of the table. We didn=t ask. They would have given the data should we have asked.

DR. VENITZ: Kathleen?

DR. GIACOMINI: I guess I feel like in oncology in

particular variation is such a major problem, and if there was anything you could do--since this question is what else are we recommending--to help develop predictive models for who are the responders to look at all the data covariates for that group of people who are responding better. I don=t know enough about modeling to know what you can and can=t do with the data that you have got, but if you could predict something about the responders the trial could be more gauged to that group of people.

DR. GOBBURU: Again, you know, this is a base platform. This is more linkage between tumor size change and survival. This is on a population level. What you are saying is, on an individual level, is there a way I can pinpoint, you know, if Joe responds or Mary doesn=t, and so on. That is the next level of detail which has to be, again, a commitment between the two parties or three parties, NIH, industry and FDA so that we plan the trial in such way so that we can populate models and grow in directions that we think, or you all think, are most useful for the public.

DR. MAGER: Again, in terms of exploratory research I think it would be very interesting to try and make a

bridge between preclinical disease models and clinical models, how very early discovery information could be translated into a clinical model, including things like physiologically based models to predict the exposure, not in plasma but in the tumor site, and how that information can be translated into the clinical level so in terms of exploratory research, and I would think you would be in a great vantage point to try and make that link given the preclinical and clinical data that are available.

DR. VENITZ: Dr. Flockhart?

DR. FLOCKHART: Just a broad comment, again from a non-oncologist but a clinical pharmacologist, but I think I see many analogies here between this approach and the approach of other biomarkers in other diseases. I would say three things.

The first is that there needs to be some more careful attention paid to, for want of a better term, validation sets. So, what kind of trials, carefully thought throughB-trials is even the wrong word--what kind of studies might usefully and most efficiently validate these kinds of things?

Now, there are things available that weren=t

available 10, 20 years ago. I mean, there are biobanks in some cases, like Marshfield linked nicely to clinical outcome data and even to genetic data sets in some very rare sets. But the biobanking craze is now large and it is possible to go into data sets tied to outcome claims data in some cases to try out these models. Ideally, if one can validate in the kind of trials we are talking about and then take it to these large, real outcome data sets for existing things, those would be tremendously valuable things down the road.

But there are other ways to validate also. There is NCI, as Howard is pointing out, and I think the new availability ofB-maybe I shouldn=t call it the new availability but the increased availability of clinical trial data to the public is a third place, and that is not going to be in the same place, that data, as these other two.

So, I think in thinking about guidances, Dr. Lesko, and other means of guiding the community in general towards doing this better it would be helpful to think about how to validate in creative ways. You guys have been really good about forcing everybody else to be creative in multiple

other settings, so this is another opportunity for you.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: I am still digesting Dr. O=Neill=s comment. I see your point about the benefit of this in Phase 3 planning. Just kind of a follow-up question on that, the comment at the very beginning of Yaning=s talk was about the poor attrition rate in oncology and looking at oncology as a therapeutic area relative to others where, you know, maybe we haven=t had this kind of success.

So, my question to you all is to what extent you thought that this attrition rate or this poor performance in Phase 3 was due to this issue of planning, or underpowered studies, or maybe a lack of realism in terms of the design element. Because if this can improve in that area then, you know, you could, as you are suggesting, have a real bang for your buck with this kind of model from the standpoint of the Phase 3 planning.

I think the difficulty for most of us around the room is, you know, this is a clinical pharmacology group and we are focused on the earlier part of this, the dose rationale, etc., so we want to see that linkage to the dose exposure, exposure response piece. But I can see your point

in terms of the value in terms of planning.

So, do you feel, based on the failures and maybe looking at some of that data retrospectively that this will make those kinds of gains?

DR. O=NEILL: Oncology is not the only area that is charged with sort of this issue. It is sort of rampant in a lot of areas. Oncology has been relatively unusual in terms of even what is called the Phase 2 study. Sometimes they are an uncontrolled study. That is not the case in any other disease. You always have a comparative controlled clinical trial in Phase 2. It is just with a different endpoint, a smaller trial, maybe a little different population. So, their dose ascertainment is compared to what kind of question. Then they use that, maybe not well but they use that to go on to the next phase.

But you are sort of looking at questions like this in the cardiovascular area. You are looking at this in the psychotropic area. You are looking at questions of better planning in many different disease areas where we have 20 years of experience on the progression of the disease.

Let=s take a Cox-2 that has, you know, average one-, two-, three-year studies and you know what the

cardiovascular outcomes are. You know what the withdrawal patterns are. You know how long people stay in the trials. If modern planning were to take all that you would have a model for everything. You would know what the risk factors are. You would know who is likely to maybe respond early or lateB-who knows?

But it is sort of a general question saying that oncology perhaps could benefit from this thinking which is based on how do I quantify the empirical stuff that I know right now and maybe use it in a more substantive way to size the trial; to know whether these endpoints-BI mean, we are looking at this in many areas.

Yaning=s exploration of this particular endpoint followed one of my colleagues, Mark Rothmann, who looked at the same database but looked at response rate potentially as a surrogate, and that essentially was not predictive at all. So, the bottom line from that was that response rates are not terribly predictive of survival, which was surprising. Yaning=s actually looking at the tumor change gave a little different picture.

But we have been doing this in terms of why do some of these trials fail. Is it the endpoint that we have

chosen? You know, there have been other issues. Is it something about the design that I can change? All my plug was is for better planning based upon what we think we might know is empirical relationships, and using that maybe to choose the dose better.

Just as an aside, there has been a big interest in adaptive designs out there for the last two years. Why? Because the feeling is I can=t be smart enough at the beginning of Phase 2 and I am going to learn something in my Phase 3 study. Can I get a shot at adapting to what I didn=t know well, and can I change it in a legitimate way in my Phase 3?

Oncology is facing a version of that, and it maybe I will start with three doses. I am not really sure what the best scheduling is but I am going to start with three and I am going to drop two or I will drop one. And, maybe this modeling and these kind of strategies can help in that kind of a design issue. That is really all I was proposing, that this is I think modern protocol planning thinking, which is you can=t size a clinical trial without knowing maybe ten unknowns that you can=t control. You don=t know the hand you are going to be dealt in terms of the trial

that is actually playing out.

So, you can simulate what you may not know based upon some models. That is all I am saying. This message is in some sense being proposed in other disease areas, other than just oncology.

DR. VENITZ: On that sobering but encouraging note, let=s take a recess. Since we are running late, I suggest that we reconvene at 3:15.

[Brief recess]

DR. VENITZ: Let=s start the second part of our second topic, the pediatric topic. Our first speaker is Dr. Lisa Mathis. She is Associate Director for the Pediatric and Maternal Health at OND, and she is going to talk about implications on pediatric studies. Dr. Mathis, please?

FDAAA: Implications on Pediatric Studies

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DR. MATHIS: Today I am going to go over the pediatric legislation. I am going to give a little bit of history and also tell you why we do pediatric studies, and the tools we have to do them. I am going to update you on the new changes to the two laws that we have to obtain pediatric studies. I am also going to talk to you about

what we have been able to accomplish by doing the pediatric studies, some of the results and also the lessons that we have learned.

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I am going to give you an overview of some general principles about why we do studies at all in pediatrics. One of the big reasons is that everybody really believes that pediatric patients should be given medications that have been properly evaluated for use in that specific population. We shouldn=t just be guessing about whether a product works or what the dose is by what has been studied in adults.

Also, the product development program should include pediatric studies when pediatric use is anticipated. One of the other things that we believe is that pediatric drug development should not hold up drug development in other areas. So, we don=t ever think that adult approvals should be held back awaiting pediatric approvals.

We also believe that developing products for the pediatric population is a shared responsibility, that industry has a role, regulators have a role and academia and society as a whole play a role in this as well.

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There are several pediatric benchmarks that I would like to cover today. One is the 1979 labeling requirement. So, this is where the FDA came out and said there needs to be a pediatric use section in labeling. However, if any of you have gone to the label to look for this, you have seen oftentimes the words Asafety and effectiveness in the pediatric population have not been established.@ That has changed dramatically with a lot of our new legislation.

In 1994 we had a pediatric labeling rule that asked drug companies to submit available information that they had on the pediatric population to be included into labeling, and also introduced the idea of extrapolation. Now, that has become a very big issue for us in pediatrics. The agency is willing to extrapolate efficacy, and efficacy only, if a product is expected to work on a disease and the course of the disease is the same in the pediatric population as it is in adults. That extrapolation should always be supported by additional studies to support dosing and also safety in the pediatric population.

In 1997 the Food and Drug Administration

Modernization Act passed, and that was where pediatric exclusivity was first introduced. In 1998 we had the Pediatric Rule which required industry to perform pediatric studies if the drug was anticipated to be used in the pediatric population.

In 2002 the Best Pharmaceuticals for Children Act passed, and that reauthorized the incentive of six-month exclusivity. In the same year the federal courts enjoined us from enforcing the pediatric rule. But in 2003 the Pediatric Research Equity Act passed which codified the elements of the Pediatric Rule.

In 2007 the Food and Drug Administration Amendments Act of 2007 passed which reauthorized both the Pediatric Research Equity Act and the Best Pharmaceutical for Children Act.

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I am going to go over those two laws now. So, for the Best Pharmaceuticals for Children Act, as I said, was reauthorized in September of 2007. This allows for the Food and Drug Administration to issue a Written Request for studies. If the sponsor does those studies per the Written Request and meets the elements of the Written Request, they

can obtain six months of marketing exclusivity. This six months of marketing exclusivity basically blocks a generic and covers the entire active moiety. So, it is an entire product line that gets protected, not just the particular drug that was studied.

This can be a substantial incentive for companies, and has actually resulted in many studies being performed. I would also say that we benefitted from this incentive in many other ways, that is, we have obtained a lot of data and we have also helped develop an infrastructure to perform pediatric studies within the United States and Europe.

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The Pediatric Research Equity Act was reauthorized in 2007 as well. This is not an incentive program; this is the required program. So, if an application comes into the FDA and its likely that that product will be used in the pediatric population the FDA does require studies in the pediatric population, unless those study requirements are waived. The reason why we would waive a study is if the studies would be impossible or highly impracticable to perform, in other words, too few patients to actually get a study together, or for any other reason, if perhaps they

couldn=t make a formulation that was age appropriate so we would waive part of the population.

This law also established an internal review committee so now we have an internal review committee in the FDA that evaluates all plans, assessments, waivers, deferrals and Written Requests for pediatric study. That is new. We never had internal oversight of the entire pediatric program before.

This law also increased transparency. We are now going to be publicly posting all medical, statistical and clinical pharmacology reviews of pediatric studies, both the required studies and the studies that are done under the Written Requests.

We also have reporting at one year of all safety events for products that are either studied under PREA or BPCA. That reporting of adverse events at one year takes place at a pediatric advisory committee. So, the Office of Pediatric Therapeutics will receive all the adverse events, will put together reports, and then we present those reports to the pediatric advisory committee, and the advisory committee can make recommendations about labeling changes that should occur based on those reports.

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This is our success story. So, under BPCA and PREA, as of the reauthorization date, we actually had requests from industry to issue 536 Written Requests. Out of those, we issued 355 Written Requests. Now, remember, those Written Requests can include one study or they can include 12 studies. So, if you do the math, we have well over a thousand studies that we have requested in the pediatric population.

We have granted exclusivity to over 150 products, and we have posted medical and clinical pharmacology summaries for 86. Now, under the old Best Pharmaceuticals for Children Act only the summaries were posted. Under the new law we post the entire review and the statistical review is included as well.

One of the most important findings from this chart is going to be under the BPCA labeling changes. At the time of reauthorization we actually had 133, but we are up over 150 now. One of the most interesting things is that in 20 percent of the cases we had new dosing or a dosing change. This is really important because before when we took an adult dose and fractionated it to get the pediatric dose,

what we have learned is that that was wrong.

What we really need to do are clinical pharmacology studies to determine the right dosage in the pediatric population. There are so many differences between adults and children that if you simply fractionate the dose you are going to end up with the wrong dose and, thus, may end up with either greater toxicity or less efficacy.

We also learned that almost 30 percent of the time we find unique or different safety signals in the pediatric population than those that we that were finding in the adult population. That is really not surprising. When you are looking at a growing and developing organism clearly you are going to have a different set of adverse events associated with drugs.

Then, another 20 percent of the time we found that the product didn=t demonstrate efficacy in the clinical trials. Does that mean necessarily that the product didn=t work? Probably not. But 20 percent of the time the trials failed. That is one of the things that I am going to be focusing on now a little bit more, perhaps exploring why those trials may have failed.

I do have here that we also had 64 labeling

changes under the Pediatric Research Equity Act. As you can see, we have gotten a lot more labeling changes out of the incentive program. However, both programs used together have really benefitted the pediatric population.

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So, if we go and look at that 20 percent where efficacy and safety were not established for products, we can discuss what leads to failed studies. I think it is really important to understand too that for all of these products, they were already approved in the adult population so these aren=t new investigational products. These are products that had demonstrated efficacy in the adult population.

So, why might we see failure in these studies? Well, one is a smaller sample size. Clearly, it is more difficult to power pediatric studies to demonstrate efficacy. You have a limited number of patients and you also in general can=t use normal volunteers. What ends up happening a lot of times because of that is that perhaps we do dose-finding in Phase 3 instead of in Phase 2. So, we may be going into Phase 3 trials without having properly identified the dose that is efficacious in the pediatric

population. That is one of the limits that we have with having a smaller population.

In addition, endpoints may be different in the pediatric population when compared to the adult population. It can be that we haven=t been able to identify an endpoint at all. We are going to talk more about blood pressure later, but if you think about the instance where you have neonates, preterm neonates that are born, we don=t have established norms for blood pressure in preterm neonates.

Even though when you go to the neonatal intensive care unit you see people using products to try and stabilize the infant=s blood pressure, we don=t really know exactly what target we should be going for. So, in some cases endpoints haven=t even been established from the scientific standpoint.

In other cases the endpoints may be different than they are in the adult population. If you look at the example of migraines, and this is just an example, we have done studies and the migraine studies have all failed in the pediatric population. When we looked at the endpoints for migraines we used the same model that we used in the adult population so we looked at the time point of cure the same

way that we did in the adult population.

And, just going back and looking at different aspects of pediatric migraines versus adult migraines, pediatric migraines seem to have a shorter time course. So, if you take a pediatric migraine and maybe use the adult time course that is a little bit longer, you are going to see that by the time you measure the effect on migraine you are going to lose any effect that you are going to have in active versus placebo.

So, that may be what the problem was. We don=t really know. We are in the process of looking at those endpoints now to try and figure out how to better improve our studies for the migraine headache.

In addition, metabolism may differ so you might have different systemic exposure to the drug, and sensitivity may also be a function of development. We know that different receptors behave differently throughout the time course of development.

Most importantly I think for this group is that the doses for Phase 3 studies have not been correctly identified. As I mentioned earlier, many of the times what we do is a population PK study in Phase 3 and we haven=t

done Phase 2 trials to try and get the best dose. So, what we may have are dose-response curves from the Phase 3 studies and failed clinical trials.

So, one area that we really have been trying to focus on in our internal review committee as we are going over pediatric plans and Written Requests is trying to make sure that we ask for adequate PK studies prior to going into the Phase 3 trials, if appropriate. Obviously, that is not always the best approach. But we really do look at that and have been emphasizing trying to get better pharmacokinetic and pharmacodynamic data prior to moving into large Phase 3 trials.

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We have had a lot of problems, and there are obviously solutions to these problems. These are some of the things we have thought through, and you will hear more details from Dr. Stockbridge and Dr. Jadhav later. One thing is that we can review results of previously failed studies to try and advance the approach for the next drug in the same or related class.

You have been hearing a lot about disease modeling and drug modeling, and what we are really trying to do is to

do that across diseases for the pediatric population. So, when we look at antihypertensives we try and study them in pretty much the same way, but we need to get those models right.

One way of doing that is to leverage adult data to model appropriate doses to investigate. We really now do have the capability to make an educated guess of where to start with these studies. One example I can give is in the world of anticoagulants. We have had situations before where we have had data on anticoagulants and our pharmacokinetics group has been able to take that data and model it, using some data that we have had from pediatric patients, to make adjustments for that data with the pediatric data and the adult data, and then report back to the sponsor so the sponsor can then verify whether or not the new dosing that we have come up with actually matches that modeling.

In at least one case what we found is that the dosing that we had anticipated using in the pediatric population was too high. So, the new recommendation, based on what we were able to model and verify in clinical studies, is a much lower starting point. So, we have been

able to improve safety by using modeling.

Another way to improve the outcome of the clinical trials is application of statistical methods to ensure interpretability. Dr. Stockbridge will talk more about this, but this really involves interim looks at the data to see if you have adequately powered the study to have a positive outcome or an interpretable outcome because, obviously, you won=t have a positive outcome if the drug doesn=t work.

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So, in conclusion, efforts have been made to obtain data to support appropriate medication use in the pediatric population. Over 800,000 pediatric patients are anticipated to have participated in the incentive program. So, we have actually asked for close to a million patients to be involved in these exclusivity studies. That doesn=t even include the mandatory program. Many lessons that we have learned have advanced the science and the public health for the pediatric population.

At this point I am going to turn it over to Dr. Stockbridge.

DR. VENITZ: Thank you, Dr. Mathis. Before we

proceed, can I ask the new FDA folks that joined us to introduce themselves for the record so we know who is sitting around the table?

DR. STOCKBRIDGE: I am Norman Stockbridge.

DR. JADHAV: Pravin Jadhav, pharmacometrics.

DR. VENITZ: Thank you. Thank you, Dr. Mathis. Dr. Stockbridge? He is the Division Director for Cardiovascular Products, and he is going to talk about pediatric studies in the cardiovascular arena.

Pediatric Studies in Cardiovascular Area: Experience and Opportunities

DR. STOCKBRIDGE: Thanks very much.

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Just so you know who we are, the Division of Cardiovascular and Renal Products is one of 15 new drug review divisions within the Office of New Drugs. Clearly, it is not a majority of our portfolio but certainly the largest single indication that we support for the antihypertensives, and there are probably several hundred antihypertensive drug products from 50 distinct chemical entities.

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Antihypertensive drugs in adults are approved on the basis of effects on a surrogate endpoint. Probably the best established surrogate endpoint is around blood pressure. We don=t ask for outcome data in an antihypertensive program. They are, for the most part, adult sized to provide a pretty good pharmacodynamic characterization of the effects and enough safety data to ensure that they will perform in clinical practice about the way other antihypertensive agents do.

Current products don=t even contain labeling that indicates a clinical outcome claim but, as a result of a fairly recent discussion we had with an advisory committee we will probably be re-engineering the labels for antihypertensive drugs to show why you actually use them.

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It is very difficult to overestimate the impact that an incentive program has created for getting useful studies in children. I am aware of only one trial that was attempted of an antihypertensive agent in children prior to BPCA and PREA. That trial was abandoned because parents would not consent to have their children in study. And, many people considered it either unethical or infeasible to

do such studies in children.

Subsequently we have issued 24 Written Requests for antihypertensive agents and that comprises about two-thirds of all the Written Requests that my review division has put in. Very few of those have been abandoned. Not all of them have been successful but only a few of them have not gone to some kind of completion.

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To get a drug approved as an antihypertensive for use in children we have asked companies to demonstrate that you get a blood pressure effect in the target age group. We do that despite the fact that there have never been any of the outcome data that support use in adults. There is no corresponding data like that in children.

Furthermore, despite the paucity of outcome data we think that hypertension in children is a pretty straightforward extrapolation of the results in adults and, consequently, we have only asked for a single successful antihypertensive effect be demonstrated in a pediatric Written Request. So, pediatric Written Requests ask for one pharmacodynamic study.

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Furthermore, we allow the first member of a pharmacological class to establish an effect in sort of the easiest age group, those that are generally able to take solid dosage forms. The second member of the class has a somewhat harder row to hoe and gets tasked with looking at younger children. Then, after that, if a third member of the same drug class wants to get a Written Request they will have to be fairly creative in coming up with a particular patient population or a novel claim to get a Written Request from us.

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Some aspects of study design that I wanted to highlight, of the studies that we ask for in Written Requests. We offer a variety of acceptable designs in a Written Request. We don=t specify any single possible design for a trial. But, because parents still have concerns, mostly about being initially randomized to placebo, the usual design in these trials is a multi-arm, parallel design where there is no placebo group, several dose levels. That is followed by a somewhat briefer randomized, placebo-controlled withdrawal. For some reason or another parents and investigators think that is a more

acceptable paradigm. We allow people to choose either systolic or diastolic pressure at the inter-dosing interval as the basis for making decisions.

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Like the rest of the pediatric Written Requests, the ones in our area call for the sponsor to develop an age-appropriate formulation. It is more of an issue with the younger children of course. That may involve having a bioequivalent study done in adults.

In general, the pharmacokinetic data that we get, we ask for it to be done in the target age range. Generally, it turns out, it is not done in the same study as pharmacodynamics, although some people will do sampling in the pharmacodynamic study. Better is if they will get you some pharmacokinetic data early enough in the program to help you decide what doses might be useful in the pharmacodynamic study.

The pharmacokinetic studies in this area are sized based on the experience of the pharmacokineticists. We generally specify a particular sample size for those studies.

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In contrast, the sample size for doing the pharmacodynamic study is not set in the Written Request. We don=t tell people how big these trials are supposed to be. Instead, what we do is establish a minimum clinically relevant effect size of interest. Sponsor assumes responsibility for estimating what the variability they expect to see is, and end up having to try to estimate how to power the study based on our estimate of minimum interested effect size and their estimate of what the variability is.

Then, we ask that as part of the study they include a late interim analysis that is intended to look at the observed variability that they are seeing in the trial. Then, they are required to re-size the study as necessary if they were overly optimistic about the variability they were expecting. The result of this is that it leaves all of the responsibility for conducting a sensibly designed, powered and conducted study on the sponsor=s shoulders.

As Lisa mentioned earlier, the goal of doing this is to try and ensure that we get a trial at the end of the day that enables us to label a drug as being either definitively useful or not for the treatment of hypertension

in children.

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Now, there is an option that some sponsors have. We will support somebody who chooses to do a study that is sized based on a much more optimistic estimate of what the effect size is likely to be. If a sponsor is successful under those conditions, they can submit to us a technically incomplete study report and ask us to amend the Written Request to coincide with the trial that they have performed.

This is, in fact, the same clause in a Written Request that allows a sponsor whose study gets stopped for some safety reason to petition us to try and get the Written Request amended to grant them exclusivity, based on having a fully interpretable result. However, no one has yet had to evoke that clause for an antihypertensive drug.

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So, as I say, we have initiated several dozen Written Requests. We have tried as hard as we could to get these data put into some shape that could address some larger community issues that are beyond the scope of single trials. A particularly fruitful such collaboration has been going on between us and some pediatricians at the Duke

Clinical Research Institute.

They have spent some time with us and done fairly limited data extraction from some of these trials, and addressed some interesting issues. One of those is based on the observation that in adults ACE inhibitors, angiotensin converting enzyme inhibitors, are clearly less effective as monotherapy in blacks than they are in Caucasians.

As a result of that, drugs in the ACE inhibitor class and closely related classes all are powered in order to try to optimize the information that is available. That is, we generally request something in the order of 40-60 percent of patients to be black in these trials. But it still turns out that they individually, as studies, don=t really have the power to address this.

The Duke group was able to pool data by race from six studies, and made a major contribution to us in showing that in children age 6-16 you see much the same reduced effectiveness of these products in black children as you saw in black adults.

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Another issue that we have addressed, as Lisa has mentioned and other people are interested in doing, we have

looked for reasons for failure of some of these trials not to have found a dose-response relationship. Again, the Duke group worked with a pool of six study results, all using the same trial design. Those six studies came from the ACE inhibitor, angiotensin receptor blocker, and calcium channel blocker classes and, for the most part, established that a limited dose range was the likely cause for failure in some of these programs.

[Slide]

Finally, another project that was undertaken between the Duke team and FDA was a look at pooling of ten trials to address the question of whether randomization of children to placebo appeared to be ethical by looking at adverse events across these studies. Their analysis shows that if there is a risk, it is well below the power of ten studies to distinguish.

[Slide]

As I say, the experience with Duke was based on fairly limited data extraction. We have now tried to team up with people at SAS to pool the data, all of the data, comprehensive data from 12 drug development programs, 29 total trials, including pharmacokinetic trials, and get

those data homogenized into a single data standard, in this case the CDISC study data tabulation model standard.

We haven=t had a lot of experience with this yet. This is only recently accomplished. But two products that have come out of that are now an integrated data set that can be used for deciding how to size trials and explore further kinds of trial designs.

In addition, an interesting data set that has been produced that is closely related to the fully integrated data set but has been anonymized so it doesn=t have any potential for disclosing personal information, but also has certain aspects of the data mangled in such a way that you won=t be tempted to use the data to try and figure out which drugs were which. The result is a product that we think is going to be fully releasable and is still a very rich data set for use in testing tools that are being developed for cross-study data analyses.

[Slide]

Finally, I want to sort of provide an introduction to Dr. Jadhav=s talk. As I have mentioned, we have identified some reasons, probably related to dosing, that have been at the core of problems in some of these trials

that didn=t work out so well. Those have had to do with problems identifying what the appropriate target exposure should be to mimic levels in adults, and also problems that have to do with the limitations on dosing you can achieve with solid dosing forms.

This has all created the incentive to try and do a very model-based approach to developing advice that we can give a sponsor, and that is really the talk that Dr. Jadhav is going to give now. Thank you.

DR. VENITZ: Thank you, Dr. Stockbridge. Our last speaker for today is Dr. Pravin Jadhav. He is going to talk about using prior knowledge to design a pediatric study.

Leveraging Prior Knowledge to Design a Pediatric Study

DR. JADHAV: Thank you, Dr. Venitz.

[Slide]

Good afternoon, everyone. Dr. Mathis and Dr. Stockbridge have explained the need to leverage prior data. So, for this part of the session what I am going to do is present to you a case study of how we leveraged prior quantitative data to design a pediatric study for drug X, which was to be investigated for immediate blood pressure control in the pediatric population.

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At the time we received this pediatric request we realized that there were a few uncertainties around the dose and exposure rate that was to be studied, and for the duration of the placebo that was going to be administered. As you heard, there were some ethical concerns about putting kids on placebo. We also had some concerns about the choice of sample size and the choice of the primary endpoint.

[Slide]

So, we decided to use prior quantitative knowledge to design a study which had adequate power, and to improve the data quality because our ultimate aim is to write good dosing recommendations for the pediatric population.

[Slide]

I should mention that in this exercise the sponsor and FDA jointly worked to create the simulations and to substantiate the choice of trial design, the dosing recommendations and dosing regimens, and the sample size.

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At the time of this exercise the following information was available to the sponsor and FDA. We had patient level exposure-response data on drug X in adults.

We also had mean exposure-response data on fenoldopam. Fenoldopam was already approved for a similar indication in pediatrics as well as adults. In addition to this data, the agency also had patient level exposure-response data on fenoldopam in adults as well as pediatrics. So, it was important to pool all this data to design an informative study for pediatric patients for drug X.

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These were the endpoints of clinical trial simulations and approach that we used to design the study based on the available data. So, there were going to be four major pieces that were needed to conduct clinical trial simulation, a exposure-response model, a placebo model. We needed some assumptions about dropout or to understand the mechanism of dropout; and we also needed a trial design.

So, for the next few slides I am going to present to you how each of this information was derived from the available data, and that is the major aim of my presentation here, how to leverage the prior knowledge.

[Slide]

We developed an exposure-response model from adults for drug X from the available data. The

pharmacokinetic model describing the time course of drug X plasma concentration was developed to obtain reasonable estimates of mean and between-subject variability. Obviously, because we were scaling it to pediatrics they were adjusted for body weight.

The pharmacodynamic model described the relationship between drug X concentrations and the percent change in systolic and diastolic blood pressure. Using this modeling, we obtained the estimates of EC50 and Emax that we could use for pediatric simulations. Needless to say, we codified this exposure-response model based on reasonable agreement between the observed data and the simulated data.

[Slide]

The second piece that we needed was a placebo model, and we used fenoldopam pediatric data to develop this model. On the X axis is time in minutes, and this was a 30-minute trial for fenoldopam. On the You axis we have percent change in response from baseline, with the red line being the diastolic blood pressure and the blue line the systolic blood pressure.

So, the model that we developed accounted for the

time course of change on placebo as well as the within-subject correlation. In other words, if a patient had high blood pressure at the five-minute time point it is likely to be on the higher end at the ten-minute time interval also.

[Slide]

Further, we needed some assumptions and some understanding of why patients dropout. From the fenoldopam data, as well as the clinical experience that was available, it was seen that most of the dropouts were dependent on subject=s observed response, and that is blood pressure. The target blood pressure for these patients was 10-25 percent decrease in systolic or diastolic blood pressure. But if the subject=s blood pressure drops more than 25 percent then, because of a potential case of hypotension, the subject is considered to be dropped out. This dropout has also given us a lot of information about the drug response. From the placebo data we realized that there could be about 7-10 percent of subjects who could drop out from the study.

[Slide]

Finally, we needed the four pieces, as I said, for the trial design. Now, there are three major aspects of

this study design which I would like to focus on. The first aspect is after the screening and the baseline run-in the patients will be randomized to five dose groups. Notice the choice of the dose groups here. There is a placebo arm, and there is the lowest dose approved and the highest dose. So, we can bracket what was approved in adults.

But given that we have some experience that the pediatric population is less responsive and less sensitive, and I will give you some data on that, we needed to include doses that are above what has been approved in adults, as well to get a good dose response, we needed some doses below the lowest approved dose. The study was a 30-minute infusion with blood pressures collected at every five-minute interval.

The original study that was proposed was a longer duration and, because of ethical concerns, we realized that it might not be feasible to put the patients on placebo for that long a duration.

So, analyzing all this data from fenoldopam and the previous experience with antihypertensives, as well as the adult data, we could justify that we can show the effectiveness of drug X within 30 minutes. The piece that

is not shown on the trial, which is an extension part of it that was also derived through objective discussions within team members, that part of the study will be useful for labeling recommendations. So, the part of the study I am showing here will be used for the primary analysis to show if the drug X is effective compared to other drugs. The extension part will be used to derive good labeling recommendations.

[Slide]

So, once we had the study, the next question was what statistical tests can be used to demonstrate if drug X is effective or not. We used several methods based on input from Dr. Jialu Zhang who was the statistician on the team. But for this presentation I am going to summarize these two methods or all the methods under two major categories.

One, a single point analysis method that will use the data collected at the end of the treatment, that is, the 30-minute endpoint. For patients who drop out of the trial, the last observation carried forward will be used for imputation.

The second method that was employed was the longitudinal analysis method. We used all the data

collected from the five-minute time point until the 30-minute time point, so we can use all the data. Because of that, we don=t really need explicit imputations. There are imputations that are explicit in the model per se.

[Slide]

So, once we have these four pieces, an exposure-response model, the trial design, the placebo model and the dropout model, this served as an input for clinical trial simulations where the simulations will be done under different scenarios.

So, under one scenario we will assume that adults are equal to pediatrics for all practical purposes, and I will call that a base design. What we also know from the fenoldopam experience as well as other antihypertensives is that pediatrics are less responsive and less sensitive compared to adults. What I show here, but I am not sure if all audience members can see it, is the change from baseline in diastolic blood pressure plotted against the fenoldopam dose or the infusion rate.

The red line represents the pediatric population and the blue line represents the adult population. As you can notice, the Emax in pediatrics was lower. So, we can

say that they are less responsive. Also, the EC50 was higher, that is to say that they are less sensitive to these drugs.

This experience and the data allowed us to come up with scenarios that I could call scenarios of 50 percent Emax and twice the change in EC50 as the worst-case scenario to develop a contour of possibilities that are likely when the drug will be tested in the pediatric population, and we also had an intermediate scenario where we assumed if there was a 25 percent drop in Emax and 1.5-fold EC50.

So, using all the data and the clinical trial simulation is allowing us to bracket what might happen in the pediatric population to generate some expectation on pediatric data.

[Slide]

This is the real power of clinical trial simulation. It allows us under different scenarios to see what the response is on an individual level as well as the population level. On the left-hand side is the percent change from baseline in systolic blood pressure over time in different dose groups, and we can visualize what is happening with an individual patient here. I am not really

showing the dropout but, for example, a patient here might be a dropout but this is the pooled data that was simulated.

It also allows us look at the response rate. So, the upper panel here is the percent of subjects achieving a certain response, that is, diastolic blood pressure greater than minus ten percent. We can clearly see a dose response here, placebo being the lowest and the highest two times the adult dose given as the highest response here.

It also allows us to track the dropout rate, what exactly are we simulating, and is the dropout and response rate in agreement with what we are expecting based on the available data?

[Slide]

The simulations also allow us to compare different statistical methods, and I really thank Dr. Zhang here for valuable discussions that I had with her. As I explained earlier, I had two major classes of statistical tests, a single point method and a longitudinal method.

For the case were we assumed the worst-case scenario we realized that longitudinal analysis was more powerful than single point analysis. And, if the expected pediatric data really belonged to the worst-case scenario

the use of the single point method had less power, in other words, less probability of success than the longitudinal analysis method.

Once we settled on using longitudinal analysis as our primary statistical test, it also allowed us to compare what is the expectation for power for all of the designs that were simulated. So, the blue curve here, the power curve is looking at the probability of rejecting the null hypothesis, saying that the power of concluding that the drug is effective versus the number of subjects. The blue curve here is for the base design where pediatrics are equal to adults. The green curve is for the intermediate case, and the red curve here is potentially the worst-case scenario.

What this exercise has allowed us to do is to understand that somewhere between 15 subjects, if adults are equal to pediatrics, to 45 subjects is a likely sample size to get good data and write good dosing recommendations. As Norman mentioned, there is no set sample size in the pediatric request. So, we recommended the starting sample size to be about 40 and build other clauses into the protocol so we can range any of the sample sizes.

[Slide]

So in conclusion, clinical trial simulation has allowed us to effectively use prior knowledge to develop a pediatric Written Request. It has also allowed us to make informed decisions about the dose range, the number of subjects, the sampling scheme that will be employed in the clinical trial, and the statistical tests by comparing the power of different tests.

It has also allowed us to design a study with adequate power and potentially get good quality data to write labeling recommendations when we have the trial.

[Slide]

This is probably the most important part of the presentation. It is the objective discussion that three major disciplines, clinical, statistics and clinical pharmacology, have had during this exercise, which were valuable to understand the basis of the decisions made for each of the aspects of the study. Actually, I have one more, the sponsor. We have had valuable discussions with them and I cannot reveal their identity here, but I would really like to thank them for getting this exercise and collaborating with us. So, thank you very much and I will

answer any questions.

Committee Discussion

DR. VENITZ: Thank you, Dr. Jadhav. Before we get started on our questions and on our assignments, any comments or questions to any of the three presenters? Dr. Morris?

DR. MORRIS: I just had a question about the 30-minute infusions that you were giving in your study design. What was that time frame based on?

DR. JADHAV: The time frame was based on the fenoldopam study. The fenoldopam was a 30-minute infusion and it successfully showed the drug effect. So, it was based on the experience.

DR. MORRIS: But wouldn=t this be dependent then on the kinetics of the drug based on the half-life? Because, you know, you are moving towards steady state so it depends on the half-life of the drug so concentrations will be changing over time.

DR. GOBBURU: I will let him answer about the PK half-life, but there is clinical relevance also to the choice here. These patients are being prepped for a procedure and this was thought to be a reasonable time point

to determine the effectiveness of the drug. So, that is one of the main reasons for the 30 minutes. It allows adequate time for a physician to control the blood pressure before the kid goes onto a procedure. I will let Dr. Jadhav comment on the PK.

DR. JADHAV: The drug doesn=t really reach steady state in 30 minutes. If my memory serves, it was taking about two hours or so. But the focus of this part of the study was to demonstrate effectiveness so we did not do that at steady state. But the little part of the study that I have not shown did have constant infusion so that patients can be stabilized either to a constant blood pressure or constant dose. So, those were built in in the other part of the study, but not the part where the major thing was to show that the drug is effective compared to placebo.

DR. MORRIS: I had a second question about your single point determination versus the longitudinal determination, and you said the longitudinal was superior. Is it just because there are multiple samples taken for blood pressure determination?

DR. JADHAV: Partly, yes. The other reason is dropouts. The single point analysis, which uses the last

observation carried forward is an imputation mechanism for dropouts, has the inherent assumption that dropouts are not related to the treatment so everything is random there, the dropouts are random. But the longitudinal analysis is irrespective of that. It allows you to model the within-subject correlation and respect for dropouts.

I did not show it here, but we did the single point analysis if patients did not drop out, and it was very close to the longitudinal. So, it is partly dropouts as well as use of multiple time points.

DR. MORRIS: Thank you.

DR VENITZ: When you did your dose scaling down you used weight. Right? So, your dose is really milligram/kilogram. What evidence did you have to support that that was an appropriate way to scale down doses? In other words kinetically? Obviously, the main focus of your simulation was to figure out if there was any difference in sensitivity and how could you account for that. But what about any PK differences unrelated to weight?

DR. JADHAV: Let me see if I can answer this. What we also did was to see if there were differences in clearance so in the PK part of the model if we had missed

the estimate of clearance by twice or by 50 percent, and the overall conclusion was that really PK was not the biggest contributor for this particular study, and I would say this particularly because of the infusion, it was more the Emax part of the equation or even the EC50 that was driving the response rate. So, we dropped the PK part of the model because too many changes to simulations would be difficult to interpret.

DR. VENITZ: Was that because you had the major source of variability in your dynamics or kinetics?

DR. JADHAV: That is correct. Dr. Capparelli?

DR. CAPPARELLI: Along those lines as well, let me back up one step and ask a question. What was the age range that was evaluated or at least simulated? From what we heard, as we get to second agents we are going further on down and as you go further on down that weight relationship to clearance becomes more tenuous.

And, my expectation would also be that there might be some sensitivity issues. There are already some sensitivity issues in pediatrics, not all children are the same. So, there are going to be some developmental changes. So, it would be interesting to hear a few more details on

that.

DR. JADHAV: Age was not explicitly assumed in the model but we were targeting ages between two and 16 years old. That is what we were developing the pediatric request for.

DR. CAPPARELLI: Would you expect similar response and clearance in the two- and 16-year olds based on weight?

DR. JADHAV: I mean, the basics of what we assume in our model do allow us to scale from adults because, although it is adult data, there were quite a few patients that were 18 and above. So, it does give us an idea of extrapolation.

DR. GOBBURU: I want to add to that. I would like to encourage the committee to consider this as not an exercise to find the right answers, but this is to map the contours and build enough safetyB-that is not the right word, but enough flexibility in the design so you can generate the data to answer the questions with more confidence. So, if we have doses half of what was the lowest dose in adults plus the highest, I mean, is there something else that you think will add to the confidence in the trial design?

DR. BARRETT: I am glad you asked that because I think that is an important statement. When you have these kind of fixed cut points in terms of the dose range considered, it assumes that the category of pediatrics is all the same when, in fact, with many drugs and drug classes there is an a priori, an up-front kind of dose adjustment made, particularly in neonates.

Now, that wasn=t part of the scope here so we appreciate that, but I think just in general terms, considering further dose subclassification in the realm of pediatrics is part of the issue, then being able to have simulations that consider variation in the response that may change within these age categories. So, incorporating simulations that have differences in variation across the strata, that is part of the issue.

DR. GOBBURU: So, where applicable we did. You know, that is not this case but there are other cases that are published. That is exactly what we have done. We tried to account for both maturation rates of the metabolism or renal function and the body size differences. So, it is good that we are thinking alike.

DR. VENITZ: Dr. Kearns?

DR. KEARNS: First let me applaud you all for doing this because for many years I have sat, reading protocol after protocol for all of these pediatric studies, as Dr. Mathis said, wondering where in the world did they get the dose. So, it is a good thing.

The perpetual struggle with whether weight is right or not is just simply that we have to use something as a surrogate for development and all the things that happen. Whether it is a metabolic difference or a body composition change difference, we need something we can hang our hat on. Certainly, the relationship between weight and clearance for some drugs is different from others. If you look at the relationship between weight and height and age, it is not linear.

So, there are all kinds of things nested in there. You know, if we are going to find something, get rid of a large molecule like a piece of a protein, we might find that resting energy expenditure is the best correlate for it. So, it is always the bugaboo in pediatrics.

But I really have two questions, the first one for Dr. Mathis and then the next one for you. In legislation we continue to struggle with this idea of substantially similar

in terms of efficacy. For me, it is always is it partly sunny or partly cloudy in trying to advise a sponsor because while you can measure blood pressure easily, if you are studying a promotility agent that happens to be on the market, most parents will not let you do manometry of a two-year old.

So, how do we, with the new regulations, really look at this? And, are we at a point with the simulation modeling that we can think about target exposures based upon adult data? Or, how comfortable are we with that, especially for things in kids that you can=t measure?

The last thing would be at what point do we allow a reasonable surrogate endpoint to be used? Because if you are really looking for the association of effect with exposure, and you are willing to buy the argument that effect and efficacy look enough and sound enough alike to be enough alike, can we use noninvasive tests of physiology, let=s say gastric emptying for instance, as a reasonable surrogate to study a drug like a promotility agent?

DR. MATHIS: I am going to start out with your first question because, obviously, it is the easiest to answer. So, initially when we started asking for pediatric

studies we were really exploring new territory, and we asked mainly for pharmacokinetic studies and some safety studies and they weren=t very sophisticated, to be honest with you.

Then we got into the realm of asking for everything. We got a lot more sophisticated about knowing what the pitfalls were of doing limited studies and we started really asking for much more expansive studies so that we would have oftentimes very complicated development programs.

Where we have found ourselves wasB-and I will think about the arena of pain, we found ourselves in a situation where oftentimes it was very hard to have an endpoint, especially for preverbal children. There are all sorts of scales where you can look at outcome data. So, we found ourselves in a situation where, because we were asking for such extensive and precise information, we were making it impossible to be able to obtain that information.

So, we have stepped back and we are trying to look at sufficiently similar enough to try and see if in some cases we may have to just do exposure, to see if we can get the same exposure in pediatric patients as we get in adults

for those conditions where we can=t necessarily define an endpoint. Again, there are a lot of different things like pain where it is very difficult in a preterm neonate to determine whether or not they are responding to the pain medication. In those situations is it more appropriate to try and get exposure data?

DR. GOBBURU: I would like to add to the second question. See, if you think about the bigger realm of disease models, that is precisely where we might be at a later stage. There are indications that Dr. Stockbridge and our Office have discussed where you cannot even measure these endpoints in pediatrics, like pulmonary arterial hypertension. You can=t do the six-minute walk with the neonates and infants.

But the most important thing for us to understand, for example in that case, is how are the hemodynamic measures in adults related to the outcome. Then, you try to get that type of data in kids. So, it is an evolutionary process and we have to start with the adult programs to understand these relationships and perhaps then apply them to the pediatrics.

DR. KEARNS: Well, something that is very practical

and that was mentioned earlier, the difficulty of doing some of these studies is because parents don=t like to consent. The hardest study to do is a drug that is on the market, used in your hospital off-label, when you are trying to study it under a Written Request.

Historically, when peopleB-people is kind of like who is Athey@B-people would recommend these huge ranges of doses if somebody would say, well, we need to give a no-effect dose. It is very difficult, as a parent and a clinical trial person and a scientist, to justify putting a child through the rigors of a trial to tell the mother or the father or the grandmother that there is a good chance that the child will have no effect from the medicine. So, that is why these efforts and the progress you are making is so important.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: To answer the question, you know, I think the approach is definitely in the direct direction and I definitely support the leveraging of the adult data, particularly where you have good portability of that kind of information content.

But I would also encourage you to continue down

this approach where you don=t think that you can parlay some of the adult experience. The example I am going to give is Dr. Stockbridge had mentioned the issue of age-appropriate formulations and the necessity of bioequivalence trials potentially in adults.

One of the things that can happen is differences perhaps in the bioavailability in children versus adults with some of these formulations. Then, you know, never having an absolute bioavailability study in children, you are left to kind of wonder where the exposure went and, you know, further make some adjustments.

The other issue potentially comes into play when you have differential food effects in children relative to adults with an oral formulation. You know, obviously with a drug product that has a bitter taste and the child won=t take it, the bioavailability is zero. So, that is not good either. So, we frequently have to live with that.

But I think this would be another issue if you could actually incorporate this into some of the simulation strategies and also potentially in the Written Requests where you suspect that these issues may be problematic from the standpoint of the sponsor doing that trial and also

giving ultimate guidance.

The other thing that comes to mind when we have the transporters involved is the issue of juice and children that is perhaps poorly studied. You know, a juice restriction in the label is really not practical. I mean, I couldn=t get my kids to do it. In any event, this is a real issue, particularly when transporters are involved.

So, some of these could, in effect, be studied very nicely in the simulation models where you have pharmacokinetic attributes that exhibit that kind of phenomenon.

DR. VENITZ: I would like to add something that we talked about a couple of years ago. There was some effort undertaken within OCP to actually look at physiological changes with age as they might impact on PK. Is that still in progress? I don=t know who I am talking to.

If it is, I would suggest that you use some of the information that presumably has been cleaned from that analysis. It goes to the heart of what we just talked about. What is it that changes the kinetics between young adults all the way to neonates?

I mean, you obviously did some simulations that

you didn=t present to us, kind of ball-parking, but you may have some additional information about basic kinetics, physical-chemical properties that lead you to believe whether it is a water soluble drug, so probably goes in proportion to body spaces. Well, then we have some elementary relationships that help us, as opposed to some lipophilic agent that goes everywhere and is very difficult to predict.

And, you can incorporate that in your model, the degree of certainty that you have, just as an addition piece of scaling. The emphasis I think right now was definitely on the sensitivity, on the PK/PK piece.

DR. GOBBURU: To answer your question, the way that we are envisioning this initiative to occur is to have a well orchestrated and not carpet-bombing approach, but focused, maybe cardiovascular, CNS, you know, very focused indications. If we put our efforts that you have seen here in those areas a part of the initiative would be two things.

One, as Dr. Stockbridge has shown, to make the clinical trial data from the previous trials more available and acquirable in a structured way. As you have seen, most of the data for the antihypertensives are in a structured,

credible manner.

The second part, which could be a proposal, is once we have attained the first part we will have a very good idea about what type of data we need, the format, and so on that can be part of the Written Request. So, we can ask sponsors to keep submitting in that format that we can readily apply to this database.

A related point, we will be able to then answer with more objectivity about what are the effects of age, and what-not, in terms of PK.

DR VENITZ: Dr. Capparelli?

DR. CAPPARELLI: I also want to echo what was stated before about the need to get these dose response data and then going beyond sort of adult doses. I think this was a very good example of when that can be done. There was a high dropout projection, but you are in controlled environments of only half an hour. That is not a large issue.

What was mentioned before, and something to keep in mind, is that they are an at-risk population and so a lot of the designs may need an adaptive component to get to some of those higher doses. To start off at high exposure levels

is going to be unacceptable for a lot of IRBs. So, the tool of simulation actually helps with that approach so I, again, applaud that.

The one other component, just to get back to the size issue, was that the presentation of the exposure-response relationship was based on dose, adult versus pediatric. It would be really nice to have that based on concentration rather than dose. At least, that was on the graph there to get at the fact this is truly a sensitivity issue or truly a PK issue. That would help us understand that a lot better so if we do find age dependency or we expect some drug interaction issues we really know how to address those.

DR. JADHAV: The graph I showed for fenoldopam was based on dose, the dose-response relationship. But for drug X we actually had the concentration-response relationship. I didn=t do the fenoldopam review but I pulled the data from there but I believe the concentration response was done. The graph was presented to make an argument on in between the sensitivity. But I agree that concentration response is more informative to us.

DR. VENITZ: Dr. Topp?

DR. TOPP: I just want to make a quick echo of some of the things that I heard and respond to the question that is on the screen. So, is this approach likely to be more informative with respect to getting better dosing? Yes, absolutely. What are our choices? Do we jump to the pediatric population and ignore the data that we took in adults, and assume that somehow preclinical data are more representative of what we are going to wee in children than data that were collected in adults from the same species? I don=t think that that makes sense. So, yes, I think this is a very effective approach and you should be applauded for taking it and I support this completely.

A question that I would ask is, okay, if we accept that this is generally a good idea, what is the potential downside? So, is there likely to be a case, can we imagine a case or cases, drugs or drug classes, where this is going to lead us down the garden path to dosing in the pediatric population that is really very inappropriate? And, can we begin to understand when this might be less than effective an approach, or less than completely effective?

DR. GOBBURU: You can call me biased but I do have an opinion. I don=t think there will be any case like that.

The only downside I can see, which is a big one and is not ignorable, is resource. Who is going to do all this work? There are 150 Written Requests that Dr. Mathis showed. We have to come up with an efficient mechanism to endure this capacity.

But other than that, again, my philosophy about the approach is to bring different disciplines and different organizations together to think about the common problem and design a study which will allow us to accept that we are not smart enough and you build that buffer into the trial design. So, you learn something useful, if not for that study, for sure for future use.

DR. VENITZ: Dr. Relling?

DR. RELLING: I think it was Dr. Mathis who mentioned that there were some examples whereby normalizing adult doses on a per kilogram basis and applying those to children where there had been unacceptable toxicity. What are examples of those, and are there physicochemical properties or pharmacokinetic properties of the drugs that make them more susceptible to that, which would call into question focusing on therapeutic areas rather than chemical drug classes?

In the cancer world I am not aware of a single example of that, and we would also never think about using body weight instead of body surface area for trying to reach such conclusions. So, I am just curious when has that ever happened, and can you learn from that in trying to avoid downsides?

DR. MATHIS: We certainly have seen pediatric-specific adverse events that we didn=t see in the adult world. One of the particularly interesting things is that we see neurologic adverse events more frequently in pediatric patients.

I think for some of the products that are used for urinary retention we actually saw aggressive behaviors at those doses that would have been equivalent to the adult dose. It should be noted, however, if I am remembering correctly and I may be wrong, that the dose was not efficacious either. So, in that case you didn=t get an indication but you did see adverse events.

I think that that brings up a good point. This is one area where I think this approach may put you in a position where you are modeling. You figure out what the dose should be based on the adult data that you have, but

you have a unique pediatric safety event. You know, if you have to go to two times the adult dose you may see an adverse event in the pediatric population that you didn=t see in the adult population.

So, I can see that as one area where you may have a downside. However, these patients are in monitored clinical trials and it would be the most ideal place to discover that versus discovering it from off-label usage, which we know occurs every day.

DR. RELLING: And why all the emphasis on body weight instead of body surface area?

DR. MATHIS: I will speak from a pediatrician standpoint. If I had to calculate the body surface area of every one of my patients I see in clinic I would go through many batteries on my calculator. So, I think that doing it by milligram/kilogram is probably in many cases a more realistic approach for the practicing pediatrician. Although I would say, with oncology obviously you always do it by body surface area and I think that is probably the more precise method for dosing. But from a practical standpoint milligrams/kilogram gets close enough.

DR. RELLING: That just seems completely

unacceptable. Let=s close down the FDA. I mean, what is the point in doing all this sophisticated modeling if we can=t get clinicians to use height in addition to weight to dose children with drugs?

DR. GOBBURU: Let me help you. The point is not about which particular use. I completely agree with Dr. Mathis. It is not just about whether to use body surface area or body weight. You just heard Dr. Kearns saying that there are other deeper issues of what drives the differences between the way pediatrics handle drugs versus adults.

The approach we, as an agency, always take is to make sure that we look at the totality of the data then, depending upon the benefit/risk, we come up with the right approach to dosing. I can tell you about two drugs, just off the top of my head, where we had to make, I would say, dosing with more resolution to capture where the variability did matter. One is sotalol. It is very hard to connect these outcome trials in pediatrics.

So, we measured the QT following its effects on QT and heart rate for this drug. When it came to the neonate population, less than two years, a month to two years, the initial proposal had no dosing. They said use caution. But

we understood the contributions of body weight and age for sotalol, which is a clean drug, exclusively excreted renally. Then if you see the label that is from modeling and simulation work, you will see there is an age factor that needs to be taken into account for the dosing. You have the nomagram in the label.

The second is bisulfan, which is an oncology drug. It is a bone marrow ablation agent. Dr. Bhutu is here, in the audience and asked about understanding the source of variability for the PK, and we said, yes, BSA is, indeed, a better predictor of the variability in PK but it Aain=t@ going to cut it by itself.

So, I would say that you explain variability in terms of dosing in a broader term, rather than, you know, trying to haggle whether it is body surface area or body weight. It will be more than that.

DR. VENITZ: On that no more haggling note, this is the first question that we are supposed to vote on. So, are there anymore discussion items related to question number one? If not, I would like to call for the vote. Dr. Kearns?

DR. KEARNS: Just one thing, I am not going to talk

about body weight. They both work until you get old and fat and you start growing this way.

The other thing that I would not challenge the agency, that is a strong word, but with regard to this question and what we are talking about, is this old notion that in a pediatric trial-Byou mentioned that they are hard to do; what would we do if we had 150 Written Requests-Bwhen we are using formulations that are not liquids and we are stuck with a fixed oral solid, or something like that, is to not go back to that old, oh, we need three dose levels or two dose levels. Because the fact is you get a range of exposures in that trial.

So, we can make the studies easier to do if we are willing to use science and look at those exposures as a function of what went down and stayed down in the gullet of the child as opposed to complicating the trial by saying, well, we need a 1 X dose at 0.5, X dose or 2 X dose.

DR. VENITZ: Is everybody ready for the vote? The question is do you think that such an approach will render pediatric trials more informative with respect to better dosing and study designs given the difficulties in conducting pediatric clinical trials?

I would ask everybody that is in favor, meaning answer yes, to raise your hand and leave it up so we can write who is in favor of question number one.

[Show of hands]

I am sorry, we have a new procedure. You have to say your own name, I can=t do it for you, Dr. Kearns.

DR. KEARNS: Greg Kearns votes yes.

DR. VENITZ: Keep your hands up until we call your name.

DR. RELLING: Mary Relling votes yes.

MR. GOOZNER: Merrill Goozner votes yes, but I still have a lot of questions actually.

DR. MAGER: Don Mager, yes.

DR. LERTORA: Juan Lertora, yes.

DR. GIACOMINI: Kathy Giacomini, yes.

DR. FLOCKHART: Dave Flockhart, yes.

DR. CALDWELL: Michael Caldwell, yes.

DR. VENITZ: Jürgen Venitz, yes.

DR. MORRIS: Marilyn Morris, yes.

DR. BARRETT: Jeff Barrett, yes.

DR. CAPPARELLI: Edmund Capparelli, yes.

DR. TOPP: Liz Topp, yes.

DR. PHAN: We have 13 yes, none no and no abstain.

DR. VENITZ: Anybody object to that? If not, let=s move to our second question. The FDA folks are looking for advice from us to help them prioritize by use of this model-based approach.

I would just say that as a general rule use it where you have good markers. Obviously cardiovascular would be good because you have lots of data. I am not sure whether you would want to start with the gastrointestinal products that Dr. Kearns likes to talk about because you don=t have any markers. So, I am not sure how much the modeling is going to help you because that is a separate question.

DR. MAGER: This is something the company has responsibility for too. It is not just your responsibility to develop the models. I think the company should do some of the PK/PD modeling.

DR. VENITZ: Any other advice? Dr. Giacomini?

DR. GIACOMINI: It seems like you have like variations in the pharmacokinetics and your pharmacodynamics and you have the response differences, you know, the headache thing that you talked about. Then, finally you

have sort of social issues. It might be that you might want to pick some representative drugs that are driven by the PK and that you know more about, and then others that are driven, like here where you have the sensitivity issue. I mean, just pick them in each category and do some modeling because you have different issues in pediatrics.

DR. BARRETT: I think you have to look also at combination of the expected utilization and the medical need where you expect the issue of getting the dose wrong to be particularly detrimental. So, kind of an overlap of utilization and medical is a place to prioritize.

DR. VENITZ: Any other comments or recommendations? Moving along, any suggestions on how to improve this approach? Dr. Kearns?

DR. KEARNS: As the agency goes forward with this and the new regulations really give you an opportunity, I would say cast your net broadly because there is a talent pool, and that talent pool resides in the pharmaceutical companies in some cases and academia in other cases. Look long for your advisors to get this stuff done, and talk to people who do the studies, who know what it is like to try to sell something, for good reason.

So, it is not a big issue but, you know, historically out of necessity there weren=t a lot of people in pediatrics in the agency. Now, you all are populating yourselves with a bunch of good people and you are kind of everywhere. Don=t misinterpret that success for a reason to be insular in your thinking about this. I am not being critical but the solutions are out there but you have to sample broadly to get them.

MR. GOOZNER: This is more of a policy observation than it really has to do with clinical trial design, but I have sort of been biting my lip so I will use this moment.

I have gone down the list of drugs that have gotten pediatric exclusivity and, as you look down that list, from my observation, a lot of them don=t have a whole lot to do with children although, obviously, there are some rare indications where that is useful.

So, my observation is that we are spending a lot of health system resources in order to generate data about the limited uses for pediatrics when you are dealing with drugs that sell a billion dollars, two billion, five billion dollars a year and you give them six months additional exclusivity. We are spending a lot of money to get, as I

look through this chart that you gave us, quality of information that at least to date is not all that high.

I was also a little bit confused about this idea that companies can submit sort of change in the Written Request. Once the trial is underway they run into problems; they are actually going to generate not that kind of data but this kind of data. So, the information that we actually get at the end of the day has not been that high quality.

I just look at the numbers, the percentages. You know, one in five trials generate new dosing or dosing change information; one in three trials new safety data. That is not a high payoff obviously.

So, I don=t know if you have the authority. That is why I say this is really a policy question, but in the field of antihypertensives, I happened to have followed the ALLHAT trial which was in adults where there was comparison, and I suspect that out of the dozens upon dozens of antihypertensives out there all the ones that are generics we have no pediatric information on, and there is no hope of ever getting pediatric information on underneath this incentive that Congress has given you.

So, given all of that, the question becomes is it

possible to ask companies to do-Bthen there was the final observation that stuck in my brain which is the ethics of having a placebo arm-Bso I guess my question becomes is it possible to ask companies, hey, why don=t you do a comparison trial between a drug that is off-patent and your patented drug for all these resources that we are going to give to you, you know, in the healthcare system which really comes from the adult population for the use of that drug when we go down to do these trials?

DR. MATHIS: Thanks for the comments, and they are really important. I think one thing to point out is that even though there have been some blockbusters that have been studied under this program, the majority of the drugs actually have not been blockbusters.

The other thing is that we are the ones that issue the Written Requests so we decide the public health benefit, and there actually are criteria that we use. We look at the severity of the disease, the number of products that are available to treat that disease, and the number of patients that are affected. So, indeed, you are right. Some of these products are used in a larger number of patients, but many of them are used for more rare indications.

The other thing is that the new legislation, actually starting with the Best Pharmaceuticals for Children Act, offered us the availability of working with the National Institutes of Health to issue requests for off-patent products, such as the older cardiovascular drugs, and we have worked with NIH, specifically the National Institute of Child Health and Human Development, to try and prioritize what products they would allocate their resources to and work on getting studies of off-patent products.

So, you are absolutely right. That is a huge area of need. And, comparative trials I think are something that you hear more and more people talking about because, of course, it is going to be very important to find out if an older, cheaper product is just as good as a more expensive, newer product.

We have actually seen a lot of data in the press about how some of the older products are equally or more efficacious than some of the newer products, not in this particular arena but in other arenas. So, you are right. Comparative data is something that we probably will be seeing more of. I know that the National Institutes of Health have been very interested in that.

In general, when we get pediatric studies, if we can=t do a placebo we do try to compare it against another active product. But that information does not always appear in labeling. So, that is something that we are cognizant of and working towards.

MR. GOOZNER: Just to follow up, do I understand you to say that the FDA does have the authority to ask a company when it comes in and says we want to do the trial because we want pediatric extra six months, can you say, fine, as long as you do this comparative trial?

DR. MATHIS: Because we write the Written Requests we can ask for anything. We really look at the totality of the data though. In some cases that may not be what we want. But if we do want to look at it against an active comparator we can. I don=t know if anybody else wants to add anything else to that.

DR. VENITZ: Any other final questions or comments? Don?

DR. MAGER: Just a quick comment. I realize that in this example pharmacokinetics were not a major focus, but I think, just to echo Jürgen=s comments, that perhaps a more physiologically based approach would be useful where you

could include sort of treating age as the disease progressionB-not that you want to call age disease, but you could include those physiological changes in the PD/PK approach, and also include physical-chemical properties of the drug, so an integrated QSPR-PD/PK approach to anticipate pharmacokinetic changes across age.

DR. VENITZ: Last chance? Then I think we are ready for wrap-up and Dr. Lesko had to excuse himself. He is a little under the weather, and I think Dr. Huang is going to wrap it up on his behalf. Shiew-Mei?

Wrap up for Day 1

DR. HUANG: Thank you. We have received very good comments from the committee. I will just very briefly summarize. On the first topic, on pharmacogenomics, there was very good input because in the preparation of our draft guidance on clinical pharmacogenomics they have got a sense of very good support to collect DNA samples in all trials premarketing.

We have also discussed the barriers and some of the possible approaches about barriers, in particular in pediatric study patient privacy issues and how to deal with IRBs.

And, we got very extensive comments on the decision tree, not only that it should apply to drugs but also to biologics, active metabolites, and we need to add a pharmacodynamic component to it, not just pharmacokinetics.

There is a common theme for all three topics that we discussed today about the utility of modeling simulation, not only to use the in silica approach combining preclinical data, some models such as the ones that are commercially available or developed by the sponsors that we need to continue to look at them. Also, to use modeling simulation to design the study better. How do you have more poor metabolizers versus extensive metabolizers?

On the second topic, which is quantitative clinical pharmacology, on the disease models I think we have very good input I think on the approach that the agency has presented.

It is very useful for better planning for additional studies, and there are several suggestions that we need to consider, systemic exposure in the consideration, and, again, bridging from preclinical to clinical using a physiological model, tumor size activity consideration, using a mechanistic view in the model development. Also,

the committee has stressed the collaboration of the FDA, the industry, NIH and other government agencies and academic institutions.

On the pediatrics we got overwhelmingly to the only voting questions for support of the leveraging of adult data to help design the pediatric study. And, we, again, have a lot of input on the simulation considering physical-chemical properties, kinetic parameters, in the modeling simulation the metabolism, the transporter effect, and I believe there was also a committee comment about using an adaptive design.

We are in the process of revising our pediatric PK guidance so these are very helpful comments to consider, and I want to mention that we did have Dr. Steve Lieder here for a month on a sabbatical, and he did help us in starting with the revision of the guidance.

And, we have additional comments about how to prioritize the studies, the possibility that we should elaborate in using this model if we have a good marker, good PK effect, and then also on the therapeutic use and finally, again, collaboration. FDA just cannot work alone unless we have unlimited FTEs.

So, again, I would like to thank all the speakers and the committee members for your very valuable input. Thanks.

DR. VENITZ: Thank you, Shiew-Mei. Thank you, everyone, for hanging in for as long as you have, and for your contributions. We will reconvene tomorrow at 8:30 for our last part.

[Whereupon, at 4:55 p.m., the proceedings were adjourned, to reconvene on Wednesday, March 19, 2008 at 8:30 a.m.]

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