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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

CLINICAL PHARMACOLOGY SUBCOMMITTEE

Wednesday, November 3, 2004

8:05 a.m.

Hilton Washington, D.C. North
620 Perry Parkway
Gaithersburg, Maryland

C O N T E N T S

P R O C E E D I N G S

[8:05 a.m.]

DR. VENITZ: Okay; good morning, everyone. Welcome to the Clinical Pharmacology Subcommittee meeting. We have a full agenda for today, and before we proceed with our agenda, I would like to go around the table and for every person sitting on this table to introduce him or herself, please. Gerry, do you want to go ahead?

MR. MIGLIACCIO: Gerry Migliaccio, vice-president, global quality operations, Pfizer.

DR. BLASCHKE: Terry Blaschke, Stanford University.

DR. BARRETT: Jeff Barrett, Childrens Hospital, Philadelphia.

DR. CAPPARELLI: Edmund Capparelli, University of California, San Diego.

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

DR. DERENDORF: Hartmut Derendorf, University of Florida.

DR. GIACOMINI: Kathy Giacomini,

University of California, San Francisco.

DR. HALL: Steve Hall, Indiana University School of Medicine.

DR. JUSKO: William Jusko, University at Buffalo.

DR. VENITZ: Jurgen Venitz, Virginia Commonwealth University.

MS. SCHAREN: Hilda Scharen, FDA Center for Drugs, executive secretary.

DR. MCLEOD: Howard McLeod, Washington University.

DR. SADEE: Wolfgang Sadee, Ohio State University.

DR. WATKINS: Paul Watkins, University of North Carolina.

DR. RAHMAN: Atiko Rahman, FDA.

DR. WILLIAMS: Grant Williams, oncology drugs, FDA.

DR. PAZDUR: Richard Pazdur, oncology drugs, FDA.

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

DR. VENITZ: Thank you, everyone.

Our next step is to review the conflict of interest statement, and Ms. Scharen is going to do that for us.

MS. SCHAREN: Good morning. The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the subcommittee participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of conflict of interest with the following exceptions: in accordance with 18 USC 208(b)(3), the following participants have been granted waivers: Dr. Paul Watkins has been granted a waiver for consulting with the sponsor and a competitor on unrelated matters. He has received less than $10,001 per year from the sponsor and between $10,000 to $50,000 per year from the

competing firm.

Dr. Kathleen Giacomini has been granted a waiver because her spouse is a member of the speakers bureaus for the sponsor and a competitor. He lectures on matters unrelated to the issues to be discussed at this meeting. He receives less than $10,001 per year from the sponsor and between $10,001 and $50,000 per year from the competing firm.

Dr. Edmund Capparelli has been granted a waiver for unrelated consulting for the sponsor. He receives less than $10,001 per year. A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12-A-30 of the Parklawn Building. In addition, Dr. William Jusko has been recused from participating in this portion of the meeting.

We would like to note that Dr. Paul Fachler is participating in this meeting as nonvoting industry representative acting on behalf of regulated industry. Dr. Fachler's role in this

meeting is to represent industry interests in general and not any one particular company. Dr. Fachler is employed by Teva Pharmaceuticals.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask in the interests of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. VENITZ: Thank you, Hilda.

Our first agenda item is Dr. Lesko, who is going to bring us up to date on the outcomes of our previous meetings and who is going to set the stage for the next day and a half.

Larry?

DR. LESKO: Thank you, Dr. Venitz and good morning, everybody, and welcome to our fourth Clin

Pharm Subcommittee meeting of the Advisory Committee for Pharmaceutical Sciences. And I'd like to say that we've been looking forward to today's meeting, and I think we have three interesting topics that we will be looking for your input and discussion of as we move forward with these particular areas.

Following the first couple of meetings, there was some interest in sort of stepping back and reflecting and recapping on some of the topics that have been previously presented to the subcommittee and in particular to reflect upon the value of the meeting in terms of what FDA has accomplished with the input from the committee. And what I'm going to do now is summarize the topics that we've discussed at prior meetings along with some of the status of the projects that we've brought before the Committee.

Let me first say that again, we have some new members on the Committee, so this will be very helpful, I think, for those individuals, but this Committee was established in May of 2002, and in

putting the Committee together, we selected individuals with very specific expertise in broad areas of clinical pharmacology that was cross-applicable across many of the therapeutic areas that clinical pharmacology deals with, and those three areas were pharmacogenomics, pharmacometrics and pediatrics, three broad areas, but as we've seen with the past meetings, various subtopics that are of interest to clinical pharmacology. The three prior meetings occurred in October 2002, April 2003 and last November.

I'll begin with some of the topics that we covered during these meetings, and you'll see that the topics were not confined to one or another of the advisory committees. We've used our meetings in a continuous fashion as the projects unfolded, and the first topic that we actually brought before the Committee was a methodology for identifying patient subgroups at risk for toxicity. These are the subgroups that represent specific or special populations such as those with renal impairment.

And what we did in the early meeting was

propose a quantitative method that was based upon a number of features that we thought would be beneficial, not only the mean exposure of the drug in test populations such as the renal impaired population and reference populations like the healthy volunteers, but also, we proposed a method that looked at the distribution of exposure values, and then, from that distribution and comparing those two distribution curves, identified a critical cutoff value at the high end of the distribution curve based on the exposure response relationship.

What we are trying to get at here is a cutoff value above which the risk of toxicity was unacceptable from a clinical perspective. In addition, we showed how we could calculate the probably of a clinically significant response beyond that cutoff, and we proposed a standardized decision tree for dosing adjustments.

The summary points of our discussion was that we linked population PK with clinical outcomes through examples with unresolved questions. We

discussed exposure response methodologies, using modeling and simulations of adverse event probabilities through drug-drug interactions. We also discussed in some of our earlier meetings decisional analysis based on exposure response methods for assessing QT risk in special populations.

These were intended to be examples of the methodology, and inherent in those examples was some methodological questions and issues that we brought before the Committee for discussion.

So what did all of this lead to? Well, the status of this project was that we've currently implemented this methodology in our NDA reviews. The methods we proposed to the Committee or a variant of them as we went through the process are routinely used in the quantitative analysis of exposure response data for efficacy and safety. The primary impact of the topic and the Committee's recommendations have been for us in the office, we use these methodologies and recommendations to formulate our dosing adjustments that we recommend

for inclusion in the package insert or in the product label.

So we really went to several methods then from our discussions here, selecting each of them on a case-by-case basis, depending on the question and the issues. That was the identification of patient subgroups at risk.

We also brought another methodology that was intended to do basically the same thing, and that was the utility function for optimizing dosing strategies. The summary points associated with this topic was that we had proposed the utility function as a methodology based on the probability of either an adverse event or the absence of toxicity taking into account the magnitude of harm if the adverse or toxicity occurs.

We worked on this project for some period of time, and the status at the moment is that we've postponed further development, not that it wasn't a worthwhile project, but the underlying approach was difficult for us in implementation. Underneath this approach was assigning relative weights to the

value of the efficacy versus the value of the toxicity, each of which can range from marginal to significant, and thereby defining a therapeutic index for the drug.

One of the ways you define these endpoints, if you will, upper and lower limits of acceptability and the relative benefit-risk is to ask clinicians, which we did. We also searched literature and looked for applications, and we found that the approach for our purposes in regulatory decision making was unsatisfactory because of the difficulty in defining targets and penalties for different measures of the utility function.

That being said, the method certainly has merit, and we have seen this in terms of drug development. It certainly has merit in its application to the selection of doses to be used in clinical trials during the drug development process, and we know of examples where this is, in fact, done by sponsors. But for our purposes, at this point in time, we have not been able to

implement it as a regulatory, quantitative tool for decision making.

The next topic that we had before the Committee was using exposure response relationships in the pediatric decision tree, which is an appendix to our exposure-response guidance that was released to the public in April of 2003. What we had is summary points from these discussions, which cover two of our meetings, was a proposal for the design of a pediatric database to effectively extract new knowledge from the in-house studies. This was a data mining exercise, so that we could use the information to update our pediatric decision tree, which right now, is used conventionally across our therapeutic areas.

We asked the Committee to comment and recommend the highest priority questions or queries from this database assuming that we could establish it, and some of the things we presented to the Committee using the database at the time was a model for pediatric clearance in order to predict it, which took into account age, adult PK and

metabolism.

We subsequently proposed a systematic pediatric research project that was fairly ambitious. We wanted to evaluate the trends in exposure response with age, using the information that we had in house. We wanted to develop a standardized approach for use across therapeutic areas for population PK studies, and we wanted to develop a computer-aided pediatric template for study design that we can use during the IND process in designing studies in collaboration with a sponsor.

So the status of this project, following our deliberations at the Committee, is that it's ongoing. The progress on the database itself has been limited for a variety of reasons. We had difficulty accessing data in our files because of the nonuniformity in the way data comes in. Some of it is electronic; some of it is manual. It became a laborious process to assemble this data, and it's still in an ongoing mode.

The other issue that we found in mining

our database was the availability of standard PK and PD information. It was heterogeneous. We could not easily take everything that we had received in the files and assemble it into a database that would be consistent across the submissions. So it was a major work effort for us to begin, but we have begun, although it's not a complete project by any means.

We had proposed to the Committee a pediatric research project, as I said, and this was funded by CDER in June. I have June 2003. It actually is 2004. Last couple of months, we received money from the Center to fund this project. It's being headed by Dr. Peter Lee, and we've just begun to get going on the project. We've hired four scientists under a contract. We've established a steering committee for this research. It has commenced, and we have some 12-month milestones.

So the input, the project are all ongoing, and we're looking forward to sharing the results of that project with the Committee as we move forward

into next year.

The next topic that we covered in the early meetings was the genetic polymorphism of TMPT. The summary points from this discussion included a presentation on the scientific and clinical evidence that linked three different TMPT genotypes with the incidence of myelosuppression. What we discussed was a general framework for consideration of analytical validation, clinical validity and clinical utility for improving benefit-risk and pharmacogenomics.

The third summary point was the discussion that we had in front of this Committee related to the revision of the label of 6-mercaptopurine that would include dosing adjustments based on genotype and the more rich information on what we know to be the case with regard to polymorphism of TPMT.

The status of this project is that with the input of this Committee and our Pediatric Oncology Subcommittee, the project is in essence complete. Both committees, if you recall some of the discussion that we had at this Committee,

recommend a revision of the label of 6-mp to include TPMT information in various sections of the label. Negotiations with the sponsor of these products are basically complete, and the updated label for both of the thiopurines will be available in early 2005.

The next topic that was really a new topic back in April of 2003 was our evaluation and labelling of drug interactions of NMEs, an important topic because we were just beginning the initiation of the revision of our in vitro and in vivo guidances for industry on drug interactions. And a summary of what we presented at the Committee was an in vitro drug interaction decision tree for CYP enzymes and associated label language that would go with that decision tree. We discussed some of the scientific basis for policy decisions related to NDA review, label language and class distinctions for drug interactions, and we discussed some specific drug-drug interaction studies involving transporters, specifically PGP and, by extension, some of the other transporters

that are sort of on the front edge of the drug interaction area.

The status of this topic is that it's complete in many ways, although we have a little bit more work to do, but the revision of the guidance, which was the process that was behind the topic we brought before the Committee is nearly complete. The working group has been working on this for some time, and we're getting close to finalizing that guidance, which would be an update of our current in vitro and in vivo drug interaction guidances.

Furthermore, the topic that we've discussed here has been included as a topic and discussion point in the office's GRP drug-drug interaction map and cross-labeling map, so again, we try to transfer the knowledge and information that we've learned through this Committee to day-to-day practice in terms of IND and NDA reviews.

A year ago, we introduced another new topic. It was the end of phase 2-A meetings, and

we had a very useful discussion on the topic. We had as a background, if you remember, the concept paper on the end of phase 2-A meeting, and what we presented was the principles of the concept, and we received again a significant input on the goals, the process, the obstacles and the metrics of success of the end of phase 2-A meeting.

With regard to the concept paper, we have worked on the development of a guidance for industry on the end of phase 2-A guidance. We anticipate this guidance will be a final guidance, in that it's not necessarily a controversial guidance. We like to get it out fairly soon.

However, the status is ongoing, and over the past year, we've had at least four significant end of phase 2-A meetings. These had to do with the questions that we had in the concept paper. They involved a fair amount of modeling and simulation. In one case, we have a disease state model that came out of the meeting that was very useful for simulating phase 2-B and 3 trials. And by all indications, these meetings have been a

success, both by comments we've received from the sponsors and by comments we've received from the medical divisions with whom we coordinate these meetings.

So we're very optimistic about this process as a so-called critical path activity that has the potential to impact the efficiency, the informational content of the drug development process.

As I say, the deliberations were very helpful to us in writing a draft guidance for industry on the end of phase 2-A meeting. It's undergone internal review, and for all practical purposes, it's complete. There is a process to release a guidance, and that would probably take us through the first quarter of 2005, when we make that guidance public.

Another topic we discussed before the Committee was the quantitative analysis of QT. The summary points that we presented to the Committee was some approaches using modeling and simulation and also metrics for assessing QTC interval

prolongation. If you recall, the metrics that we talked about were pros and cons of maximal change from baseline area under the QTC time curve, et cetera. And we asked for input from the Committee on these methodologies that we could begin to apply in the review of QT studies within the NDA database.

Status of this is still ongoing. There's a lot of current discussion on standardization of both study design and data analysis of these kinds of studies. We've made recommendations and presentations that have stemmed from our discussion here at the Advisory Committee to the CDER QT working group, who was favorably impressed by what we delivered in terms of a quantitative approach to assessing the risk of QT.

We also discussed drug interactions involving somewhat unrecognized and underappreciated potential drug interactions involving CYP2B6 and 2C8. The summary of our presentation and discussion here at the Committee was that we sort of took an inventory of our

current understanding of inhibition reactions in particular that are based mechanistically on the 2C8 and 2B6 pathways.

We discussed some of the reliability of the in vitro and vivo associations of these drug interactions, similar to what we do for the more common CYP enzymes to see to what degree these in vitro studies can be a guide to the need to do clinical studies, and if we do clinical studies, what are the model drugs? So we did present some examples to the Committee with model drugs, and I've listed a few of them there asking for comment on the methodology and the use of the information.

So the status of this project is ongoing. The input was seriously considered in the context of our CDER working group on drug-drug interactions, and there's probably a good chance we'll be discussing more of this in subsequent Committee meetings.

So anyway, that in a nutshell is what we've brought before the Committee as topics. I think you can see how they fit into those three

broad areas of pharmacogenetics, pharmacometrics and pediatrics. We've branched out into the drug-drug interaction area as the need arose for us to bring this to a public discussion.

So my reflections on the first three meetings as we move into our next one is that the topics we've brought before you as an advisory committee have been challenging. We recognize they have been diverse. They've been as diverse as the expertise of the membership.

Just so you appreciate how we bring topics to the Committee, we try to select topics that are relatively new and important to NDA reviews such as the quantitative methods. You've noticed that they are not usually drug-specific, because we bring general topics that are cross-applicable across many therapeutic areas. We've brought topics to the Committee that I think are cutting-edge science, the drug interaction area in particular with transporters and some of the new CYP enzymes are areas that we have a lot of issues to resolve in terms of what we would recommend to drug

sponsors and their drug development programs.

And finally, some of the topics we've brought here had an element of controversy, because they were new, and I would say in our pharmacogenetic area, we've had a lot of good discussion and clarity about the integration of pharmacogenetics into product labels and into the assessment of benefit risks.

So in short, a compliment to the Committee. The value of this Committee has been tremendous. I think it's the only committee that has dealt with those topics. It has given us significant guidance on decisions we have to make in terms of the specific areas that we've brought forward, and it has had a very significant influence on our clinical pharmacology program at FDA.

And finally, many committees do vote. Usually, this is characteristic of committees in which specific drugs are brought forward for voting on one issue or another associated with that. We haven't done that very much in this Committee. The

nature of our topics really haven't lent themselves to voting, because they are more general. We anticipate we will be doing more of that, including some of the topics that we will bring before you today, but the primary benefit is not the voting, necessarily; the primary benefit that we've received is the copious notes that we've been able to take and the benefit that we've had from the discussion of the Committee.

So for all of this, I would thank you for your service to the FDA and service to the public as members of this Committee and, frankly, look forward to further very interesting discussions with you all.

I will pause at this point, and it looks like if there's any questions, I'd be happy to answer those. I'll turn it back to the Chair before I move on to a specific topic.

DR. VENITZ: Thank you, Larry.

Any comments or questions by Committee members?

I'm interested in the end of phase 2

status. What are the metrics of success that you're considering right now to evaluate whether this program is going to be a success?

DR. LESKO: Yes, the metrics of success really have been a questionnaire that we're preparing to send to the company. We also call the company to try to get feedback on what we did as a process and what recommendations we gave them in terms of value. We interact both with the clinical group at sponsors. We work with the biostatisticians and the clin pharm folks as well as the regulatory folks at the various companies.

We also survey the medical division that we coordinate the meeting with to see if what we brought to the table in terms of the quantitative methods was perceived to have value, and then, finally, we have, in one form or another, a debriefing of the internal team that worked on that preparation for the end of phase 2-A meeting to get back into lessons learned and see what we can do better.

What has it all meant? I think we need to

have more experience with it, but as I said in my remarks, I think the feedback we've gotten both from the company and the internal participants has been very encouraging for us to go forward. These have not been small efforts. We're somewhat overwhelmed by the effort that goes into preparing for these meetings in the short time frame that we have, and it is very resource-intensive, so it's important to us to actually get good metrics of success, and we're going to be collecting those, and I'd like to share that, maybe, with the Committee at some point in time.

DR. VENITZ: And I was exactly going to encourage you to do that, because as you remember, the discussion that we had, even though the Committee was very much in favor of this initiative, there was concern about resource allocation and so on, so you really have to demonstrate that there is a value in doing this.

DR. LESKO: Exactly, and I remember those comments exactly. And there was no rebuttal to those. We just had to get into it and try it, and

indeed, we have gotten into it and tried it. But, you know, aside from what the impact was on drug development, the impact on us in FDA being able to work together in a quantitative way to discuss drug development and benefit risk in a way that you can put on the table in terms of a model and do a lot of what-if scenarios has really been good for us, and I think it's, again, made us a stronger group within the agency aside from whatever impact it had on drug development.

It's oftentimes spoken about in the context of critical path now, which came out this past March of one of the leading initiatives of the critical path project that has the potential to influence in a positive way the drug development process so--

DR. VENITZ: Thank you. Any other comments, questions?

[No response.]

DR. VENITIZE: Then why don't you proceed with the topics for the next day and a half?

DR. LESKO: Okay; so, now, switching to

the topics for the next day and a half, we're bringing three projects, topics, to the Committee. The first of those this morning is going to be in the area of pharmacogenetics. Specifically, we're going to be discussing the scientific and clinical evidence that surrounds the UGT1A1 polymorphism and its relationship to the pharmacogenetics of Irinotecan.

This afternoon, we're going to bring to the Committee a topic in the area of drug-drug interactions. We'll be talking about metabolism and transporter-based interactions, and again, this is a relative topic to the revised guidance for industry on the on-drug interactions. And thirdly, we're going to bring to the Committee a topic from the world of pharmacometrics, but it also is from the world of the critical path.

We're beginning to focus on specific critical path activities that we would like to advance, and tomorrow, we'll be talking about one that deals with the greater use of biomarkers within the context of drug development and their

systematic progression to potential surrogate markers. We'll primarily be talking about the project and the project plans in the latter area but not necessarily on any specific biomarker in any given therapeutic area but a more general plan that we hope to get input on as we move forward with it.

So those are the three topics, and I think what I'll do now is really launch into the first topic, but I want to pull up the slides for that.

So the first topic of the morning is the pharmacogenetics of Irinotecan. And we'll be talking about the scientific and clinical impact of UGT polymorphism. And my role up here right now is to present a background to the topic and then turn it over to the individual presenters that we've scheduled for the morning prior to the discussion with the Committee.

I'll start out with the labeling regulations that apply to both new and to previously-approved drugs, and the labeling regulations are that if evidence is available to

support the safety and effectiveness of the drug only in selected subgroups of the larger population with the disease, the labeling shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug. Obviously, this is not pharmacogenetic specific but certainly I think encompasses pharmacogenetic testing and information.

Pharmacogenetic information on drug labels in general is not anything new. There's no current barriers to including this information in product labels. Many of you, I'm sure, are familiar with examples of Herceptin, which is probably one of the most well-known examples of pharmacogenetic information on product labels. That is one example of where a test and a drug therapy are used in conjunction with one another.

If one were to survey the PDR and look at package inserts over the years, about 35 percent of the approved drugs have pharmacogenetic information in the label. That doesn't necessarily mean that that information is clinically important or

clinically relevant. Much of it is descriptive, and much of it doesn't really translate into what physicians would do in clinical practice having that information in hand.

On the other hand, this is reflecting many years of pharmacogenetics in terms of the well-known biomarkers of cytochrome enzymes, and it's only now that I think we're beginning to see evidence that some of these enzymes are clinically important and ought to be considered more seriously in dosing of approved drugs.

A couple of other examples: Thioridazine is a previously-approved drug, and if you look at the package insert for that, there's a black box warning in there that warns physicians and patients that they ought to avoid this drug in 2D6 poor metabolizers because of the toxicity risk associated with poor metabolism, and Thioridazine, of course, is a 2D6 substrate.

Atomoxetine is an example of a relatively new drug for attention deficit disorder. There was information from the clinical development plan

about the relationship between pharmacogenetics, specifically poor metabolizers and extensive metabolizers and clinical outcomes in terms of efficacy and safety. This was information that both the sponsor and the agency agreed is worthwhile to put in the label, and in fact, we included it in the label in seven different sections, ranging from the laboratory test section to the clinical pharmacology section. However, there was no reason to require or suggest that a test would have to be done prior to using the drug.

Cetuximab is a drug that was approved that includes genomic information and particularly tumor genomics about receptor positivity. This drug is an EGFR inhibitor, and there's some general in there about the relationship between the drug and its pharmacology and its receptor positivity from a mechanism standpoint. Again, there was no recommendation to require a test prior to prescribing the drug.

Finally, as I mentioned in my opening remarks, we have discussed before the Committee

6-mercaptopurine and azathioprine, and these labels, for all intents and purposes have been updated to include the polymorphism information in multiple sections. That was deemed important.

With regard to the outcome of the 6MP and TMPT polymorphism, in many ways, it was a step in a general framework for assessing the pharmacogenetics of approved drugs. We are trying to create a structure for that type of discussion as we look at approved drugs that may benefit in terms of the inclusion of pharmacogenomic information, so we start out in this case with the absence of information in the label, which was then discussed at the Clin Pharm Subcommittee as well as the Pediatric Oncology Subcommittee.

The new labeling, as I said, has been revised in consultation with FDA and includes, now, data on increased risk of severe myelosuppression associated with genotypes of TMPT. So we think the label has been updated with useful information for clinicians and patients as they weigh their options of using TMPT testing to guide along with other

adjunctive tools and clinical information to guide the treatment of 6MP.

The general process that we've tried to create as a general framework for assessing pharmacogenetics, particularly of previously-approved drugs, where we don't have the benefit of new drug development plans and prospective trials, is to think about the general process of approaching the assessment of pharmacogenetics and its value in inclusion on label.

In this meeting, we wouldn't mind having comments on this. It's not one of the specific questions, but I think we need to think about a general process where we develop the appropriate questions. What is the question we're asking of a pharmacogenetic test or a piece of information? We try to capture the relevant evidence. Oftentimes, that comes from the published literature. You'll see today how we try to abstract and summarize in a sort of meta-analysis the scientific and clinical evidence that allows us to go forward and make a

decision.

We think it's important to evaluate the quality of the studies, and that's what we've done in this case of 6MP as well as the Irinotecan we'll talk about. We look at the overall strength of the evidence from the individual studies, and we consider other factors in the relabeling decision that has to do with test availability, test performance and things of that sort, and then, finally, we move to the specific language for the label.

So it's a general framework that we walk through as we think about this drug or that drug or the next drug where pharmacogenetic information may possibly be pertinent to the improvement of benefit-risk or dosing.

Now, today, you're going to hear about the current understanding of pharmacogenetics and neutropenia with regard to Irinotecan. What I've summarized in this table is on the left-hand side, groups that begin with all of the patients and then moving over from left to right the prevalence of

genotypes and the risk of toxicity that we currently feel is the case. And this comes from the data of one paper that's been published by Innocenti in 2004, and what this shows basically is that all patients have a relative risk of 10 percent of developing grade three/grade four neutropenia.

Breaking down the general population, we have a subgroup that represents the 7/7 genotype for UGT. Prevalence of that genotype is approximately 10 percent. The relative risk of toxicity, that is to say, the penetrance of toxicity is 50 percent. Patients that are heterozygous, prevalence of 40 percent with a relative risk of toxicity of 12.5 percent, and at least in this study, patients that were 6-6 had a prevalence of 50 percent and a relative risk of toxicity of zero percent.

So you see more of that data, but this is the compelling data I think that facilitated bringing this before the Committee. So we see the potential for a test for UGT testing in this figure

that oftentimes is used to represent the value of pharmacogenetics. And basically, we're looking at patients with the same diagnoses that require this drug for its approved indication and an overall risk of 10 percent for neutropenia.

We know, however, in this general population is a mixture of people with different genotypes, and the value of the tests and the way we'd like to consider this is what would this test bring to the table as an adjunct piece of information to use this drug in the most optimal way? We have on the top the profile for the high risk patient that we could identify with a genomic test. Not all of those patients identified, as you'll see, will develop frame toxicity. We have a middle group that represents those at moderate risk, and we have the bottom group based on the data I've showed you that has a relatively low risk.

So I think the goal of pharmacogenetics in general and in this case specifically is to try to differentiate and discern the differences between

patients who otherwise would be perceived to be those patients with the same disease and the same indication for the drug and bring that differentiation as a tool to the clinical practice for improving benefit-risk and drug and dose selection.

So that's the context for what we want to do this morning. So we'll begin with a discussion of the scientific and clinical evidence that links the UGT polymorphism with severe neutropenia. We'll discuss, then, the role that testing can play in identifying patients predisposed to severe toxicity.

Now, I want to share with you that we have had very positive interactions with the sponsor on this topic. The sponsor is committed to providing informative and understandable labeling as is the FDA for all its drug products. Both agree that information on UGT polymorphism and the risk of toxicity on the label is of great importance. Both sponsor and FDA agree to update the label to fully inform prescribers and patients about

pharmacogenetics.

However, in this discussion today, we're not going to get into what the label will say or what the specific wording will say. We'll be talking primarily about the scientific and clinical evidence and the strength of evidence and the questions that we've brought before the Committee.

I'll say this once now, just to sort of create a framework for what you're going to hear. We'll go back to the questions, obviously, near the end of the morning. But basically, we're going to ask is the clinical and scientific evidence that you'll hear sufficient to demonstrate that homozygous genotypes, the 7/7 genotypes, are at significantly greater risks for developing neutropenia and/or acute and delayed diarrhea from therapy.

We're going to ask based upon what is known on this relationship between Irinotecan containing regimens and toxicity three subquestions: do we know enough to recommend the starting dose of the drug in the single agent and

combination therapy? What would be the risks and benefits of the recommended starting dose? And if we need more information, what is the appropriate study to evaluate dosing in these types of patients?

We'll ask how information about genotype can be used in combination with bilirubin. This is, like a lot of genetic tests, not the end all and be all, but it's an adjunct piece of information that, used in conjunction with other indicators like bilirubin, can be used to improve clinical decision making.

And finally, you'll see some information where we're going to ask is the measurement of the genotype sufficiently robust in terms of its clinical sensitivity and specificity to be used as a response predictor test for Irinotecan dosing?

So those are the questions and my introduction. I could pause and turn it over to the chair, or we can launch into the next presentation.

DR. VENITZ: Any quick questions or

comments by the Committee before we start off on the first topic?

DR. SINGPURWALLA: I hesitate to raise these questions because I'm new here to this Committee, but I'd like to draw your attention--I'd like to go to that particular chart, where you had prevalence and risk of toxicity. If I were to understand correctly, the purpose of this chart is to show that patients who are 7/7, and I don't know what that means, have a 50 percent risk of toxicity.

DR. LESKO: That is correct.

DR. SINGPURWALLA: There are two concerns I have. One is why is the 10 percent prevalence important? Because if you know the patient is 7/7, then, the risk of toxicity is 50 percent. So the fact that there are only 10 percent of individuals who are of that particular category is not relevant, unless you are giving the drug blindly, without taking into consideration the characteristics of them. So that's the first question I want to ask.

DR. LESKO: Okay.

DR. SINGPURWALLA: Then, I have a comment to make, and I'm not sure if this is appropriate, but there's something called Simpson's Paradox that arises in these particular contexts. And I'm wondering if that has been taken into account.

DR. LESKO: Well, let's go to the first question. I think in the first question, what I've showed is that in the overall population, and you use that term blinded. If you're blinded, and we were all sitting around the room as potential patients, the overall risk of toxicity is 10 percent. The question is which of the one out of 10 people are going to be most at risk for that toxicity?

Without a test, you wouldn't know that. You could obviously use other information that's available on the drug and currently is in the label regarding age or bilirubin levels. What the genomic tests would do is to begin to differentiate those people in the room, those 10 people around the table that would be more at risk than the 10

percent risk for the general population, because you're teasing out, obviously, the people that would have a very low risk or no risk at all and identifying those with a higher risk.

So if we took the general population, subdivided it by genotype, then, the overall risk would be 10 percent. It's only a reference mark. I didn't mean to say more about it than that. However, in this group of patients identified by a genotype, by a test, the risk is much higher. It's about 50 percent.

And what you'll hear in some of the presentations is the likelihood ratio and relative risk of developing this adverse event in that defined subset by the genomic test, so that's the relevance of the test and comparing it to the current situation without and the future situation with a test.

DR. SINGPURWALLA: Yes, but I'm still not clear. If there is a 7/7 patient, I'm sorry; you wouldn't blindly give the drug to anybody, any person who shows up at random. You'd find out if

that is a 7/7 and then act accordingly; isn't that correct?

DR. LESKO: Well, clinically, I'd think you'd want to do that, because that would have a role in making your decision to give the drug, what dose to give and to consider other choices, but you need something to identify that patient, and currently, that information is not contained in the package insert to guide the physician to make that decision.

DR. SINGPURWALLA: I see. So now, given that that is the case, then, I would strongly encourage you to look at this notion, this concept of Simpson's Paradox before you arrive at a 10 percent risk for patients overall.

DR. LESKO: Can you tell me what Simpson's Paradox is?

[Laughter.]

DR. SINGPURWALLA: Well, yes, what is good for--a drug is good for men, and a drug is good for women, but a drug is not good for the population as a whole. That's the paradox. Okay; some of your

statisticians will help you with that.

DR. LESKO: Okay.

DR. SINGPURWALLA: If not, I'll charge you a fantastic consulting fee and help you.

DR. LESKO: Sounds good. I don't know if you'd be on our advisory committee.

[Laughter.]

DR. SADEE: Larry, I have a comment, maybe a different type of question that's brought up by this polymorphism for Irinotecan.

The optimal dose, unquote, optimal dose has been derived before these considerations, and that includes a patient population that's really inappropriate to calculate the optimal dose. So what would be the position of the FDA to--in new trials, where you combine Irinotecan? Do you go by the old optimal dose, unquote, that included a patient population that really shouldn't have been included?

So the question would be how do we define optimal dose in future trials to the normal population, which is the inverse of saying what is

the optimal dose for those people who are at high risk?

DR. LESKO: Right; yes, I don't think we have the data to make that call. We'd like to know the answer to that question, but I don't think we have enough information to say what the optimal dose would be for these subtypes. I'm not sure we have enough information to talk about the optimal dose for any of the patient groups.

However, we're going to discuss that as we get further into the morning. In fact, I think that's one of the questions we'll talk about: in the absence of credible information to discern the dose, what type of study and what type of study design would be appropriate? And I think you'll hear about some of the ongoing studies that will be along those lines. So maybe we can leave that as a partial answer and wait for the rest of the presentations.

DR. VENITZ: Thank you, Dr. Lesko.

Then, our first speaker on that topic is Dr. Atik Rahman. He's going to review for us the

clinical evidence of the role of UGT1A1 in Irinotecan.

DR. RAHMAN: Good morning. I am Atik Rahman, the acting deputy director of the Division of Pharmaceutical Evaluation I, the Office of Clinical Pharmacology and Biopharmaceutics. I'm also the chair of the OCPB Pharmacogenetic Working Group.

This morning, you have already heard from Dr. Lesko regarding the approach that we took with 6MP and thiopurine methyltransferase enzyme. The pharmacogenetics of thiopurine methyltransferase, TMPT enzyme, and 6MP toxicity was discussed by the Advisory Committee of the Pharmaceutical Sciences in November of 2001. Subsequently, the topic was also discussed by this Committee on April 23 and also by the Oncology Drug Advisory Committee, Pediatric Subcommittee on July 15 of 2003.

I will briefly discuss or update the Committee on 6MP label modifications that resulted from the Committee's deliberations and the FDA interaction with the manufacturer of Purenithol. I

will follow that with the scientific and the clinical evidence from the literature that we have in the agency to demonstrate a relationship between UGT1A enzyme polymorphism and its association with Irinotecan toxicity.

6MP is inactivated by TPMT. TPMT is a polymorphic enzyme. Ninety percent of the caucasian and African-American population have normal gene and normal enzyme activity. Ten percent of the population have intermediate enzyme activity, resulting from one deficient TPMT allele, and one in 300 has low or no TPMT activity because of two deficient allele in their gene.

There is a strong correlation between genotype and phenotype, which is expressed as either TPMT enzyme activity or as the levels of 6-thioguanine nucleotides in red blood cells.

A clinical study showed that 100 percent of the homozygous patients required 6MP dose reduction to prevent toxicity, compared to 35 percent of heterozygous and 7 percent wild type patients. Currently, prospective trials are

ongoing to evaluate appropriate dose of 6MP in acute lymphoblastic leukemia patients.

6MP is given with other myelosuppressive therapy in the treatment of acute lymphoblastic leukemia or ALL. Literature information indicated a potential benefit of reducing the dose of 6MP in patients with low to intermediate TPMT enzyme activity. This reduction of approximately 50 percent 6MP dose in heterozygous and approximately 80 percent 6MP dose reduction in homozygous patients allowed other myelosuppressive agents to be given in full dose with 6MP during the entire course of therapy.

Most of ALL protocol now avoid radiation with 6MP because of the higher incidences of brain tumors observed in TPMT-deficient patients in previous trials.

Based on the advice of the advisory committees and the manufacturer of Purinethol, Tiva collaborated to include the information on TPMT polymorphism and its relationship with 6MP toxicity in the package insert of Purinethol. A new

subsection is included in the clinical pharmacology section to describe the metabolism of 6MP and TPMT polymorphism.

In the warning section, bone marrow toxicity subsection includes a warning for substantial dose reduction for homozygous TPMT deficient patients. Information on the availability of genetic tests is indicated in the precaution section.

The availability of the test is mentioned in the dosage and administration section of the label, and substantial dose reduction is indicated for patients with TPMT deficiency. In the future, we hope to provide specific dosing recommendations for both the homozygous and the heterozygous TPMT deficient patients for 6MP therapy.

Now, I al provide you with the scientific and clinical evidence that relates Irinotecan pharmacogenetics with toxicity. Irinotecan is indicated as a first line therapy in combination with 5-fluorouracil and leucovorin for colorectal cancer patients. The drug is also indicated as a

single agent for patients with metastatic colorectal carcinoma, whose disease has recurred or progressed after initial 5-fluorouracil-based therapy.

Two phased randomized controlled multinational clinical trials show that Irinotecan in combination with 5-fluorouracil and leucovorin increased the survival in first line colorectal cancer patients compared to Irinotecan alone or 5-fluorouracil alone. Two multicenter randomized clinical trials show significant increase in survival for colorectal cancer patients whose disease has recurred or progressed after prior 5-fluorouracil therapy.

Irinotecan is metabolized by carboxyesterases to SN38, a metabolite which is 1,000 times more potent than the parent drug. SN38 is glucuronidated in the liver by UDP glucuronol transferase family of enzymes, predominantly by UGT1A1, and eliminated via biliary route. Deficiency of UGT1A1 results in increased SN38 levels in plasma and in bone marrow cells, causing

hematologic and nonhematologic toxicities. These toxicities result in dose delay, dose reduction and hospitalization and even sometimes in deaths.

UGT1 gene is located on chromosome 2 and contains at least 13 different promoter axons which are spliced to common axons 2 through 5. UGT1A1 is an isoform that is associated with bilirubin glucuronidation. The isoenzyme has more than 30 variant alleles. UGT1A1*28 is a variant allele that contains seven TA repeats in that TATA box of the promoter region instead of six TA repeats.

Today, we will focus on UGT1A1*28 variant only, because the agency believes that we have the most mature data on this variant's association with Irinotecan toxicity. I will use the term 7/7 genotype to refer to UGT1A1*28 variant in my presentation.

Fischer et al studied the relationship between UGT1A1*28 genotype and estradiol glucuronidation mediated by UGT1A1 enzyme. Liver, kidney, lung and intestinal tissues were tested for UGT1A1, 1A6 and 2B7 isoenzymes. In the 7/7

genotype liver samples, the apparent Micholas Mentin constant KM was not altered, but the V-max was altered, compared to 6/6 wild type liver samples. Liver samples with 7/7 genotype had a fourfold lower activity of the enzyme compared to the samples with normal gene expressions, as shown in this bar plot.

As you have already heard, that in the caucasian population, the frequency of homozygous deficient 7/7 genotype is approximately 10 percent, with a range from 5 to 15 percent. The heterozygous 6/7 genotype is approximately 40 percent.

This slide illustrates the relationship between the risk of severe neutropenia and diarrhea and SN38 exposure. These data are from the phase 2-3 studies of Irinotecan in which weekly doses of 100 to 150 milligrams per meter square were administered to patients with colorectal cancer. In absence of individual PK data in these studies, mean AUC data from earlier studies were used. Despite the limited data, logistic regression

analysis suggested that the risk of severe neutropenia and diarrhea increases with SN38 exposure.

The first article that I'd like to present today is a clinical study that was conducted at the University of Chicago by Dr. Mark Ratain and his group. The article was published in the Journal of Clinical Oncology this year. This was a prospective study in 66 solid tumor or lymphoma patients. The study evaluated the association between the prevalence of severe toxicity and UGT1A1 genetic variation.

The patients received 350 milligram per meter square dose of Irinotecan every three weeks. This is an approved dosing regimen for single agent Irinotecan therapy. Toxicity was assessed during cycle 1. Fischer's exact test was used to relate genotype with pharmacokinetic parameters, pretreatment bilirubin and absolute neutrophil count.

I'd like to mention some of the highlights of this study. The study has certain unique

features compared to the other studies that I'm going to present subsequently. This is a prospective trial with an adequate number of patients who had 7/7 genotype. The study is clean in terms of not having any contribution in toxicity from other agents. Sometimes, it's hard to pin down the culprit for toxicity in combination regimen chemotherapy trials.

The onset of toxicity was rapid with the first cycle of therapy. The PK assessment was reliable, being conducted in a lab that has pioneered an assay for this complex and unstable molecule.

There was a significant difference in the dose normalized AUC exposure between 7/7 genotype and 6/6 genotype patients. A significant difference was also noted between 6/7 and 6/6 genotype patients. This is a combined data set, including 66 patients from the Innocenti study and 20 patients from another phase one study conducted in the same institute, using 300 milligram per meter square dose of Irinotecan.

This slide shows the relationship between the maximal decrease in absolute neutrophil count ANC as a function of SN38 exposure. Patients with 6/6 genotype are shown in blue. Those with 6/7 genotype are shown in green. And patients with the 7/7 genotype are shown in red. The square symbols are the mean ANC nadirs and SN38 AUCs for the three subgroups. The data were log-transformed and fit using linear regression models. The blue line shows the predicted curve for 6/6 and 6/7 genotypic groups, and the red line shows the predicted curve for the 7/7 patients.

The 7/7 genotype has a greater effect on the ANC nadir versus SN38 AUC relationship compared to the 6/6 and 6/7 genotypes. For the same AUC, the 7/7 genotypes show a lower ANC nadir.

Overall, the study showed 50 percent of the 7/7 genotype patients had grade four neutropenia compared to 12.5 percent heterozygous patients, and no wild type patients had grade four neutropenia. There is a significant difference in the exposure to SN38 between the

homozygous-deficient 7/7 patients and the 6/6 genotype patients as shown in the previous slide. Also, the pretreatment bilirubin levels between the 7/7 and the combined 6/7 and 6/6 genotype patients was significant.

The prevalence of grade four neutropenia and grade three diarrhea in the overall population--sorry, the prevalence of grade four neutropenia was 9.5 percent, and the grade four--or the severe diarrhea was 5 percent in this study. Notable in this study, one patient died of neutropenia-related sepsis who had 7/7 genotype and had the highest total bilirubin level.

In the study, the grade four neutropenia was significantly higher in 7/7 patients compared with 6/7 and 6/6 patients. The relative risk for grade four neutropenia for 7/7 patients was 9.3. Only three patients in this study had grade three diarrhea. One was a 7/7 patient, and the two others were patients with 6/7 genotype. None of the patients with 6/6 genotype had severe diarrhea. The study conclusively established an association

between genotype and neutropenia.

This is a prospective phase two study designed to evaluate the influence of UGT1A1 polymorphism on the toxicity profile, on the response rate and on the overall survival in 95 colorectal cancer patients treated with four Irinotecan containing regimens. Irinotecan regimens were 350 milligram per meter square every three weeks; 80 milligram per meter square weekly; or 180 milligram per meter square biweekly. Toxicity was evaluated during the entire duration of treatment. No PK samples were collected. Various statistical tests were applied to assess the differences between the categorical variables and between the related or unrelated continuous variables.

Logistic regression was used as a multivariate method to assess of genotype independently predicted toxicities. I will not present any efficacy data from this trial.

Neutropenia and diarrhea in this table includes both grade three and grade four

toxicities. Forty percent, four out of 10 7/7 genotype patients had grade three/four neutropenia compared to 15 percent patients with normal alleles. Seventy percent of the patients with 7/7 genotype had severe diarrhea compared to 17 percent patients with normal alleles. The cumulative dose of Irinotecan received by 7/7 genotype patients was 1,398 milligrams per meter square, compared with 1,725 milligrams per meter square received by patients with 6/6 allele.

The prevalence of grade 3/4 neutropenia and diarrhea in the overall population was 21 percent and 31 percent respectively. Notable is the incidence of diarrhea, which was higher in this trial compared to what we have seen with other Irinotecan-based trials.

Both univariate and multivariate analysis showed statistically significant association between appearance of diarrhea and 7/7 genotype compared with 6/6 genotype. Hematologic toxicities increased from 6/6 patients to 7/7 homozygous patients from 15 to 40 percent but didn't achieve

statistical significance. Cumulative dose of Irinotecan received by 7/7 patients were lower than the dose received by 6/6 patients because of the dose reduction that was necessary for the appearance of severe diarrhea. This study demonstrated a significant relationship between genotype and severe diarrhea. The statement by the author of this article shows a need for genetic-based chemotherapy treatments for cancer patients.

This is the third study that I'm going to talk in detail about. This is a retrospective study of 75 metastatic colorectal cancer patients receiving two common Irinotecan containing combination regimens. Irifufol regimen contains 85 milligram per meter square weekly Irinotecan, given with 1,200 milligram per meter square weekly infusional 5-fluorouracil plus 100 milligram per meter square bolus leucovorin. Folfiri regimen contained 180 milligram per meter square biweekly Irinotecan given with 2,500 milligram per meter square infusion of 5-fluorouracil and 400 milligram

per meter square leucovorin. No PK samples were collected in the study. Kruskal-Wallis test was used to assess the statistical difference among the three populations.

Seventy-one percent of the 7/7 patients, five out of seven, compared with 10 percent 6/6 patients, three out of 31, had grade 3/4 neutropenia. Sixty percent of the 7/7 patients had neutropenic fever compared to no 6/6 patients suffering from neutropenic fever. Neutropenic fever was associated only with patients who carried at least one deficient allele of UGT1A1.

Irinotecan courses had to be delayed in five out of seven patients in the 7/7 group compared with 21 out of 35 in 6/7 and 10 out of 31 in 6/6 group. 100 percent of the 7/7 patients whose therapy had to be delayed for toxicity had to be hospitalized compared with no 6/6 patients with delayed therapy requiring hospitalization.

The prevalence of grade 3/4 neutropenia and diarrhea in the overall population was 30 percent and 7 percent respectively. There was no

association between genotype and diarrhea because of the low frequency of diarrhea in this trial. There was a strong correlation between genotype and grade 3/4 neutropenia. 100 percent of the 7/7 patients who had severe neutropenia needed delayed therapy and hospitalization compared to none of the 6/6 patients who had neutropenia and/or diarrhea.

The authors mentioned in this article that hematologic and digestive toxic events were not due to 5-fluorouracil because all of the patients had 5-fluorouracil dose adjusted individually to avoid severe 5-fluorouracil toxicity.

Literature includes other adequately-sized studies that I'd like to summarize for the Committee. These are the two PK studies that evaluated the effect of variant alleles on Irinotecan disposition. Mathijssen's study evaluated a number of genes associated with the metabolism, transport, and disposition of Irinotecan. UGT1A1 genotype did not correlate with Irinotecan disposition. Notable, there were only two UGT1A1*28 patients in this study.

On the other hand, Paoluzzi's study showed a significant decrease in the exposure ration of the SN38 glucuronide to SN38, indicating a reduction in the formation of the SN38 glucuronide in 7/7 patients.

Font, et al., published a phase two study evaluating the activity of docetaxel and Irinotecan in 51 non small cell lung cancer patients. Irinotecan 70 milligram per meter square was administered with 25 milligram per meter square docetaxel. The study did not see any correlation between genotype and toxicity. The overall incidence of grade 3/4 neutropenia and grade 3 diarrhea in this study was low. Also, the dose of Irinotecan used in the study was 70 milligrams, compared to 100 to 125 milligram per meter square dose used in combination studies of Irinotecan.

A retrospective analysis of 118 Japanese patients who received Irinotecan containing regimen showed that UGT1A1*28 genotype was a significant predictor of severe toxicity. In this analysis, 55 percent of the patients, irrespective of genotype,

who had grade 4 neutropenia also had grade 3/4 diarrhea, and 73 percent of the patients who had grade 3/4 diarrhea also had grade 3/4 neutropenia.

Sai et al in Japan conducted a PK study to evaluate the relationship between SN38 PK and UGT1A1 haplotype. UGT1A1*28 was associated with reduced SN38 glucuronide to SN38 area under the curve ratio and increased total bilirubin.

Iyer, et al., published a prospective PK study in 20 patients that related genotype with reduced SN38 glucuronidation rates and lower absolute neutrophil counts in 7/7 patients compared to 6/6 genotype patients.

In the evaluation of the clinical data provided to the agency for the approval of this drug, certain predictive factors were related to increased toxicities. These are observations only and not statistically powered data that allowed the agency to recommend a reduced starting dose of camptazar for patients equal to or older than 65 years; patients who received prior pelvic or abdominal radiotherapy, patients whose performance

status was two, and patients with increased bilirubin levels.

The reduction was by only one level. That is for the 350 milligram per meter square every three weeks regimen, the starting dose will be 300 milligram per meter square. Similarly, if the normal starting dose is 125 milligrams per meter square weekly, the predictive factors will recommend a dose of 100 milligrams per meter square. If the patients tolerated the reduced starting dose, the dose in the next cycle is increased to the standard dose.

In the geriatric use section of the label we have the statement the starting dose of camptizar in patients 70 years and older for once every three week dosage schedule should be 300 milligram per meter square, a 50 milligram per meter square reduction from the standard dose. Based on the scientific and clinical evidence available in the current literature, the agency believes that genotype is a predictive factor for Irinotecan dose limiting toxicity. The agency also

believes that SN38 level is a likely predictive factor for toxicity.

Based on Innocenti's article, UGT1A1 polymorphism information will help to reduce the overall incidence of grade four neutropenia from 10 percent to 5.7 percent, almost a 50 percent reduction in the incidence of grade four neutropenia. Irinotecan can be given as a weekly, biweekly or every three weeks regimen. One of the regimens may be more appropriate for the 7/7 genotype patients. Genotype testing, combined with bilirubin levels and other predictive factors shown in the previous slide, will allow the physicians to select Irinotecan therapy more judiciously in the high risk patients. Alternate therapy, either in the first line or in the second line setting, may be a choice for the 7/7 genotype patients.

I'd like to thank my colleagues from the Office of Clinical Pharmacology and Biopharmaceutics, Dr. Larry Lesko, Dr. Shiew-Mei Huang, and Dr. Felix Frueh for helping me out with this presentation. I'd like to thank my colleagues

from the Division of Pharmaceutical Evaluation I for helping me out with or for providing the PK analysis of the Innocenti's and the Phase I data. They are Dr. Roshni Ramchandani, Dr. Yanning Wang, Dr. Brian Booth, and Dr. Joga Gobburu. I'd like to thank my boss, Dr. Mehul Mehta, for giving me the time to prepare for this meeting, and last but not least, I'd like to thank my colleagues from the Division of Oncology Drug Products, Dr. Grant Williams and Dr. Richard Pazdur, for challenging me to translate the principles of clinical pharmacology, especially pharmacogenetics, to clinical practice and clinical use.

Thank you.

DR. VENITZ: Thank you, Atik.

Any questions or comments by Committee members?

And what I'd like to do is after each of the presentations, give everybody an opportunity to ask questions for clarification. We have a whole hour reserved from 11:00 to 12:00 to discuss the specific questions that Dr. Lesko wants us to

address.

So, any specific questions?

DR. GIACOMINI: Yes, I had a couple of questions.

Was race specifically or ethnicity specifically looked at in any of the studies that you reviewed?

DR. RAHMAN: I would say no, because the Japanese study included only the Japanese population, and the other studies in Europe and the United States included only the caucasian population. So we at this time don't know the prevalence in blacks, in the African-American population, or in other populations. I think the polymorphism is less prevalent in the Asian population. Dr. Howard McLeod might correct me on that.

DR. MCLEOD: There is ethnic variation for the frequency both of the 6 and 7 allele but also the presence of either five repeats or eight repeats seem to be more common in the, I think, the racial minority groups found in the United States.

The impact of those other alleles is not completely clear, although Dr. Ratain may address that in his presentation.

DR. GIACOMINI: Okay; and as a followup to that, then, maybe you can explain it to me: what is the difference? I mean, you've called it the star--I think, is it 28 haplotype versus 7/7. What is in the haplotype besides the promoters? Are there some other snips in the haplotype, and what are they? And are they functional in any way?

DR. RAHMAN: Dr. Howard McLeod?

DR. MCLEOD: It's a genotype, Kathy, not haplotype. Star-28 is the name that was stuck on the 7/7 repeat, so folks that are homozygous for the 7/7 genotype are called star-28 by the powers that be in determining a nomenclature for UGT1A1.

DR. GIACOMINI: So it's not like there's any other snip in there.

DR. MCLEOD: Correct.

DR. GIACOMINI: It's just simply not.

DR. RAHMAN: Can I clarify that a little bit? Actually, that was not an appropriate term,

but there was a haplotype study that has been published by Dr. Margaret Eng's group that are associating star-28 with other variant alleles, star-60 and others, and there is a paper out on that. So I kind of was alluding to that, that in that study, the number of star-28 patients, homozygous patients, were low, and they were associated with other risk factors.

DR. GIACOMINI: Okay; but we can assume when somebody says star-28, they mean the 7/7; they're homozygous, they mean the 7/7 genotype.

DR. RAHMAN: Seven, yes.

DR. GIACOMINI: Okay; one other question: in terms of mechanism, I didn't see you quote any, you know, like a reporter assay or something in which we're seeing a transcription rate difference between the 7, some biochemical mechanism which supports what you're seeing clinically in terms of that. Are there biochemical data like that? Mark's saying yes. You can't talk, Mark.

DR. MCLEOD: In the--I don't know if everybody received--there was a packet that we

received of light reading. Within that is a number of papers addressing those issues, including a paper from Dr. Boiler Scripps that looked at both the racial issue as well as the promoter variance in terms of luciferase assays, seeing this stepwise inverse relationship between length of the TA repeat and the amount of transcript that's produced.

DR. GIACOMINI: Okay; thank you.

DR. VENITZ: Go ahead.

DR. HALL: Can you give some idea as your part of the agency as to your views on why, you know, you know, several or a significant number of the 6/6s get the toxicity, and a significant number of the 7/7s don't get any toxicity? Do you have some kind of rationalization for this?

DR. RAHMAN: As I've shown in this, in my presentation that the toxicity in the 6/6s definitely lower than 7/7 patients. As you can see, 71 percent versus 10 percent. In one of the studies, none of the 6/6 patients had toxicity. So I'm not sure if there is a significant--the

statement that you made, there is a significant toxicity in 6/6 patients is really true. But there is toxicity in the 6/6 patients also, and that could be attributed to not only Irinotecan depending on the studies if there were a combination of regimens used. It could be also attributed to the others. But it also could be attributed to Irinotecan.

DR. HALL: So have you considered other mechanisms other than this 1A1 polymorphism as a contributor to the toxicities?

DR. RAHMAN: Yes; as I've shown that other predictive factors have been associated for predicting the toxicity, like the bilirubin levels is one of the predictors that has been kind of alluded to being related to toxicity

DR. HALL: But bilirubin would be metabolized by the enzymes. So they would be somewhat correlated.

DR. RAHMAN: Yes.

DR. HALL: Other enzymes? Other genes, perhaps?

DR. RAHMAN: There are papers out in the public domain which are trying to associate other UGT1A1 enzyme, and the factors that could also contribute is the sensitivity of the individual patients to specific neutropenia or to severe diarrhea, and that is something I am not aware of the magnitude of. But there is an understanding that some of the patients might be overly sensitive to a certain kind of regimen compared to the others, even that don't carry any of the homozygous deficient alleles.

DR. VENITZ: Jeff?

DR. BARRETT: I had a question about the prevalence rates in your responses both in the grade 3 diarrhea and in the neutrophil count. It seems that there's quite a bit of interstudy variability, and I know in your pooled analysis, you were basing this on mean data, but is there any--and now, with the Innocenti PK information available, you really could use some of that information to back-project some of the individual variance in those models. Is that going to happen?

DR. RAHMAN: So, first of all, I'm trying to address the question about finding differences in the neutropenia and diarrhea in different studies. What happens is that in certain trials, the patients were allowed to take premedication for diarrhea, so that might have helped. It is approved in the label for using of loperamide and other agents for controlling of diarrhea.

Now, there are two components of diarrhea. One is the early phase diarrhea, and the other is the late phase diarrhea. I have kind of focused on Innocenti's article, because that truly was trying to address these toxicity issues. And their study was trying to look for diarrhea as well. However, the incidence was pretty low.

Now, we are exploring the pharmacogenetics of this drug. However, we're trying to see if SN38 could be a good predictor or could add on to to come to a kind of dose for 6/7 and 7/7 patients, but this is still in the earliest stage, and I think we need some more solid data to show the relationship and then can make a difference.

DR. SADEE: The star-28 genotype is associated with Jorbert's syndrome.

DR. RAHMAN: Right.

DR. SADEE: And so my question is how often is this diagnosed, and what is the correlation between having a patient diagnosed with Jorbert's syndrome and toxicity? So, in other words, could we substitute a genotyping with a diagnosis for Jorbert's Syndrome?

DR. RAHMAN: I haven't come across any article to address that question.

DR. VENITZ: Larry?

DR. LESKO: Yes, just on the last question, you know, another way to think about this is as an adjunct test. You could actually think of tests being done in parallel. If you think of a screening test, you're screening an entire population with or without an elevated bilirubin. You could increase, I think, the sensitivity of a UGT test by maybe screening people that signal by their high bilirubin that they may be at potential risk for the genotype.

So either in parallel or in serial, I think you could enhance the value of the test by thinking of it as an adjunct to the current information that somebody would have. When you look at--getting back to the prevalence issue, when you look at prevalence of Jolbert's syndrome as a function of the ethnic or racial group and the prevalence of the UGT, there are some parallelisms there.

In a review article that appeared last year, the range of prevalence of UGT was anywhere from 2 to 3 percent in Asian populations; up to 23 percent in blacks and Africans. So that's sort of the 2 to 23 percent range that people have reported for the prevalence of the polymorphism.

I was going to maybe add this other information, because Atik showed the slide, and it was shown as average values, but we were looking at the question Steven Hall raised about the 6/6s becoming toxic and the 7/7s not, but I think what we have here is a probabilistic issue that if you look at the variability in SN38 area under curve in

each of the genotypes, there's clear distinctions based on mean values. However, the low end of the 6/6 area under curve and the high end of the SN38 area under curve for the 7/7s does overlap.

So I think what we're seeing, then, is some risk in the 6/6 homozygous and some lack of risk in the other people as one possible explanation. I think another explanation is that in most of these cases, more than the target allele was not looked at, so there could be other alleles that would be predisposing individuals to risks that weren't measured, perhaps because of, you know, the ethnic or racial background. But these are some of the possible reasons anyway, but certainly, the pharmacokinetic explanation seems to make sense based on what we know about area under curves related to nadirs of neutrophils.

DR. MCLEOD: Back to Dr. Sadee's question: in the prospective study in the GI intergroup throughout North America, the N9741 study, Jolbert's syndrome was one of the flags in the inclusion criteria or exclusion criteria. Yet, we

had an 8 percent frequency of the 7/7 genotype. But just kind of highlights the lack of diagnosis of Jolbert's syndrome, because it is a subclinical benign hyperbilirubinemia syndrome.

It's out there, and so, plenty of people are getting this drug without that diagnosis, because it's not something that's really evaluated in common practice.

DR. WATKINS: I was the only--as the only hepatologist here, I'd just reiterate that it's a subclinical diagnosis that can be brought out by fasting and certain other conditions, like certain protease inhibitors.

But in the studies that have looked at, I believe, even the majority of 7/7s have bilirubins within normal limits, so it would not be a surrogate. I guess one question is how much does the genotyping add in a multiple regression if you include in serum bilirubin, which I haven't heard, but I'm sure someone is going to address it.

DR. SINGPURWALLA: Your slide 15, retrospective analysis, you showed two pictures,

one on the left, my left, and one on the right. You have predicted versus observed. How did you get the predicted?

DR. RAHMAN: Okay; the predicted line came from the regression analysis.

DR. SINGPURWALLA: So the predicted is based on the observed data.

DR. RAHMAN: Right.

DR. SINGPURWALLA: I'm curious why you didn't fit a straight line. I know if you fit a straight line--

DR. RAHMAN: Right.

DR. SINGPURWALLA: --it would go out, but why did you choose that particular form?

DR. RAHMAN: It was done by our pharmacometric folks, and they have got a better understanding of the modeling that they did. And I think they thought that this was the appropriate regression to use rather than a linear regression.

DR. SINGPURWALLA: I understand, but there were three points, and you can draw all kinds of curves.

DR. RAHMAN: Yes, that's true. Actually, the intent was to show that there is a relationship that we have seen, but it's very soft at this time, as I've said, because these are all the mean values that we are lumping together; it's not the individual ones, which would have given us a much better fit. And also, in large clinical trials, the PK is not collected.

So we kind of lumped them together and had only three reliable mean values that we could do something with predictions.

DR. SINGPURWALLA: So rather than saying predicted, you should really say fitted.

DR. RAHMAN: Fitted.

DR. SINGPURWALLA: Because when you say predicted, I'm thinking of some theory that tells you what's the probability.

DR. RAHMAN: Right, right.

DR. SINGPURWALLA: As the dose increases.

DR. RAHMAN: Right.

DR. VENITZ: Ed?

DR. CAPPARELLI: Yes, I just wanted to

echo a little bit of what Dr. Watkins was saying, and one of the studies you mentioned that there was an evaluation of bilirubin levels as well as genotype, and you'd expect them to be, you know, highly correlated, and one of the questions is what's the independent component that the genotype is going to give in conjunction with the fact that there is some induceability of this enzyme, and so, genotype may not fully predict especially, and a single genotype differential may not predict.

The other sort of related question that I have is has there been any look at inducers of CYP3A? Because the APC metabolite actually represents a larger portion of the compound that ends up in urine and feces. And so, if that goes by 3A4, again, you may have some differential there as well as if you have some inducers, you may have some confounding of the genotype.

DR. RAHMAN: One thing I can tell you is that there are studies going on, I think, which Pfizer will present showing that they are looking at, besides UGT1A1*28, other genetic factors and

other 3A4, 3A5 to show if--to see if they have any association with the toxicity. So there are studies going on. That's how far I know. But I have not reviewed or looked at any articles focusing on that.

And also, Dr. Ratain's and Dr. Howard's group are looking at all these various factors in association with toxicity for Irinotecan.

DR. DAVIDIAN: My comment just pertained to Nozer's comment a minute ago. This is a logistic regression, right? Is that what was done?

DR. RAHMAN: Yes.

DR. DAVIDIAN: I think it was a logistic regression.

DR. RAHMAN: Right.

DR. DAVIDIAN: So this is just the fitted probability curve.

DR. RAHMAN: Right.

DR. DAVIDIAN: Was this based on these three mean values? Or was it based on--or are you just showing the mean values on the plots?

DR. RAHMAN: It is based on the three mean

values.

DR. DAVIDIAN: And that's all.

DR. RAHMAN: Right.

DR. DAVIDIAN: Oh, okay.

DR. VENITZ: Okay; Atik, let me ask you one final question for my clarification: the Innocenti study is the only one that's a single agent study. All the other studies are multiagents.

DR. RAHMAN: That is correct.

DR. VENITZ: So that is really the only study that allows us to look at Irinotecan as opposed to the contribution that other chemotherapeutic agents might play--

DR. RAHMAN: That is true.

DR. VENITZ: --in toxicity.

DR. RAHMAN: As far as I know, that is the only prospective study that was actually conducted to address this association of genotype with Irinotecan toxicity. So this was kind of--this was a focused study looking at these specific issues, which was based on another phase one trial which

they conducted early on with 20 patients, so they kind of, you know, expanded on that and moved on to do this prospective trial to address the issue.

DR. VENITZ: But all the other studies that you reviewed either prospective or retrospective in nature, they involved other agents as well.

DR. RAHMAN: Yes, like in the four different regimens in the second trial that I talked about, Markelos' trial, I think they had one arm with a few patients who received a single agent, Irinotecan, and then the other arms. So there are blips of single agent here and there, but the other studies definitely had other components besides single agent trials.

DR. VENITZ: Okay; if there are no more questions, then I thank you.

Our next presenter is Dr. Parodi. He is the director of clinical pharmacogenomics at Pfizer, and he's going to give us the Pfizer perspective.

DR. PARODI: Good morning.

I would like to thank Dr. Lesko, Dr. Rahman for inviting Pfizer to participate in this meeting. I would like also to acknowledge my colleagues Dr. Mark Morrison and Dr. Akitunde Belo, who are here to answer any questions that may be in regards to clinical or pharmacokinetic issues during the meeting.

During this presentation, we would like to reiterate the commitment of Pfizer to the safety of all of our products. In addition, we would like to talk about how we are applying pharmacogenetics at Pfizer. At Pfizer, pharmacogenetics is getting important information during the whole drug development process, from early discovery research through development and through the safety and efficacy of our marketed products.

Today's discussion is around Irinotecan, a cytotoxic agent that has been proven to be an effective therapeutic choice for patients with metastatic colorectal cancer and colorectal cancer in general. Since the late nineties, there have been several publications reporting a relationship

between Irinotecan's safety and genotype. We have kept abreast of these publications, and we have provided for the Advisory Committee a summary of those published reports in the background document.

We will review this data, and we will present to a highlight of what Pfizer is doing to continue to expand the database regarding the Irinotecan pharmacogenomics. We will also talk about how we're working in collaboration with the FDA to provide useful information in the label that may refer to this particular genotype.

We believe this forum is going to be an important meeting, where we can share our views and our ideas about the subject and present activities that we are currently undertaking to address these issues. I would like to outline how pharmacogenomics is being used at Pfizer. At Pfizer, we use pharmacogenomics as a generic term which also encompasses what may be traditionally called pharmacogenetics. We use disease genetics to select targets. We use the knowledge of the variation of our targets to improve the safety and

efficacy profile of our drug candidates. And in some cases, we are using the genetic variation to define subpopulations for conducting proof of concept studies.

For our marketed products, we are also looking into the effect that genetic variation has on the safety and efficacy of our drugs. Today, we're focusing on the effect of genetic variation on the safety and efficacy of Irinotecan.

We have been interested in this area since the first studies that were reported reporting the relationship between Irinotecan safety and genotype. Later, Dr. Ratain, who has been a leader in this effort, will address and present his ideas on the subject.

During recent years, we have supported and sponsored many clinical trials that contain a pharmacogenomics component. We will go through a detailed list of the projects we are supporting or sponsoring later in the presentation. Most recently, we have engaged in a collaboration with a company in Germany called Epidaurus to explore the

significant variation of transporters in metabolizing genes in pharmacogenomics.

Today, we will focus on our knowledge of the variation in the genes involved in the Irinotecan disposition and metabolism. This is a representation of the genes involved in Irinotecan metabolism, taking into account only what's going on in the gastrointestinal lumen, where we have more information. We have very little information regarding the genes involved in the disposition of both Irinotecan and its metabolites, both at bone marrow level or at tumor level.

In general, we can say that the mechanism for disposition and metabolism of Irinotecan is complex, and it involves several genes. We want to also note that all of these genes are very polymorphic, and those polymorphisms are known to be functional. As pointed out earlier, there is a great deal of variability in the frequency of the different alleles of these genes in the different ethnic groups, which makes extrapolations from one ethnic group to another very difficult.

The UGT1A1 polymorphisms are probably the best known, but information is constantly being accumulated about the polymorphisms in other genes. As recently as a couple of weeks ago, there has been a couple of reports reporting on novel polymorphisms in the carboxylesterase genes.

Our discussion today will focus on one of these genes, UGT1A1, in particular, one snip in one of these genes, and we would like to address the relevance of the published data associating that polymorphism, specifically what has been called the 7/7 or star-28 polymorphism, in regards to neutropenia and diarrhea.

By now, you are familiar with these studies. We have basically conducted an extensive review of the published literature and have selected these studies which are full papers, because they provide the frequencies of diarrhea and neutropenia as well as the frequencies of genotypes for the UGT1A1 gene.

Something we would like to note is that these studies contain a rather small number of

individuals included in the studies. Given the low frequency of the 7/7 genotype, very few patients in this group have been actually included in these studies.

Again, all studies don't include the same type of cancer patients. Two of these studies include only colorectal cancer patients, while the other three include primarily lung cancer patients. Probably more significantly is the issue that these studies all use different dosing regimens, both in the intensity of the dose of Irinotecan and the schedule, and more significantly yet, the inclusion of 5-fluorouracil, a known agent that causes neutropenia.

Although there are many differences in these studies, we have attempted to look at the data in a comprehensive way. So we realize that this data can be interpreted from multiple perspectives, so what I'm going to provide for you in the next few slides is a statistical analysis of the data. All of the analysis has been done based on the raw data presented in those papers and are

unadjusted for any known factors.

First, we would like to look at the rate of neutropenia in the UGT1A1 7/7 patients compared to the rate of neutropenia in the group containing the 6/6 plus the 6/7 patients. A simple look at this table tells us that the frequency of neutropenia in the 7/7 patients is higher than the frequency of neutropenia in this other group. In order to establish a comparison between the different rates recorded in the studies, we calculated the odds ratios and the 95 percent confidence intervals as represented by this statistic to quantify the association between genotype and neutropenia.

The odds ratios vary from study to study and have very wide confidence intervals. Based on the 95 percent confidence intervals, the odds ratio was statistically significant in three out of the four studies.

Without adjusting for known risk factors, this univariate analysis shows a statistically significant association between UGT1A1 7/7 genotype

and neutropenia, although we note that the association varies among studies with odds ratios between 2.5 and 16.7. This variability could be due to the small sample size, differences in the dosing schedules and the contribution of 5-fluorouracil to neutropenia; the fact that we are not controlling for known factors such as baseline bilirubin levels, age, performance status, and prior pelvic radiation; and indeed, differences in the population's treatment, both from the ethnic perspective and also from the tumor type.

In a similar fashion, we have done the same analysis for diarrhea, grade three plus. In this case, we have included the Font study, because the Font study reports the rates of diarrhea for the different genotypes. It was not included in the analysis of neutropenia because Font did not provide the data for neutropenia separately in his publication.

Again, we would like to note that this analysis has been done without adjusting for known factors, and if we look at the diarrhea rate

between the 7/7 genotype and the group of 6/6 plus 6/7, simple inspection of the rates shows that it's difficult to draw a general conclusion. Here again, we calculate the odds ratios and 95 percent confidence intervals as a representative statistic to quantify the association between genotype and severe diarrhea.

The odds ratios vary from study to study and have wide confidence intervals, and based on the 95 percent confidence intervals, we can say that two out of five studies were statistically significant.

In summary, we have performed a comprehensive review of the published literature and selected publications that provided genotypes and rates for neutropenia and diarrhea in Irinotecan-treated patients. Although there are significant differences among studies, we analyzed the data without adjustments using odds ratios and confidence intervals as a representative statistic. We conclude that there is a statistically significant association of UGT1A1 genotype in the

development of neutropenia. The association of genotype in diarrhea is not as consistent among studies.

Now, if we want to translate this association data to a predictive performance of a test, we need to assess multiple parameters. We have used the same published rates for neutropenia in genotypes used for the association analysis to calculate the test performance parameters.

The following analysis assumes that the genotyping test is 100 percent accurate for the detection of UGT1A1 7/7, 6/6 and 6/7 genotype. We have calculated the performance parameters based on the reported rates in the publications that were examined previously for neutropenia.

First, we look at the clinical sensitivity. The clinical sensitivity can be interpreted as the probability that those patients that have neutropenia will have the 7/7 genotype. We note that the clinical sensitivity varies from 15 percent or 0.15 to 50 percent.

Probably for our discussion, it's more

important to look at the predicted values. Ideally, we would like to have a test with high predicted values, maybe approaching 100 percent possibly. Under the assumption that we know that a patient has the 7/7 UGT1A1 genotype, the overall probability that the patient will develop neutropenia will be about 50 percent.

These values are not highly predictive for developing neutropenia. Given that we cannot accurately predict the development of neutropenia, we have to be cautious when balancing the risk for neutropenia and the benefit of treatment. Neutropenia is generally manageable, and dosing reductions for all UGT1A1 patients would result in unnecessary reductions for 50 percent of the patients, and the outcome is unknown.

We think that this data furnishes a provocative signal hinting at the biology and provides guidance for additional ongoing research in this area. We recognize the importance of this data that has been collected so far, but we also feel that more research is necessary. As mentioned

earlier, we have many ongoing sponsor and supported trials that investigate the UGT1A1 and other genetic factors and their association with severe neutropenia and diarrhea. In parallel, we have ongoing discussions with the FDA to understand the implications of the published data and what may be an appropriate use of this data in the Camptosar label.

These are the sponsored or supported studies that include Irinotecan-treated patients and that have a pharmacogenomics component. These studies may address some of the limitations of previous published studies, in particular, sample size, the analysis of multiple genetic factors, the possibility for controlling for known factors, and the inclusion of current standard of care regimens for first line metastatic cancer or colorectal cancer patients FOLFIRI and FOLFOX.

Although most of these studies are ongoing, we would like to highlight that study N9741 is finished, and the NCCTG has almost completed an analysis of pharmacogenomics data for

15 polymorphic markers on 10 genes. A publication is planned in the near future by the NCCTG.

The future looks very promising. The data from these studies will provide important new information in addition to other efforts and other studies that are being conducted by other investigators. We hope that from these studies, we can better define the magnitude and strength of the association between UGT1A1 and safety; we can also identify other potential covariants of severe neutropenia and diarrhea, and as the data matures from the ongoing studies, we look forward to providing additional information for health care providers and patients to aid their treatment decisions.

I would like to acknowledge a large team of Pfizer colleagues who have worked together to provide this presentation this morning. Thank you.

DR. VENITZ: Thank you.

Any questions, comments by Committee members?

Can I ask you to go back to your slide

where you discuss the performance of the test? You focus on the sensitivity. Would you care to discuss the specificity and the negative predictive value?

DR. PARODI: The clinical specificity basically gives the overall probability that given that a patient has neutropenia, does not have neutropenia, will not have a 7/7 positive test. In general, the clinical specificity seems quite high. The negative predicted value gives a probability that given that the test is negative for 7/7, what is the probability that that patient will not develop neutropenia?

The overall values that you see there are averages. They are not weighted averages. We feel that a negative predicted value is relatively high and much better than the positive predicted value.

DR. VENITZ: So would it be fair, based on this analysis, then, to say if you did the test on a large number of patients, you may not necessarily predict neutropenia with a 50 percent sensitivity, but if your star-28 is negative, you have a very

small chance of developing neutropenia?

DR. PARODI: Certainly, if you get a negative value--a negative test for 7/7, you have a high probability of not developing neutropenia than if you had a positive value for 7/7; basically, a 50 percent chance of developing neutropenia is equivalent to a toss-up.

DR. VENITZ: Right, but that's from your perspective the bad thing, but the good thing is, on the other hand, if you have a negative test, you're unlikely, very unlikely, to develop neutropenia; is that correct?

DR. PARODI: That is correct, but overall, given the incidence of neutropenia, the likelihood that you will develop neutropenia anyways is low.

DR. VENITZ: Any other questions?

Yes?

DR. SINGPURWALLA: Yes, I was just looking at your first slide where you had the odds ratios and the confidence limits around the odds ratios.

DR. PARODI: Which one? For neutropenia or diarrhea?

DR. SINGPURWALLA: Well, let's just take that one.

DR. PARODI: Okay.

DR. SINGPURWALLA: I can't pronounce all these things.

DR. PARODI: Oh, me neither.

DR. SINGPURWALLA: So let me try and understand the objective of this slide from a layperson's point of view.

DR. PARODI: Right.

DR. SINGPURWALLA: If I was 7-7, and if I took this medication, then, it appears that there is a 50 percent chance that I'll get an adverse reaction; is that correct?

DR. PARODI: That is correct. You have a higher probability of having an adverse reaction.

DR. SINGPURWALLA: And if I was either a 6/6 or a 6/7, I have a lower probability.

DR. PARODI: That is correct.

DR. SINGPURWALLA: If I pool all those numbers, I find the answers to be 50 percent probability and 25 percent probability roughly, if

I just add everything now.

DR. PARODI: Yes, yes.

DR. SINGPURWALLA: So I'd still be scared if I had a 25 percent chance of an adverse reaction.

DR. PARODI: Yes, and you should be.

DR. SINGPURWALLA: Is that the point you're making?

DR. PARODI: The point we're trying to make is we try to really provide--we'd have liked to have done a meta-analysis of this data. Given the differences, significant differences in these studies, it's really unfair to pool all this data together in a meta-analysis exercise. So we are basically presenting this data in a tabular form, using a calculated statistic as a comparator between studies, because not all studies reported the same statistic, as Dr. Rahman indicated. I mean, some people used one statistic; some the other.

So it made the tabulation and the comparison between studies a little bit difficult

but--

DR. SINGPURWALLA: I see your point, but look at the confidence limits. They're so wild.

DR. PARODI: The confidence limits are very wide, and that is primarily due possibly to the fact that these are very small sample sizes.

DR. SINGPURWALLA: That's right. Therefore, it makes sense to pool them.

DR. PARODI: It makes sense to pool them, but, I mean, we're doing this in a highly abstracted way, because I think pooling the data is really not warranted. This is basically an exercise, and also, we have not adjusted for known factors, because it is difficult to extract from the policy literature what was the performance status of the patient, what was the baseline bilirubin. All of these adjustments will have to be made, since these are known covariants in the incidence of neutropenia.

DR. SINGPURWALLA: Can I suggest that you consider the use of prior odds and the posterior odds in these kinds of studies?

DR. PARODI: Can you be more explicit?

DR. SINGPURWALLA: Well, prior odds are you put prior distributions on these ratios, and you compute the aposterior using these.

DR. PARODI: Okay; prior probabilities and--

DR. SINGPURWALLA: Right.

DR. PARODI: We could do something like that.

DR. PAZDUR: I wanted to bring up some clinical issues here, and perhaps I realize that the company Pfizer kind of got this drug from Pharmacia, who did most of the development on this, and feel free, obviously, to discuss these with your clinical colleagues--

DR. PARODI: Right.

DR. PAZDUR: --if they have an issue with this. But I think it's very important for the Committee here to understand the clinical development of this drug, and obviously, we'll be talking about an effect on dose reduction and potentially a potential reduction in efficacy. And

I wanted to give the Committee some idea about how the dose of this drug was selected on either schedule. There's two schedules on the product label: a weekly schedule times four and then an every three weeks schedule.

How is that dose selected in the 1990s here? And that has carried us forward here throughout the entire clinical development, and I was wondering if you could give us some idea: how did you get this dose? What was it based on?

DR. PARODI: I would like to defer to one of my colleagues to answer that particular question.

MR. MORRISON: Okay; thank you. I'm Mark Morrison. I'm the medical team leader for Camptosar in the U.S. I've been with Pfizer, so I don't have first hand experience of the development at Pharmacia; however, the dose was arrived at by the standard mechanism of looking at MTD and pushing the dose up to the MTD and then backing down to a tolerable dose just below MTD. So it was a standard development.

DR. PAZDUR: Well, I guess the point that I wanted to bring out here, when the dose was selected, we were looking in a 5-FU refractory population, and the dose was being looked at in terms of response rate here, okay, which was relatively modest. We were looking at 15 percent response rate. And the point that I want to bring out is what is the relationship that the company has with dose and a clinical outcome of an impact on survival? Because here again, if we talk about perhaps changing the dose, you have to be cognizant about any missing data that we have on a dose and the ultimate clinical outcome and what is that level of certainty that we have regarding that dose, the package insert dose and clinical outcome?

MR. MORRISON: That's actually something that we proposed to look at going back into the databases. What we do know, in the first line setting, we use a combination of bolus IFL is that with dose reduction after cycle one and follow them out, each group is dose-reduced, and you do see a slight trend for a difference in efficacy; however,

it's not statistically significant, so that you'd have to come to the conclusion that the overall efficacy at the end of the day was very similar, because both wind up being dose-reduced more.

We do need to look at that in the single-agent setting going back to the second line studies. One thing I'd like to point out, if we go back to the probability slide, looking at negative predictive value, I think a very important point to make in looking at the label, the incidence of grade four neutropenia would be expected if you average the two trials, which isn't statistically valid, because they're two different populations, but it comes out to about 18 percent.

So the negative predicted value tells you that you have a 17 percent chance of having the effect or an 83 percent chance of not having the effect, and that's what we know to begin with. So the test actually is more indicative of the standard population. The positive predictive value of 50 percent gives us added information that these patients are at increased risk over the general

population; however, we would like a test with a positive predictive value of 90 or 95 percent.

So what other factors are coming into play? Is it the carboxylesterase, for example? Is it transporters? Camptosar itself is present in micromolar concentrations versus SN38 in nanomolar concentrations.

So given the difference in efficacy between the two compounds, they're both present at therapeutic concentrations, and UGT is important for SN38 much more so than for Camptosar, and the carboxylesterase may be a very important factor. We don't know whether it is; upcoming data from our clinical trials will hopefully give us an answer, and likewise, transporters in the bone marrow and in the gut and in the liver may help us unwind the story of selectivity and look at the therapeutic index and try to figure out what combination of factors might give us a positive predictive value greater than 90 percent.

So we're striving to do that, and we will have data available in the near future from a

number of trials that Dr. Parodi has mentioned to try to improve on that ratio.

DR. PAZDUR: Just one last question. We spent a lot of time on this slide. I've seen it put up now three or four times, and it addresses severe neutropenia. However, you know, if you ask medical oncologists that actually use this drug, if you ask them what are the top 10 toxicities with Irinotecan, one to nine would be diarrhea, diarrhea, diarrhea, diarrhea, diarrhea, diarrhea, diarrhea, diarrhea.

So is it really a fair--just to look at neutropenia here, are we really missing something by not really looking at what is the most clinically relevant toxicity, and that is either diarrhea alone which leads to the hospitalization or, more importantly, diarrhea in the presence of severe neutropenia, which generally is very problematic and is usually associated with the deaths that we have seen on this drug?

So I would like to make sure that the Committee understands, you know, the clinical

relevance of neutropenia that we're talking about here. Severe neutropenia in oncology circles, we deal with on a daily basis here. The real toxicity with this drug that we should be paying attention to is diarrhea and severe diarrhea that will lead to the patient's hospitalization.

One last question, just to give the Committee an idea of kind of the softness on the dosing on this drug. If one would take a look at the single agent use of Irinotecan before it went into combinations, at the labeled doses of 125 milligrams per meter squared, how many people could actually be maintained on that full dose?

MR. MORRISON: I think the dose intensity for the various drugs ranges from about 70 to 80 percent.

DR. PAZDUR: Okay; but how many people would require dose reductions, I'm asking basically?

MR. MORRISON: By cycle two, I know in the IFL data, for example, in first line--

DR. PARODI: Single agent.

MR. MORRISON: Yes, single agent, I don't have that figure.

DR. PARODI: It's usually the majority, usually a high, high number of people.

MR. MORRISON: And if I could comment on the diarrhea issue, this is something we're absolutely looking at, and we're very concerned about neutropenia occurring in the presence of diarrhea when we've got endothelium or epithelium is compromised. And we would like to see what correlates with diarrhea, and I think more importantly, we're urging the medical community to use the infusional regimen of 5-FU, which has been shown to cause less diarrhea and actually seems to be more efficacious.

So we're actually advocating use of the FOLFERI regimen, which is a two-day infusion of 5-FU preceded by a bolus of 5-FU, and the Irinotecan and 5-FU are given once every two weeks. So that seems to be a much more tolerable regimen; requires less dose reduction; and appears to be more efficacious, and we are looking at these same

pharmacogenomic correlates for UGT and a whole host of other genes with that regimen in our ongoing trials.

DR. WATKINS: Just a quick point, which is obvious to everybody, I'm sure, on the panel here. But as a newcomer, it obviously would be very nice if the genomic DNA and the clinical data was available on the patients who went through the studies back in the early nineties, that would greatly be to patients' benefits. And I guess since you started off the talk talking about Pfizer's global role in pharmacogenetics and as a leader in R&D, is Pfizer now routinely collecting genomic DNA and creating databases and bank so that when such questions come up in the future for drugs, you can very quickly go back and--

MR. MORRISON: Yes.

DR. WATKINS: --verify these rather than doing large phase four studies?

DR. PARODI: Absolutely. We have a very large commitment in the company to pharmacogenomics, including systematic collection

of DNA samples, and we are actually developing the right infrastructure to store and retain this valuable asset for future investigations.

MR. MORRISON: And we're actually looking at this not just in terms of Camptosar, but we're looking at genes involved in a number of other compounds as well. We're looking at genes involved in metastasis; for example, in a protocol that we're just getting ready to launch, we're going to have tumor samples from the primary tumor and from liver metastases in a neoadjutant program.

So we're looking at genes that are involved in invasion metastasis and responsive therapy, so we're trying to look at everything across the gamut.

One thing I neglected to mention was we're also looking very carefully at bilirubin levels, and we do have in our label a statement concerning data looking at bilirubin in the normal range, even. In the range of 1.0 to 1.5 milligrams per deciliter, there is a significant increase in toxicity. And that is within the label, and it's

brought to clinicians' attention.

And this is statistically significant compared to patients with bilirubins less than 1, so we're very concerned about this. And we would like to see how bilirubin correlates with UGT, and maybe Luis can comment more on that, because I know in the analysis by Dr. Innocenti, that was addressed.

DR. VENITZ: Steve.

DR. HALL: Yes, I noticed on your initial slide talking about the metabolism of the drug and its metabolites that only the UGT1A1 was mentioned. And that seems to be the theme so far.

Now, there's a growing literature, and Kathy's just done a literature search here on the computer that, you know, other UGTs are involved, and in your own materials that you supplied to us, there was a study from the Foxchase Cancer Institute, I think, that implicated for sure the 1A7 UGT also as a contributor.

So I wondered if you had any information on the impact of the other UGTs, and secondly, I

noticed in the list of genes that you plan to look for in the studies you listed again in your materials, there were no other UGTs mentioned, and I wondered if that was something that in the short-term, you would be able to get some concrete insight into rather than in the longer-term studies.

DR. PARODI: I think we have, as I indicated, sponsored the N9741 study, which has established a collection of DNA samples from Irinotecan-treated patients. And maybe there is an opportunity in using those samples to investigate other candidate genes that may be associated with outcomes.

In our earlier studies, we had not collected a DNA sample from the earlier registration studies, but as I indicated in another slide, we had on the other collaborative studies that we're conducting right now, we are collecting samples for future analysis. So if we wanted an answer about, well, what about UGT1A7, I think a more immediate answer can come from maybe

genotyping those samples from the 9741 and getting an answer.

Maybe Dr. McLeod would like to comment on that.

DR. MCLEOD: In the context of several of the GI intergroup studies which I am involved in as well as several others in this room, Dr. Ratain, Dr. Giacomini, we have tried to take a drug pathway approach that does not focus on any one particular element of the disposition of the drug. And so, missing from this slide here is also many of the pharmacodynamic markers that are starting to come out of the some of the screening systems we have.

And so, taking this pseudoholistic approach as much as our knowledge lets us, we're trying to understand these issues. So any genes that come out of these screens are fair game and hopefully will complement the additional data that's available.

DR. SADEE: I just want to bring up the issue of how we use genotype and also as a question on this. Obviously, and just looking at the 6 and

7 alleles for the gene, including the enzyme, we will have three genotypes. One is you get both 7/7; that's homozygous for one; and then, you have homozygous for 6/6; and then, you have the third population that's heterozygous.

Now, you have chosen, in most of your slides, to combine the homozygous 6/6 with the heterozygous 6/7. And in this particular case, it's very likely that there is additional functional polymorphism in this gene. So you have a much greater chance for a large variety in the heterozygous population that you included with the 6/6 or the 6/6 and the 6/7. They're very different. And you also have, in the 6/7 population, clinical symptoms for--suggesting that this is truly, again, a different population.

So my question is how do we deal with, if we make dosage recommendations, and we have one population where it's very uncertain; we have one population--that would be the heterozygous population; one where it's--and the two others are more certain, I would say, or we have better

predictors.

So can we actually combine them, those populations, heterozygous and homozygous, and would that be a basis of making decisions along the lines of dosages?

DR. PARODI: The reason which we combined 6/6 and 6/7s was basically because we saw that those groups, at least in the reported data, behaved almost equivalently. So from the phenotype that we're looking at was almost indistinguishable. So that was the reason why we--of course, when you--I take your point that even within one of these genotypes, like the--even including the 7/7, it can be genetically very heterogeneous, because any of these groups can be genetically heterogeneous.

But from the point of view of the phenotype, it certainly made sense to us to combine 6/6 and 6/7s and compare that to the 7/7s.

DR. LESKO: Yes, it's really two questions with regard to the information provided. The first is thinking about risk factors separately versus

complements. You mentioned there appears to be a relationship, albeit imperfect, between pretreatment bilirubin levels and the level of toxicity and neutropenia, and that's consistent with the literature. There's been several articles that have pointed in that direction with modest predictive values, let's say.

However, if I were to--and this may be something that's worth calculating--if I were to take individuals with certain preexisting bilirubin levels and then add to it as a complement the genotype information, would I then increase predictive value in terms of my risk of toxicity, my individual risk of toxicity, to the point where it would be higher than it is?

That would be sort of the one question, and one could go back and look at that, I'm sure, with the data in the files, and taken together, those two indicators, I think, would give a pretty good indication of an individual's risk of developing toxicity.

The second question is with regard to

dosing. I mean, from our discussions, it's clear that dosing in the label is based upon some clinical studies, but there's also, as I recall, some dose reductions recommended in the label. And I don't have it in front of me, but I think elderly was one of those. And there's some measure of dose reduction in the elderly. And I'd wondered if there's any information on either--well, the information on what was used to lower that dose, and is there any exposure data in elderly that would be related to the exposure you would see in genotype?

In other words, I'm trying to draw an analogous situation between lowering the dose in terms of elderly, because they have a certain exposure of SN38 area under curve and then comparing that to the area under curve that we see in the genotypes and see if there's any logic to using that as a guide to what dosing reductions would be done.

DR. PARODI: If I can answer the first question, and maybe Dr. Morrison can answer the

second, with regard to the correlation between baseline bilirubin levels and the neutropenia, actually, the Innocenti paper models this correlation and actually, in the electronic version of the paper, they offer to deposit the data at the publicly available genomics database.

I have checked the database, and it was not publicly available yet. So it might become available. And then, once that data is available, we could attempt the modeling. They report a multivariate analysis adding a genotype with baseline bilirubin, and in their modeling, both genotype, baseline bilirubin and sex were determinants of the correlation.

MR. MORRISON: Regarding the second question, I can't comment on exposure to Irinotecan or SN38; however, the decision to use clinical judgment to perhaps decrease the dose level in the elderly was based on an increase in late diarrhea that was seen in that population.

DR. PAZDUR: But didn't Upjohn do a study? Perhaps Dr. McGovren could comment on this, on the

elderly, and it had a PK component?

DR. MCGOVREN: Yes, yes.

DR. PAZDUR: And I believe I was one of the authors on that.

[Laughter.]

DR. VENITZ: Would you introduce yourself, please?

DR. MCGOVREN: For various reasons, that data has been a long time being put into a report form, and--

DR. PAZDUR: Yes, I know that.

DR. MCGOVREN: And in fact, that data will be filed with the agency very soon. Age is probably not the best example to go into here, because in fact, in that study that you participated in, there really was no association between age and diarrhea or age and PK.

DR. VENITZ: Can you introduce yourself for the record?

DR. MCGOVREN: I'm sorry; it's Pat McGovren from clin pharm group at Pfizer.

DR. PAZDUR: And for the record, that long

time was how many years?

DR. MCGOVREN: It was probably about five or six years, yes.

DR. VENITZ: Okay; thank you.

DR. MCGOVREN: For the record, do you want to indicate what that gesture means?

[Laughter.]

DR. VENITZ: Speaking about the record, I think it's time for a break. We'll take a break until 10:45 and reconvene for the Committee discussion. So at 10:45, we'll reconvene.

[Recess.]

DR. VENITZ: Okay; welcome back, everyone. Our next and last speaker for our first topic is Dr. Mark Ratain. He is one of the authors of the paper that was discussed in detail earlier on, and he's going to give us his perception and perspective as to how to use the test for UGT1A1*28.

DR. RATAIN: Good morning. Thank you. I very much appreciate the opportunity to speak here. I want to thank Dr. Lesko and Rahman from FDA for

inviting me. I really want to thank Pfizer and their predecessor companies for providing drug for my trials. Actually, it goes back into the early nineties with our initial trial. And I thank the indulgence of the Advisory Committee.

Some of you are totally overexposed to Irinotecan already.

[Laughter.]

DR. RATAIN: And that goes long before this particular meeting.

Now, I've been working on this drug since the early 1990s, and I was specifically asked today to speak to you as a clinician, as a medical oncologist, and how I would see from with obviously a biased view how this test could be used to enhance the treatment of patients.

So, many of you have seen a poster child before. The poster child is the one on the right here, 6-mercaptopurine. And you're very familiar with this, as was alluded to in the important work that's been done by many, particularly the group at St. Jude, and this is a figure from the Nature

Reviews cancer paper by Mary Relling and her colleague showing the relationship of TMPT polymorphisms to the therapeutic index of 6-mercaptopurine in children with acute leukemia.

Now, here's another poster child. This is from pharm GKB. This is the Website of the NIH pharmacogenetics research network, and this was our poster child. This was the first pathway that went up. This is a pathway that some members of this advisory committee have agonized over, and I would urge you to take a look at it. It is a clickable interface. And in theory, it should get you the data that you're looking for; at least that's what we're told. Some of us have actually been able to retrieve the data out of this database.

But I think it's pretty clear that this is a very complex drug. You see the parent drug here. The parent drug is inactive. The only way the parent drug becomes active is when it's hydrolyzed by carboxylesterases, and there are carboxylesterases within cells. So you can, if you expose cells to Irinotecan and the cells contain

carboxylesterases, the drugs will get hydrolyzed to SN38 and become activated. But by itself, it is inactive. And the primary enzyme responsible for the hydrolysis is CES-2.

Irinotecan is also a substrate, as shown here, for CYP-3A. Both CYP-3A4 and CYP-3A5, although CYP-3A5 has a relatively minor role; the major oxidative metabolite is APC. That is formed only by CYP-3A4, and I will add we have looked at CYP-3A polymorphisms in our studies. We have not been able to correlate it with anything.

SN38 is a substrate for glucuronasil transferases. As far as the glucuronasil transferases that are expressed in the liver, UGT1A1 far and away is the most important enzyme. There is probably a minor contribution of UGT1A9. We have not been able to demonstrate any role for UGT1A6 in the metabolism of SN38.

And there are other UGT1s that are expressed in the gut, particularly UGT1A7 and UGT1A10 that do have the capability of glucuronidating SN38.

And finally, SN38 as well as the parent drug and the glucuronide are all substrates for a variety of transporters, and we are actively looking at the relationship of polymorphisms in these transporters to the pharmacokinetics and toxicity of the drug. We have not been able to find any relationship between polymorphisms and MDR1 or ABCB1 and clinical outcomes, but we have some preliminary data that was presented at the American Society for Clinical Oncology meeting this year on a polymorphism in ABCC2, also known as MRP2, and the pharmacokinetics plasma concentrations of parent drug as well as APC and SN38 glucuronide, and we currently have some work in progress looking at possible relationships of subtleties such as haplotypes and other clinical outcomes, but that is all work in progress that has not even undergone any internal statistical review.

So I really want to focus you on the subject of today, UGT1A1. Because as you've heard, this is a polymorphism that, one, is common, and two, for which there have been multiple studies.

Now, this is a study, and I can't remember whether this was a pharmacy or an Upjohn study, the mass balance study of Irinotecan. And I think that this paper, published in Drug Metabolism and Disposition in 2000, gives you some idea of what happens to the drug.

And in a mass balance study, 55 percent of the drug is found, is excreted as parent drug. Nine percent is SN38; 3 percent is SN38 glucuronide. Only 11 percent is this oxidative metabolite APC. Only 1.5 percent as NPC, another oxidative metabolite. So as far as metabolites, you can see that this pathway, down SN38 and SN38 glucuronide is pretty important, but also, there's a lot of parent drug that comes out unchanged, which does make you wonder about the importance of polymorphisms and transporters.

Now, as you've heard, Irinotecan is a cytotoxic agent approved in the United States for metastatic colorectal cancer. It is usually administered these days in combination with 5-FU, and I will add is also active in many other

malignant diseases, and it's commonly used off-label for other solid tumors.

Its usage is definitely limited by toxicity, both actual toxicity and perceived toxicity. The toxicities include life-threatening neutropenia and associated infection. This appears to be most common on the every three week schedule. And the other major toxicity, clearly the one that is more problematic when it occurs, is severe or life-threatening diarrhea, requiring parenteral fluids and/or hospitalization, and this occurs primarily on the schedule, the weekly schedule, which consists of four weeks on, two weeks off.

And in our hands, at least, this diarrhea really is not very common on the every three week schedule. So clearly, we have different pharmacodynamics going on on these two different schedules. And so, it is very important not to lump studies together, particularly when looking at the diarrhea, because of the schedule-dependent effects, as well as the confounding issue of concomitant drugs such as 5-FU, which commonly

causes diarrhea.

Now, I think from a clinician's perspective, Irinotecan is one of many FDA-approved choices for metastatic colorectal cancer. And the discussion to date has focused on if one chooses to give Irinotecan, what does one do? And I think from a clinician's perspective, one has to also ask the question: might genotyping help the clinician decide among the various choices?

So for first-line therapy, you have 5-FU, which nowadays is always given with leucovorin, folinic acid, a modulator of 5-FU, Irinotecan, oxaliplatin, which is a platinum analogue that has a totally different mechanism of action from any of the other approved drugs; capecitabine, which is an oral fluoroprimadine and is very similar to 5-FU, and bevacizumab, Genentech's monoclonal antibody against veg-F. And these are all approved for first-line therapy in various combinations.

For second-line therapy, one has a choice of Irinotecan, oxaliplatin, 5-FU with leucovorin, or cetuximab, the monoclonal antibody against EGFR

marketed by Inclone and Bristol-Myers-Squibb. So again, one has many choices.

So how might clinicians choose among various choices? Well, one is clearly personal experience. Two is interpretation of phase three data; three, marketing influences; four, reimbursement; five is a very controversial piece, chemosensitivity testing. There was a recent story in the Wall Street Journal suggesting that this should be done. The American Society for Clinical Oncology has reviewed this and really, there are no good data as to how one might use chemosensitivity testing in an infectious disease kind of model to decide among treatments. And then, the one we're talking about today, genotyping, whether one can predict toxicity or one can predict activity or efficacy. These might influence how a clinician would choose among the various options.

So I want to review with you some of the clinical data, so you can see the dilemma. So this is a study from the North Central Cancer Treatment Group, and this was a prospective randomized study,

three different regimens: N9741. And you see that two of the regimens, IFL and IROX, included Irinotecan, and one regimen, FOLFOX4, did not include Irinotecan.

And this study demonstrated that the two Irinotecan regimens were both--that FOLFOX4 was superior to IFL, p value 0.0001, and that IROX was superior to IFL, so that the conclusion of many clinicians from this study was that FOLFOX4, a regimen that does not contain Irinotecan, was the preferred first-line therapy.

Here is a more recent study from the New England Journal of Medicine. This regimen used IFL. This is a regimen that was shown to be inferior in the previous study, and combined it with Genentech's monoclonal antibody, bevacizumab, and this study showed that IFL plus bevacizumab is superior to IFL, and this study led to the approval of bevacizumab for the first-line treatment of metastatic colorectal cancer. And the label does not say in combination with this IFL regimen; the label says in combination with any 5-FU

leucovorin-containing regimen.

So again, the clinician is still struggling with what to do. The only published data is in combination with IFL here.

And then, there is this trial by Tournigand, a European trial, published in the Journal of Clinical Oncology this year. This was a randomized trial that compared FOLFIRI, an Irinotecan-containing regimen, to FOLFOX, a regimen that does not contain Irinotecan. Prospective randomized trial; 113 patients per arm, and then, second line patients crossed over to the alternative therapy.

And what this study showed was that basically, for first-line therapy, the two regimens, the Irinotecan and the non-Irinotecan regimen, were comparable from the standpoint of response rate. Again, bringing the clinician back to wonder what's appropriate first-line therapy? And when one looks at survival, again, you get the same survival no matter what you start with.

So the clinicians treating colorectal

cancer need all the help they can get.

Now, Oncoscreen, a German company, has taken advantage of this dilemma and is marketing a commercial test for UGT1A1 genotyping, and you can go to www.oncoscreen.com, I think, and you can read--part of it's in German, and part of it's in English, and part of it's in misspelled English--about the side effects of Irinotecan, also known as CPT11, and polymorphisms in the promoter region of UGT1A1. And it gives you the address, and you can send blood here. I've never tried, and I have no idea how well they're doing, but they've taken advantage of this opportunity to actually market the test.

And this is the data from our study, the Innocenti study that you've heard about, shown in greater granularity. And this was 66 patients enrolled prospectively as you've heard. And the study was powered around trying to show a trend, a significant trend, 6/6, 6/7, 7/7, although the original study design was powered to look for diarrhea, which at the time we started the study,

we did not understand the schedule dependent differences in the diarrhea, and so, we ended up looking at neutropenia as the endpoint.

As you've also heard, there are other polymorphisms: allele 5 and allele 8. Allele 5 has been suggested to have higher glucuronidating activity than a 6, and allele 8 has been suggested to have lower glucuronidating activity than the 7. And in response to the question previously asked about ethnicity, the study was primarily caucasian, not exclusively caucasian. I believe there were one or two Asian patients, and there were certainly some African-American patients in the study, but there were certainly not enough within any population subgroup to stratify for that.

And you see that there was a significant trend with the 7/7s having a lower absolute neutrophil count nadir than the other two groups, with the 6/7 being intermediate, but clearly, the difference between 7/7 and 6/7 is greater than the difference between 6/7 and 6/6.

I will also add that if you want to

translate absolute neutrophil count nadir to grades of neutropenia, grade three neutropenia is less than 1,000. That's probably not clinically significant, although it can affect subsequent dosing. It might result in delays of treatment if you develop grade three neutropenia.

Grade four neutropenia is an absolute neutrophil count nadir of less than 500, and a patient who has grade four neutropenia, who develops a fever, is essentially automatically admitted to a hospital and treated with parenteral antibiotics. And so, it is very common to get fevers when you're neutropenic, and so, that that is a real morbidity and a real cost issue.

So others have addressed the issue of sensitivity and specificity, and I'm just going to again go through our data, and again, this is a single study: 350 milligrams per meter squared every three weeks and looking at grade four neutropenia, the clinically significant neutropenia, this is the extreme, less than 500. And again, we agree with the Pfizer analysis. The

sensitivity is 50 percent of patients who have grade four neutropenia who are 7/7. Specificity: 95 percent of patients who do not have grade four neutropenia are not 7/7.

And the positive predictive value: 50 percent of patients who are 7/7 have grade four neutropenia, and the negative predictive value, 95 percent of patients who are not 7/7 do not have grade four neutropenia.

Now, let's put this into the context of without testing and with testing. Without testing, 100 percent of patients are treated, and 10 percent have grade four neutropenia. If you chose not to treat the 7/7 patients, with testing, 90 percent of patients are treated, and approximately 5 percent would have grade four neutropenia. You would have a 5 percent absolute reduction. You would test 20 to protect one.

So I put out what is my bias but I believe is still hypothesis that pharmacogenetic testing will improve outcomes in metastatic colorectal cancer. That's really what we're here to discuss.

And I believe it will allow the clinician to select a drug regimen based on patients' genetic, and now, we're talking germ-line polymorphisms, genetic characteristics, that this will lead to reduced toxicity and potentially will lead to increased efficacy, something that we've not previously talked about.

My opinion is that sufficient data exist to recommend that patients who are homozygous for the star-28, the 7/7, should not receive Irinotecan at standard doses. Some might say that you could treat at standard dose and accept greater toxicity. Some might say you could reduce the dose. I believe that these patients would be most appropriately treated with an alternative regimen such as an oxaliplatin-based regimen that has the same survival outcome as an Irinotecan-based regimen. I cannot sit here and recommend reduced dose, because we have no clinical data to show that patients treated with 7/7 at a reduced dose have comparable activity and comparable survival outcomes to patients treated with alternative

regimens.

On the other hand, the optimal treatment of patients who are at reduced risk of Irinotecan toxicity star-one, star-one, or 6/6 is unclear. Should they be treated with standard Irinotecan-based regimens? Should they be treated with high-dose Irinotecan-based regimens? There's one European study that took patients treated with standard dose, escalated patients who did not have significant toxicity; they escalated them up from 350 per meter square to 500 per meter square. It's a single-arm study, but it's got the highest single agent response rate of any study in the literature, and so that this may be an opportunity to reexplore dose in a low-risk group of patients representing 50 percent of patients that are candidates for this drug.

Or is oxaliplatin the best regimen for these patients? We have no data to support that, particularly for the low-risk patients.

I want to contrast this with other drugs and other polymorphisms, because I think this is a

great opportunity to use pharmacogenetics to individualize treatment of colorectal cancer. And this is Bob Diazio's Website, www.dpdenzyme.com, where you can learn about screening patients for DPD enzyme deficiency. Oncoscreen also offers this test.

What do we know about this test? And here, you see the Oncoscreen Website, and it says this test is supported by the German health insurance companies. Actually, the German health insurance companies initially--the German oncology group initially recommended this test and then retracted the recommendation, which is kind of interesting. There's a history there.

And the most common mutation in DPD is an exon 14-skipping mutation. This has an allelic frequency of approximately 1 percent. The star-7 polymorphism has an allelic frequency of approximately 35 percent. So there's a big difference in allelic frequency here. DPD testing, if you test this exon 14-skipping mutation, and your endpoint is grade four, life threatening 5-FU

toxicity, without the test, all patients would get treated, and approximately 3 percent of patients have this toxicity. So only 3 percent of patients have grade four toxicity from 5-FU as a single agent.

With the test, you would treat 98 percent of patients, and approximately 2 percent of patients will still have toxicity, a 1 percent absolute reduction. You would test 100 to protect one, so much lower efficiency of this test.

And then, there's another important polymorphism that may predict for toxicity and efficacy of fluoroprimadines, and that's a polymorphic repeat sequence in the thymidylate synthase gene that has been suggested to affect translational efficiency but not gene expression. And this is quite polymorphic.

Here, you see the population distribution of this 28-base pair repeat. This is data from Howard McLeod's group. And you see that the three repeat is more common than the two repeat, and that there's also a four repeat present in African

populations.

So with parting words: oncology is widely anticipated to be the best model for demonstrating the clinical importance of pharmacogenetics as it relates to germ line polymorphisms. Colorectal cancer is an important model, because of the large number of active agents. We have candidate genes, candidate polymorphisms and abundant clinical data.

And I want to thank my colleagues in the PAR group, pharmacogenetics of anticancer agents research group. I want to thank my colleagues in the PGRN, pharmacogenetics research network, those sitting here today, those I've collaborated with, and those who have had to sit through far too many discussions of Irinotecan.

So, thank you.

DR. VENITZ: Thank you, Dr. Ratain.

Any questions or comments by the Committee before we start our overall discussion?

Paul?

DR. WATKINS: Just a question about the UGT1A7, which is in the gut, and we've heard that

diarrhea is probably a bigger issue than neutropenia. What work has been done looking at UGT1A1 polymorphisms and diarrhea?

DR. RATAIN: It's a very difficult problem, because there are definitely polymorphism 1A7 that have shown to be functional that are strongly linked to UGT1A1, because it's all one gene. And, in fact, the linkage in UGT1A1 goes five prime at least down to UGT1A9. So to actually distinguish the independent effect from 1A7 from 1A1 requires a very large study.

One would not--since 1A7 is not expressed in the liver, one would not expect it to have a significant effect on the plasma pharmacokinetics or on the neutropenia, but it certainly is a candidate gene for gastrointestinal toxicity. But we really need a lot more data, because this really will require haplotype based analyses of the whole UGT1 gene.

DR. SADEE: Mark, this comes back to my earlier question about dosage escalation in populations. You mentioned that here that in

patients who are apparently protected against the cytotoxic effects, you can go to higher doses and get higher efficiencies. So I think that really sets an important example to pursue that.

Do you have any other examples where that has been pursued, so rather than looking at the negative side, one would look where you want to avoid things. You exploit the patients that really should get a different dose.

DR. RATAIN: Well, I mean, you know, there have been some studies in oncology where patients sometimes get intraindividual dose escalation, but there's really not a large data set on that. I mean, Dr. Pazdur may have some comments.

DR. VENITZ: Howard?

DR. MCLEOD: Mark, we heard from Dr. Rahman's talk about how the current package insert includes data on age and bilirubin and some other factors that I'm forgetting, public radiation and one other thing, as risk factors and with a need for dose reduction.

I wonder if you could put the 7/7 genotype

into the context of those existing risk factors.

DR. RATAIN: Well, we've looked at age in our data set, and we have not found at least in our study of 66 patients a significant impact of age. So I would say from the standpoint of neutropenia, genotype is certainly more important than that. Bilirubin, in our hands, is a pretty good poor man's genotype, but this is a single institution where the bilirubin is collected in a standard way. Once you get into multiple laboratories, and bilirubin is tested at various times of the day with various degrees of fasting, you're going to really obscure the relationship between genotype and bilirubin.

And so, I think that yes, patients with higher bilirubins, particularly if it's unconjugated, are very likely to be 7/7, because many patients within the normal range of bilirubin are 7/7. So, but I think even there are some subtleties. I think again, patients with very low bilirubins probably are not 7/7, and I've used that in my clinical practice to help determine dosing in

the absence of an approved test.

DR. GIACOMINI: Yes, Mark, in your study in which you documented the neutropenia, did you also measure pharmacokinetically the SN38, and was it higher in those patients with the 7/7?

DR. RATAIN: Yes, we did measure SN38. SN38 is higher in the 7/7. SN38 correlated with neutropenia. As I said, we have some evidence that polymorphisms in ABCC2 through our collaboration with Deanna Krebs may relate to the pharmacokinetics of SN38 glucuronide, which makes it difficult to interpret SN38 to SN38 glucuronide ratios, which we previously assumed to reflect solely glucuronidation. It quite possibly is determined by both glucuronidation as well as excretion.

DR. GIACOMINI: Let me ask a followup on the bilirubin thing. Does bilirubin actually competitively inhibit the glucuronidation of the SN38 to SN30 mechanistically? Is it a competitive inhibition, so when the levels of bilirubin are low, it's telling you two things, one, about the

genotype but also about just direct competitive-competitive inhibition?

DR. RATAIN: You're asking me does bilirubin inhibit--

DR. GIACOMINI: Yes.

DR. RATAIN: We've not looked at that. I don't know of any data. I would not expect it to. And there is certainly some evidence not for--it's possible that SN38 could inhibit bilirubin glucuronidation if the levels are pretty low, but there are certainly examples of other drugs, particularly the protease inhibitors, that inhibit UGT1A1 and do competitively inhibit bilirubin glucuronidation.

DR. GIACOMINI: Okay; but you wouldn't expect the bilirubin and the high bilirubin levels to be inhibiting the SN38.

DR. RATAIN: Not in--not in--I don't think so; I mean, Dr. Watkins would have a better feel for that.

DR. DERENDORF: I'd like to come back to your mass balance slide. If I understood it right,

only about 9 percent of the parent drug gets converted to the SN38. So what do we know about the other metabolites?

DR. RATAIN: Would you like for me to put that back up?

DR. DERENDORF: Yes, you can. It's the number five.

DR. RATAIN: Messed it up; sorry.

So, this is the mass balance slide you were referring to. And I'm sorry--

DR. DERENDORF: Only 9 percent gets converted to the SN38, right?

DR. RATAIN: Well, 9 percent is found as SN38, and 3 percent is found as SN38 glucuronide.

DR. DERENDORF: Oh, okay.

DR. RATAIN: And again, this is a limited number of subjects. These subjects were not genotyped, but approximately 12 percent, I think it's fair to say, goes down that pathway. I think that's a reasonable estimate. And you see 55 percent in this study was--the parent drug was excreted unchanged. About 12 percent is oxidative

metabolites, metabolites known to be formed by CYP3A, and then, we don't know the rest of this. And again, I was not an author of this study; just presenting it for perspective.

DR. WATKINS: Just to address that issue of can bilirubin itself interfere with the glucuronidation of SN38 or any other drug, in theory, that's possible. It certainly works the other way around. There are some drugs that will inhibit glucuronidation in patients who have a genetic predisposition of Jolbert's. But I'm unaware of any studies that have looked the other way, so I don't think I can address that.

But the question I wanted to ask myself, one of the concerns with using genotypes of the host as opposed to the tumor in cancer chemotherapy is the fact that genotype and phenotype don't always go together, particularly in an ill cancer patient on multiple drugs with cytokines, and certainly, if their liver is completely replaced by tumor, genotype is irrelevant.

And one of the very unique things here is

this particular phase two enzyme has an endogeneous substrate, so in effect, you have a phenotype measurement. And my assumption up until what you just said was that that endogeneous probe for UGT1A1 was not very good. But what you're saying at your institution, it's in fact very good.

DR. RATAIN: There are two studies that address this. There's our study that within a single institution, all patients were on a research protocol; the bilirubins were collected at, you know, in a fairly consistent way just by nature of our research practice, and it looked pretty good. There's also a study that I was a coauthor on that relates to a Pfizer study in which a large data set was analyzed, and bilirubin really wasn't a very good predictor, and this was just published in the Journal of Clinical Oncology this year by Meierhard is the first author, and the company may want to elaborate on that further.

DR. WATKINS: Because if I can just follow up, I mean, the key question is what does genotyping add to the existing tool kit of the

oncologist? And my assumption in all the background reading was that it adds a significant amount. If an alternative is just standardizing indirect bilirubin measurements, that's another option that could be considered, I think.

DR. RATAIN: Again, you know, from an analytical perspective, there's a gray zone, and it doesn't--bilirubin doesn't, you know, in a large data set may not correlate as well as something that is a discrete answer like a 7/7 genotype. I think also, it might be tough to distinguish 6/6s from the 6/7s, and I think that the 6/6s are potentially appropriate candidates for phase four clinical trials looking at higher doses of Irinotecan which I think is another important reason to find a way to get this test in the hands of the clinical oncologists and the research oncologists to help further explore the dose-response of this drug.

DR. HALL: So in part to follow on from that, then, in your hands, what would your recommendation be for the heterozygotes? Are they

to be treated or given an alternative?

DR. RATAIN: I would see no reason not to treat the heterozygotes, given the data today.

DR. MCLEOD: One of the things you commented on was that neutropenia is an important toxicity, and I certainly second that. And during the discussion, hopefully, we will elaborate on that more, because it's a common problem that is less of a worry but probably more of a problem to the patients.

The question I have for you is you made the comment that you thought the 7/7 patients maybe--might represent a data set that should get a different drug, oxilaplatin or something like that. But with the current state-of-the-art and the one for probably the foreseeable future is that every colorectal cancer patient at a decent center will get Irinotecan. If they don't get it first line, they will get it second line.

And so, we can't really avoid the issue that Irinotecan is going to appear. This is a real drug for colon cancer. And they're going to get it

at some point, first line, second line, third line. So it would be worthwhile, either now get your comments or in the discussion, trying to think about that issue, because the drug is approved in both these settings, and so, we do have the remit to actually talk about it in first line, second line, et cetera.

DR. RATAIN: Well not everybody gets it second line. There's some patients--

DR. MCLEOD: Not everybody does, but they should.

DR. RATAIN: What I'm saying is if--some patients don't get to second line. If you were to give Irinotecan first line and have a grade five, a fatal event, they won't get to second line. So you would say, ideally, the clinician would like to reserve the more toxic drug for second line rather than first line.

DR. MCLEOD: But I totally agree with your thinking behind it. I'm just--we can't avoid it. I mean, the patients that make it through first line because they didn't get Irinotecan, and they

were 7/7, the selection now, you've just taken one drug off the table. It's now either single agent Irinotecan or Irinotecan and bevacizumab, whatever.

We may not be able to come up with those things, because like you said, there is no prospective studies. But certainly, it is an important issue.

DR. RATAIN: You know, I think as you think about it as a clinician, you know, if you have a discussion with a patient, and you sit down with them, and you talk about Irinotecan versus oxaliplatin as first line therapy, when you talk about Irinotecan, you have to talk about neutropenia, diarrhea, which can be severe, life-threatening or even fatal. And as you talk about oxaliplatin, you have to talk about neurotoxicity that can be persistent.

And, you know, patients have to make choices, and I think being able to inform patients about their relative risk, particularly of the toxicity that scares a lot of both patients and clinicians, which is the neutropenia/diarrhea

complex, I think, is useful, and I think if one could reassure a clinician that their patient is at relatively low risk of these toxicities of Irinotecan, a clinician would be more interested in prescribing Irinotecan first line.

And so, I think that this actually is helpful, very helpful to the clinician and I think potentially very helpful to the sponsor who is marketing the drug.

DR. BARRETT: You mentioned the lack of prior appreciation of the scheduled dependence on diarrhea, and I wondered, back on your recommendations as far as not reducing the dose, would you feel the same with neutropenia and the diarrhea? And I guess the followup question there is most of this data has been summarized outside of the time dependency, so do you feel if that kind of information is brought to light through either dose reduction in the context of managing toxicities that you could perhaps devise a schedule for one toxicity versus another?

DR. RATAIN: Well, the diarrhea is a lot

messier to model; no pun intended. And the neutropenia is pretty well correlated with plasma SN38 exposure, and we can understand that both in the context of these studies as well as in the context of other studies, anticancer agents and neutropenia.

The diarrhea is not fully understood, and we've tried to model it in the past to somehow try to model biliary excretion of SN38, and we have one study that actually came up with a surrogate endpoint, or, actually, biomarker would probably be a better term for it, which was the CPT11AUC times the SNC38AUC over the SN38 glucuronide AUC.

But it's very complicated. I think that the thing one is most concerned about is the neutropenia/diarrhea complex and particularly in the context of schedules that are more frequent than the every three weeks, which is where you see this problem.

DR. VENITZ: Mark, as you know, the Committee is asked to review the evidence to see whether we would concur with the recommendation to

include pharmacogenetic testing. I'd like to know what the competition is. In other words, I'd like to know right now what is being done to come up with a starting dose. How do you choose a starting dose for Irinotecan with the information right now without genetic testing?

DR. RATAIN: Right now, people just rely on clinical evidence, which is one size fits all based on body surface area, even though body surface area has been shown not to correlate with the pharmacokinetics of this drug.

DR. VENITZ: Followup question: how do they adjust the dose once the patient is being put on Irinotecan?

DR. RATAIN: I think clinicians do it to some extent by the package insert and some extent by their personal experience.

DR. VENITZ: Okay; thanks.

Larry, I think you had the last question and then maybe frame the questions for the Committee so we can start the questions.

DR. LESKO: Okay; thanks.

Yes, Mark, and I think you may have answered this in the last couple of minutes, but I was looking at the relationships that Atik had presented looking at the probability of neutropenia and diarrhea respectively as a function of SN38 area under the curve.

They're remarkably similar, although they were based upon mean data. So the question is is there an indirect benefit in reducing the risk of severe diarrhea from paying more attention to, let's say, the neutropenic problem? In other words, do they go together, and to what degree do they go together?

DR. RATAIN: Yes, there's certainly an association of the two, but they don't always go together. But a patient with neutropenia is more likely to have diarrhea and vice versa.

DR. VENITZ: Good. Thank you. We appreciate your comments.

Larry, why don't you frame your questions for us?

DR. LESKO: How about if we bring them up

on a slide?

DR. VENITZ: That's fine.

DR. LESKO: I'll just scroll through these.

Okay; so, as the time proceeds, I'll scroll through the individual questions, but the first question that we have for the committee discussion is regarding the scientific and clinical evidence that we're all aware of at this point. So the question is is the evidence presented sufficient to demonstrate that the homozygous star-28 genotypes or 7/7s, as we call them, are at significantly greater risk for developing a, neutropenia, and b, the acute and delayed diarrhea that we've heard about as an adverse event?

DR. VENITZ: And you would like for us to vote on this?

DR. LESKO: Yes.

DR. VENITZ: So as far as the Committee is concerned, any comments, discussion items for FDA before we vote? And by the way, the vote is going to be by voice vote. I'm going to call your

individual names, and you're going to have to tell me whether you're a yes, no or abstain for the individual questions as we go along.

DR. SINGPURWALLA: Jurgen?

DR. VENITZ: Nozer.

DR. SINGPURWALLA: Would you consider removing the word significantly?

DR. LESKO: What would you suggest as an alternative? Just--are you thinking of it because it's a statistical--how would you convey a small risk versus a large risk?

DR. SINGPURWALLA: Well, I'm not sure if I could subscribe to the view that the risk is significantly larger.

DR. LESKO: Could we use markedly greater? Clinically important?

DR. SINGPURWALLA: I made my point.

DR. LESKO: I think the question is intended to convey a magnitude of risk. If we want to say clinically important, markedly, I think it's fine. I think it conveys the same thing.

DR. SINGPURWALLA: You mean you insist on

an adjective?

DR. LESKO: I think a qualifier would help.

DR. VENITZ: Any further comments?

DR. SADEE: Are we to consider these two together, A plus B, or A separate from B?

DR. LESKO: I think we need to, based on the way the evidence was presented today, it's probably better to consider them separately.

DR. VENITZ: So we'll have two votes. We'll have one on neutropenia and one on diarrhea.

DR. LESKO: Yes.

DR. VENITZ: Any other comments before I call for the vote?

[No response.]

DR. VENITZ: Okay; then, the first question is is there sufficient evidence of a greater risk of developing neutropenia. And as I said, you have three choices: yes, no or abstain. So let me go down my list.

Dr. Barrett?

DR. BARRETT: Yes.

DR. VENITZ: Dr. Capparelli?

DR. CAPPARELLI: Yes.

DR. VENITZ: Dr. D'Argenio?

DR. D'ARGENIO: Yes.

DR. VENITZ: Dr. Davidian?

DR. DAVIDIAN: Yes.

DR. VENITZ: Dr. Derendorf?

DR. DERENDORF: Yes.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes.

DR. VENITZ: That doesn't count.

DR. VENITZ: Dr. Hall?

DR. HALL: Yes.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: Yes.

DR. VENITZ: Dr. Sadee?

DR. SADEE: Yes.

DR. VENITZ: Dr. Singpurwalla?

DR. SINGPURWALLA: Yes.

DR. VENITZ: And Dr. Watkins.

DR. WATKINS: Yes.

DR. VENITZ: Okay; then, the second part

of that question is is there sufficient evidence to substantiate a significantly greater risk for the delayed diarrhea and acute delayed diarrhea? Oh, before--I'm a yes, too. So we have unanimous.

Okay; second question, then, what about diarrhea? Does the Committee feel there is evidence to support significantly the increased risk?

Dr. Barrett?

DR. BARRETT: No.

DR. VENITZ: Dr. Capparelli?

DR. CAPPARELLI: No, not yet.

DR. VENITZ: Dr. D'Argenio?

DR. D'ARGENIO: No.

DR. VENITZ: Dr. Davidian?

DR. DAVIDIAN: No.

DR. VENITZ: Dr. Derendorf?

DR. DERENDORF: No.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: No.

DR. VENITZ: Dr. Hall?

DR. HALL: No.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: No at the moment, but the data looks like there's something there.

DR. VENITZ: That counts as a no.

Dr. Sadee?

DR. SADEE: No.

DR. VENITZ: Dr. Singpurwalla?

DR. SINGPURWALLA: I abstain.

DR. VENITZ: Dr. Watkins?

DR. WATKINS: No.

DR. VENITZ: And I would add my no, but it does appear not only that there might be something but it may be limited to patients that have colorectal cancer; in other words, diarrhea may not be present in patient populations that don't have it.

Okay; any other comments about question number one? So we have a unanimous vote on the first part, and we have an almost unanimous part on the second part of that question.

Okay; Larry, you want to present us with the second part of this question?

DR. LESKO: Yes, I think on this second question, if I can propose that the way this is worded, it's not in a sense a votable question, because I think we're looking for discussion; for example, what would be the risks and benefit, what is an appropriate study design, and it strikes me that it doesn't lend itself to a vote. So if I can propose that we look at this question and address the questions that are posed on the slide in a discussion context as opposed to a voting context, I think that would be useful to us.

DR. VENITZ: Okay; then, I open the discussion.

DR. GIACOMINI: Yes, one of the things I didn't see, and I don't even know who I'm addressing this to, this question to, but did we ever see any data and, like, Kaplan-Meyer curves? I don't even know if--Kaplan-Meyer curves, where they've factored, you know, where they've looked at survival data over time and then genotypes, put them in categories, like the people with the star-7 genotype or the star-28 genotype are they having a

better survival or worse survival?

Can I ask Mark, or is he not allowed to talk? Can I ask this to Mark? He can't talk?

DR. VENITZ: Yes, you may.

DR. GIACOMINI: Mark, I mean, just to get an idea of the benefit to--

DR. RATAIN: There are no published data. Dr. McLeod has a data set that may provide some insight into the answer to your question.

DR. GIACOMINI: Oh; Howard? I guess what I'm trying to do is get a feel--

DR. MCLEOD: Yes, there are no published data on colorectal. There are two studies included in the papers from--provided by Pfizer that looked at the UGT1A1*28 genotype and survival. They were both in the context of non-small lung cancer, if I recall correctly. And one of the studies found that the 7/7 genotype group from the star-28 homozygotes had a poorer survival. The other study didn't separate the groups quite the same way, but the group that contained the 7/7 genotypes had an improved survival.

Now, neither of them met statistical significance. They were all 0.06, 0.07 type things; small studies, no covariance; I mean, a lot of different issues. So my interpretation is we really don't know the effect of UGT1A1 on survival.

In the context of colorectal cancer, there is sufficient data, in my mind, to show that any one study is not really going to have the full answer on patient survival. So if you look at patient survival for the impact of first-line therapy is confounded by the presence of good second-line therapy, good third-line therapy, et cetera. And the Chornagon study demonstrated that. Didn't matter what you gave first from what Mark showed. If you gave the other one second, then, it was a wash in the end.

And so, in the context of response, there is some data that UGT1A1 may have an influence on response, although the numbers were small and not definitive. But there was no impact on time to progression or survival, and so, it's inferior data. It's as good as we have at the moment.

There are large studies in the cooperative groups that are going to be able to address this in a much more aggressive fashion because of sample size.

So I don't really know the answer. It appears there may be an influence on response, but there certainly does not appear to be an influence on time to disease progression, so time until the tumor grows again, or survival influence.

DR. VENITZ: Jeff?

DR. BARRETT: In thinking about dosing this agent, I'm struck with Dr. Pazdur's original comments when he talked about the fragility of the original dose selection of this compound and the modest response rate. So while I think most of the discussion is focused on managing toxicities, the loss of efficacy looms very high with this compound. But I guess the other curious thing I had in my mind is do we have any of the historical data in which dose reductions were, in fact, monitored where you could look at the responsiveness of these markers or responses as far as diarrhea and neutropenia go relative to a dose

reduction, so you can get some sense of, you know, how, in fact, responsive those toxicities are to dose reduction?

DR. MCLEOD: So that would be dose reduction regardless of the cause?

DR. VENITZ: Atik?

DR. RAHMAN: I'd just like to comment on something that we have in the package insert already. We have data on 100 milligram per meter square weekly dose, 125 milligram per meter square weekly dose, and 150 milligrams per meter square weekly dose, and what we have seen is that there is not a whole lot of differences in the response rates, although numbers are very small, so you cannot do a cross-study comparison here.

But the observation that we have from the package, and also, it is in the package insert is that the survival, median survival across those dosage groups is not a whole lot different so is not the response rates.

DR. PAZDUR: The additional point is that we do not know the relationship between response

rate as a surrogate for survival in this situation. I would like to point out that this drug had in the 5-FU refractory disease population a 15 percent response rate, yet it was able to show an overall survival advantage compared to best supportive care in two trials, which indicates to me that perhaps disease stabilization or some influence on time to progression is far more important than simply tumor reduction size.

DR. VENITZ: Dr. Williams?

DR. WILLIAMS: I think one of the most important questions to answer is what you're going to base your dose selection on for the 7/7s. Mark suggested, you know, not treating them as one option, but obviously, you are going to have to treat them. You cannot base it on a survival observation. You just don't have enough patients to make that observation.

So you're going to have to decide what to select a dose on, and your new study, perhaps, that's going to be done to look at dosing in that population. So what are you going to base it on?

I was sort of interested with Mark, would you base it on a targeted dose of AUC of SN38? That's a little unsettling, because the slide that Atik showed suggested that even with the same AUC, these patients had a higher degree of myelosuppression. You know, they were having grade four neutropenia all along the bottom of that graph up and down the AUC spectrum, so that's a little mysterious, and then, you ask, well how about from the pharmacodynamic standpoint for the tumor? Is the tumor equally sensitive to the same AUC of SN38?

So, I mean, I think you're going to have to target something. You can't, you know, you just can't look retrospectively at toxicity, and I'd be interested in what the Committee thinks when you do this new study to try to individualize dosing for these patients, what are you going to target?

DR. RAHMAN: I'd like to make a comment about the starting dose. What I have shown in my presentation that there is already a nice algorithm for a starting dose for standard therapy and continuous therapy and dose modification based on

toxicities in the package insert. And as I have mentioned that we have some predictive factors already in the package insert which are bilirubin levels, prior radiation therapy, performance status. Those are already indicating, recommending a dose level lower than the standard dose as a starting dose.

And then, if the patients do not have any complication with that, the package insert allows to go up to the standard dose and then move on with that. So here is the starting dose that we can be thinking about that can we do anything different for the UGT1A1 patient, 7/7 patient, I mean?

DR. MCLEOD: And to follow up on that, I wonder if maybe Dr. Morrison or one of the Pfizer team could comment on whether dose reduction is a covariant in terms of outcome, time to progression, whatever your favorite is, coming back to try to get at Jeff's initial question.

MR. MORRISON: Maybe if I could defer to Pat to comment on that, because this was actually before my time.

DR. MCLEOD: Lucky Pat.

DR. MCGOVREN: Yes, I don't have an answer. It has not been modeled. So I don't know--I think that the various risk factors were arrived at very empirically, and dose reduction was not done in any systematic way.

DR. MCLEOD: Well, Atik clearly and correctly mentions that there is a range of doses that seem to be equal. Those patients may have declared themselves as being different not only in their sensitivity to the drug but also for other factors, and so we can't say that just because we can start low, that means that people who are sensitive will still do well.

DR. PAZDUR: But there is an inherent bias in looking at the data that patients that may get the dose reduction are poor performance status or other issues that lend themselves to poor either responses or poor survival outcomes. I think it's clear, though, you know, having worked with this drug before I came to the agency and have had a long history, I think it would be fair to say that

we do not have a really good handle on what is the dose in its relationship to the eventual outcome.

You know, could we have achieved a similar outcome with a reduced dose? Remember, this drug was developed in a time when oncology had the mantra more is better, more is better, more is better, and we kind of were hitting toward what is the absolute highest dose that we could deliver, and this is common in many of the oncology drugs that we have developed over the past decade, and now, we're trying to step back and ask this question, which is very difficult to do.

You know, should we look at, for example, at these patients that have this genetic mutation to do just simply a phase one study, as we suggested, sometimes through the company to take a look at what would be the appropriate dose, starting out at an artificially dose reduction and seeing actually what the dose, because we really don't have a good handle, even in the general population, of what is a dose response for this drug. And we're basing it on toxicity, basically,

and that's--we have to be realistic on the development of this drug. That's how it happened over the past decade.

DR. VENITZ: Let me make a--

DR. MCGOVREN: Yes, go ahead.

DR. VENITZ: --followup comment that gets to item number B. I think right now, the concern is that if you reduce the dose, we might compromise efficacy. Well, but can you not turn that argument around? If you improve tolerability and compliance on a long-term treatment, don't delay treatment as a result of a lower dose, you might actually improve efficacy, not just compromise it. So to me, I don't know which way to go. As you pointed out, this drug was developed under the paradigm of an MTD.

So by actually backing off of the dose, you might get improved efficacy just by keeping more patients on drug.

DR. MCGOVREN: Yes, none of the trials, I don't think, were large enough to actually dissect out the efficacy in patients who started at the

standard dose and continued on the standard dose until their tumor progressed versus patients who started with the standard dose, were dose-reduced because of toxicity and then continued on a reduced dose versus those who started on a reduced dose because they had a risk factor at the time they went on treatment, performance status or whatever, and then continued on that reduced dose or even had that dose reduced because they couldn't take the -1 level dose.

So it's just very difficult to tease out of the available trials all of these factors which, of course, complicates how do you design to determine the appropriate dose for the 7/7s?

DR. VENITZ: Then maybe let me focus the Committee on the third part of this question: what would be needed, what would need to be done in order to figure out what to do with those patients in terms of coming up with a starting dose for patients that are 7/7 genotypes?

DR. SINGPURWALLA: Jurgen? As an outsider looking at this, the question is what is an

appropriate study.

Now, I can't answer that question as to what is an appropriate study, but one thought goes through my mind: electrical engineers use control theory to control the movement of something or to control the behavior of something. Has any thought been given to using a similar kind of a paradigm in this particular business? You start with a certain dose; you make a prediction as to what the effect of the dose will be; then, you observe the actual outcome and make a correction subsequent to that and keep on doing it in some kind of a filtering scheme.

That is a suggestion that I would like to put forward.

DR. MCLEOD: There are study designs that have used a variation on that theme, both in terms of trying to reduce the number of patients required to study in early evaluation and also try to make them more rapid. They've had variable success, and in the end, we've kind of fallen back to the status quo. But people are certainly aware of sort of

iterative-type processes. We just haven't figured out how to do them very well.

DR. SINGPURWALLA: Well, I'm surprised that you've said you've fallen back, because control theory is one of the most successful applications of process control, which is really a part of this, and I'm surprised why the study failed or why they regressed.

DR. MCLEOD: Well, it's a very successful theory in many industries. Biomedicine is not one of the areas where it has been a blazing success. And so, I think with the greater understanding of systems biology, it will be successful.

Currently, the endpoints that we talk about in phase one are incredibly crude, and crude endpoints don't lend themselves to intricate approaches such as what you described.

DR. SINGPURWALLA: Are these studies published? Is there any way I can read up on them?

DR. MCLEOD: Certainly.

DR. WILLIAMS: Let me sort of restate my question earlier. I think from a practical

standpoint, certainly, you could do a phase one study in these patients, right? And I think the question would be that's probably what you should do, right? Do a phase one study in the 7/7s; you find a reasonable toxicity.

But then, what are you going to use to provide yourself with the assurance you're in the right place? Will it be that you have the AUC that everybody else had with SN38? Would that provide you assurance, or would there be some other route? So I guess I'm just throwing out the possibility that you would do a normal type phase one study looking at toxicity and pharmacokinetics.

But then, what would you do, you know, to assure yourself that you're where you want to be?

DR. VENITZ: Marie?

DR. DAVIDIAN: I just wanted to bring up, related to that, there's been some recent work in the statistical literature by Peter Fall, who is at M.D. Anderson, and I was just wondering if any of his work would be relevant in looking at toxicity and efficacy jointly?

DR. WILLIAMS: I mean, I wonder, you know, in this setting, do you think that--I guess the only thing you could look at would be response rate in that kind of setting. I don't know--we have to talk to the statisticians, whether you could really study enough patients to do that.

DR. DAVIDIAN: I agree.

DR. VENITZ: Just a followup to your, I guess, subquestion here. I think that's the only way you can approach it with what we know right now. Doing a phase one dose escalation study and see what area do you accomplish? What's the corresponding dose?

DR. PAZDUR: But we really don't have a good pharmacodynamic relationship between any parameter and efficacy, either if one tries to look at response rate or any other clinical endpoint with this drug, and we have to be realistic about that. And I think also, it depends on what type of dose reduction that we're talking about with these 7/7 patients. If we're talking about a 75 percent dose reduction, that could be quite problematic.

If all we're talking about is a 25 percent dose reduction, I would feel a little more comfortable.

DR. WILLIAMS: Let me push back to my boss here. But what if it was a 25 percent dose reduction, and you had the same AUC? Would that help you? That's what I'm sort of trying to get at.

DR. PAZDUR: Yes, but we don't know as far as that would involve some comparison here, but we don't know, basically, that AUC correlates with response rate or doesn't.

DR. MCLEOD: And Atik's data says that AUC is not AUC in terms of risk of neutropenia.

DR. WILLIAMS: For these patients, anyway, right? There somehow seems to be a little bit of a difference in these particular patients' sensitivity to AUC than the other patients. That's what I took away from this graph.

DR. PAZDUR: But, Grant, I think that would give you a degree of some comfort here to have some parameter that you're achieving.

DR. VENITZ: Final words, Larry?

DR. LESKO: If we're thinking of dosing adjustments, whether it's a drug in oncology or not, we generally try to bring a quantitative analysis to the probability of an adverse event based on exposure, whether it's a renally-impaired patient or whether it's a drug interaction, and depending on the outcome of that analyses, we would reduce the dose to achieve similar area under curve. This is pretty much how labels are derived in terms of dosing adjustments for specific populations.

So that concept isn't all that foreign. It's actually the first principles of the way that drugs work. So I think in any study that would be conducted, the area under curve of the species that has been shown to correlate with neutropenia to date, which is the SN38 area under curve, would be extremely important to measure and then use as a guide along with other measures to determine what the appropriate dose would be.;

I also think you don't necessarily need a

prospective study. There are many studies discussed today, and not knowing the details of all of them, one could imagine that a study would be conducted in which efficacy or safety would guide the treatment and then having some genotype information in a retrospective fashion to associate the dose that was given and the appropriate outcome that was previously decided upon would be an extremely powerful correlation to have, coupled with area under curve to figure out what the right dose reduction ought to be.

MR. BELLO: Hello. My name is Akintunde Bello. I work for Pfizer clinical sciences. We just thought it's interesting and important to point out that there is actually a study that's going to be starting shortly that's actually looking at different doses and will be looking at genotyping as well as exposure, PK exposure for various moieties related to CPT11. So this is work that's ongoing. There's a study that's forthcoming and may give us the answers that we're looking for.

DR. VENITZ: Howard?

DR. MCLEOD: In the context of the cooperative groups, this issue has also come up, not just so much from a regulatory standpoint but from a clinical trial standpoint, and I'm wondering whether Dr. Ratain would be able at this point to comment on some of the discussion that's going on in the context of these patient genotypes. It may be too early for that, Mark, but if you want to comment, here's an invitation.

DR. VENITZ: Are you willing, Mark?

DR. MCLEOD: And if I put you on the spot, I'll buy you a beer.

DR. RATAIN: Thank you.

Yes, the CLGB has a study in development--CLGB is Cancer and Leukemia Group B--in which patients will be genotyped; patients with 6/6 genotype will be enrolled in a trial to establish the safety or potential safety of higher doses, as high as 500 milligrams per meter squared, based on the evidence from this European trial that some patients can tolerate 500 milligrams per meter squared, and the hypothesis that these are 6/6

patients.

And if, indeed, we can establish that, the next step would be a prospective randomized trial in the 6/6 genotype patients of 500 versus the standard 350.

I also, since I'm up here, I thought I would follow up on some of the previous comments about the pharmacodynamics of the activity. I don't think we know what correlates with activity. I think there is a fair amount of evidence that it's not the SN38 AUC, and in fact, in a study that we've completed and is in press in Clinical Pharmacology and Therapeutics, we have modulated the pharmacokinetics of Irinotecan with cyclosporin A as an inhibitor of transport and also inhibits CYP3A as well as phenobarbital is an inducer of glucuronidation, and activity is preserved in some patients despite very, very low SN38 AUCs.

So I would not recommend that one titrates dosing to--from an efficacy perspective to particular SN38 AUC. I think that is useful to guide neutropenia considerations but not from the

standpoint of efficacy.

DR. VENITZ: Okay; Larry, you want to move along to the next--

DR. LESKO: Yes, I'll just say the next two questions are obviously up there, and the first is not, I don't believe, a voting question, but nevertheless, it would be useful, again, to have some discussion of a context. Some of this has been covered already, I think, in the prior discussions, but if there's any other remaining comments on the question number three in terms of how a genotype could be complementary to preexisting information on risk and how it might be integrated into predelivery of the drug or simultaneous delivery of the drug would be beneficial.

Question four refers to some of the terms we had about performance and probability content information of a test, and one of the things that hasn't been discussed is the relative value of the expressions of a performance of a genomic test to clinicians in terms of understanding. We've heard

sensitivity, specificity, predictive value, odds ratio. There is one other, and that is the likelihood ratio, all of which are used in the literature to different degrees for these tests as screening tests, basically, and any discussion or comment people have on the relative value of these different tests in conveying the probabilistic nature of these genomic tests would be useful.

DR. VENITZ: Okay; then, I start with any comments to question number three. How would you incorporate PG information?

DR. WATKINS: Well, the point I made before is that this is, to my knowledge, a unique situation where you've got a xenobiotic--polymorphic, xenobiotic metabolizing enzyme that has an endogeneous substrate. So one of the biggest concerns in using host genotypic information to predict dose, particularly to escalate dose in the 6/6 individuals is that in fact, there might be a nongenetic factor or additional polymorphisms that would make that person susceptible.

But in this case, you have an endogeneous marker. You've got indirect bilirubin, which is a safety valve. So if you're missing environmental reasons or other snips, the bilirubin should go up, with the caveat that in total liver failure, serum bilirubin only rises about a milligram and a half per deciliter per day, so this would not be a sensitive measure of acute changes.

So, apropos question number three, I think the main unique situation here is there is an endogenous, built-in marker for the rare individual, or it doesn't matter how rare, the individual that would be 6/6 genotype but in fact would have low activity.

DR. VENITZ: Any other comments to question number three?

DR. MCLEOD: Just to follow up on that, Paul, I mean, it should be a surrogate marker, biomarker, bilirubin, but, I mean, from some of the data that was presented and some of the discussion, it doesn't seem to be a good biomarker. I mean, genotypes seem to offer something beyond the

current approaches. And I know there are approaches out there where you give a single dose of rifampin and then six hours later take a bilirubin level, look at induction or induction but the increase in glucuronidation. And there's other tests like that.

But in terms of something that could be used in clinical practice, baseline bilirubin in the context of multiple centers, from what Mark described in his JCO paper, wasn't a good marker. But yet, genotype wouldn't be influenced by those things. So genotype wouldn't be the answer, but it seems like an achievable answer.

DR. WATKINS: No, and I think the overall data is that bilirubin is not as good a marker as genotyping in this case. That wasn't the point I was making this time, which was the comforting thing is there's a built-in marker for someone who's very deficient in UGT1A1 but genotypes as having normal activity. So there's a built-in safety valve, which is really unique, to my knowledge, to this situation, which is very

reassuring and, I think, makes it easier to go ahead and push genotyping, knowing that there's a safety factor involved.

That wasn't implying bilirubin is better; it's just a safety valve here.

DR. VENITZ: Steve?

DR. HALL: I think one of the features of the UGTs is they don't have a high degree of specificity, you know. So maybe the 1A1 is a major determinant of bilirubin conjugation, but many others contribute a small part, and in the absence of one, they kind of all contribute something to the remaining activity.

So I don't think it would be surprising that the bilirubin wouldn't work as a good index of the enzyme, and I think the 1A family of the UGTs is complex. They're all this single locus. They have highly related polymorphisms that probably all contribute in some part to the overall bilirubin thing. So I don't think it's likely to be the surrogate for that single enzyme defect.

DR. BARRETT: I think if the question is

how to use this information relative to the other factors, I mean, you have a clear idea with the bilirubin and these other factors in conjunction with genotype as far as the directionality goes with Irinotecan, so as far as using it, I mean, I think there is a practical guidance that could come out of this, independent of the fact that it's not a perfect correlate.

So, you know, where you are today in terms of your understanding of this polymorphism, there is a directionality there. Whether or not people use it is another thing. I mean, I think the comment from Dr. Raitan was very interesting. You know, for the most part, there is a default to what's in the label as far as dosing guidance, but there's still a lot of empiricism. So the extent to which you can provide educated information to that empiricism, you should do it.

DR. VENITZ: Okay; then, let's move on to--Wolfgang?

DR. SADEE: Since you bring that topic up, I have to agree. Clearly, we have, for the star-28

allele, we have good information that it does make a difference. But what is missing is the information on what is the variability within these genotypes? And I don't think it's all that difficult to get. In fact, while we're listening to it, motivated to maybe look into this and maybe provide definitive numbers as to in a population of 500 people, when you look at 1,000 alleles, how often do you see that one is less than the other? And what's the variability within this one genotype?

I see this again and again with pharmacogenetics that translate into clinical trials, where there's a single genotype that's been isolated; for instance, the LPR for the serotonin transporter. And every single clinical study is using this, and there isn't even evidence that it does make a difference in where the gene is really expressed.

So I think in this case, there's very good evidence that we have a clear difference. We still haven't defined here how much does this difference

really cover of what's actually happening in the body? And so, I would like to really see that we take the first step, and we have all agreed that there is a correlation already with neutropenia, but the second step must be--we must have quantitative information: how often is this predictive? How soft is this information? And I think this needs to be clarified.

DR. VENITZ: Okay; then, last question, Larry, do you want us to vote on this, question number four?

DR. LESKO: Yes.

DR. VENITZ: Okay; so, first, let's have a discussion on do we believe as a Committee that current test has sufficient sensitivity and specificity to be used. And I'm assuming response predictor means toxic response predictor.

DR. LESKO: Yes, it does, and if there's any discussion of the question or other measures we haven't brought up to the Committee, that would be appreciated as well.

DR. VENITZ: Let me start making my

comment first. Obviously, the numbers that we've seen, that both Dr. Raitan and the Pfizer group has presented, the positive predictive value looks pretty low: 50 percent. The negative predictive value, 83 to 90 percent, very high. So now, we have to use my favorite concept of the utility concept. In other words, we have to use judgment, not just statistics.

So is a 50 percent positive predictive value, is that something that we deem clinically important? In other words, is that enough assurance for a patient and/or a health care provider to start treatment or vice versa? Is a negative predictive value of saying I'm 90 percent certain that with a 6/6, you're not going to develop neutropenia, is that comforting enough? And in my assessment, it is, based on clinical judgment, not based on the statistics empirically per se.

DR. PAZDUR: Could I just ask a question before we go on? And maybe this is to Larry or Atik: the meaning of this question, are you trying

to implicate in this question that all patients, before they go on Irinotecan, should have their status known? Is that what we're after here?

DR. LESKO: That's a different question. I don't think that's the question we were intending to ask. It was more directed towards if, as a physician, I'm going to treat a patient, and I'm going to use this test, I have to have some information about what the test conveys in terms of probabilities.

I think we heard about the sensitivity and specificity, and then, we moved to predictive values and odds ratios, so it's, for example, the question on the likelihood ratio would be if I tested positive, I would have a ninefold greater chance of becoming neutropenic. That's what the likelihood ratio would say for this. Now, what would that mean to the clinician in terms of, a, using the drug; monitoring the patient; using a lower dose; making other decisions, coupled with the knowledge of the bilirubin or other preexisting risk factors?

And I think it's important not to take the test in isolation in making these decisions but coupled with and complementary to the other information that would normally be at the disposal of the patient and the physician to make a decision. So I don't know if that answered the question. I don't think it's asking is there a need to prerequisite do the test before deciding to give the drug, but it certainly would seem to be useful, very useful a priori information.

DR. WILLIAMS: One of the points we had discussed internally was to look at the current label and some of the information that suggested you might want to dose-reduce based on these things, such as age, et cetera. And realizing that--thinking about, I wonder what the basis of that was?

So some things, we may have put in the label. You might wonder about how strong the evidence was there. I don't know if that relates to this. It seems to a little bit.

DR. VENITZ: Howard?

DR. MCLEOD: My followup question, the reason I asked Mark that question is is there performance data for these other factors, for bilirubin, prior pelvic radiation, performance--

DR. PAZDUR: It's very poor.

DR. MCLEOD: Okay.

DR. PAZDUR: And a lot of this has to do with how the clinical trials were done that led to the registration of the trials, because what we put in the labeling usually reflects the patient eligibility of the clinical trial that was done. For example, age was put in the label because the European trial restricted entry based on age. Whether or not that would occur now, I don't know, and we've heard from Pat that that probably doesn't make a lot of sense, and we need to revisit this.

So the data on this are probably not as robust as what we're seeing here, to be honest with you.

DR. BARRETT: You're going to appreciate you framing the question, because if I had to answer number four the way it's written, I would

say no. However, if you said to me would I vote for a test in which the negative predictive value was greater than 90 percent as far as an aid to dosing, I would say yes.

DR. VENITZ: Larry?

DR. LESKO: Yes, another way we tried to think about this question is really the question that we're trying to ask: are we trying to rule in a risk or rule out a risk? And I think that really reflects on the usefulness of the predictive values. If we're trying to rule out a potential risk with a high specificity, that would seem valuable to know that in terms of making judgments about the therapy with the drug as opposed to trying to rule in someone with toxicity. It gives an indication, but it's a little bit softer because of those predicted values.

So I think there's a context for these tests that have to be what is the question we're asking?

DR. VENITZ: Well the positive predictive value in my mind is so low because you have low

prevalence. It is only an average 10 to 20 percent of neutropenia. So you have to have a very specific, I mean, very, very sensitive test to have a high positive predictive value.

DR. LESKO: Well, the other question is you're exactly right: the predictive value is a function of the prevalence, and we know that's relatively low. Another way to think about the question is how does it perform in the context of other tests that are used routinely in therapeutics, in particular in oncology, where some of the predictive values are down around 10 percent?

Another way to ask the question is what is the predictive value in sensitivity and specificity if I want to detect a variant allele, namely, a 6/7 or a 7/7 patient? Now, you have a prevalence of about 50 percent, and then, you begin to look at predictive values; they're probably moving up on the positive side to 85 or 90 percent at that point, with a 50 percent prevalence.

DR. VENITZ: When you've seen Mark present

that it takes 20 patients tested in order to avoid one bout of toxicity relative to TMPT, where it takes 100 patients that need to be screened.

DR. LESKO: It was 300 to find one in the TMPT, so this is fairly efficient.

DR. VENITZ: Any additional comments in terms of question four before we vote?

Nozer?

DR. SINGPURWALLA: I was not sure whether you wanted some kind of a reaction to odds ratio versus likelihood ratio. Is that correct?

DR. LESKO: Yes, I think that would be useful, because both are used in the field of testing, of screening tests, and we'd like to hear what the Committee thinks or what you think about that.

DR. SINGPURWALLA: Well, perhaps I'm wrong, and maybe Marie can correct me, but I thought that the likelihood ratio is, in fact, the odds ratio when the model is a binomial model. So I think they are the same thing. And I was wondering why you wanted a comment on the

distinction between the two.

DR. LESKO: Because I'm not a statistician.

[Laughter.]

DR. SINGPURWALLA: Okay; so, here is my contribution to this meeting: they are the same thing.

[Laughter.]

DR. VENITZ: Any other comments, statistical or not?

DR. WILLIAMS: Another comparison that might be of interest is the design of a phase one oncology study. We usually consider, you know, you have one toxicity in three patients, and then, maybe you should look at a little more; or you have less than that, it's okay; you have more than that, it's not.

Well, here, I think 50 percent is--of grade four toxicity, it is kind of interesting. That really is above what we would say is the MTD, and so, to that extent, you might consider it's relevant. You're getting a patient population here

saying is above the MTD. So from that extent, you might consider it relevant.

DR. VENITZ: Okay; any other comments before we call for the vote?

[No response.]

DR. VENITZ: Okay; so, we are voting on question number four. The only friendly amendment, predictor means toxic response predictor, right? Because we're not talking about efficacy.

Okay; so, you have three choices: yes, no, or abstain, and I'm going to call your name.

Dr. Barrett.

DR. BARRETT: Yes.

DR. VENITZ: That's a yes but, right?

DR. BARRETT: Yes but.

DR. VENITZ: Okay; Dr. Capparelli?

DR. CAPPARELLI: Yes.

DR. VENITZ: Dr. D'Argenio?

DR. D'ARGENIO: Yes.

DR. VENITZ: Dr. Davidian?

DR. DAVIDIAN: Abstain.

DR. VENITZ: Abstain?

Dr. Derendorf?

DR. DERENDORF: Yes.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes.

DR. VENITZ: Dr. Hall?

DR. HALL: Yes.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: Yes.

DR. VENITZ: Dr. Sadee?

DR. SADEE: Yes.

DR. VENITZ: Dr. Singpurwalla?

DR. SINGPURWALLA: I'm afraid I have to abstain.

DR. VENITZ: The statisticians abstain.

DR. SINGPURWALLA: Well, I'll make a comment that if somebody starts with a yes, there is a high probability that the yeses will--

[Laughter.]

DR. VENITZ: Okay; Dr. Watkins?

DR. WATKINS: I'm going to abstain. I mean, we've all agreed that the test predicts neutropenia, but this is somewhere between that

answer and do we think all oncologists should be doing it, and I'm just not sure where the question really is in that spectrum, so I'm abstaining.

DR. VENITZ: Okay; so I'm going to vote yes, so we have three abstentions and nine yes, for a total of 12.

And I think that does conclude our morning session, so I appreciate you all's contribution.

We'll take a break until 1:00 for the open public hearing, and the Committee members have a room for lunch reserved in the restaurant right here in the hotel, Martindale's.

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

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

[1:08 p.m.]

DR. VENITZ: Our next agenda item is the open hearing, and we do have one letter submitted by Dr. Rowling, a member of the Committee who was, unfortunately, not able to attend. She submitted a letter for your information that is attached to your packages and will be posted on the Website.

Other than that, we have nobody here for public hearing.

Then, our next order of business is conflict of interest statement.

Hilda?

MS. SCHAREN: Hello.

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such.

Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability, and there are no products being approved. Unlike issues before a

subcommittee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special Government employees have been screened for their financial interest as they may apply to the general topics at hand.

To determine if any conflict of interest existed, the agency has reviewed the agenda and all relevant financial interests reported by the meeting participants. The Food and Drug Administration has granted general matter waivers to the special Government employees participating in this meeting who require a waiver under Title 18, United States Code, Section 208. A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

Because general topics impact so many entities, it is not practical to recite all potential conflicts of interest as they apply to each member, consultant and guest speaker. FDA

acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the subcommittee, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Paul Fachler and Dr. Gerald Migliaccio are participating in this meeting as nonvoting industry representatives acting on behalf of regulated industry. Dr. Fachler's and Mr. Migliaccio's role at this meeting is to represent industry interests in general and not any one particular company.

Dr. Fachler is employed by Teva Pharmaceuticals USA, and Mr. Migliaccio is employed by Pfizer. In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participant's involvement and their exclusion will be noted for the record.

With respect to all of the participants, we ask in the interest of fairness that they address any current or previous financial

involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. VENITZ: Thank you, Hilda.

The second topic of today's meeting is in regards of drug-drug interaction and will be introduced by Dr. Shiew-Mei Huang, who is the deputy director for sciences of the Office of Clinical Pharmacology and Biopharmaceutics.

DR. HUANG: Thank you, Jurgen.

Good afternoon. Before I talk about relevant principles of drug interaction concept paper that is published as part of the background information for this Committee's discussion, I'd like to briefly summarize some of the publication and discussion that happened to lead to a revision of this guidance.

Back in 1997 and 1999, we in CDER, with CBER, published two guidance documents for industry: the 1997 on in vitro drug interactions and 1999 on in vivo drug interactions, focusing on study design, data analysis, and recommendations

for labeling. Subsequent to the publication of these two guidance documents, we had various public workshops discussing different topics related to drug interactions.

We also had a lot of internal discussions, including CDER-wide scientific round discussions. There is one example of publication on one of the public workshop, and you have heard from Dr. Lesko. We have various internal documents. Some of them are published, such as the good review practices, where we have included important drug interaction questions to ask during the review of the applications. And we also have drafted a MAP, which is Manual for Policy Procedures about cross-labeling and also about in vitro evaluation of drug interactions.

PhRMA has published a white paper last year on general drug interaction issues, and as Dr. Lesko summarized earlier this morning that this advisory group, the Advisory Committee for Pharmaceutical Sciences and the Clinical Pharmacology Subcommittee, at a meeting last year

in April, we discussed the proposal of classifying CYP3A inhibitors, and we also touched upon PGP inhibition-based interactions, and in November, we talked about some of the emerging important enzymes, such as CYP2B6 and 2CA and their role in the evaluation of drug interactions.

So based on these discussions, the CDER working group with the contribution from CBER, we have drafted an interaction guidance, which is in internal review right now. And this will be published soon as a draft for comments, and when the guidance is finalized, this will replace the two in vitro and in vivo guidance documents currently posted on the Internet, where we have updated information and recommendations on drug interaction evaluation.

We also have this guidance to address some of the recent labeling rule change. In 2000, we had published a proposed rule about professional labeling of prescription drugs. The final rule will be published soon, with accompanying various guidance documents to talk about various segments

of the labeling.

So I'd like to talk about some of the principles that we discussed and the drug interaction concept paper which was released for discussion purposes only.

In this concept paper, we stress the importance that metabolism and drug interaction information to benefit-risk assessment for new molecular entities prior to market approval. We have learned our lessons from recent U.S. market withdrawal from 1998 to 2003. Note that this table was constructed prior to the withdrawal of Vioxx, so we did not include Vioxx in the table.

However, if you look at these 10 drugs that were withdrawn between 1998 and 2001, where they had been approved between 1985 and 1999, these 10 drugs with different characteristics and use; there are some antihistamine or cholesterol lowering. But if you look at these, the risks, five of the 10 drugs, the risk of drug interaction has contributed to withdrawal. And out of these five drugs, if we look at Terfenadine, Astemizole,

Cisapride, Cerivastatin, these are substrates of cytokine p450 enzymes or other enzymes or transporters, while Mibefradil is an inhibitor of CYP enzymes, PGP and possibly other transporters.

So these examples demonstrate that it is important to evaluate other drugs' effect on the new molecular entity and the new molecular entity's effect on other drugs. We have a recent example where a new molecular entity is a CYP3A inducer, and the risk of drug interaction has contributed to that drug's nonapproval. So again, we want to stress it's important to evaluate inhibition-based interaction as well as induction-based interaction.

Second principle I'd like to talk about in the concept paper is to talk about an integrated approach to evaluate drug interaction in vitro, in vivo, specific and population pharmacokinetic studies where when you look at the totality of data to estimate the potential for drug interaction, and this, hopefully, will reduce the number of unnecessary studies and to optimize our knowledge.

In the concept paper, we discuss that for

the evaluation of metabolic interactions, as far as evaluating the new molecular entity as an inhibitor, we said it's important to study the five major CYP enzymes: 1A2, 2C9, 2C19, 3A and 2D6. As far as evaluating as an inducer, since the 2D6 has not been shown to be inducible, here, we're stressing the importance to study the other four major CYP enzymes.

We know it's important to study other drugs' effect on the new molecular entity, so it's important to evaluate the metabolic profile of the new molecular entity. We think it's important to evaluate those five CYP enzymes, but when none of these enzymes are found to be responsible for the metabolism, it may be important to evaluate other CYP enzymes such as CYP2B6, 2C8, rarely 2E1 or other phase two metabolizing enzymes.

This morning, we have discussed how the genetic variation would affect a drug with a substrate for UGT1A1. Unless we know this drug is metabolized by UGT, we probably won't know how the genetic component would affect its metabolism and

its clinical response.

As far as inhibition, we have included an appendix to talk about how to evaluate in vitro, and we have indicated one parameter to look at possibility of in vivo inhibition based on in vitro data is to look at the I over KI, I as the concentration of an inhibitor, which we like to use a CMAX at a steady state at a highest dose and compare to a KI of get a five major CYP enzymes.

The PhRMA paper indicated I over KI of 1 or 0.1. More than 1 is likely to be an inhibitor. We did not specifically indicate what ratios, although we did mention when the I and the KI were separated by a very large--such as 50, then, it's not likely to have an interaction. However, we also indicated that we could rank order the in vitro data to determine and prioritize the in vivo studies.

For example, this is one new molecular entity. And here, the five major CYPs are evaluated. We like to look at the KI value. Sometimes, we don't have the KI values, because

when you have very high concentration, you still don't see inhibition. Sometimes, IC50 will be expressed as higher than the concentration being evaluated. So in this case, if you look at I and KI, you would say, well, this is a very likely event, and this one falls into probable, and this may not be likely.

In order for us to--we don't have a definite number to work with, I over KI ratios, so the suggestion would be to look at the KI in rank order, and you probably want to evaluate the CYP that's most potently inhibited first in vivo. If the results are negative, then, you wouldn't have to evaluate the other that's less potently inhibited, but if the results are positive, we couldn't extrapolate, and we need to evaluate the other CYP enzymes.

As far as induction, we have a new message in the concept paper. We say that induction can be addressed with in vitro methodology. In our previous guidance documents, we mention that induction can only be evaluated in vivo as a

technology for evaluation has not--there's insufficient data to support a use of in vitro. So we said we would look at the induction data based on in vivo at this point.

I have mentioned earlier, it is important to evaluate CYP1A2, 2C9, 2C19 and 3A. However, we are suggesting that the initial in vitro evaluation can be done with 1A2 and 3A. Part of the reason we thought the 3A could be coinduced with 2C9 and 2C19, so if the results from CYP3A is negative, then, you don't have to evaluate 2C9 and 2C19. Dr. LeCluyse is going to show us some data to support that argument later.

Again, we say negative results may preclude in vivo evaluation of the other important CYPs that we have mentioned that are important to evaluate in a submission. Unlike the inhibition study where we only say a positive control is optional, for induction, we say a positive control is recommended. For example, if you're evaluating CYP3A, we think it's important--we could use revamping as a positive control.

We think it's very important, since our recommendation is if the data is negative, then, you don't have to do in vivo. If it's positive, then, you need to do an in vivo study. So it's important how we define when it's positive. The original concept paper, we said we can either use a 40 percent of positive control as a cutoff or twofold of the negative control.

With subsequent discussion that when we look at both 3A and 1A2, there may be too much false positive if we use the twofold negative, so we have dropped it right now, and we are discussing, we are asking the Committee to comment on the appropriateness of using a 40 percent of positive control to suggest a possible induction, and this 40 percent number was based on the PhRMA white paper.

Ever since we have started to discuss the appropriateness of using in vitro induction methodology to evaluate induction, we have received quite a few comments. Well, then, it's now a need to conduct in vitro inductions for all new

molecular entities. And our answer is no. However, it's important to address induction. You can either use in vitro or in vivo. It's important to address, but you don't necessarily have to use in vitro, but it may be a good approach to start with in vitro. And then, if the results are negative, then, you're done, but if it's positive, then, you continue. This is sort of what I just said. Positive in vitro needs to be followed with in vivo.

And I want to mention that induction can be part of evaluation of in vivo inhibition studies. Oftentimes, we have seen inhibition studies carried out with Midazolam when we're evaluating the possibility of inhibition of CYP3A with Midazolam. And when the sponsor conducted a study with multiple dose, multiday evaluation, when the results are negative, you could claim that this is not an inhibitor. At the same time, you could also say it's not an inducer.

Study design data analysis is key and should be well thought out so that we can provide

important information for proper labeling. In our concept paper, we said we need to design a study to maximize seeing an effect. And we said that when you are starting with an inhibitor, we'd like to use the highest dose, shortest-dosing interval of an inhibitor.

A common question is always, well, if we are evaluating inhibitor effect using ketaconazole to evaluate a CYP3A inhibition, should we use 400 or 200 milligrams? Many of our submissions use multiple doses. And so, the question is really whether what is the dose level that should be employed.

The literature data has many studies using 400 or 200 milligrams. However, they have varied study design. The difference in study length, timing of coadministration or different populations, so it's difficult to compare intrastudy. And that's why later on, I will show a study where we compare within study, where the subject was given both 200 and 400 and make a direct comparison.

However, in one literature data, one publication has shown that ketoconazole CMAX concentration appeared to show a correlation with the inhibition effect on Midazolam. If you look at the AUC ratio where Midazolam was given with ketoconazole versus when it's given alone, you can see the ratio increase as ketoconazole levels increase.

This study was conducted only with one dose of ketoconazole, but this is the initial base of our recommendation to sponsors that we should use a higher dose of ketoconazole when conducting interaction studies, however, we did include a study to evaluate 200 versus 400 milligrams of ketoconazole as part of a collaborative research and development collaboration with Indiana University, and Dr. Steve Hall is the principal investigator for the collaboration.

And this is a preliminary result that was shown from that study, where Midazolam, after IV and oral were compared when it's given together with 200 milligram dose of ketoconazole or 400

milligrams of ketoconazole given for six or seven days. You can see that after IV administration, the extent of interaction is smaller as compared to oral. It's about fourfold after the 400 milligram dose, and it's about threefold after the 200 milligram dose.

After oral administration, the extent of interaction is much higher. The AUC ratio is about 15 after the 400 milligram dose; it's about tenfold after the 200 milligram ketoconazole dose. So based on the literature data and the study comparison that I just showed you demonstrate that CYP3A inhibition after ketoconazole is dose dependent with 400 milligram dose having a higher effect than a 200 milligram dose. And we believe that inhibition studies with ketoconazole should be conducted at a 400 milligram dose.

However, we have seen in many applications that a study is already being done with 200 milligram doses. So questions always come up: well, if you're already studying at 200 milligrams, do you need to conduct another study with 400? And

there are several cases where the sponsor went back and conducted a 400 milligram dose, and it showed a difference. The 400 milligram produced a higher extent of interaction.

There is also a case where a 200 milligram dose was already demonstrated to have a very large extent of interaction and is likely to result in a contraindication. In that need, may not need to have an additional study, because if you already know what 400 milligram results will--data will result in what kind of labeling; it's probably very similar. It's a contraindication. So in that case, you don't need to conduct another study. We need to look at the results and other information such as exposure response before we automatically request an additional study.

What about other study design issues? This one was not directly addressed in the concept paper, but it was frequently asked: can we use the cocktail approach where, in vivo, a mixture of pro substrates for three to five of the major CYP enzymes were given together with the new molecular

entity to evaluate the new molecular entity as an inhibitor or inducer?

We say yes, they can be used if they are properly designed; probes are specific; they do not interact with each other, and there are a sufficient number of subjects that are used in the evaluation and if the results are negative, then, we could preclude further evaluation. However, many of these cocktail studies used a ratio such as metabolic ratio in the urine or plasma level, and it's difficult to extrapolate to assess what would be the extent of interaction, unlike the studies that we used where you look at AUC ratios, where you know it's a fivefold increase or a tenfold increase. In that case, then, we may need additional evaluation to provide some quantitative information.

And again, we have seen cases where some of the older cocktails were used, and one of the probes may not be specific, and it may interact with one of the--it also affect the other CYP. The other--the data from the other CYPs can still be

used, and it could be used in combination of other in vitro-in vivo data. It could still provide useful information. Again, we don't automatically throw away data from a study just because it's not well designed and certain parts of a design.

Again, the design issue, we were often asked what kind of substrates or inhibitors or inducers that should be used both in vivo and in vitro? What concentrations of substrates should be used in vitro? We've been asked so many questions, and this happened always in a sponsor meeting. So the working group thought it would be good if we can provide tables in the concept paper on some of the proven or good in vivo and in vitro probe substrates, inhibitor inducers.

Earlier, we thought this may be too proscriptive, and the tables may be outdated frequently. And we thought we could address it by using a Web link so we can provide more frequent updates of the tables than the guidance itself.

And this is just one example of in vivo probes that we have included in the concept paper.

You can see, in addition to the five major CYPs, we also included information on 2B6, 2C8, since these are emerging, and 2E1, and you can see that in some of the well-defined polymorphic enzymes such as 2C9, 2C19 and 2D6, we also think that the evaluation of pharmacokinetics in poor metabolites of those enzymes and compare that to the extensive metabolizer, and this could be done in lieu of a drug interaction study.

We also indicated that for 1A2, since we couldn't find a good inducers, since omeprazole has not been consistently providing induction effect based on some of the criteria that we mentioned in our table that made these drugs onto the list, so we provided that perhaps the pharmacokinetic evaluation of smokers versus nonsmokers could be conducted in lieu of an induction study.

And this, I already mentioned, that the kinetic evaluation in poor metabolizer or smokers can be used, and we also mentioned, we put a statement that it may be important to evaluate interaction based on a pathway in poor metabolizers

of enzymes, of the other pathway, which is considered to be major and the extensive metabolizer. For example, if the drug is a substrate for both CYP2D6 and 3A, then, in poor metabolizer, the CYP3A may be an important pathway, and you may want to consider the evaluation of that pathway.

In addition, based on information that we know about herb, dietary supplement interactions, juice, food interactions, we thought it's important to also start to look at the protocols, and we provided some sample language that should be included in a clinical protocol when we evaluate drug interaction, so that when we look at the interaction results, they're not compromised by the unknown factors that are contributed by these other factors.

The concept paper not only discussed metabolism-based drug interactions, but it also included transporter-based drug interactions, although right now, we focus only on PGP-based interactions. In our concept paper, we mentioned

that if a new molecular entity is an inhibitor of PGP in vitro, then, we think a clinical study using digoxin may be appropriate. And we have discussed this in the April meeting last year, and this was just a summary of some of the data that are presented at that time.

This is the digoxin plasma AUC or steady-state concentration that's the ratio when it's given with these drugs or without. And you can look at some of the known inhibitors of PGP: quinidine, retonavir, verapamil, has increased the ratio to 1.5 to 2.5-fold. Here, grapefruit juice, aprepitant did not show an interaction.

The known inducers of PGP, St. John's wort, rifampin, has shown to reduce the plasma concentration by 20 to 30 percent. And we'd like to ask the Committee to comment on this point again.

So we talk about the new molecular entity as an inhibitor. What about it as a substrate? And we thought it's important to discuss it with the status of its CYP3A, whether it's a CYP3A

substrate or not. So we said in a concept paper if a new molecular entity is a substrate for PGP and CYP3A, and we have a lot of cases like this, then, the clinical study with a dual inhibitor or a multi-inhibitor may be appropriate. We just put in ritonavir as an example, because ritonavir affects multiple pathways, and here, we're just using example data from vardenafil labeling, where you see the AUC ratio of vardenafil when it's given with these compounds as compared to when it's given by itself.

And you can look at ritonavir, indinavir, ketoconazole. Vardenafil is a CYP3A substrate, and you can look at the strong CYP3A substrates have shown a large degree of interaction. It's more than tenfold, and here, ketoconazole is only given as 200.

The moderate inhibitor, I will explain about in the classification on CYP3A inhibitors later, but erythromycin has shown a little bit lower than fivefold increase in vardenafil.

This should show even these three

compounds are classified as strong 3A inhibitors, but they did show some differential effect. And so, there's a possibility that ritonavir, because of its effect on other pathways, in addition to PGP and other transporters that contributed to a much larger effect on the substrate.

So we say if a new molecular entity is a substrate of PGP but not a substrate of 3A, then, a clinical study with regular known PGP inhibitor may be appropriate. Again, it's hard to differentiate, because some of the compounds that are listed here are also 3A inhibitors, but they're not as strong an inhibitor.

And here, this is the same table I have listed earlier with digoxin, so you can see one of these PGP inhibitors could be used when we have a new molecular entity which is a substrate of PGP but not 3A. So we're asking the Committee to consider whether CYP3A status should be a key factor when we decide what kind of inhibition study to conduct, when the drug is a PGP substrate and also whether we have sufficient data to recommend

routine evaluation of PGP interaction if a substrate, if a drug is a substrate of PGP.

Finally, the last issues regarding study design: we put in some statement in the concept paper about the use of multiple inhibitors or multiple impaired system. When we evaluate the possibility of a serious adverse events such as we use the QT prolongation to assess the probability of trassar DuPont's, we have recommended in the QT concept paper, actually, it's an ICH document right now, to use perhaps a strong inhibitor of the major pathway.

In addition, we have seen examples where either the reviewer has recommended or the sponsor has conducted that multiple inhibitors--this is different than multi-inhibitor. It's a multiple inhibitors to attack different pathways or, using one inhibitor for one pathway in poor metabolizers of the other pathway in the evaluation.

And we have examples such as telithromycine. An inhibitor such as ketoconazole was used in the evaluation of a QT prolongation to

obtain maximum exposure. We also have cases where a strong inhibitor was used, for example, when we evaluated vardenafil. A separate study prior to the QT evaluation was conducted to estimate what the maximum exposure that's attainable with a strong inhibitor; then, use that information to design a high dose study to evaluate QT prolongation.

Finally, though not directly related to this issue, we think the use of multiple inhibitors of one pathway is also important. Particularly, right now, we're talking about possibility of classifying CYP3A inhibitors to moderate inhibitors and possibly monoinhibitors. That was suggested in the PhRMA position paper, and we have research ongoing again with Indiana University, looking at multiple moderate inhibitors' effect, whether they would be additive or synergistic or producing an effect like you're giving a strong inhibitor.

Next point I'd like to stress is this is the same point that we have stressed in the previous guidance in 1999, that it's important to

establish a therapeutic equivalency boundary for the new molecular entity, so we will be able to interpret the extent of interaction based on interaction studies and what to put in the labeling.

And here, I am going to present a hypothetical case where we use combined data from different applications. This new molecular entity was given with ketoconazole, a strong 3A inhibitor. This new molecular entity is a 3A substrate. And you look at the CMAX increased by fourfold.

The moderate inhibitors: erythromycin, verapamil, increased by threefold. The AUC showed similar effect. I put CMAX here because one of the adverse events was believed to be related to a maximum concentration.

And we look at exposure response data, where from the safety and efficacy database, we try to relate the exposure to one of the endpoints for efficacy, and one of the endpoints was adverse events. Here, I simplified the outcome. Actually, we have several endpoints for both efficacy and

safety. And based on the data, between 15 and 60, the exposure, consider that the drug will be efficacious and safe. However, because of ketoconazole's effect, it's varied. It's very large. We think it's important to advise against abusing strong inhibitors with this drug.

For moderate inhibitors, if you approve the dose of 15 and 30, since if you give 30 milligrams, and the moderate inhibitors will increase the exposure to outside the safe and effective exposure range. So we would recommend to use a lower dose.

My final point is that labeling language needs to be useful and needs to be consistent. In our concept paper, where we said that if a drug has been determined to be a sensitive substrate or a CYP3A substrate with a narrow therapeutic range, and I'll explain a definition later, and it does not need to be tested with all strong or moderate inhibitors of 3A in order to warn about it in the labeling.

And in the concept paper, we gave

examples. We have many tables. And one table is, well, strong, examples of strong 3A inhibitors or moderate CYP3A inhibitors. Here, the strong 3A inhibitors, we have included. The definition is any substrate, any--if an inhibitor, if that caused more than fivefold increase in the area under the curve of a CYP3A substrate. And that's not limited to Midazolam, then, we listed it as a strong inhibitor.

The PhRMA paper specifically talks about Midazolam. But since there are many strong CYP3A inhibitors, we do not have Midazolam data, and we think it's important to include these strong inhibitors in the table, since we do have information from the other.

The moderate inhibitors, we have similar definition with a PhRMA white paper, except we added some specifics. We said that a moderate inhibitor is one that caused a more than two but less than fivefold increase in area under the curve of a sensitive substrate. It has to be a sensitive substrate, and the inhibitor needs to be given at

the highest dose and lowest, shortest dosing interval, so that we won't misclassify a strong inhibitor because a study was conducted with a low dose, a long dosing interval, or it's not--it was conducted not with a sensitive substrate, so you may underestimate the extent of interaction and therefore misclassify.

And one example I've already shown that even the study was only conducted with ketoconazole for a strong inhibitor but it does not prevent us from labeling it with other strong inhibitors. And for moderate inhibitors, even only done with erythromycin and verapamil, we will be able to label with the other additional moderate inhibitors.

In the concept paper, we also mentioned that if a drug has been determined to be a strong inhibitor of 3A, it does not need to be tested with all sensitive substrates or substrates here specific about CYP3A with a narrow therapeutic range. And in the concept paper, we included examples of sensitive substrates or substrates with

a narrow therapeutic range.

This is a new definition. The PhRMA white paper did not discuss a sensitive substrate in the definition. And here, we defined that sensitive substrates are drugs that AUC will increase fivefold or more with an inhibitor. It doesn't have to be a strong inhibitor; any inhibitor.

A CYP3A substrate with a narrow therapeutic range: this would be applicable to drugs that are not a sensitive substrate. However, the increase in exposure because of coadministration with a CYP3A inhibitor may result in serious safety concerns, such as trussar DuPont, so you can see there are quite a few drugs: cisapride, astemizole, terfenadine; these were removed from the market but are included in the table just for illustration purposes.

An example of a labeling based on this table would be--I'm using telithromycin as a case. This drug, when, it's given with Midazolam, increased the area under the curve by sixfold, so in definition, it's a strong inhibitor. So in the

labeling, we said telithromycin is a strong inhibitor of the cytochrome p4503A, and we also said the use of simvastatin and other statins here concomitantly with telithromycin should be avoided.

We also said that the use of telithromycin is contraindicated with cisapride and pimozide. And you will notice, based in the information in the summary of our study, we did not evaluate all of these drugs that are listed here. For sensitive substrates, we only evaluated with simvastatin, but it does not prevent us from listing other sensitive substrates.

For substrates, CYP3A substrates with narrow therapeutic range, the pimozide was not evaluated. But again, because of what we classify it as a substrate with narrow therapeutic range, we put it in our labeling. Right now, we have various discussions on how to label strong inhibitors; what sensitive substrates to put in the labeling when we are evaluating one, and we may come up with a different list. Therefore, we think it's important that we publish the labels and constantly update it

so that we have consistency among the labeling of different drugs.

So in summary, we think metabolism drug interaction is key to benefit-risk assessment, and I think based on today's discussion, we probably will add some transporter information as well. An integrated approach may reduce the number of necessary studies and optimize our knowledge. Study design data analysis is important and information for proper labeling, and we have devoted many pages of our concept paper on study design, and we've also added an appendix on the conditions of in vitro evaluation: what are the study design and data analysis issues?

The thing we need to establish, therapeutic equivalency boundaries, so we can have proper interpretation of the clinical outcome and put it into a useful information in the labeling, and we have added tables of classification of CYP3A inhibitors, substrates, to hopefully that we have consistent and useful labeling.

And I'd like to acknowledge the drug

interaction working group. It consisted of many members from our office, the Office of Clinical Pharmacology and Biopharmaceutics; from individuals outside our office, the Office of Pharmaceutical Science; individuals from CBER; some of them have joined us after the reorganization and also from the Office of Medical Policy.

I think my time is up. Do you want to take any clarification questions?

DR. VENITZ: Thank you.

Any comments or clarification questions for Shiew-Mei by the Committee?

DR. JUSKO: I have one.

DR. VENITZ: Go ahead.

DR. JUSKO: Shiew-Mei, that was very clear and impressive. With the study of the ketoconazole interaction that you showed, I didn't see that using 400 milligram ketoconazole was that much better than 200, and I would have come to the same conclusions with either dose. Why are you so firm on 400, where there may be some additional negative aspects as opposed to 200?

DR. HUANG: The example, since we use a sensitive substrate with Midazolam, you probably can see, well, 200 milligrams already gives you a tenfold increase, and we probably will classify to say not to use it together with some more sensitive substrate already.

If the exposure response data are such that, then, you don't need to do another study. However, we have a lot of compounds where CYP3A is part of the pathway. So in that case, the results are not clear cut. We did have one example where a threefold and fivefold difference, from these two different doses, and it would make a difference. For example, one of the examples that I showed you, the moderate inhibitor and strong inhibitors, one shows fourfold; one shows threefold, and we do have a different proposal for labeling, because depending on the compound's exposure response, fourfold increase is going to take you outside that safe and effective exposure range; then, you would contraindicate. But if it's threefold, it may still be within the range, and you can either using

a dose reduction in the labeling to address that issue.

So for less sensitive substrates, the difference, three to fourfold or versus one to twofold, it will make a difference in the proposal and the labeling.

DR. GIACOMINI: Do I have that--yes, Shiew-Mei, that was an excellent and very clear presentation. I just have a couple of comments related, of course, to transporters and how we have to begin thinking of not really metabolism but more metabolic pathways, which would include maybe an influx transporter, the enzyme and then an eflux transporter, which may be all part of a pathway.

So when you've indicated here, and you've got particularly sensitive substrates, and you have examples of inhibitors, and many of these are dirty; they'll inhibit different things along the pathway, and I think it would be helpful in this paper at some point to at least indicate what may be a dual substrate and a dual inhibitor, and are you planning to do that dual, triple, whatever?

DR. HUANG: There are a lot of publications that did suggest this, and what we want to put in the guidance is where it's going to be useful in the study design or in the labeling, what's going to be translated to a clinical setting. So any information that may not be helpful; for example, if we say we evaluate this drug as an MRP substrate, and we know it's both CYP3A and MRP.

However, we really couldn't recommend to a sponsor a certain type of study to conduct besides a PGP. We do have some proposals; or we don't know what to do with the data, and how would that help prescribing a physician or health care provider's? Then, we don't think that that will belong to the guidance. It will belong to the literature, and we have enough information to make a recommendation under this case, what should you do in your study design? Then, we will include that in the guidance.

DR. GIACOMINI: I mean, I agree with you. I hear what you're saying, but it seems to me like

if somebody has done some kind of an inhibition study, they may make an interpretation; they're going to use that to make some kind of an interpretation, and you're focused mostly on the interpretation as it relates to the dose of the drug. But I'm just wondering about even a mechanistic interpretation by at least indicating that certain substances may, certain compounds may be inhibitors of both a transporter and an enzyme, that some caution in the--especially, you're going to extrapolate, right? Because you're going to say well, now, that we showed this, you better be careful for all of these, all of these compounds, which may also be substrates of CYP3A4 when, in fact, the transporter was the bigger part of the interaction, and that wasn't--

DR. HUANG: Yes, well, I would welcome the Committee's discussion, because I did have some question to see what other transporter that should be evaluated. But you will notice, even we put all the tables, when we want to translate one study to the others and put in the labeling, we only provide

some very specific information. For example, we say ketoconazole, an inhibitor, and whatever happens with that result, you can translate to the others.

When a study was conducted such as a cyclosporin study, and with rosovostatin, when we couldn't translate that in the labeling, we only said when cyclosporin increased rosovostatin by sevenfold, and therefore, the initial dose should be this, and we do not translate that to others.

So until we know more, then, I think we will be able to put in the table and put in the guidance you're suggesting.

DR. DERENDORF: I'm very happy to see that induction is addressed, and that was overdue in both in vitro and in vivo. Now, in the in vitro part, I have a question: it says if 40 percent of positive controls suggest possible induction potential, does that mean, first of all, 40 percent of what? What will be the measure? And the positive control will be defined, because otherwise, you can change, you know, the percentage

based on your control.

DR. HUANG: Yes, you will hear more from the subsequent speakers, but I can say in our guidance, we--sorry, concept paper, we did recommend that, for example, with CYP3A, you look at revamping induction, and we use the enzyme activity, the fold increase in enzyme activity. So if it's increased tenfold, then, 40 percent would be fourfold.

DR. DERENDORF: With respect to the in vivo, you have the classification of strong and moderate with two and fivefold increases in exposure. If we apply that to induction, would that mean that a fivefold decrease in exposure would also be the border between moderate and strong?

DR. HUANG: Well, we did propose that at the April Committee meeting last time, and the comments from all of you was that we don't have sufficient data to indicate which one is a strong inducer, and we just don't have the information. But I'll be happy to revisit that if the Committee

thinks it's proper that we do that.

DR. HALL: Yes, could you comment on--you've done a really good job of talking about when to conclude something is an inhibitor, but when it came to concluding that it was not an inhibitor, you somewhat skirted around that. And I think, you know, there are clearly labeling advantages to being able to conclude it's not. You mentioned you have no recommendation, but the former working group did come up with a recommendation.

And it seems like that would be an important thing to address.

DR. HUANG: Well, I'd love to hear the Committee's recommendation. The PhRMA white paper, as far as inhibition, it says if I over KI ratio is more than 1, it's likely; if it's between 0.1 and 1, it's probable, and I believe it's--when it's less than 0.1, it's at least--well, I don't remember the exact words, but it's not likely. And we do have, we have cases where the ratio of 0.1, you still see some interactions.

So it is difficult to say--I mean, rare occasions to say that it directly translates, especially for 3A, since the inhibition, I mean, the induction could happen--I'm sorry, fall back; inhibition could also happen in the GI tract. So when you use the equation, you might be able to come up, to derive an equation to say, well, 0.1, it's going to result in very small extent of interaction.

But if you consider the other components in the GI and also the uncertainty of the concentration in the hepatocyte as compared to what we are using right now, plasma concentration, and that's why we are using a more conservative approach. We did not use exactly 0.1, although we did mention when you have a large gap between I and KI, and we put in the numbers and say if it's fiftyfold, then, it's not likely there's interaction. I know it's a very conservative number.

And that's why we're proposing perhaps we could use a rank order evaluation. Any time in

doubt, you probably want to study with the one with the strongest inhibition, that is, the smallest KI. And if the in vitro data, in vivo also show no interaction, then, you do not have to do the other studies. If there are other alternative approaches, the working group will be very willing to listen to the suggestion.

DR. SADEE: Shiew-Mei, I have a comment and maybe a question about HIV therapy, which takes advantage of many of the agents that you have shown to be interacting, so we expect a lot of interactions. Now, in that case, physicians use retonavir to, in fact, as a dosage sparing agent; in other words, you block probably PGP; you block 3A4 and a number of other cytochromes by adding retonavir; then, you systematically adduce the other agents because of that knowledge.

Unfortunately, these patients are also given statins. They're given antineoplastic agents, antidepressants, you name it. So this is the inverse usage of the information of inhibitors, and it appears to me that it has tremendous effect

on the adverse effects that are pretty prevalent in HIV patients. So is this something you also want to look at, or I was personally very surprised to hear these relatively nonchalant views of the inhibitors to spare other agents, whereas, to me, it would induce a lot more problems.

DR. HUANG: Yes, you mentioned kalitra, which is a combination of retonavir and lopinavir, and a low dose of retonavir was used to increase the exposure of lopinavir to its HIV therapeutic effect. In that case, there's no difference in how we treat the evaluation of kalitra as an inhibitor or inducer if it's submitted today. So we have the package included many interaction studies based on that we already know retonavir is a CYP3A inhibition, and there are many studies that were conducted because of the nature of the HIV therapy, and many of these studies, the results were summarized in a table format, and there's also certain for kalitra, I think most of the study results were summarized in tables. I don't think there's extrapolation of the conducted study.

And this is true for most of the HIV therapy. When you submit a new molecular entity, this drug's effect on others will be evaluated as a standard procedure almost the same as what we have described in the concept paper. If you're going to evaluate multiple inhibitors, how that would effect, and I think there's some ongoing research project that we hope to conduct using modeling and simulation and just see how different the various inhibitors or various pathways will result in an extent of drug interaction.

And the study that we're conducting with Indiana, and it's only a very first step to looking at multiple inhibitors of one substrate, how would that conduct? How would that compare to a simulation outcome? And what you envision is much more complex.

DR. WATKINS: You know, that was a great presentation, and I think it's a great idea to try to merge the two old documents and come up with new guidelines, but I suspect to industry, it's not going to be reassuring that the reason to do this

is that we can now Web link the different substrates that could change week to week is sort of the implication.

But I think the document then needs to stress the fact that unfortunately, this is still a work in progress. We really haven't refined the probes, for instance, for PGP and the issues Cathy was bringing up of separating out transport from metabolism and the interactions of transport and metabolism. And the last thing you would want is with the publication of this guidance for upper management in a major pharmaceutical company to feel that this had been solved and that the scientists could be put onto other projects, because there's so much work left to do in the area.

DR. HUANG: Right, we--the idea of the Web link tables is, I think, because the last guidance was published in 1999, and this is not likely to be finalized until 2005. So it's a six-year gap. And with the Web link, I think we can do maybe more frequent than every six years.

DR. REYNOLDS: I just wanted to address the ritonavir issue. When a company is evaluating an HIV droug, and ritonavir will be part of the regimen, we really consider the drug plus ritonavir the drug. So if the drug will be given alone, or if it will be given with ritonavir, we expect them to look at it both ways, and we consider the interactions very seriously.

DR. SADEE: On that also, interactions with statins, for instance, which are very often given or metabolized and transported by very similar gene products.

DR. REYNOLDS: Right, so we would expect to understand the interaction of the protease inhibitor plus ritonavir on the statin.

DR. BLASCHKE: I think coming back to Wolfgang's point, as you're saying, I think, virtually all patients who are getting a protease inhibitor for HIV are also getting ritonavir, and what I think it speaks to is probably the importance--and they're also getting these multiple other drugs, whether they're statins or CNS active

drugs and so forth, and it probably really speaks to the importance of most drugs in which we think there's any possibility of using that in HIV-positive patients, that the ritonavir should be one of the drugs that is studied rather than some alternative.

DR. VENITZ: One comment: as you know, I'm very much in favor of using this approach to minimize the amount of studies that need to be done. One concern that I have, and I mentioned that before, is whenever you talk about dose adjusting based on either inhibition or induction data, you're basically trying to match areas under the curve or something like that for the parent drug.

What you don't necessarily consider, and I suggest you incorporate that in your paper, in your guidance, the change in the metabolite profile. You're reducing the dose. It's not the same as inhibiting a particular pathway. You all of a sudden have a metabolite in higher concentrations than it would be, okay? So I'm not sure whether

that's relevant for specific drugs, but it may well be, depending on whether the metabolite contributes to activity, meaning safety or efficacy.

But it's something that I haven't seen in any of the documents that you've provided us.

DR. REYNOLDS: Correct, yes.

DR. VENITZ: Okay; any other comments or questions?

[No response.]

DR. VENITZ: Then, thank you, Shiew-Mei, and our next speaker is Dr. Keith Gottesdiener from Merck, who's going to give us the scientific perspective.

DR. GOTTESDIENER: Thanks very much for inviting me here today. Before I start, I'd just like to also let you know that many Merck colleagues helped me to put this talk together, and I just wanted to acknowledge some of the people who had actually worked on this talk as well.

It's a real pleasure to be here today. I'm in charge of early development and clinical pharmacology at Merck, and to a great extent, what

I do or a major part of what I do every day, every month, every year is really looking at this question from inside the industry as opposed as to from outside. Of course, the FDA is very interested that the packages we put together and we submit for registration of a drug be complete.

In a sense, I get to do that sometimes months and years ahead of the FDA, and it's really my job to really make sure that package is robust and to try to put it together. And so, in a sense, I think that both myself and the people in the industry who do these kinds of things have a very unique perspective. We get to see a lot of compounds that never really make it past this evaluation stage as well as those that actually go forward to filing, and I hope I'll share some of my thoughts with you today.

I can assure you that senior management does not think that this problem is solved yet today, and I'll point out some of the issues. I wasn't able to really participate in the last meeting where you talked about induction, but some

of the questions that came up to Shiew-Mei are exactly very similar to the kinds of questions that I would pose as well: how difficult it is sometimes to do this in a real life situation.

So what I'm going to do is talk just a minute about the approach to assessing drug interactions. I'll talk about the many areas of agreement with the concept paper that exist, which I really have to applaud. It's a real step forward. I'll mention a couple of areas where I think there's really some further discussion, and I just pick three today: induction, transporters, and this issue of multiple inhibitors, multiple impaired.

I'm not going to cover specific comments on the concept paper. I do have many. I've shared some of them with Shiew-Mei as well. The study designs, the tables, et cetera; when that comes out as a draft guidance, I'm sure I'll have plenty of opportunity to comment, and nor was I going to spend much time talking about specific comments on the questions to the Committee.

What I wanted to do was focus on the approach to some of these issues. When I think about approaching, assessing drug interactions, I'm really probably saying this slide or two, I'm probably talking to the wrong audience. I often have to explain to people what the approach is. But clearly, the issue is how should we adjust the dose of a substrate drug in the presence of an interacting drug? And which DDIs and which drug interactions to study, how to answer that question?

And clearly, we're moving from the past, when this choice was largely empirical by the likelihood of coadministration, clinical consequences of the interaction towards a science-driven approach, particularly where feasible. You know, we're using preclinical in vitro studies to determine in vivo studies, in vivo studies using probe substrates and really robust study designs. But clearly, I think there's ideas where the science is evolving and the necessary tools and the probes are still lacking.

We also think it's important, again, like

the FDA, that there be prespecified criteria to compare the PK or PD measures to the drug in the presence and the absence of the interacting drug, and clearly, this is based on the safety and the efficacy profile of the substrate drug, the therapeutic index, the clinical context of the use of the drug, which I think actually is quite important and very hard to capture in the guidance and the concentration and response data for the substrate, which is obviously something this Committee is very interested in, and so are we.

One thing, though, I do want to emphasize is often, this is not clearly positive or negative. It's very difficult if something is or is not an inhibitor; it does or does not have a clinically relevant effect on one drug or another, and actually, probably, the one comment I'd make about the questions today, it will probably be the only one, is the questions are really framed as either-or. If it is an inhibitor, this is what you should do.

And in many cases, I think the guidance

the Committee is going to give, and it's going to be quite interesting; my problem is trying to decide is it an inhibitor or not in many ways, and I know that the FDA struggles with that very question. For the NCE or the NME, the data is often quite limited; concentration response info is always better for efficacy than it is for safety, and I still think there's many areas for probe substrates, where there really isn't much consensus, even though I think we've come quite far. And as I'll point out today, induction in particular is problematic.

But let me talk first about all the good points. I think that the integrated and scientific approach is clearly the right step forward. I think we've made a lot of progress and clarity on CYP interactions, especially the in vitro-in vivo correlations and the clarity on the substrates, inhibitors or inducers, though I do have to comment: somehow, simvostatin is on the list of sensitive inhibitors twice, and I didn't know if that was a hint from the agency to Merck or not or

whether it was just a typo.

I'd certainly agree with the use of PK in poor metabolizers where appropriate. I think the robust study designs is really important, and in many ways, I applaud the efforts and the question, the slides that Shiew-Mei showed, for example, on doing a ketoconazole interaction study. Having read that literature for many, many years and struggling with that issue day by day, the issue of whether you're going to do 200 and 400, whether you're going to dose one day, three days, five days or a week, those are real issues that have real impact on how the results come, and it's all too easy to pick a study design that really will, in a sense, manipulate the result so that it comes out the way you'd like it to rather than the way it's most scientifically correct.

So I think really, we're going to be in much better shape as we start to look at robust designs and receive, you know, gain a little bit of clarity on which ones really give us the best information.

I also applaud useful and consistent labeling language. Part of my job is to read to every new label that comes out and see what the FDA says about every new drug, and I understand the desire to be consistent, really quite hard in the field of drug interactions, and I'm always so struck about how difficult that is. And of course, then, I also get to compare it to what happens in the EU and the rest of the world, where a whole new variety of approaches come forward as well.

So I think that this is a real step forward, but I do think there still needs some discussion on how to label moderate inhibitors, how to define sensitive CYP substrates, and I must admit: all the devil is in the details. So while I agree with the principles the FDA has said, it's really going to be what's in the tables and how it's translated into labeling language, I think, that I'm going to be very curious to see.

So let me talk now about some of the issues that I think are worth discussing, where I'm not sure I fully agree with the concept paper or

some of the issues that you may grapple with today. And I think about things very, very practically. You know, where are we today with in vitro predictions of in vivo drug-drug interactions? And I think ready for prime time. You know, we really understand where we are; things related to CYP inhibition, particularly for the five major CYPs.

I think almost ready for prime time are some of the PGP interactions, UGT and some of the other CYPs, I won't talk about them today, and CYP induction. And there, actually, I think there are some issues with the tools we can use in vitro, but I also think there's many more issues actually in the in vivo studies that follow, because in the end, as I look at this, it isn't only an interest; it isn't only of interest to me to try to predict from in vitro what is going to happen in vivo, but there's also the issue of how do I interpret what happened in vivo, obviously, into something that's useful, so that we can actually use the drug properly?

And then, I really think that many things

are not ready for prime time, though I applaud the science moving forward. Most transporters, to me, still are in this gray, murky area where I have a very difficult time understanding how to use them. And I'll also point out some of my difficulties with multiple paths of inhibition as well.

So induction, I don't have to talk to you about. There's a lot of concerns for induction. Mostly, it's related to the reduction in therapeutic efficacy. Auto-induction is also a big concern; rarely the imbalance between toxification and detoxification. It's dose and time dependent. The study designs become really quite important here. It's dependent on clearance and route of administration. Again, a study design issue, and I should also point out it's a concern with both initiation and discontinuation of an interacting drug.

We have many models or many tools now to talk about CYP induction, and animal models were previously used. You know, it wasn't that long ago that that happened. When I arrived at Merck nine

years ago, the only way we really assessed induction was by doing high dose, short-term studies in rodents instead of looking at liver weights and science of induction.

You know, nine years is a very short time. And today, we're talking about, really, a whole new category of tools. Dr. LeCluyse is going to talk about that. But clearly, those were poor predicters. We looked at those, and we shrugged, and we went ahead into the clinic, and we had no idea what to do with the information.

Nowadays, the in vitro models are much better: the assays, the primary culture of human hepatocytes, and they're very, very--clearly, very, very helpful in the selection of drug candidates. And in fact, in many ways, that's where their most helpful nature is. We rule out enormous numbers of candidates, because they're really positive in these assays overall.

But I will also tell you it isn't always that easy. It sounds like it's great: you set a criteria; you cross off a drug candidate, and you

move on. As targets become more complex, the chemistry becomes more complex; the size of molecules increases, more and more whole areas of structures actually carry some risk of induction. So in many cases, we're not able to cross off those candidates, and we have to bring them forward into the clinic.

But the problem I have is still is it quantitative in vitro-in vivo prediction possible for induction? And I think there's many factors that complicate that in vitro-in vivo extrapolation, particularly inter-individual variability; plasma protein binding; multiple mechanisms as well.

Now, I wanted to share with the Committee some idea of what I actually see as a vice-president of clinical, you know, pharmacology, drug development. This is the kid of data I see. These are hypothetical drugs. None of them is real. But they're all based on drugs that actually have made it into the clinic. And as you start to look at this, you can see some of the things that

come forward and some of the complexities.

I picked five drugs where the mouse five-day study was actually negative, okay, just to sort of get that off the table. You can see the human PXR data, the mRNA data. Those are percent activity of a rifampin control at 10 micromolar; the enzyme activity in human hepatocytes, and I put over on the side something that I also think is important is really what the CMAX concentration was in the clinic. Sometimes, that's a predicted value; sometimes, it's an actual value when we get into the clinic, and we understand efficacy.

And you can see, if you looked at any one of these drugs here, the question about should we or shouldn't we do an in vivo induction study is really quite difficult. Now, I wish I could tell you what these five drugs were. More importantly, I wish I could tell you what the results of, for example, Midazolam studies were for those five drugs. Many of them have not progressed far enough in the clinic to have that evaluation, but this is the kind of data we grapple with every single day.

And the question I ask myself is which ones really need an in vivo study? And I don't really know. So at present, I could probably only say that we can predict a likelihood of CYP induction; highly possible on one hand; less likely on others. And I kind of gave some examples of things where at least they fell into the possible range going forward, and most likely, we would have done an in vivo study to follow up what's going on.

I should also point that clinical data does sometimes help. For example, we see--often, we see evidence of autoinduction, which helps to clarify the issue in a particular clinical dose. But I think once again, it really depends to some degree on what kind of exposures one has in the clinic, and that helps in some ways to really interpret the data.

Now, of course, I think that's the easy part. I think the hard part is actually interpreting an in vivo study. I think there's less consensus on probe substrates, their clinical interpretation. I wasn't here for the Committee

deliberations last time about the issue of induction, but I find these questions quite difficult.

And this is just a slide showing the percent of baseline exposure for a variety of known inducers. I don't think you have to pay attention to the specific data. Many of these were studied on numerous occasions. But this is the effect on oral Midazolam. And I look at this data, and I'm asking myself really, is this where we think the bar should be? This is just about a fivefold decrease, or should the bar be here? We know the glucocorticoids and St. John's worts do have clinical effects on certain drugs, or where should it be?

And in the end, I still struggle with really the interpretation of induction, whether it's the in vitro or in vivo going forward. Now, more recently, the role of transporters has been recognized, and I think there's clear examples of transporter-mediated drug interactions. A couple of years ago, I don't think I would have actually

said that there were clear examples. I would have said hypothetical or potential examples.

And I certainly think the understanding of peak lack of protein is advanced greatly. But the in vitro methods are not really standardized, and they're not really quite as available as we'd like. And I think a quantitative in vitro prediction of in vivo relevance is still quite difficult. And of course, it's complicated by the fact that the transporters really are just not an issue of metabolism but also absorption, tissue distribution, excretion; as someone said earlier, the whole pathways can be involved as one is looking at this influx, eflux, et cetera.

Now, probably peak lack of protein is the best study, and I don't have to say much to this particular Committee about that. But even there, the in vitro methodologies are not quite what I would like. The transgenic MDR naga mice are a very powerful tool, but we have numerous examples where the human and rodent differences occur.

The in vitro tools are clearly becoming

more sophisticated, but some of the PGP substrates don't follow simple kinetics. There's a lot of overlapping substrates between PGP and CYP3A4, many inhibitors affect both, and of course, there's the issue of other transporters as well. The tools are most useful to identify PGP substrates. We can certainly identify PGP inhibitors, but it's still comparatively laborious and time consuming to do so.

And what might I, as a clinical pharmacologist, actually get as an evaluation of a PGP substrate? This is a paragraph, actually, from a real drug. I changed the numbers once again to make it a little hypothetical, but you can read this. What we see is what happens in the MDR mice. We can look at transport ratios going back and forth. I have a B to A ratio from the two sides of 1.7. I'm not really sure if that's a substrate or not; what should I do with that particular data?

Now, if an in vivo study is indicated, and I've told you I struggle with what that actually, you know, how do I actually decide that, I think

for assessing a potential PGP inhibitor, digoxin clearly is a suitable probe. I do think that most other probe PGP substrates are less than ideal.

But I've borrowed a slide from Shiew-Mei just to talk about some of the difficulties I have about thinking about assessing PGP substrates. This is the same slide that Shiew-Mei showed before. These are all PGP inhibitors, and you can see in vardenafil what the tremendous difference there might be between all those, and of course, part of the difference is that ritonavir, as we pointed out, oops, doesn't work, ritonavir, as we pointed out, clearly is an inhibitor not only of PGP but of CYP3A4, but in this particular case, it's also an inhibitor of 2C9, which is probably the other pathway by which vardenafil is actually metabolized.

And you can see there's a widely divergent variation in terms of the results one would see. I'm not sure here that I think that that's really the kind of data I'd like to be generating to help understand how to extrapolate datas to new

situations.

I think the situation in terms of inhibitors and doing a study on a substrate with an inhibitor is even worse. If you look at the compounds that we have that are inhibitors, there's quinidine, ritonavir, verapamil, cyclosporin, okay? These are all very difficult compounds to work with. We don't use quinidine in volunteers. We really think it carries too much risk. Ritonavir, as I've already mentioned, is a 3A4 PGP substrate, inhibits 2C9.

We've had studies where we've seen tremendous induction of UGTs, a whole variety. Some have gone up, some have gone down. In the end, when we do studies with ritonavir, what we do is we conclude this is what ritonavir does and nothing else, because we really just don't know how to interpret the individual data.

Verapamil, also very complicated; similar on PGP and CYP3A4, but we stopped using it in our clinical trials. When we gave it to volunteers, Dr. Vago in the back there who used to be at Merck

did studies for us where we showed that we clearly saw, you know, PR lengthening in all of our healthy volunteers, and we just really thought that the risk-benefit really wouldn't allow us to do that.

And of course, cyclosporin has myriad effects. The interpretation is difficult, but it carries a significant risk to volunteers, and we've been unwilling to do more than single dose studies in volunteers because of the effects it has on the kidney and on immunosuppression. As a matter of fact, this is very real to me. Last Friday, Merck spent a couple of hours, a whole crowd trying to design a study requested by the agency to really try to understand the effect of a model PGP inhibitor, cyclosporin, on one of our drugs, and we just found it almost impossible to design a study that we thought would really be able to answer the question without significant patient risk.

Other transporters are far less standardized and available. Many cell-based systems contain multiple transporters, making it hard to interpret in vitro. There's few

well-defined substrates and inhibitors. The correlations are difficult. Many of the interactions can't even be linked to a single transporter system. And we just don't know how to generalize these.

So I think that in general, my feeling about other transporters are that the science doesn't support an in vitro-in vivo correlation. Clearly, we're moving that way. I have high hopes that five years from now, if I stood in front of the Committee, I'd have a different answer, but this is what I think today.

Now, I wanted to just close and talk a little bit about the multiple inhibitors, multiple impaired. Just like with induction, Dr. LeCluyse is going to be talking about that; someone is going to be giving a presentation about this as well, and I think there's some really elegant work there. But I have to admit, I'm not a big fan of this particular approach. I understand the agency's desire for higher exposures when evaluating QTC issues, which I think is probably the primary

driver for many of these studies.

But the new hurdle for QTC is very, very stringent. And we certainly agree, I certainly agree that the margins are critical. But the real question I ask myself is for how many of the drugs that are coming forward are extraordinary efforts justified? And of course, not everybody would agree with me that some of the things that we're doing with multiple inhibitors are truly extraordinary efforts.

But I want to just lead you through a little bit about how this actually works in practice you can understand why I take that approach. First of all, the QTC effects of many inhibitors are not well-characterized. That's a solvable problem. And again, I hope that in a couple of years, we'll know that ketoconazole and itriconazole and, you know cyclosporin or whatever we're going to use in these studies, ritonavir really has no effect on QTC that could mess up these definition QTC studies.

But the important thing to realize is

while the industry agrees with all the agencies around the world that these studies are important, these studies are extremely costly and difficult to do, and the carrot to the industry, okay, is the fact that if we do these right, and we get an answer that really satisfies the agency that this drug does not have a QTC effect, we really need that information to prevent us from doing extraordinary efforts in terms of monitoring in phase three. So it kind of puts a limit on when we need to really have this data to be most useful in terms of designing a QTC study.

If it isn't available for us at the end of a phase 2B study, honestly, it's much less valuable to us overall. And so, we have to work hard to get that in. Now, what do we have to do to do a multiple pathway study? In most cases, we have to do a clinical study first to really define the in vivo metabolic pathways. It takes nine months to set up, six months to analyze. We need clinical data on each inhibitor separately, really, to understand the usefulness to increase PK exposures.

We have to get that data, we have to model it to make a prediction what is going to happen when we look at multiple pathways.

And in most cases, I would argue, you actually need to test the concomitant administration of the inhibitors before the QTC study because of the issue of safety and tolerability. These studies are not really done at sites that are really set up to carefully evaluate sort of phase one type issues, and in many cases, you'll be giving a new exposure to drug that no one has ever seen before.

And of course, these QTC studies get quite complex if people feel dizzy or nauseous or vomit, have diarrhea, okay? I have to tell you: I am senior management, but if I went back and said we couldn't complete our QTC study and that a million or two dollars are really down the drain because people were unable to tolerate the drug, I would not be well received. And so, we have to do that stuff as well.

Special populations also are needed in

some cases, and I think there are some elegant studies, like the telithromycin study, because recruiting those particular people is really quite difficult and time consuming as well.

Now, to make it even worse, those are logistics issues. This is what I might see, actually, from a particular drug where we're considering a multiple pathway. And this is, again, patterned after a real drug. In vitro data incident that 3A4 plays the major role, but there's 10 percent from four other CYPs. What inhibitors should we use? How should we actually design such a study?

And lastly, I also question are we really as smart as we think? Despite all our knowledge, can we really predict the effects of inhibition of multiple pathways? And I just wanted to give one example of some data that will be presented at ASCPT the next year about a study we were asked to do, which I think was actually a very good study to request, so I certainly support it, but one where it showed me that I was a lot less smart than I

thought I might have been.

Aprepitant is a moderate CYP inhibitor. It's used in combination with 5HT3 antagonists, and dolasetron is a 5HT3 antagonist we had not studied in our clinical program. It's metabolized by 2D6, with 3A4 being an important pathway. And because of the concern of QTC prolongation with the dolasetron, we did a study at the agency's request to conduct an aprepitant interaction study in 2D6 extensive in poor metabolizers.

All of the data that we had would have suggested we should have had a remarkable effect. And in that study, as you can see from that data, if you take a look at what happens with dolasetron, with aprepitant, APR, and dolasetron together, we were able to show, in fact, yes, poor metabolizers do have higher levels. But closing off the CYP3A4 route with a moderate inhibitor really had no important effect at all on the levels. Very reassuring in this particular case, but clearly not what we would have predicted overall.

So overall, I think that we really are

making a lot of progress. I very much applaud the efforts of this Committee and the FDA, and I think, though, that we're really not there yet in all of the things going forward, and this is sort of my summary of what's ready today and what I hope will be ready in the future.

Thank you very much for your patience.

DR. VENITZ: Thank you.

Any comments or questions?

[No response.]

DR. VENITZ: Thank you again.

Our next speaker is Dr. LeCluyse. He is the chief scientific officer of CellzDirect, Inc., and he's going to talk about induction.

DR. LECLUYSE: Excuse me while we do a technology switch here.

[Pause.]

DR. LECLUYSE: It worked.

Okay; I also would like to thank the Committee for this opportunity to speak to you. The way I interpret my role in all of this is that I think I'm supposed to condense this labyrinth of

information that's out there on nuclear receptor biology and what it all means in terms of human gene regulation, P450 induction and how to do in vitro screening for that.

So with that task in mind, let me start out by just first putting up the questions that it's my understanding that we are asked to address, and this is very limited as compared to a number of issues that Keith brought up and addressed in terms of the in vitro-in vivo correlations, et cetera, and some of the complications associated with that.

So I am specifically going to focus on these questions that were placed in the paper or at least suggested in the papers, questions that need to be addressed, such as if a drug's induction effect on 3A4 in vitro is negative, then, it is acceptable to not recommend any in vivo studies with substrates of 3A, 2C9, 2B6 and 2C19, yes or no?

Also, the other question that was meant to be addressed today is if the in vitro induction or increase in enzyme activity is more than 40 percent

of the positive control, then, there is a need to recommend an in vivo induction study, yes or no? I'm going to focus predominantly on this first question, because I think that's the one that's most complicated and involves a little bit more of a mechanistic understanding of what our current understanding of regulatory of the human liver genes, and this, you could argue, is as much of a philosophical one.

So before we can address that specific question, especially the first one, let's start off by first reviewing the enzyme induction in humans as we currently understand it or as observed in the clinic.

So, for example, if you take compounds, and certainly, this is not a complete or comprehensive list, but it serves to represent the point that for most drugs that are known to cause clinically significant drug interactions, and that's the point, our current understanding of which CYPs are involved in their interaction is pretty evident these days, especially by the number

of drugs that we use as probes as well as the in vitro data to support that.

We also know the relevant plasma concentrations at which we see a clinically significant interaction event. And then, also, now, we're very much aware of the particular pathways that mediate these events. And notice that for the most part, these center around three receptors, namely, CAR, PXR and the AHR. And I'll go into much greater detail on those in a second.

Another way to look at this is if you actually look at the inducible P450 enzymes in human liver, with the exception of CYP1A, which is predominantly induced by aromatic hydrocarbons, some dietary components and cigarette smoking and with the exception of 2E1, which is basically induced by solvents and drugs like isoniazid but mostly involves a mechanism of stabilizing protein and RNA, for the most part, the rest of these often are induced by compounds represented by the anticonvulsants, antibiotic rifampin, et cetera, suggesting that there is some overlap or

commonality in their mechanism of regulation.

It's now fairly apparent that especially for the regulation of the human hepatic enzymes, that there's three major receptors that are involved: predominantly the aral hydrocarbon receptor, the AH receptor; constitutive androstane receptor or CAR; and the pregnane X receptor, PXR.

And there's three main points that I want to basically draw from this particular slide: number one, each of these receptors contains a ligand or drug binding domain which determines, basically, which drugs are going to activate it, and also, they contain a DNA-binding domain, which determines which DNA sequences or response elements that they're going to bind to upon activation by drugs.

Now, the other point I want to bring out is that these all form heterodymers with other proteins, and for the most part, the AH receptor is distinct, in the sense that it partners with a protein called the aral hydrocarbon receptor nuclear translocase protein. I didn't name it. It

was given that name a long time ago. The acronym AHRNTP is given to that.

On the other hand, CAR and PXR both heterodimarize with another receptor called RXR, but basically, it's gratuitous in its function here. It's predominantly driven by--it's the partner CAR and PXR. Now, the other point I want to make is that upon activation, each of these nuclear receptors induces a number of genes, not just a single subfamily or, you know, a limited class of genes, but, for example, upon activation of PXR, you're upregulating a number of phase one enzymes; also, transporters as well as phase two enzymes as well as others, including the carboxylesterases, by the way.

So bear in mind that also, CAR and PXR share a number of these target genes in common. So, for example, 2B is upregulated by both CAR and PXR; 3A4 and the 2Cs, beginning to suggest that there are some common regulatory mechanisms of these genes by these nuclear receptors. And we actually understand now enough about the particular

promoter region sequences and the response elements that are in the promoters of these genes to explain mechanistically now that they can be and ought to be coregulated by activators of these receptors.

So our first evidence for coregulation that we observed in my lab, and we've been looking at this for over a decade, I would hate to admit now; basically, our first evidence was a study that we set out to do to explore the effect of 14 different compounds that were known to induce 3A4 to various extents, either in vivo or in vitro, and our intention was to relate that to their PXR activation profiles.

Now, interestingly, when we extended those studies to include 2B6 activity, we basically found something very interesting, which is summarized in these tables over here. So if you basically look at the most potent or the strongest inducers of 3A, you'll notice that clotrimazole, rifampin and ritonavir are also very potent inducers of 2B6 in this particular case.

Notice also in the 2B6 column that there

is a couple of others, including phenotone and phenobarbital that are strong 2B6 inducers, but they're either moderate or weak inducers of 3A; however, upon more extensive evaluation, even these compounds are known to induce 3A, here again showing some common regulatory mechanisms.

Now, if we extend these studies to include CYP2C9, we also find very similar profiles; for example, potent inducers of 3A and 2B6 also induce 2C9. Now, this is represented nicely in this particular slide, where we looked at the coregulation of CYP2C9 and 3A4 by avasomid, which we discovered to be a very potent PXR activator. It's also been shown to interact clinically with warfarin and midazolam and digoxin.

You can see here in two separate donors, if you look at 2C9 versus 3A4 in hepatocytes from one particular donor how the response concentration curves basically are almost superimposeable. Also, in a second donor, the same situation, suggesting here common regulatory mechanisms via PXR in this particular case.

Now, if we extend these studies to include additional inducers of 2B6 and 3A, but then, look at the induction now of multiple 2Cs, including 2C8, 2C9 as well as 2C19, in this particular case, we're looking at RNA, not activity, but it still exhibits the point that I want to make that basically, all these compounds that are inducers of 2B6 and 3A via activation of CAR and PXR also upregulate the three 2C enzymes.

The other point I want to make is that the most efficacious inducers are actually transactivators of these 2C9 genes have a tendency to be rifampin and/or phenobarbital in all three cases.

And finally, the other point that I want to make, because it's going to play a role in terms of why we're proposing looking at a limited number of endpoints is if you actually look at the induction of 2C9, it's basically between two and threefold, with even the most potent inducers, positive controls, if you will, suggesting that it's actually not a very sensitive target gene if

you're trying to actually elucidate the induction potential of a particular drug, and since we've now discovered that there's a lot more coregulation between these genes, we propose a more mechanism-driven type screening strategy than what has typically been proposed in the past.

So in essence, what this boils down to is we think we're at a point now where we understand the regulatory mechanisms of the relevant human P450 genes to where we can now do a more mechanism-driven screening strategy with a goal to screen efficacious activators of these particular dominant nuclear receptors and these clinically relevant induction events where we propose screening protocol using a sensitive endpoint for each nuclear receptor being the goal with the premise that potent activators of each of these individual nuclear receptors will induce a number of target genes but differentially.

So for example, potent PXR activators will induce 3A, 2B, the 2Cs, even some of the phase 2 enzymes like 1A1, UGT1A1, transporters like MDR1,

but 3A4 is the most sensitive. Likewise, potent CAR activators will induce a number of these same genes that overlap with PXR, but 2B6 is the most sensitive. And then, finally, potent AH receptor agonists will induce 1A2, phase two enzymes such as UGT1A1, GSTs. But 1A2 is the most sensitive in terms of screening for that.

So, finally, an example protocol that we would advocate, and we currently use, is to treat human hepatocytes. That's a given with our protocol. Treat with a new drug at three to four relevant concentrations, especially where clinically relevant concentrations are known; treat for one to three days; include positive controls, which is very important in terms of making appropriate comparisons, so, for example, the most robust 1A, 2B and 3A inducers ought to be used for positive controls, in our opinion, where some sort of maximum is obtained that's possible with the particular preparations of cells.

Now, one has the ability to measure RNA, certainly, protein as well as enzyme activity. We

would advocate that the enzyme activity is probably the best representation of the induction response. Protein content is semiquantitative at best, and the relationship between RNA content and enzyme activity is still yet to be completely characterized, although I think we're nearly there.

And finally, the last point here is that a major CYP target gene for each nuclear receptor ought to be the focus of these initial screens; so, for example, looking at CYP1A2 as an endpoint for AH receptor agonists, 3A4 for PXR, and possibly 2B6 for CAR, although all 2B6 inducers and CAR activators that we've come across thusfar also turn out to be inducers of 3A4.

So finally, one other point that I want to make in terms of looking beyond enzyme activities, in this particular case, where we're looking at a mechanism-based inhibitor such as ritonavir, if you limit yourself to looking at enzyme activities, which is the case in this particular study, where we evaluated seven different inducers of 3A, you can see that if you only evaluate things on the

enzyme activity, which is normalized enzyme activity to the negative control, here, you can see that ritonavir actually knocked out the activity significantly in these microsomal assays that we did. And as we all know, ritonavir is one of the most potent mechanism-based inhibitors that we've come across.

However, if you actually were to look at its effects at the ability to upregulate 3A4 gene expression at the RNA level, you'd find that ritonavir is every bit as efficacious as positive control rifampin at that level, suggesting that it's actually a very potent PXR activator and inducer.

So finally, some of the other important factors to consider in terms of study design: the interdonor differences in the control and basal activity between preparations of hepatocytes can often be a caveat. We suggest that that's why it's important to compare it to a positive control rather than fold over a negative control. We also believe that it's possible that depending on how

high the basal activity is, it may exclude some preparations of hepatocytes from maybe being appropriate for induction studies.

Also, the relevant concentration range of your drug is important, focused on plasma and tissue concentrations; appropriate choice and concentration of a positive control is an important consideration; certainly, the major species differences have to be acknowledged in terms of nuclear receptor activation as well as induction of specific P450s, so for example, it still surprises me that some of the studies that I come across where dexamethasone is still used as a positive control in human hepatocytes, it's a very potent inducer, as is PCN in for rodents, but there's about an order of magnitude difference between dexamethasone's ability to induce the 3A enzymes in human hepatocytes compared to, let's say, a positive control like rifampin.

Also, the expression of the data in the relevant endpoints is very critical, and that's been also an issue that's been addressed and

relating that to a positive control. Exposure time is important, especially for the particular subforms that you might be evaluating, shorter for CYP1A, for example; longer for 3A; and then, finally, one must bear in mind that solvent effects on P450 expression and activity are observed. DMSO, for example, is an activator of PXR itself at sufficiently high concentrations, and also some of the alcohols are known to even inhibit some of the P450s.

And finally, just in summary of the key points: our mechanistic understanding of enzyme induction in human liver has increased markedly in the past decade. Most inducible human P450s, UGTs and transporters involved in DDIs are regulated by a few receptors, namely PXR, AH receptor and CAR. Screening for potential inducers during drug development, in my opinion, can be achieved using a single, selective and sensitive target gene for each of these nuclear receptors through following a 3A4, 1A2 and/or 2B6, and activity data from in vitro induction studies for a new drug should be

normalized to a negative control, compared to an appropriate positive control at appropriate concentration, considered significant when they are greater than or equal to 40 percent of the positive control, and that's actually a question that I'd be interested to hear others' opinion on that and also complemented with protein or RNA data if time dependent inhibition is involved.

So, with that, I'll be happy to answer any other questions that you may have.

DR. VENITZ: Thank you, Ed.

Any questions for Dr. LeCluyse?

Go ahead.

DR. HALL: Ed, one of the biggest concerns with hepatocyte work has always been the preparation, the treatment, the handling, and the sort of somewhat unique capabilities of one group versus another group in just the way the hepatocytes work. Do you believe that is now sufficiently robust that this can be done independent of supplier, source of the liver, they're all going to work?

And if they are going to work, how many do you have to use in order to come up with a reliable answer?

DR. LECLUYSE: Yes, that's an excellent question, and I think that's been part of the historical issues with the use of hepatocytes is depending on whose hands the studies are conducted in, you can get some variability. And I think that goes back to how important the study design is and the appropriate use of the positive controls as markers or indicators of whether the studies have been appropriately done, and I think, you know, I think John is going to maybe discuss that a little bit more in terms of those criteria, but I think we're there now to where we can start stipulating those issues and at least minimize poor results.

And personally, I think you're pretty much going to have a good indication as to whether your drug stands a possibility of being an inducer in three to four preparations of hepatocytes. So I think if you get--certainly, in this case, where we're talking about negatives, if you haven't seen

induction in three preparations of hepatocytes where you've gotten adequate and sufficient induction with a positive control, then, I think you can pretty much rule that out so--

DR. HALL: So to sort of follow up that, the 40 percent number seems reasonable, but is this 40 percent N statistically significantly different? I mean, if you had a 0 of 40 and an 80 percent change, is that okay, or how would you deal with that issue?

DR. LECLUYSE: Is that between donors--

DR. HALL: Yes.

DR. LECLUYSE: --you're talking about? Yes, and it is very possible that you may get that kind of variability, although it may not be that significant, but, you know, certainly, you may get, in some donors, and it may be on the border; less than 40, certainly.

And I think to me, it's more about the potential. So if you've got one donor where you exhibit greater than 40 percent induction, then, that's letting you know that your compound

certainly exhibits the appropriate properties; that it's likely or stands a chance of inducing, at least assuming that your study was designed around appropriate, you know, in vivo or physiologically relevant concentrations, it stands a chance of inducing.

So, you know, I mean, we can go into a long dissertation about why it may be lower or higher in certain donors, but certainly, if you see it in a single donor, then, you know, greater than 40 percent, then, that's telling you what you need to know, I would argue, so--

DR. SADEE: My question is a little bit along the same lines. You have a basal activity of transcription of all of these genes, which is usually reduced, and those are a whole set of other transcription factors like the HNF transcription factor family, and if you have a high expression of those, your induction will be percentagewise much lower. So in vitro, you apparently exclude those where you have high basal activity.

But I wonder whether, in extrapolating,

then, the data you obtain with hepatocytes in vitro which have minimal basal activity to the in vivo situation, that you're not somehow exaggerating the importance of induction compared to the situation where you have reasonably high basal activity, which may be more prevalent in the in vivo situation, and variability actually comes more from basal rather than from induced activity in vivo.

DR. LECLUYSE: Yes, I mean, I think obviously, that's a very good point. In fact, the one thing I like personally about the use of human hepatocytes is you do get some feel for what that range may be in the clinic, because I think they are representative of true donors. And so, you know, here, again, to me, it's more about getting an indication as to whether you should--whether a compound is going to stand a chance to be an inducer in an in vivo setting and about whether you're going to get a negative or not, not about what do you do when you get to a positive? I mean, that could be another whole discussion we could have, which I'm happy to engage in.

But you know--

DR. SADEE: Do you have any information on the interaction between, let's say, HNF4-alpha with a CAR, or are they additive, or do you have any feeling for this?

DR. LECLUYSE: Yes, they're supportive. You may be aware of Richard Kim's data as well as that of others now that suggests that there are a number of transcription factors as well as cofactors that are supportive or even necessary for a normal induction event to occur. And so, it's almost the equivalent or the way I look at it is all of these factors are necessary to drive the car, so in other words, in order for you to get in your car and drive down the street, you have to know that your engine is working, the tires are okay, et cetera, et cetera.

So without any of those things, you may not get very far, either, but what's driving the bus, basically, or what's critically driving it is these nuclear receptors. So something like HNF4-alpha, as well as other cofactors and

transcription factors, are necessary for just the normal events to occur. If anything, that argues the point of why human hepatocytes are a relevant model, because they retain their normal profiles of those factors, cofactors, transcription factors that I think is actually written in the concept paper as to why cell lines, for example, might be inappropriate.

But you're exactly right: I mean, all those things that just go into factoring maybe some of the donor differences in how the hepatocytes and in vitro setting respond, they're also operative in vivo, so, you know, like I say, to me, what I like about it is that it's probably more reflective of what you're likely to run into in vivo.

DR. WATKINS: Ed, as you know, I'm a big fan of cultured human hepatocytes, but there are some practical issues as an academician. We find it very hard to get human livers. And I don't know if that's been solved by cryopreservation, but clearly, it's, I think, a limited resource that's very expensive if you talk about doing all these

validations and multiple, you know, with multiple donors' hepatocytes and doing multiple experiments.

And, of course, there are problems when you culture human hepatocytes, which is they no longer have canaliculi, so all the canalicular transporters presumably just spread out over the basolateral membrane. So some of the theoretical advantages of having the relevant cell with the relevant transporters, I think, is gone, and I would imagine can be deceptive.

So one of the questions is now that you've whittled it down to basically two relevant receptors or maybe three with two endpoints, I mean, wouldn't the first step be some sort of in vitro transcription factor activation or transgenic mouse or something to actually look at the effect of your compound on the transcription factors directly rather than marching right into human hepatocytes?

DR. LECLUYSE: Well, yes, in fact, exactly. What you've described is exactly generally what industry is doing is they're

starting with the least common denominator, which is the nuclear receptors. And whether their compounds either bind to or transact or activate the nuclear receptor, you know, these reporter assays, as you know, full well, people are using fairly extensively.

But the relationship between nuclear receptor activation and a reporter assay and how that translates to, then, an hepatocyte assay and then, further yet, in vivo is still, I think, a long ways from being clear. I actually view them as nice, complementary tools. I mean, you're going to get a lot of information from using both to complement one another, in my opinion.

But back to your point, Paul, about the availability of resources. You know, that has been limiting for both industrial scientists as well as academic to do these kinds of studies, and we're slowly making headway on that both in terms of more sensitive assays, where we can do maybe what used to could only be done in a petri dish, we could now do in multiwell plates, much more high throughput

fashion.

We are, I think, on the cusp of being able to understand the relationship of the RNA, level, changes in RNA levels with those of activities, so that allows you to even make these much more rapid throughput assays much more amenable to less material being used and all those things. And also, you mentioned cryohepatocytes. There are batches of cryohepatocytes now that are available to do these studies, so you can basically stock up on those, if you will, or have better access to whole donors where they would be available to multiple investigators or multiple departments within the same institution or company.

And that's oftentimes what companies have turned to now is just buying whole lots of cryopreserved hepatocytes that do plate out and are inducible and respond well to positive controls to doing their screening. In our understanding of what makes a good cryobatch of hepatocytes that will then attach has advanced significantly, too, from years ago, so--

DR. WATKINS: If I could follow up, I mean, I think the data undoubtedly exists, and you may have it, but it would be awfully nice to see stories of drugs that were positive for the in vitro transcription assays, and you went into hepatocytes and more negative or vice versa and then went into man, and it turned out hepatocytes were the right answer and well worth the resources and, you know, provided all this additional information.

I just have not seen that kind of data put together that would at least from my perspective justify recommending human hepatocytes as somehow muscling to the front and an assessment of potential drug interactions.

DR. LECLUYSE: Let me tell you off the top of my head the reason for it is remember, these nuclear receptor assays only evaluate a single pathway at a time, and we actually do not have a good assay for human CAR that's similar to the reporter assays that exist for PXR. And we do, for a fact, know that there are compounds that

induce--that are 3A4 in human hepatocytes actually to the same degree as rifampin that show up as negative in a PXR assay.

So I think, you know, like I say, the technology just needs to come along a little bit further. I don't disagree with you. I mean, I think we're getting there. I just think we're not quite there yet, so in this particular case, I think hepatocytes are going to cover more of your bases, more of the signalling pathways, cofactors that we just described, nuclear receptors, alternative pathways and even working in synergy all exist together in a human hepatocyte system so--

DR. DERENDORF: Yes, I'd like to come back to my previous comment. I'm a little uncomfortable with that clean cut cutoff of 40 percent as a threshold for significance or relevance, particularly we need to define what we're measuring. We need to define what is an appropriate positive control. We need to define what concentrations should we look at, what time

point. And I think unless we do that and have a correlation with, if it's really meaningful, that 40 percent seems arbitrary.

DR. LECLUYSE: Yes, and that's honestly been the ongoing debate over the last, I would argue, couple of years. And by the way, I think we have defined all those other parameters that you've mentioned, and now, it's just, and this is where I'd like to open the floor for discussion, and I think that's part of what the point is is how comfortable are we with that 40 percent mark? I think that's--I would argue that's where we need to focus. I mean, there's other things that have been brought up around hepatocytes and doing these in vitro studies where I think is more away from the point.

But I think those kinds of issues are valid points that still need to be up for discussion somewhat so--

DR. GIACOMINI: I think I just wanted to echo what Paul said about the transporters not really being in place in the hepatocytes. I don't

know if this is still the best system, you know, to test for inducing the nuclear receptors.

The other comment I had was we've tried making constructs, you know, reporter constructs and then transfecting them into hepatocytes. Have you tried that kind of--so that you get a more quantitative readout at the end of the, you know, comparative quantitative readout?

DR. LECLUYSE: Right, yes, no, actually, we do that, too. I mean, we basically, you know, I should qualify this: my academic lab does do--takes all those measures. In fact, you do get normal disposition of human CAR using the primary cell versus these, you know, the immortalized cell lines, where CAR translocates constituitively to the nucleus, as you're aware.

So, yes, certainly, you know, here again, you're still using primary hepatocytes to get to the answer. And I think the complementary tool here, again, of following endogeneous gene expression with your reporter assays is probably even the best way to do those particular

assessments, I would advocate, so--

DR. STRONG: I think generally, at least in our guidance, we do accept the fact, though, that this issue of induction of 3A4, if we see that's negative, that we probably don't have to worry about C92C19. My concern, though, comes back to the same issue that I think is really pertinent today, and that is what's the way we define an inducer and not inducer, the 40 percent?

In fact, what I did was one of the slides that you showed with the comparison between 2B6 and 3A4 with the number of compounds, I looked at phenytoin which is a strong CAR inducer, and compared it to rifampin. When you do that, it shows that the induction of 3A4 defined by the 40 percent rule, phenytoin is not an inducer.

And so, the question is what's going on here? Well, I think it comes back again, and some folks have alluded to it, is the hepatocyte experiment and the hepatocytes themselves. I think all of us agree that you can find hepatocytes that have been induced to their maximum, and you see

very little additional induction. And if you look at the particular figure he showed, the basal activity in that set of experiments with the 14 compounds, whatever they were, it was considerably higher than what you saw, say, in the 2B6. So it may be just experimental design.

And again, I think this is a question that we have to really grapple with if we're going to use hepatocytes for induction. Maybe we need to define better some parameters with respect to the hepatocytes we're using.

I wanted to make one other comment off the subject, but I think it's great. I think again, we believe that enzyme activity is still a gold standard. On the other hand, Ed brought up the issue of ritonavir, an inducer and inhibitor, and how some of these other measurements like MR8 can come in and add additional information.

Another way to look at that, though, is that we're looking at mechanism-based inhibitors. And in most of these drugs, when you're doing your inhibitor study, you'll already know that your

compound is or is not a mechanistically-based inhibitor, so that you can put a red flag up with regards to induction studies.

DR. VENITZ: Ed, I have two questions: how do--your CYP induction, how does that compare to UGT inductions? Have you looked at that at all?

DR. LECLUYSE: Yes, in fact, I don't know if you got my background slides, but I did include some UGT1A1 data in there, too, and basically, as you may be aware, UGT1A1 is unusual in the sense that it's regulated by all three receptors. And so, activators of those three receptors will induce UGT1A1 in human hepatocyte preparations, according to the potency of the compound, and there, it's the compound's ability to activate those nuclear receptors.

So, you know, here again, you see the most potent induction of UGT1A1 with things like rifampin, phenobarbital, and also activators of the AH receptor like 3-methylclanthrine, homeprizole.

DR. VENITZ: The second thing: can you help predict hepatic enzyme induction for GI enzyme

induction, 3A4?

DR. LECLUYSE: Well, that's an interesting point, because that's also a debated issue currently right now, and the fact that the gut enzymes are regulated by other factors that are unique to the gut--now, bear in mind that the profiles of these nuclear receptors are tissue-specific, so you will find PXR, for example, in the gut. And so, inducers of hepatic 3A or activators of PXR will induce hepatic target genes as well as the gut.

But there's other things going on in the gut that are not operative in the liver and vice versa, like with the vitamin D receptor, for example. So there are additional mechanisms that might be operative in the gut that may cause upregulation of transporters of P450s that you wouldn't observe in just an hepatocyte model, for example, so--

DR. VENITZ: Any other questions or comments?

[No response.]

DR. VENITZ: Then thank you again.

DR. LECLUYSE: Thank you.

DR. VENITZ: Shiew-Mei?

DR. HUANG: About the 40 percent, I just wanted to throw this question out. Initially, we got this from the PhRMA paper, although I know that there is still discussion on whether this is too high a value; should we be more conservative, 20, 25, or 30 percent. But I think the cut-off should be supported by data, and as John mentioned that based on some of the existing data, perhaps 40 percent is too high a cutoff.

And so, I was going to say in our concept paper, we recommend the evaluation of 3A along with 2C9, 2C19, and we have not included 2B6 or UGT1A1, although this will be some time to come. So I thought perhaps it's important maybe we consider to have different cutoffs depending on what information we would like to get from 3A. If you want the information of the certain cutoff to support that, if 3A data is negative, then, we don't have to do 2C9, 2C19. Perhaps 40 percent

would be sufficient.

But if you're going to include 2B6 or UGT1A1, then, perhaps there's a different cutoff. And I'd like to see what your opinion, really, because I think it's data-driven. We need to know very carefully what data we have.

DR. LECLUYSE: Well, I can look at it from a number of different perspectives, Shiew-Mei. And I'd like to hear the panel's views on these, too, because the one issue is, you know, just the views on enzyme induction as an event in itself, especially the clinical relevance of it as an event. Now, I can tell you that I have my own opinion on the chronic activation of these nuclear receptors by not only drugs but any xenobiotic can be an issue, especially the more potent ones, and that you would want to stay away from those. But, you know, that would be like the rifampin type activators.

So the question is like where do you start worrying about it, you know, where you're more in the gray zone or where are you comfortable saying

that it's a negative result, which also can be interpreted as a not significant enough of a result is another way I look at it, because, you know--so the assumption is if you've done everything else right, and at the optimal concentration, your drug or a particular drug never induces more than 40 percent of your positive control like a rifampin. What's going to be the clinical outcome of that? Is it really going to be noticed above and beyond, you know, the normal distribution of the population, et cetera, et cetera? I mean, we've had these discussions before.

And so, you know, but that's different than asking the question, does it have a potential to cause an interaction, you know? And so, I think that's where the debate really lies. And, you know, I could argue both ends of the argument, depending on how conservative you want to be. So, you know, I think that's--I'd like to hear the agency's view on that as well as the panel's view on that so--

DR. SINGPURWALLA: I'm surprised that our

chairman on the matter of cut-off, our chairman has not raised his pet issue, namely utilities. Is there no discussion of utilities in these cut-off points?

DR. VENITZ: He's not really dealing with clinical yet. This is purely in vitro. The utility has something to do with what happens if this turns out to be clinically relevant.

DR. SINGPURWALLA: Factored in subsequent to utilities.

DR. VENITZ: Yes.

DR. SADEE: I still have just a quick comment that we haven't mentioned that, for instance, CAR consists of multiple, multiple isoforms, spliced isoforms. And so, that not only changes between tissues but also between individuals and the splices contain 14 different proteins that are all differentially expressed, too.

Do you consider this as a potentially problematic factor, or is it a factor that could account for the finding that sometimes, you find an

adoption, sometimes, not?

DR. LECLUYSE: Yes, I think that's an excellent point. I mean, that's sort of where our current understanding leads us to believe that variability in things like the particular receptor and differences in the cofactors that even regulate these receptors all factor into some of these interindividual differences. Bear in mind that even with 3A4 or the difference between 3A activity baseline that we brought up that you've got 3A5 contributing to the baseline activity that's not really very inducible compared to 3A4.

So you've got all these things operative in vivo, and that, here again, goes back to the point that we raised again: while I like human hepatocytes, and it's probably more indicative of all these factors, now, I don't think we have a complete understanding as to what the--whether there's an individual subpopulation of individuals that are going to be maybe on one extreme of the spectrum or another.

Interestingly, as you may be aware, that

the known polymorphisms for these receptors suggest that for PXR, anyway, that most of them don't really have a functional relevance. Now, CAR, on the other hand, seems to show a lot more variability in a lot of different ways, including the expression levels. It seems to be more susceptible to shifts, ebbs and flows, you know, in a person's social life, you know, genetic makeup, et cetera, et cetera, whereas PXR, for whatever reason, through evolution, it's pretty stable. It's pretty amazing what we've been able to do to try to vary PXR expression in human hepatocytes, and you can imagine we've done everything that's possible to vary its expression. It's fairly stable. It's almost like a housekeeping gene, in that sense.

Whereas, CAR can be variable. So, I mean, I think--but the net results is over the course of looking at three to four donors for the same drug at the same concentrations, you know, we generally get a good clue as to whether a compound is likely to induce or not so--

DR. VENITZ: Okay; last question.

DR. JUSKO: It looks very promising that this type of screen using human hepatocytes would allow one to anticipate enzyme induction for multiple CYPs. But this is partly based on the premise found with rifampicin and anticonvulsants that these drugs are a bit ubiquitous in inducing many CYPs. Has the reverse type of literature review been done to see how many drugs may induce one CYP and not others? I notice in your list, you have CLZ as an inducer of CYP3A4. Does it induce the other CYPs?

How many sort of false negatives, or I'm not sure which way it's going to go, how many misleading results will there be because of the lack of ubiquitousness of this kind of thing?

DR. LECLUYSE: Yes, well, actually, I was hoping early in my academic career that that was exactly the case. So then, we could get excited about these unique kind of compounds that were very selective or specific inducers. When I first started my career, I hate to admit, again, that it

was over a decade ago. We kind of went into this with this biased impression that there's, like, 1A inducers, there's 2B inducers, there's 3A inducers, suggesting that there's, you know, some distinction between them.

And one of the first things I became disappointed in is the fact that the human doesn't seem to operate that way so much. In fact, for whatever reason, the receptors have evolved to where generally, if you have inducers of 3A, you always see induction of 2C9. And same way with 2B. I don't know why it is, but it seems to be the case.

So we've been out there searching. I honestly have been looking for compounds that will just selectively induce particular subfamilies of the human P450s and not come across--and a lot of that data, admittedly, you know, partly due to time but partly due to proprietary nature, et cetera, you know, we've not come across over the, you know, years and years we've been doing this of compounds that are that selective.

And it kind of makes sense. I mean, you know, the other thing I didn't get to do, and it's part of my background slides, I actually have, like, some of the promoter sequences for all the promoters of the 2C promoters, 2B and 3A, and what they share in common, and it begins to make sense why they are coregulated and why it would be very difficult to come up with a compound that selectively induces any one of these, because on a molecular level, it just wouldn't make sense that it would happen, number one, because of the overlapping specificity of the nuclear receptors themselves and the fact that they share a lot of commonality in their DNA binding domains.

So basically, they're meant to kind of overlap and to crosstalk on these specific isoforms, so--

DR. VENITZ: Okay; thank you again.

Our last presentation, right, for today, is Dr. Reynolds. Kellie is in the Office of Clinical Pharmacology and Biopharmaceutics, and she is a team leader in Division Three.

DR. REYNOLDS: I just have a brief presentation to open up a topic that's been mentioned in two other talks today. It's a topic, I think, that's been bounced around at several other meetings, so we finally want to bring it to the Committee for you to discuss.

The term that's used is multiple inhibitor studies, and it really does refer to a lot more than just multiple inhibitor studies. That's just the terminology we've used. So I just want to address what we're actually talking about, why we think we need this information or may need this information in some cases and how we might collect the information.

So what we're actually referring to are studies that are conducted to determine the effects of a new molecular entity at the maximum exposure that's likely in patients. And by effect, we mean adverse effect.

And there's several different reasons we might need this information. The primary reason is to define the safety at the top of the exposure

response curve for adverse effects. And the example that is brought up most often is for QT prolongation. So this is actually mentioned in the ICH draft document for the clinical evaluation of QT prolongation, and there's also similar wording in our draft concept paper for drug interactions.

So it mentions that if there aren't any safety concerns, it may be useful to look at the effect of the drug at substantial multiples of the anticipated maximum therapeutic exposure, and if you can't get to that exposure by giving higher doses of the drug, you may do different types of inhibition studies.

And another reason we may need this information is to really just define what the worst case scenario is for the drug. There are numerous reasons that patients might be exposed to elevated drug concentrations above what was observed in clinical trials. It may be due to drug interactions, genetic polymorphisms of the drug metabolizing enzymes, renal impairment; it could be hepatic impairment or multiple combinations of

these factors.

So there are several different ways that we can get this information. We can give a higher dose of the new molecular entity, if that's possible. We can give the drug with a high dose of a potent enzyme inhibitor. We can give multiple inhibitors if the drug is metabolized by different enzymes. If it's a drug that's metabolized by an enzyme that has different genotypes, we can give it with poor metabolizers to help higher concentrations, or we can combine these factors, and that's why these are called multiple inhibitor studies. You may give the drug to patients with renal impairment in combination with an enzyme inhibitor, or you may give it to 2D6 poor metabolizers in combination with a 3A4 inhibitor.

But there are some special considerations for the studies. We need to consider what safety data are available, both in animals and in humans. Do the safety data actually support the conduct of the studies? And we also need to consider the relevance of the high exposure: what is the

expected dose in the clinic? Have higher doses already been given? Did they start out looking at a much higher dose and then settle on a lower dose?

What are the expected concomitant medications? Is it likely that inhibitors will be given with the drug? And that's an important consideration. And also, what is the target population?

So there's several steps in the process: first, if you're going to do a multiple inhibitor study, you need to know the effect of individual factors by themselves first, and then, you can simulate the effect of the multiple factors. And if there are safety concerns, it's probably a good idea to study lower doses first to see what the actual fold increase in concentration is before you actually give a higher dose with the potent inhibitor. And so, it is multiple step process that would take quite a bit of time.

And there are not a lot of examples. We don't have a whole lot of data on this. And I guess that's probably one of the concerns. But we

did find two examples. The first example is for repaglinide, and this drug is a substrate for CYP2CA and CYP3A4. And there was an interaction study conducted in 12 healthy subjects. It was a four-way crossover study. They received the repaglinide either with placebo, itraconazole, which is a 3A4 inhibitor; gemfibrozil, which is a 2C8 inhibitor; and also, the combination of itraconazole and gemfibrozil.

And you can see that there was an increase in the effect. When we gave it with itraconazole, there was a 41 percent increase in the AUC. With the gemfibrozil, there was a 712 percent increase. And with itraconazole, it was almost a 20-fold, with itraconazole plus gemfibrozil, both inhibitors, it was almost a 20-fold increase in concentrations.

Another example is telithromycin, and this example is actually in the label. This drug is a substrate for CYP3A4. Thirteen percent of the dose is excreted unchanged in the urine, but that may serve as a compensatory elimination pathway when

metabolic clearance is impaired. So if you give ketoconazole with telithromycin, there is a 95 percent increase in the AUC, and in patients with severe renal impairment, there's about a 90 percent increase compared to normal, healthy volunteers.

And very limited data is just from two subjects. But in two subjects with severe renal impairment who are also given ketaconazole, the AUC increased four to fivefold compared to normal volunteers who did not receive ketaconazole.

So in summary, just to prepare for the questions that we have, what we're referring to here when we say multiple inhibitor studies is any studies where we're trying to determine the effect of the new molecular entity; its adverse effects at the maximum exposure possible. And we think it may be important in some cases to consider this, because some patients may be exposed to the worst-case scenario. We want to define what that is and evaluate what happens there.

And the way we can evaluate it in some cases, just a single factor will be enough to do

this. And in some cases, we may need multiple factors. But there are a lot of different unanswered questions that we need to consider for this: first, how practical is the approach? It does take a lot of different steps, and if you need the answer at a certain point in drug development, you need to get all the information prior to conducting the study.

Are there certain cases where we think we need this information and other places where it may not be necessary? And do we actually have enough information about the effect of multiple factors to make a specific recommendation? I guess that's kind of the same as are we smart enough? Do we really know what we're doing here?

And there are just limited data. There's probably one or two other examples that we have, other than the two that I showed here. And is the general recommendation acceptable, or do we need to make it more specific? There are some general recommendations in the ICH guidance and also in the concept paper. Do we need to be more specific

about when we actually think we need to make the recommendation?

And also, is there a possible role of population pharmacokinetics for determining what the effect of multiple factors would be? If we actually enroll patients who have the multiple factors on board into the clinical trials, with appropriate population pharmacokinetics, we may be able to determine what the effect is.

And so, there are going to be two questions posed to the Committee regarding this: first, is it acceptable to recommend this under certain circumstances, and also, if we do recommend this, what other issues should be considered first?

DR. VENITZ: Thank you, Kellie.

Any quick questions or comments?

As I said, we will discuss the individual questions at the full discussion after the break. Are there any quick comments or questions to the presentation?

Steve?

DR. HALL: Could you clarify, is there

sort of an agenda that would lead you to include this in this drug interaction guidance? It seems to me that it's not truly in the spirit of the overall document, that it's a separate issue. Is there some reason that you believe it should be in there?

DR. REYNOLDS: I think--well, one reason, Shiew-Mei may be able to address it better, just because it's been talked about a lot, and it seems because it does involve drug interactions, and it does involve specific study design concerns, that's one reason it is in here. It is a little bit different from the rest of the tone of the document, though. If Shiew-Mei wants to provide more insight--

DR. VENITZ: Jeff?

DR. BARRETT: You mentioned that on the why was to define the worst case scenario. But under what conditions would you say you need to define the worst-case scenario? What properties of a drug would lead you to say that I need to know that?

DR. REYNOLDS: I think it really would depend on what we know about the safety of the drug. I mean, if we feel like there are situations where patients may be exposed to higher concentrations than they were exposed to in the clinical trials, and we have special concerns about the drug, then, maybe one situation. It would depend on, like, in phase two, what the dose finding was, whether they actually ended up settling on the highest dose they looked at or whether they actually looked at doses several fold lower and settled on one of the lower doses.

DR. VENITZ: Larry?

DR. LESKO: Yes, just in the context of Kellie's presentation, the adverse event that comes up often and is spoken about in this context is QTC prolongation. Now, the question would be what else is there beyond that that would be sort of a characteristic of this concern about multiple inhibition? I don't think it would be dry mouth, for example, or things of that sort, of course.

So we have to sort of think about when is

this concern a legitimate concern. And one thing that wasn't mentioned is how we ought to be thinking about the exposure-response relationship that we do know about prior to making the decision on these multiple inhibitors, and how does that factor into the decision? That is to say, how can modeling and simulation play a role here based on an analysis of the data that's contained within the clinical trial program, to look at worst case scenario and simulate its settings as a prerequisite to doing something live.

DR. VENITZ: Any other questions or comments?

Paul?

DR. WATKINS: Being responsive to the ethical concerns of putting together combinations of drugs or medical conditions like renal failure with another inhibitor, would this be proposed during drug development as--I'm just curious--as this is something you have to do to establish safety in patients that may be out there, or would be you either have to fess up and put in bold,

black letters that ketaconazole shouldn't be given with this drug in people with renal failure based on what we know, unless the company is willing to do this study to see if that could be removed from the label or both?

DR. REYNOLDS: We're certainly not to the point yet where we're saying you have to do that. We haven't said that to anyone, as far as I know. And as far as whether or not there may be situations where there need to be special warnings in the label, I think that's going to be very drug-specific.

DR. WATKINS: Because my interpretation is that Merck was being asked to do something that they felt they couldn't do, not that this was something that you wanted to do and couldn't do.

DR. GOTTESDIENER: Could I respond to that? The answer is Merck has not yet been asked to do that for a specific compound. There are other members of industry who have told me that they have been asked to do that, specifically in relationship to a QTC study, or at least it's been

proposed.

In at least the one case I know the details of, the company was able to convince the agency that in the end, it really didn't make a lot of sense, because again, this is anecdotal, so I'm not sure I'm capturing everything, but the idea was that the particular risk of QTC effects for that particular drug appeared a little more remote than most, and I think in fact, the agency must have made a decision that in this particular case, the risk-benefit of going to those high doses didn't quite exist.

I do think that the issue of, though, how high you're going to go in the QTC studies is something that every company faces every day, and I think as mentioned, there are many ways to get those kind of margins overall. But it's clear that there are situations where without these kinds of what I still call extraordinary efforts, it may or may not be possible to do so, and then, I think the question is what are--as Dr. Lesko said, what is it you're worried about, and how concerning is that

issue overall?

I think Merck, as well as other companies, would say that if there were a very specific issue that needed to be addressed to use a drug safely, such an approach might very well make sense. But I personally believe that those examples are very far and in between.

DR. VENITZ: Anything else?

[No response.]

DR. VENITZ: Okay; then, let's take our last break for today. We'll reconvene at 4:00, and the Committee will discuss the 11 questions put in front of us.

[Recess.]

DR. VENITZ: All right; our final task for today is to work through 11 questions that Dr. Huang has put in front of us. And the way I'd like to manage that, I'd like for Shiew-Mei to introduce each question with help of at least one of our Committee members, and then, have a brief discussion before we vote. And just like we did this morning, I'm going to have to go around the

table, make a voice--collect voice votes and then tabulate them.

So, Shiew-Mei, go ahead.

DR. HUANG: All right; thanks, Jurgen.

Our first question: the next few questions will be related to inhibition of CYP enzymes and transporters, so the first question is related to inhibition of CYP enzymes.

So based on what we have said in the concept paper, we say five major CYPs are important to evaluate for inhibition. So if a new molecular entity is not an inhibitor of the five major CYPs, based on in vitro data, then, there is no need to conduct in vivo interaction studies based on these CYPs.

DR. HALL: So could you define "not"?

[Laughter.]

DR. HUANG: I mean, one approach is to use the I over KI ratio, and the other one is to use the rank order. The approach I have mentioned, we do not say it very clearly on. We didn't specifically say if I over KI ratio is 0.1, then,

there is no need to inhibit, although we did mention if the ratio is 0.02, you definitely do not need to evaluate. And further, we have talked about using a rank order. If a more potent or smaller KI were used, you don't see any inhibition in vivo, then, you do not have to do the others.

DR. HALL: But the rank order, you have to do a study in vivo, right, based on the rank order approach so--

DR. HUANG: Right, so if we use our definition, we could vote; you could answer a question based on our ratio, I over KI, of 0.02, or you can--at 0.1. So maybe when you answer, you can say yes for 0.1, no for 0.02 if we come down to that it's a critical issue. That would be very helpful for us also.

DR. VENITZ: So we do allow yes buts? Is that what you're saying?

DR. HUANG: No, I'm saying since Steve, Dr. Hall, has asked me to define what in vitro data, and we always look at I over KI, and I we have defined as CMAX at steady state at a highest

dose, projected CMAX, and it's a total concentration, not free concentration, versus KI. So sometimes, we use IC50 when KI is not available.

And so, currently, it could be interpreted that we set in our concept paper a ratio of 0.02 or lower. We would not need a study. And I think Dr. Hall is bringing up another issue. Perhaps that number is too conservative. Maybe we should look at 0.1. So I would recommend that you could amend your answer to say I would say yes if the ratio is 0.02. But it's better if it's 0.1.

DR. SADEE: So, let me clarify. I'm not quite sure. Then, there's no need to conduct in vivo interaction studies. Does that also include, well, PGP or--

DR. HUANG: No, just CYP interaction studies.

DR. SADEE: So if we know about a compound that is metabolized by these enzymes, but we--we would have to know that there's no other possible--

DR. HUANG: Here, we're talking about--the guidance talks about the effects of a new molecular

entity on others; also, others on this enzyme. And right now, we're talking about the effect of this new molecular entity on others.

DR. SADEE: Okay.

DR. CAPPARELLI: Just a clarification of downstream from that, making the answer no. If I recall, there's pathways, then, though, to screen in population approaches or potentially other modalities rather than a straight, you know, in vivo study of a specific substrate.

DR. HUANG: Yes, I'd like to clarify. This is only one approach. So you could use population kinetics or other specific studies to say there is no interaction. But I'm saying we could extrapolate from in vitro when using I over KI ratio. When there is no inhibition, then, we do not have to do a study in vivo.

One of the comments that I've heard from outside FDA is that the drug may affect transporters, and that indirectly affects metabolism. And so, that's one of the reason there is some suggestion that even though it shows a drug

may not affect this CYP enzyme, but if through affecting transporters, they may still affect the CYP enzymes. So that's one of the reasons everyone's throwing the question.

DR. VENITZ: So how do I vote if I believe that in vitro trumps in vivo? In other words, if I have evidence in vitro that there is no inhibition, that there is no necessity for an in vivo study, how should I vote? Because I think that's what most of us agree with, but I'm not sure how to vote.

DR. HUANG: Well, you're saying most people agree?

DR. VENITZ: No, I'm saying I'm not sure how I can vote on your question, but I know what I believe: I believe that if you have in vitro evidence that there is no inhibition, that there shouldn't be any necessity or any need to do an in vivo study.

DR. HUANG: Right, for inhibition, yes.

DR. VENITZ: If that's what I believe, how should I vote on this question?

DR. HUANG: Yes.

DR. VENITZ: Okay.

DR. SADEE: But I think you have to add there, there's no need to conduct in vivo interaction studies based on these CYPs targeting only these CYPs.

DR. VENITZ: That's what it says.

DR. SADEE: Okay; well, if it's clear--

DR. VENITZ: Okay; so everybody then understands the question.

Okay; then, let me randomize the way we vote, because I was advised by our statistician that I was biasing the Committee.

[Laughter.]

DR. VENITZ: So let's start with Dr. Watkins.

DR. WATKINS: I agree with that statement as a general statement. I could think of specific instances where even if you didn't show inhibition, it might be prudent to do an in vivo interaction study. And the other thing is just to emphasize that the devil is in the details. For instance,

we've talked about, Shiew-Mei, it's standard, I believe, within industry to use two different substrates for 3A4 and in vitro studies, a big one, a little one, reflecting the fact that it can act like two different enzymes.

And since that survived through the Basil consensus and the PhRMA document, there would have to be new data, I would think, to take it out of the FDA's guidance now, which then leads to the problem what do you do with that information if one substrate group inhibits and one doesn't?

I mean, those sorts of details, I think, will come back as industry response. But as a general statement, yes.

DR. VENITZ: Dr. Sadee?

DR. SADEE: I think I agree with it with some hesitation, you know, that it doesn't state that you don't need to do in vivo interaction studies. It's just that you don't need to do it for that reason. So if I understand that correctly, my answer is yes.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: Yes.

DR. VENITZ: Dr. Jusko?

DR. JUSKO: Yes.

DR. VENITZ: Dr. Hall?

DR. HALL: Yes.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes.

DR. VENITZ: Dr. Derendorf?

DR. DERENDORF: Yes.

DR. VENITZ: Dr. Davidian?

DR. DAVIDIAN: I'll abstain as a statistician here who doesn't have the expertise to judge.

DR. VENITZ: Okay; fair.

Dr. D'Argenio?

DR. D'ARGENIO: Yes.

DR. VENITZ: Dr. Capparelli?

DR. CAPPARELLI: Yes.

DR. VENITZ: Dr. Blaschke?

DR. BLASCHKE: Yes.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: Yes.

DR. VENITZ: And I would add my yes, but I don't--

[Laughter.]

DR. VENITZ: --I don't like the way you define absence of inhibition in vitro. 0.02 to me is too conservative.

DR. HUANG: Okay; before I go to the next question, I just want to clarify: in our concept paper, we did recommend to use two different CYP3A substrates, and if either of them shows positive, then, this, then, you would need to do an in vivo study.

The next three questions are related to PGP transporter, and this was a very statement from the April discussion of this Committee that if a new molecular entity is an inhibitor of PGP in vitro, then, there is a need to conduct an in vivo study using digoxin or other suitable substrates.

DR. VENITZ: Okay, any discussion?

DR. DERENDORF: I think we have to define is.

[Laughter.]

DR. GIACOMINI: Shiew-Mei, are we going to use the same I over KI in the same way, in the same spirit that we do?

DR. HUANG: Well, for the PGP, what we have seen, at least, in the submissions is you use the in vitro system such as CAPO2 or other system where you look at A to B--or, I'm sorry, this is an inhibitor, so you'd look at the effect on digoxin, a labeled digoxin transport, and when there is an effect, which we do not define, but you could look at, such as quinidine effect, as a positive control.

I mean, we did not specify the detail in this guidance, but if the Committee thinks it will help to have a detailed appendix just like we have for the CYP enzyme, we could do that. We have not done it, because as we have heard earlier, there are different ways of conducting it. There's not a standardized way, although based on the digoxin study, we often can conclude that this drug is an inhibitor of PGP, based on its effects on digoxin or other substrates transport.

DR. DERENDORF: But you need some quantitative cutoff here, some quantitative cutoff to make that decision whether it is or it is not. So what would that be?

DR. HUANG: Okay; we have not specifically stated, but usually, when we have this submission, it will say this is an inhibitor, based on either a statistically pure t-test. I mean, that's what we have seen in the submission, to show there is a difference in the transport, A to B, B to A for the digoxin or compared to a quinidine effect, and it's comparable, or maybe a certain percentage of it.

DR. DERENDORF: But that wouldn't really be consistent with the first approach, because there, we standardize it to the I, to the concentration that we have, so I think we need to do that as well.

DR. HUANG: Okay.

DR. GIACOMINI: I mean at least be measuring in the therapeutic range, you know, somewhere in the therapeutic range and then look at the inhibition then.

DR. HUANG: I'm sorry; for some reason standing here, it's hard to hear.

DR. GIACOMINI: So I'm just saying, I'm just agreeing with Hartmut that in fact, it's good to at least standardize that in some way. So I like your idea of comparing, having a comparison with quinidine and dig, that comparison, but I also like the idea of, you know, making sure you're in the therapeutic range, where you're seeing an inhibition in and around this. I kind of like I over KI as being just sort of a guidance.

DR. HUANG: Okay; so, should I amend the question so that it would be similar to the first one, that we are going to recommend something on in vitro data? We probably will use I over KI, the ratio, and suggest, say, for example, with--this is what you see, and compare to a standard. Then, based on that, we'll come to this question.

So I guess the recommendation is we have something in our concept paper, in the guidance.

DR. HALL: I think staying away from the phrase therapeutic range would be good, because at

this point, they have no idea what the therapeutic range would be at this point in the history of the drug, right?

DR. WATKINS: The other part of that is the choice of probe, and I think if you say digoxin or other suitable substrate, everyone will do digoxin until there are other suitable substrates in the document. And, you know, it's a dilemma, because digoxin may be the best substrate, but we know it's transported by other transporters.

Furthermore, you give, you know, a tenth of a milligram, and it all gets in. So it gets by an absorption MDR-1 gene product, p-glycoprotein. So there's some intuitive disconnect about using a digoxin, and you're clearly not evaluating the intestinal component, and whether something else like fexofenadine would be better; you know, unfortunately, we still don't know the answers to it, and that's the reservation that I have at this stage about recommending, you know, an in vitro-in vivo algorithm. But I don't know the alternative; I don't know what else to do.

DR. VENITZ: And that's exactly the reason I'm going to vote against this question. I don't think the science is there yet. I don't think we know necessarily which in vitro transporter--not transporter but probe substance to use. I'm not sure whether digoxin is the most informative clinical substrate, so maybe in a couple of years, we'll know that. Right now, I don't think we can make the same jump that we make in terms of your question one.

DR. HUANG: Yes, in the current submissions, we have seen studies done with digoxin and fexofenadine.

DR. GIACOMINI: Can I comment on that also, on the digoxin?

DR. VENITZ: Absolutely.

DR. GIACOMINI: I mean, digoxin, there's multiple lines of evidence, certainly, that it's a PGP substrate: cell culture, knockout mouse; there's a quinidine interaction that's gone through--in my mind, it goes through sort of all of the tiers in terms of levels of evidence in terms

of whether it is, it's not metabolized, so it's an ideal substrate to use, and then, the specific inhibitors, even if they have studies of the drug-drug interaction in a knockout mouse, which they're looking at quinidine-dig interaction, and the quinidine-dig interaction doesn't occur in the knockout mouse, and it does occur in the wild-type mouse.

So that, again, suggests that that particular interaction is pretty--

DR. VENITZ: I don't doubt that digoxin is an in vitro and in vivo PGP substrate.

DR. GIACOMINI: Okay.

DR. VENITZ: It's just that the main thing that we're concerned about is PGP as it relates to drug absorption, and I don't think that's where the major--where digoxin has a problem. Digoxin has a variability of 70 to 90 percent.

DR. GIACOMINI: Right, right.

DR. VENITZ: So I don't think that's the best in vivo substrate to find out whether some in vitro inhibitor is actually going to change

protease inhibitor absorption. That's my concern.

DR. GIACOMINI: Okay.

DR. VENITZ: So I'm not doubting that digoxin is a PGP substrate, but I don't think we're testing for absorption interactions, which are the ones that I'm personally most concerned about.

DR. GIACOMINI: But then, in the absence of that, I mean, if you don't put something in the guidance, then, even a dig study isn't even done at this point, because this is a recommendation to say that we need a clinical study. If you've got a PGP substrate inhibitor, your enemy is that PGP inhibitor.

Should you carry out a clinical study with digoxin--

DR. VENITZ: Maybe in a couple of years, we'll find fexofenadine or some other model substrate is a better one. Maybe we'll find better ways of assessing the in vitro potential to interact.

DR. BARRETT: I think the original intention of this was to be purposely vague so that

you would have a little bit of freedom to define it as you saw fit. So, you know, even though the original comment was to standardize between the first two questions, it may be written okay as far as the spirit of being able to recommend, assuming the sponsor has done some studies here, not to do an in vivo study, assuming they have some compelling data on the in vitro side.

DR. SADEE: Your concern may be mostly related to bioavailability, but this also relates to other endpoints, such as do you get your drugs into lymphocytes in HIV patients, and that may be a very large effect. You cannot assess this with pharmacokinetics necessarily.

So is that--you're only talking here about an in vivo study that includes measurement of drug levels in plasma and area under the curve; is that correct?

DR. HUANG: Yes.

DR. SADEE: And if you have that, say, you know certain target tissues, you would not necessarily consider that--

DR. HUANG: Right, right, and just to remind the committee that there is some recommendation from the April meeting that digoxin even is not the perfect substrate for PGP for all the reasons we just heard, because of the clinical significance on the change in digoxin, and that was, at that time, digoxin was proposed as one substrate to consider if the drug is a PGP inhibitor. I know not everyone from that committee was here today, are here today.

DR. VENITZ: Okay; any other comments, questions?

Then, let's go the opposite way. So, Dr. Barrett, you go first this time.

DR. BARRETT: Yes.

DR. VENITZ: Okay; Dr. Blaschke?

DR. BLASCHKE: Yes.

DR. VENITZ: Dr. Capparelli? Oops; sorry.

DR. CAPPARELLI: Took my spot.

DR. VENITZ: I'm going alphabetically according to the seating order.

DR. BLASCHKE: My answer is yes, but I

would also just comment that I think that there's been a couple of important points made, and that if a drug is a PGP inhibitor, there may be a lot of other kinds of clinical studies that might fall out of that, as was suggested, perhaps those that affect drug transport into cells, et cetera. But I think this is an appropriate place to start.

DR. VENITZ: Dr. D'Argenio?

DR. D'ARGENIO: Abstain.

DR. VENITZ: Dr. Davidian?

DR. DAVIDIAN: Abstain.

DR. VENITZ: Dr. Watkins?

DR. WATKINS: Yes, if it is further quantified what degree of inhibition and at what concentration.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes.

DR. VENITZ: Dr. Hall?

DR. HALL: Yes.

DR. VENITZ: Dr. Jusko?

DR. JUSKO: No.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: Yes.

DR. VENITZ: Dr. Sadee?

DR. SADEE: Abstain.

DR. VENITZ: Dr. Watkins?

DR. WATKINS: Yes, and just to comment, I was glad Shiew-Mei clarified that, because I remember when the first guidances were put together, the point was made that the FDA has to be concerned about safety and should not be dictating science, and in that sense, digoxin is a very relevant interaction. A lot of people on it; neurotherapeutic index. And so, it's a reasonable substrate from that aspect, although scientifically, it's not perfect, so yes.

DR. VENITZ: All right; and my last vote is a no, which according to my count, gets us two noes, three abstains and eight yeses.

Okay.

DR. HUANG: Yes; the next question is about a new molecular entity as a substrate for PGP, and I need to clarify this here. When we have the concept, when we have the guidance, we would

talk about how do you determine as a substrate, and this would be one of the ways is to look at one of cell systems and look at A to B, B to A, base lateral to applicable transport and look at the difference between these two.

And so, if you determine it to be a substrate in vitro, and actually, the next two questions are related: number one is to consider the CYP3A status in making the recommendation, and then, number two, the question is whether it's proper to evaluate PGP-based interaction when the new molecular entity is a substrate. So they could be commented together. And when you say yes and no, I think it's probably more informative to also discuss the examples we used here, whether these are appropriate examples to give.

DR. VENITZ: Any comments?

DR. GIACOMINI: Yes, so, in terms of three and four, when you conduct a clinical study, what we would be interested in at that point when a clinical study is conducted is since this is the substrate is what the inhibitor is, what inhibitor

to use in a clinical study. And since, of course, this is one of those cases where we're going to have to use an inhibitor that's going to be an inhibitor, probably, of a transporter and an enzyme, PGP and CYP3A4, for example, something like that; so I guess I want to say that from my point of view, three and four are hard to pull apart, you know, because I don't see that I could pick an inhibitor for three that didn't work for four. So I would lump the two together, whether your NME is a substrate of PGP alone or whether it is a substrate of PGP and a CYP 3 and 4.

DR. HUANG: One of the reasons I did that, because if this drug is a substrate of 3A, when we assess interaction, we would recommend to use a strong inhibitor.

DR. GIACOMINI: Okay.

DR. HUANG: The inhibitor that we recommend in question three, four, they're not strong 3 inhibitors.

DR. GIACOMINI: Okay; okay.

DR. HALL: So I guess it again comes down

to the details of whether such--whether there are such inhibitors that can be used in some sense ethically in these types of studies, and, you know, ritonavir, for sure, there are concerns with it. We've heard cyclosporin, verapamil, there are concerns with those that the IRBs commonly express, and so, in practice, I think there are some issues with this.

I think, you know, the general principle of the question, I don't think people would disagree with. But whether you can execute that on a large scale is another issue. And I'm not convinced that these are reasonable choices of inhibitors to be used for these types of questions.

DR. HUANG: Yes, one standard for us to be putting on something the guidance to make a recommendation is we have to have something that is a general inhibitor that we will agree to, and it can be used in a study. So if none of these are practical inhibitors, then, we probably would not be able to put that in the guidance or recommendation.

DR. VENITZ: And that means we should vote no, right?

DR. HUANG: If we couldn't think of any, or we could put in a general statement instead of putting the examples if these are not--well, one question is we have to agree that when we found that a drug is a substrate, then, we would routinely conduct a study in vivo. That was one of the important questions.

DR. VENITZ: Any other comments?

Go ahead, Terry.

DR. BLASCHKE: Well, just a comment about the ritonavir. I think single dose ritonavir, Steve, would not be a concern; certainly not a multiple dose study with ritonavir, but certainly, I think a single dose study with ritonavir would not be a safety concern.

DR. HALL: Would that work, though, to get the full interactive effect of ritonavir?

DR. BLASCHKE: We've done single-dose studies with ritonavir looking at interactions, and it's certainly a potent inhibitor even with a

single 400-milligram dose, yes.

DR. CAPPARELLI: But there still is a specificity issue with ritonavir. In terms of depending on the compound that you're looking at, it's not just 3A and PGP, so you still have those issues of what's, you know, how do you apply the results that you get.

DR. WATKINS: Can I--yes, just I realized it was helpful to me to think about, you know, why we're being asked these questions. So with digoxin, you know have a PGP inhibitor. You go to a digoxin study. If it's a negative interaction study, unfortunately, it doesn't mean you won't inhibit PGP in the intestine and other things. But here, I think the implication is if you have a substrate for both PGP and 3A4, and you don't have an interaction with ritonavir, you can stop. There are no more rocks to turn over. That's the end of the drug interaction considerations.

And I actually agree with that. But I think that's the question. And then, the next thing is if it's a PGP substrate but not 3A4, of

course, you could do ritonavir again. But being a little more specific, again, sticking with clinically relevant interactions, you do the cyclosporin study. If that's negative; you're done. You don't have to do anything else. And I think I agree with that, too.

DR. HUANG: Yes, one of the reasons we put in cyclosporin here for discussion, because it affects a lot of transporters, not just PGP. And so, as you said, if you do a study, and it's negative, it's a very good information.

DR. WATKINS: With a positive control, obviously. You've got some other probe; you're showing that cyclosporin got in the right place in the right concentrations, et cetera, but--

DR. HUANG: Right, right.

DR. VENITZ: So is this question, then, supposed to read if the NME is not a substrate for PGP and not a substrate for 3A4, no clinical study will have to be done? Because I think that's what I heard you say, Paul, right?

DR. WATKINS: Yes, I think we already

decided that, didn't we? I mean--oh, I guess no, we didn't. You're right, no, no, we didn't decide that.

DR. VENITZ: We talked about inhibitors; we didn't talk about substrates.

DR. WATKINS: That's true.

DR. VENITZ: So are we here saying if the in vitro is negative, stop; no further clinical study? Are we saying if the in vitro is positive, a clinical study has to be conducted? Because that's the way I read this question.

DR. HUANG: Right, but Paul was going one step further: if it's a substrate, and you did a study with a cyclosporin or ritonavir, then, you're pretty confident that other future transporter inhibitors will not have an effect. It's just cyclosporin and ritonavir inhibits a lot of pathways, not just PGP.

DR. WATKINS: In other words, it doesn't matter that it's not specific; it's just the maximum way to knock out those two pathways. And if that has no effect, and the study is done right,

you're done. You don't have to do anything else.

DR. BARRETT: Shiew-Mei, it strikes me when I look at the questions that there's a decision tree that's going to fall out of this, assuming that the yeses and noes fall in the right path. And if you could superimpose history on top of what you're going to come up with at the end of this, is there some idea of the sensitivity and specificity of what that kind of a proposal would look like, or can you do a kind of scenario testing to this? I mean, you have the benefit of looking back on a lot of development programs that have made it to market.

So if you look at the decision tree based on, you know, taking away those kinds of studies, you know, would you arrive at the right--where you think you want to be, I guess, with this kind of a guidance?

DR. HUANG: I think this will be the beginning of gathering some information. I don't think we are at the stage yet that once you did a study, if it's a positive, what else do you need to

do? I mean, with the cyclosporin study, if it's a positive, you probably will report this in the labeling. If it's negative, you could say a lot of things that it does not affect, and probably, the other PGP inhibitors will not be able to--

DR. BARRETT: You know, I know you're laying this out prospectively. This is something we want to put forward as, you know, moving forward, but if you applied this kind of an approach back to historical agents, where you had the benefit of in vitro signals and in vivo studies, you know, I just wonder where you think we would end up. Do you have that kind of information, or has the working group looked at any of that?

DR. HUANG: We started to construct a decision tree based on in vitro and how that compares with digoxin; then, we decide whether to do an in vivo. But once we reach an in vivo, we haven't had enough information to say what to do.

For CYP3A inhibition, it's very easy. We say if there's no interaction with medazolam, you

stop. If it does, then, you continue with other sub, like, sensitive substrates or other coadministered drugs. And we do have that layout in our good review practices.

For PGP, we don't have that, partly because many of the inhibitors that we're talking about are not specific for just PGP, but I would be happy to have any input from the Committee members.

DR. VENITZ: Are we ready to vote?

Go ahead.

DR. JUSKO: When I look back at your slides and look at the severity of the interactions, the first question we examined looked at digoxin AUCs and the presence of quinidine, and there's a 2.5-fold increase in AUC. So it's a moderate interaction. The ritonavir interaction is extremely strong, a 50-fold change, it looks like to me.

But for question four, the single interaction, it goes back to about a 2.5-fold, so some consideration needs to be made upon what we're going to learn and how important these interactions

are, and it looks like number three there is a very important one; but going back to number two and number four, they're not quite so important that we need to do these clinical studies.

DR. HUANG: When you say number two, number four, you mean the questions?

DR. JUSKO: The degree of interaction demonstrated in previous studies in relation to the benefit gained from doing these kinds of studies.

DR. HUANG: Okay; as mentioned earlier, digoxin, because it's a high bioavailability and others, so the extent of interaction may not be as great. But we know for digoxin, 2.5-fold increase is definitely important. And so far, since it's probably the best substrate that we have as far as PGP specificity is concerned and also the clinical significance that the change in digoxin is important; that's why we recommended it.

But if you're talking about the drug as a PGP substrate, then, we don't know yet. Perhaps the ritonavir and cyclosporin will have a very high degree of interaction, cyclosporin and rosuvistat,

and that's one other transporter, has sevenfold increase. So it depends on the substrate that we're talking about right now. We're talking about the new molecular entity as a substrate, so depending on its kinetic or disposition characteristic, you probably will have much higher extent of interaction compared to digoxin.

I use digoxin just because it's what we have. If you look at fexofenadine or others, those are nonpure PGP substrates. You might see a different extent of interaction.

DR. VENITZ: That's exactly the problem I have with both of those questions. I don't know anything about the NME. I don't know anything about the degree of absorption. If it's 90 percent absorbed, PGP, it's probably not particularly important.

DR. HUANG: But we did see--we don't know the mechanism of interaction, but we know about ritonavir--

DR. VENITZ: I understand.

DR. HUANG: But for ritonavir and

vardenafil, we have 50-fold increase. Cyclosporin and rosuvistat, we have sevenfold. So we're seeing a great degree of interaction, possibly because of some transporters.

DR. VENITZ: But you don't know whether it's based on the fact that they're PGP substrates is my point, so you're using some in vitro tests that may have nothing to do with the interaction that you're going to find when you look at ritonavir interaction.

DR. HUANG: If they're a substrate of PGP, we know ritonavir and cyclosporin, they do inhibit.

DR. VENITZ: Right, but it could be that by giving ritonavir, something else is going on. They did it in--

DR. HUANG: Correct.

DR. VENITZ: Okay; the second question or concern that I have, what is the exposure response, and what's the side effects or the negative utility that--what are the stakes, basically? I mean, here, you're not looking at the effect of the drug on something else but of something else on the

drug.

DR. HUANG: Correct.

DR. VENITZ: So unless you know that, I'm not sure whether you can give it a clear-cut yes or no answer.

DR. HUANG: Right; we definitely put that into consideration when we interpret a drug interaction. For a drug that's a substrate of 3A, we don't ask what is the exposure response before we recommend an interaction study. We want to look at interaction, what is the maximum effect of interaction, and then, see whether they're within that exposure response or not. And we don't say that this drug has a very wide therapeutic range; therefore, you do not need to study an interaction.

DR. VENITZ: But I think we know more about 3A-4 interactions than we knew about PGP interactions.

DR. HUANG: Okay.

DR. VENITZ: That's my--

DR. HUANG: All right.

DR. VENITZ: Any other--

DR. CAPPARELLI: I still have a question on the yield on number three, and, you know, if you really look at 3A substrates, are you really going to catch anything extra by doing a ritonavir interaction study? In other words, are there examples where doing these interaction studies surprises you and shows you no interaction? Because the single dose PK is not going to reflect what's going to happen in any clinical situation; in other words, it will show you sort of the maximal effect of wiping out a lot of systems, but it's not going to tell you--you know, I'm wondering if it's going to tell you enough to really justify that study versus doing something more specific and moving on from there.

DR. HUANG: Right. But doing a single dose study might be able to tell us whether there's a pharmacokinetic interaction, and we may not be able to assess a dynamic or other additional response. We know that.

DR. VENITZ: Okay; are we ready for a vote?

Then, let's start with Dr. Watkins: question number three.

DR. WATKINS: Yes; do them one at a time, or should I do four with that?

DR. VENITZ: Do both of them.

DR. WATKINS: I would say yes to both, and the only suggestion I would have, and I understand the problem probably with doing it, is having been involved with certain drug approvals, often, the interpretation of guidelines differs not only from company to company but even within the agency.

So I would suggest rewording. It says that you should do this. I would say that if you do this, and it's negative, you don't have to do anything else; I mean, just to clarify what I think is really the essence of the message that will get upper management and pharmaceutical companies very excited about the work they don't have to do.

DR. VENITZ: Okay; Dr. Sadee?

DR. SADEE: So, what am I voting for?

DR. VENITZ: Three and four.

DR. SADEE: Well, as it stands, on three,

I have to abstain, and four, I say no.

DR. VENITZ: Okay; Dr. McLeod?

DR. MCLEOD: Three yes, four no.

DR. VENITZ: Dr. Jusko?

DR. JUSKO: Three yes, four no.

DR. VENITZ: Dr. Hall?

DR. HALL: Three yes, four yes.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Three yes, four yes, and I like Paul's suggestion.

DR. VENITZ: Okay; Dr. Derendorf?

DR. DERENDORF: Three yes, four yes.

DR. VENITZ: Dr. Davidian?

DR. DAVIDIAN: Abstain and abstain.

DR. VENITZ: Dr. D'Argenio?

DR. D'ARGENIO: Abstain to both.

DR. VENITZ: Dr. Capparelli?

DR. CAPPARELLI: Three no and four no.

DR. VENITZ: Dr. Blaschke?

DR. BLASCHKE: Three yes and four yes as amended by Paul.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: Three no, four no.

DR. VENITZ: And I have no on three and no on four. So we've got seven on question number three; we've got seven, yes; four, no; two abstain. Is that right? On question number four, six yes; five no; and two abstain.

Okay.

DR. HUANG: This question is trickier, because right now, we say for inhibition interactions, focus on the five major CYPs and their emerging data on the importance of CYP2B6, 2CA, UGT1A1 and possibly other drugs. So this is more of asking whether there are other CYPs that seem important, because we know there are quite a few drugs that are a substrate of 2CA. So whether it's important to evaluate the inhibition potential, of the other drugs, when you answer, you could include others or maybe a specific set, only certain CYPs that are important to evaluate right now.

DR. VENITZ: Any comments?

DR. WATKINS: One of the issues in the Bay

Call litigation is whether 2CA inhibitions should have been routinely part of drug development back in the, I guess, the midnineties, and it would certainly seem, for those who don't know, gemfibrizol inhibiting 2CA appears to be a relevant mechanism for the rabdomyalisis there. And it would seem to me if you knew and demonstrated that your drug was largely metabolized by 2CA, it would now be incomprehensible why you wouldn't do interactions at least with gemfibrizol.

So certainly, for 2CA, it would seem to me that should be part of the guidance.

DR. HUANG: We actually have a case where we did recommend a study with gemfibrizol with a 2CA substrate. And now, the question is if a new molecular comes in, do we need to ask routine evaluation of in vivo interaction with CYP2CA substrate?

DR. WATKINS: So for clarification, are you saying when there's no evidence from in vitro studies that it's metabolized by 2CA?

DR. HUANG: Yes, right now, we're talking

about the effect of new molecular entity on others. If this new molecular entity is a CYP2CA substrate, because they're not the substrate of the other five major CYPs, and 2CA is a major substrate, then, we would recommend a study with the two CYP2CA inhibitors that based on literature data.

But my question right now is if a new molecular entity, when we evaluate its ability to affect other drugs, do we routinely ask to evaluate CYP2CA?

DR. WATKINS: I think I understood it correctly, and my answer would be yes, that that's a relevant pathway for certain statins and already has a track record of problems. It's Taxol's major pathway; rosyglydazone; it would make sense to me to incorporate that into the document.

DR. HUANG: So we would add to the five major CYPs perhaps CYP2C8?

DR. WATKINS: I would say so, yes.

DR. VENITZ: What would be your UGT1A1 inhibitor that you would recommend be studied?

DR. HUANG: Right, actually, I would not,

but this is thrown out as a question partly because we haven't seen significant interaction. I think earlier on, there was a question about UGT1A1 inhibition or actually this morning about irinotecan. I don't think we have seen an inhibitor which can deplete the activity as much as a poor metabolizer status that would cause the depletion of the UGT activity, so we have not putting that as a recommendation of evaluating a drug's ability to inhibit UGT1A1.

DR. VENITZ: You want to take it off the question, then?

DR. HUANG: We could, unless there are others.

DR. MCLEOD: Is it known how many companies are not currently screening for these three? Because many companies are already looking at these three because of the known polymorphisms and trying to predict risk.

DR. HUANG: For a new molecular entity as a substrate of these, yes. This has been done. But as routinely to evaluate its ability to inhibit

these, no, not consistently. And the latter one is my question.

DR. MCLEOD: Right, thank you.

DR. SADEE: I think that clearly, we should be somehow going on record to say that the potential for interaction should be assessed. Whether we would want to recommend for all these three genes and their products to recommend clinical drug interaction studies, that's a different question. But I think we need to go forward and say these are important potential factors in drug-drug interaction.

So in particular, if we don't have any inhibitors, it would appear to be difficult to recommend at this point clinical studies.

DR. VENITZ: Larry?

DR. LESKO: Yes, I just wanted to make sure I understood Paul's comments, because I don't think this fits the Bay Call situation, because the question, as Shiew-Mei's asking it, is if I have a drug that is a substrate for these enzymes, not a substrate affected by another drug for these

enzymes. So, in other words, if the enemy was a substrate for these enzymes, would you want to do clinical studies based on the in vitro? Isn't that what you just said?

DR. HUANG: No.

DR. LESKO: Okay; could you just rephrase that so I understand the question?

DR. HUANG: Well, in our guidance, we actually said as a substrate, it's important to study other than the five major CYPs, because if there are not substrates for those five major CYPs, you need to evaluate, for example, 2B6, 2C8 and others and UGT 1A1. You need to know if it's a UGT substrate, so later on, we can see the variation in genetics, how that affects the pharmacokinetics.

But right now, I'm asking whether it's prudent to recommend routine evaluation of a new molecular entity's ability to inhibit--that's not the same as the substrate--to inhibit these enzymes.

DR. LESKO: Yes. That's my point. Bay Call didn't inhibit gemfibrozil. It was the other

way around.

DR. HUANG: No, no, no, but Bay Call, cerebrostatin is being found to be a substrate of CYP2C8 and other transporters and UGT. So gemfibrozil would affect the part of the interaction of gemfibrozil and cerefostatin could be through CYP2C8.

DR. LESKO: Well, creating the scenario, the scenario is the cerebrostatin is the new molecular entity, and the question is does that affect the metabolism of other previously-approved substrates for these enzymes?

DR. HUANG: Right; it would not.

DR. LESKO: Yes.

DR. HUANG: But to come back to Paul's question, now, with a new molecular entity such as cerebrostatin, if we have, if we know that it's a CYP2CA substrate, based on the new concept paper, we would have recommended a gemfibrozil type of study. We did have that statement in our guidance, our concept paper. We have said that if it's a substrate.

DR. LESKO: Right.

DR. HUANG: But as an inhibitor, okay, if cerevosin is right here, other drug that's being approved which may affect its, okay, say it's 2CA or many of these glydazones, they're CYP2CA substrates. So if another NME that we're reviewing, should we ask that it be evaluated as an inhibitor of CYP2CA, because they may interact with many of the glydazones?

DR. LESKO: Yes; it's just two different questions.

DR. HUANG: But I'm asking this question, not the other question.

DR. LESKO: The new molecular entity could be the so-called offending drug, or it could be the--

DR. HUANG: Yes, offending drug.

DR. LESKO: Yes.

DR. HUANG: We're only talking about offending drug here.

DR. LESKO: All right; it's the offender.

DR. HUANG: Yes.

DR. WATKINS: And just, Larry, because it's getting late, and I'm getting confused, too, about the two different things, but it would be like if somebody developed a new gemfibrozil which was an inhibitor of 2C8, and that appears to have contributed to the recall of Bay Call because of a drug interaction, and so, we already have a precedent that caused a serious problem, it only makes sense to me to included 2C8 inhibition in the, you know, the next test tube and the line of, you know, recombinant enzymes.

DR. GIACOMINI: It says clinical study. It's not whether to put it in the test tube.

DR. WATKINS: All right; so you meant in terms of coming up with specific probes for 2C8, for instance?

DR. HUANG: Yes, and I'm actually asking a general question: should we evaluate the other pathway besides the five major CYPs?

DR. WATKINS: Okay; because that's the way she rephrased the question is that we know 3A4, you know, 1A2, et cetera. Should we be adding 2B6 and

2C8 all the way back to everything? And my answer is yes, that should be done, and I think an in vivo study should be done if there's evidence of inhibiting 2C8 in vivo. So I'm just going to carry it, like, 3A4 through the whole process. That's what I meant, anyway.

See, I realize this says just clinically but--

DR. HUANG: But it's clear based on what you said.

DR. WATKINS: Whereas 1A1 and 2B6, I think, is much less clear, but 2C8, there's a track record.

DR. HUANG: Thank you.

DR. HALL: I think given, of course, that it passes the test of your definition of not or is--

[Laughter.]

DR. HALL: So if the I over KI ratio is a certain number, then, whether we have other inhibitors of 1A1 or not, the new entity would be a good inhibitor of 1A1 predicted from that in vitro

study, correct?

DR. HUANG: 1A1? You're talking about UGT1A1?

DR. HALL: The UGT1A1, for example.

DR. HUANG: Yes.

DR. HALL: So, you know, in 2B6, even though there's not many 2B6 substrates that are sufficient, if you were to coadminister it with one, you would be concerned if the I over KI ratio, however we define it, is sufficient.

DR. HUANG: Right.

DR. HALL: So I don't see why these would be special. You would simply treat them just like 3A.

DR. HUANG: Right. One of the reasons we put it this here, in order for us to put in a guidance, we need to have probe substrates, inhibitor, inducers to recommend. So if we have a good probe to recommend, then, we would put it in the guidance. If we don't have a good probe--we're talking about metabolizing enzymes, not the transporters--then, we usually do not. But we did

put in 2CA, 2B6 substrates and inducers. I don't think we have an inhibitor for 2B6 yet based on our discussion in November. But I know what you're--I understand your comments.

DR. SADEE: But I think there needs to be another qualifier here. Those are minor cytochromes in terms of quantity, and if a compound is a substrate for 2C8, let's say, and it's also a good substrate for 3A4, then, it doesn't make any sense to study this in further detail. So it needs to be said that the evidence suggests that there are substrates and that this is the major pathway of metabolism.

DR. HUANG: Correct, correct.

DR. VENITZ: Okay; are we ready for a vote?

Okay; then, I think I'm going to start with Dr. Barrett.

DR. BARRETT: Yes.

DR. VENITZ: Dr. Blaschke.

DR. BLASCHKE: As amended, yes.

DR. VENITZ: Dr. Capparelli?

DR. CAPPARELLI: Yes.

DR. VENITZ: Dr. D'Argenio?

DR. D'ARGENIO: Abstain.

DR. VENITZ: Dr. Davidian?

DR. DAVIDIAN: Abstain.

DR. VENITZ: Dr. Derendorf?

DR. DERENDORF: Yes.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes.

DR. VENITZ: Dr. Hall?

DR. HALL: Yes.

DR. VENITZ: Dr. Jusko?

DR. JUSKO: Yes.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: Yes.

DR. VENITZ: Dr. Sadee?

DR. SADEE: Yes.

DR. VENITZ: Dr. Watkins?

DR. WATKINS: Yes.

DR. VENITZ: And I put my yes in, so we have 11 yes, no noes and two abstains.

DR. HUANG: Jurgen, can I clarify, because

I have heard some say yes with the amendment. So I assume the amendment was based on Dr. Watkins' comment that we consider 2C8? And the others are just as-is, correct?

DR. VENITZ: Yes.

DR. HUANG: Okay.

DR. SADEE: What about the other--it has to be the major metabolic pathway.

DR. HUANG: Right; that's on the substrate side. Here, we're talking about inhibitor.

DR. VENITZ: Okay.

DR. HUANG: The next question is related to the transporters. We said does the current evidence support recommendations that drug interactions based on other transporters, such as OATP or MRP, be recommended for clinical study during drug development? And I believe because the answers from questions 2, 3, and 4 are relatively positive, so I guess we could move on to this one. If those were negative, then, we wouldn't ask this question, because PGP is much more developed a field.

So I would go ahead and ask number six.

DR. GIACOMINI: I think it's hard to do this at the end of the day, to present all of the evidence to suggest that something might be clinically relevant for us to begin to put this in the guidance. So I have some thoughts about it, but it's--there are some other transporters: OATP1B1 in particular is one that we should be thinking about.

And what is the evidence there? Well, there's good evidence, first of all, in cell culture that OATP1B1 and the statins, interacts with the statins. There is a genetic polymorphism in OATP1B1 that has now been shown in three or four clinical studies that when that transporter is polymorphic, pravostatin levels then go up. So there's polymorphism evidence; there is in vitro cell culture evidence; there is drug-drug interaction.

Now, these are, again, not clean. So you take a drug like pravastatin. It interacts with OATP1B1. It's not a CYP substrate. And when you

give it with cyclosporin, which is dirty, you get a profound eightfold increase in the area under the curve. Similarly, pitavostatin, which is another one which is primarily--it's not a CYP substrate. It's primarily a transporter thing. When you give pitavostatin, when you give cyclosporin with pitavostatin, you see, like, a four and a half fold increase in area under the curve. So they're increasing clinical drug-drug interactions showing or suggesting highly that OATP1B1 is involved, and then, there's genetic data.

So it's one that I think we should certainly be considering as part of this guidance. That's one that you're asking me to present at 5:00. And then, the other area, which I don't know how the Committee feels about this, is just renal transport interaction. So I had read the 1997 guidance, and there's nothing in there about--at least I didn't see anything in there about renal transport interactions, and there are known probenecid versus penicillin, even therapeutic interactions that people use those two drugs

together, actually, to enhance the effects of penicillin.

So if I have some thoughts about, you know, if a compound is secreted or if your in vitro studies are suggesting that they're interacting with some of these OATs, kidney-specific OATs, particularly OAT1 and OAT3 or kidney-selective OCTs, OCT2, which is only in the kidney, then, you may want to consider doing a probenecid interaction study for the N ions, and then, for a CAT ion, you might want to consider doing, for example, a somatadine interaction, if that's--so those are renal transport points, and I think it would be appropriate to mention, at least in this guidance. It's drug-drug interactions that should only concern the liver.

DR. HUANG: And just to clarify, so if we--I mean, we do have certain studies that we look at the competition of ectosecretion on renal levels, although the labeling only states the drugs. We do not extrapolate to other transporters, and we do not currently name the

transporters. Do you think we're at the stage to name the transporters when we report this type of interaction?

DR. GIACOMINI: Well, okay, so, for OAT3, there's a knockout mouse that when the OAT3 is knocked out, the cephalosporin renal elimination goes way down. So you've got knockout mouse studies, and then, you have studies showing, you know, certain affinities for OAT3. So those are the two levels that you have for OAT3.

For OAT1, there's not a knockout mouse. You just have cell culture evidence. And you know that these anines are interacting.

DR. MCLEOD: Kathy, do you think it needs to be so specific, though, in the language? Because you've identified several different families where it's important. There will be more coming. You didn't mention the transporters, which from your own work and others, are also going to be important. I almost think, like, that the language needs to be more general, saying transporters, any transporter that's shown to be--any drug that's

shown to be a substrate for a transporter needs to be followed up if it's a main route of transport; if there's some data.

Because if we get into the point where it has to be a--only a named transporter on the list, even if you have it on the Web, and it's dynamic, you know, it's too new--the field is moving too fast for this guidance to be changing every couple of minutes.

DR. GIACOMINI: Yes; I guess what I did when Shiew-Mei asked me to consult was I just looked for the most compelling examples, not the ones that, you know, the field is moving fast, and I think we would be changing every week. But the statin interactions are pretty strong; in particular, the statin interactions with OATP1B1 look pretty compelling right now. And then, of course, the renal transport interactions, which have been historically around for so many years are more or less compelling.

But again, I feel like the--I, personally, feel like it would be nice if people saw the papers

and got the irinotecan book, you know, something like that on some of these so that they could see the evidence themselves.

DR. MCLEOD: And I've had the benefit of seeing you present this data and others.

DR. GIACOMINI: Right.

DR. MCLEOD: And there is very good data for a lot of these.

DR. GIACOMINI: Right.

DR. MCLEOD: So I think you're right that these are at least on people's radar screens.

DR. GIACOMINI: Right.

DR. MCLEOD: I think the companies, most of the big companies, you know, it is on their screen.

DR. GIACOMINI: Yes, it is, but I don't know whether it's ready for this guidance.

DR. HUANG: Just for information, we do have--we have seen in vitro data or animal data on various transporters. So the question from our reviewers is are we ready to recommend a followup when it's shown to be a substrate or an inhibitor?

And that's why I put in this question. And these are real-time review questions.

DR. VENITZ: And I guess my sense is I think we are ahead of the science. I mean, here, you're setting rules for large regulated industry, and I don't think we're there yet. So maybe if you come back in a year or two years from now, we'll have more information. That's my personal opinion. We'll have more information. But right now, I can't agree with that.

DR. GIACOMINI: And I think he can't agree with it, because we didn't have the time to present, although you didn't see the papers and all of that, so you have to look at that and see where the evidence is. But we just didn't have time to, because there is, on one of them, at least, there's more and more compelling evidence, but I agree.

DR. LESKO: Yes, one of the questions I have is how do you translate information in a sort of cutting edge area into a label? I mean, with the CYP enzymes that we're quite familiar with, there's studies done in vitro; there's studies done

in vivo, and then, we label compounds with information about drugs that were not studied, necessarily, but are part of a class of 3A substrates that are sensitive or modestly sensitive or something like that. So the value of the information becomes larger in magnitude, because you can extrapolate.

My question then becomes, in this area of transporters, when you say this cephalosporin or that cephalosporin, is it then only that interaction that's of relevance? I.e., can you go beyond that to say, well, it isn't just the two drugs I studied in the clinical study, but it also would apply to this drug and that drug and other drugs. Do we know enough about the information to get more out of the study than simply two drugs interact; that is leveraging the information for the package insert?

DR. BARRETT: I come back to Howard's point here, though. I don't know that we need this level of granularity. I mean, I think if you rephrase this in a more open fashion, and you don't

need to tell your child don't put your hand on the stove if you told him not to put it in the fireplace. So I don't know that you need to do that.

DR. DERENDORF: Well, I also think that it really depends. I think the general answer to that is very, very difficult, and coming back to what was said earlier about the exposure response relationship, if there is a likelihood that this may be relevant, that depending on the PKPD properties of the compound, it's a different story than when I have a very safe compound, am I really, you know, if it happens or not, it's nice to know, but it really wouldn't make that much of a difference.

So I think that needs to enter the decision tree, too, at some point.

DR. VENITZ: Any other comments?

Okay; ready for the vote, Dr. Watkins?

DR. WATKINS: I know it's a tough one. I mean, it's so clear that transporters and uptake transporters are going to be so important in the

disposition of drugs. And to come back to Bay Call, there was some evidence of OATP inhibition and things. But unfortunately, the science is so new, there aren't good probes or understanding of regulation-specific inducers. So I think anything more than just encouraging, you know, more research in the area is very hard at this stage. So I don't know whether that's a yes or a no.

I guess it's a no, because, well, I guess we don't even have--oh, there it is, yes, because you're saying clinical study, and I don't think we really have the tools to clinically study it other than maybe pravacol for 1OATP, so I guess I'm no.

DR. VENITZ: Okay.

Dr. Sadee?

DR. SADEE: I agree with the principle that wherever you find a single gene product to be important in drug-drug interactions, it is essential to study it further. And the evidence is beginning to appear, but I cannot see that we can prescribe clinical studies at this point. So I would like to abstain, but I like a more general

approach here.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: Yes.

DR. VENITZ: Dr. Jusko?

DR. JUSKO: On one hand, it seems highly advisable that if a drug is following a certain pathway, it's the major pathway, that any interactions with it should be studied. But we haven't been given enough evidence for this whole arena for me to say yes as yet, so I'm going to say no.

DR. VENITZ: Dr. Hall?

DR. HALL: I think I would go with a no as well given the context that others have already mentioned.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: I'm going to go with a yes that there are specified transporters that we could be looking--requiring clinical studies on and drugs, specific drugs.

DR. VENITZ: Dr. Derendorf?

DR. DERENDORF: I go with a no unless

there is evidence that there is a high likelihood, so not as a general recommendation.

DR. VENITZ: Dr. Davidian?

DR. DAVIDIAN: Abstain.

DR. VENITZ: Dr. D'Argenio?

DR. D'ARGENIO: Abstain.

DR. VENITZ: Dr. Capparelli?

DR. CAPPARELLI: For the specific transporters listed there, I would have to say no, but I think that the issue of putting a general statement in would be highly recommended.

DR. VENITZ: Dr. Blaschke?

DR. BLASCHKE: I would agree with that. I think there should be something in there about transporters, something that can be updated.

DR. VENITZ: And Dr. Barrett?

DR. BARRETT: Yes.

DR. VENITZ: And I would put my no in with the recommendation to maybe come back at a future meeting and talk about specific transporters and probe substrates, probe inhibitors.

DR. HUANG: One clarifying question, when

Dr. Watkins says maybe with the exception of prevastat and OATP1B1, is that--did you say that or--

DR. WATKINS: Maybe. Was it intelligent? I can't remember.

[Laughter.]

DR. HUANG: That's all right.

DR. WATKINS: I mean, that's why I'm sort of torn with this. I mean, there is the pravacol example, so there's a probe, but I don't know the studies that have validated it. I think as Kathy said, we really haven't heard much about transporters here, so, you know, I'm all for clinical study of these things, and that's all I can say right now.

DR. HUANG: Okay, thanks.

DR. VENITZ: Okay; the final vote is three yes, seven no, and three abstain.

DR. HUANG: The next questions are related to induction.

Okay; so there are two questions: one of them is on--maybe I'll go to question A first,

because that's how it was presented: if a new molecular entity induction effect on CYP3A in vitro is negative, and it's acceptable not to recommend in vivo studies, not only just CYP3A but also 2C9, 2C19 and 2B6; if you do not agree with 2B6, we could take it out, because right now, we're only recommending the major CYPs: 1A2, 3A2, 2C9, 2C19.

DR. VENITZ: Paul?

DR. WATKINS: If I could just ask for clarification from John, actually: you were saying that phenytoin was negative, at least in one human hepatocyte induction study, and you thought that was because the hepatocytes might have been maximally induced, in which case the positive control would have been negative?

I mean, my question is, and maybe I should put in a context, because I've talked to Shiew-Mei. What we're really voting on here is the concept that every single drug ever developed from here on either is given to people and probes either singly or in a cocktail are done to see if they induce it. And if you don't want to do that, you can do

cultured human hepatocytes and see whether the induction is 40 percent of a positive control, and if it's not, then, you don't have to do those studies.

And since the clinical studies are further in development and requires a lot of drug and everything, what it's basically saying is every single drug ever developed from now on, you can correct me if I'm overstating the case, has to go through a human hepatocyte study at some point in its development. Practically, I think that would be the outcome.

And the concern that I have is just that I'm unaware of the data that would really standardize this thing as being a routine part in drug development, and we heard about all of the different cells, and if the liver is ischemic, the pericentral hepatocytes are gone, and you just have the periportal hepatocytes, and maybe people can cryopreserve a whole bunch of hepatocytes from 50 different donors, so genetic polymorphisms is important, and you can refreeze the same aliquot,

and it will all be standardized, and it will all make sense.

But from my perspective, I have just not seen any data to suggest it's that robust. Now, that would be acceptable in my opinion because I think it is the best single test for induction if it weren't such a precious resource to us academicians. I mean, I don't know how industry is getting all these to do all these studies. I just know that we academic people have a very hard time getting them.

So I think there's a cost of, you know, of doing this, and so, that's the basis of what I'm saying. You mentioned that there is a clear clinical significant drug interaction with phenotone. It's on a short list of drugs where induction is really important, and didn't you say that it was negative in a human hepatocyte culture study?

DR. STRONG: Yes, this was in some data that Ed had in his slide. You know, I think in most studies, you'll find that it would meet that

40 percent criteria. I think what I was pointing out was design of experiment is very careful, you have to be very careful with; i.e., these particular hepatocytes appeared to, you know, be induced with their background or basal activity for three or four was very high, compared to, say, even looking at the figure A, which was the 2B6.

So what I was talking about was I still don't know what number quantitatively would be good myself, and I think that's what we're trying to discuss here. I think a lot of it may be just due to the particular hepatocytes you're using and the design of the study.

You were mentioning, you know, the availability. You know, that's a question I don't know either myself. Certainly, folks here in PhRMA would know. I agree with you that they're expensive, but--

DR. WATKINS: Well the price is going to go way up.

DR. HUANG: Right.

DR. WATKINS: --if we endorse this,

obviously.

DR. HUANG: I'd like to clarify. The in vitro methodology is only one additional method that we think that could be used to evaluate induction, but it's not required to have hepatocyte studies done. It obviously can be achieved through in vivo study. It could be a specific study; it could be a cocktail study; it could be a population study. We're just adding an additional tool that we think is acceptable to study.

So it's important to the issue that you raised, but this is only one additional tool. So with that, I would like to amend my question: based on the mechanism of induction that we have heard through various nuclear receptors, I would like to say if the induction in 3A is negative, which could be in vitro or in vivo, that we do not need to assess 2C9 or 2C19, because they would have been coinduced. So if a negative 3A could prevent us from conducting an additional study about 2C9 or 2C19, that's my question.

So it could be a different, because of the

mechanism of induction, so I'm amending my question, number eight. Number seven is specific about in vitro methods, so we can come back later, but I'd like to amend my question, so that we don't have to be considering the appropriateness of the hepatocyte preparation.

DR. HALL: I think again, we have to discuss the not or the negative part, how that's defined. And I think, you know we could define it rigorously like Dr. LeCluyse did, which incorporated many aspects, including RNA quantitation, which is quite rigorous and would be comforting, I think. But that's an enormous burden, then, I think, on the industry to not only procure all the hepatocytes but to do all the other parts to that that would make it a water-tight conclusion that it's negative.

So I think again, it's one of those questions where you really have to state what being negative means. What would you accept as being negative?

DR. HUANG: So what about if we have

conducted an in vivo study with medazolam, and it shows no change in medazolam AUCs with this new molecular entity? Could we say that you do not need to investigate whether this drug also induced 2C9 or 2C19? And perhaps you're hinging on the in vitro data to make that conclusion. I'm doing an additional leap of--not leap of faith; if you look at mechanism of induction. If they're coinduced.

DR. JUSKO: When you do inhibition studies, you very nicely take into account an I over KI ratio. These in vitro induction studies lend themselves to calculating EC50 values for the induction, and in addition, you can bring in a CMAX for the exposures, expected exposures in animals or humans. It seems like these kinds of quantitative indices are needed to augment this kind of recommendation.

DR. MCLEOD: We were presented with data showing that hitting the nuclear receptor caused induction of 3A4 and 2C9 and a bunch of others. I didn't remember seeing any data saying that that's the only mechanism for inducing 2C9, 2C19, and

whatever else you want to write up there.

So do you have any data to share with us to help on the voting how--if there are any other realistic mechanisms of induction? Because it seems like there's got to be something else.

DR. HUANG: Maybe Dr. LeCluyse can address based on in vitro. But I think the information was that if you induce 3A through PXR, if the 2C9 and 2C19 through PXR, then, you would have seen it. But as for other mechanisms, so far, we don't have a drug which is a pure CAR--

DR. MCLEOD: I'm thinking of false negatives, basically.

DR. HUANG: Right, we don't have a drug. So far, we don't have a drug that's based on in vitro data to show that's the case. Until we have a drug which is a pure CAR receptor effective, then, for now, then, I don't think we'll see a false negative.

DR. LECLUYSE: So basically your concern is is there something that might be missing mechanistically, and is it as simple as we portray

it as these three nuclear receptors, which is really what I'm proposing. And we have come, you know, round and round with this ourselves over the years. We've asked ourselves the same questions: is it as simple as if you don't see a compound activating CAR or PXR, is it sufficient to exclude any other possible mechanism?

And what's interesting is that seeing all the evidence to date, not only our own but out there in the literature, including if you look at all the observed, clinically significant drug interactions that are due to induction, and to me, that's the question, I think, that's at hand, you can explain every one of those through these three nuclear receptors. And I think, you know, I think Wolfgang brought up a point about some of these other cofactors and some of these other transcription factors that are involved in just normal gene regulation, and, you know, whether it's basal expression or induced expression, they play a role.

But the question was the clinically

relevant drug interactions that have been observed in those events could all be explained by these three nuclear receptors or these three receptors. And it seems at least for the human P450 enzymes that they're regulated by these three receptors and can be explained through these.

So, you know, we're convinced to, like, here I say our evidence as well as others that you're pretty much covering all your bases or most of your bases through these mechanisms; that at this point in time, that's where the science is at.

DR. MCLEOD: Thanks. You're on the record.

DR. BARRETT: Shiew-Mei, instead of maybe considering whether or not this test is adequately sensitive to protect against induction of the other CYPs, I just wonder if this guidance needs the burden of having that statement in it, because I think if you don't have it, it's going to be up to the sponsor to investigate induction where they think it's appropriate.

If they see CYP3A4 not involved as an

inducer, they're not going to do those studies. However, you may see, either with population analyses or otherwise, some evidence for induction, and in that case, they're going to have to investigate it.

I mean, I understand the spirit of trying to reduce the redundant studies or eliminate unnecessary or noninformative ones, but this seems to be an additional burden to the guidance that maybe it doesn't need.

DR. WATKINS: Sorry, and then, I will shut up, but there are things called gratuitous inducers; there's things that induce pathways that aren't involved in their own metabolism; so just that it's not a 3A substrate doesn't mean that it couldn't induce, you know, bind and activate PXR.

Let me give a hypothetical example: there's a drug that there's been no induction study in two animal models and an in vitro, you know, PXR, you know, binding and transcriptional assay; there's no effect at all. The question is what--show me the data that the human hepatocyte,

cultured human hepatocytes is going to add significantly to the decision making of whether an in vivo study should be done there. I mean, what is the human hepatocyte--I mean, just where is this data that this is going to be worth this precious resource on an industrial scale?

Relatively early in development, which is where I would do it if this guidance came out, and right at lead candidate selection is when I'd try to do a cultured hepatocyte study just to know what was, you know, coming down the line. And it just strikes me that I've not seen this data. I mean, for instance, all the drugs that are known to be clinically relevant inducers, say, through PXR, and the whole list of drugs that aren't at all, like niphetapine, for instance, is a PXR ligand, activates PXR, but there's no drug interaction that I'm aware of that's due to niphetpaine inducing metabolism through PXR. And Ed, you may know about it.

But where is the data that really critically evaluates the added value of early human

hepatocyte studies for induction? We know the receptors; we should be able to see whether they bind them and activate them, and that should be the initial step, and if it's negative, I want the data that going to human hepatocytes is adding the enormous costs and resource that that represents.

DR. VENITZ: Okay; Shiew-Mei, why don't you rephrase the question so we can vote on it? Because you were going to make an amendment, if I remember correctly.

DR. HUANG: Yes, although no committee members have commented on in vivo. If in vivo 3A shows negative induction, and we should--

DR. VENITZ: Should say in vitro or in vivo.

DR. HUANG: Yes.

DR. VENITZ: Okay; so what we're voting on is question eight with the addition of in vitro or in vivo.

DR. HUANG: And I would just comment on 2C9 and 2C19. If a new molecular entity induction effect on CYP3A in vitro or in vivo is negative, it

is acceptable to not recommend any studies with substrates of 2C9 and 2C19.

DR. VENITZ: Okay; I think we are starting with Dr. Barrett this time.

DR. BARRETT: No.

DR. VENITZ: Dr. Blaschke?

DR. BLASCHKE: As rephrased, I think it's acceptable. I'd say yes.

DR. VENITZ: Dr. Capparelli?

DR. CAPPARELLI: In the definition, in the rephrasing of it, if there is no in vivo or in vitro indication of inhibition, then, I would say yes. So there's the situation where you may mask induction by having inhibition as well.

DR. HUANG: We're talking about induction here.

DR. CAPPARELLI: No, I understand.

DR. HUANG: Oh, okay.

DR. CAPPARELLI: But, like, with ritonavir, if you gave a drug that induced but also inhibited, you may miss it in a 3A screen, and it may still have an impact on induction if it's not

inhibiting the 2C system.

DR. VENITZ: Dr. D'Argenio?

DR. D'ARGENIO: Abstain.

DR. VENITZ: Dr. Davidian?

DR. DAVIDIAN: Abstain.

DR. VENITZ: Dr. Derendorf?

DR. DERENDORF: Abstain.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Yes.

DR. VENITZ: Dr. Hall?

DR. HALL: I think as rephrased, then, I agree with what Paul is saying, but this doesn't say anything about hepatocytes. It could equally well be a reporter system. So in that context, I think I would say yes.

DR. VENITZ: Dr. Jusko?

DR. JUSKO: Yes.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: Yes.

DR. VENITZ: Dr. Sadee?

DR. SADEE: Yes.

DR. VENITZ: Dr. Watkins?

DR. WATKINS: I'm just getting irritable, but I feel like saying no at this point. But I think the qualification--

[Laughter.]

DR. WATKINS: --is if you know that it acts through PXR, if you know that, at least from the evidence I know, then, demonstrating it does one of these things in vivo, you know, gives you your answer. You don't have to test for all of them.

So if that means my answer is yes, then, it's yes.

[Laughter.]

DR. VENITZ: You tell me.

DR. WATKINS: I still think that the human hepatocytes is hooked in here somewhere into this, but, I mean, they only go together if they're all being activated by PXR. And it sounds like all the data makes that acceptable. So the real issue is does your drug activate PXR? And then, you can see whether it induces one of these and assume the rest go along. But there has to be that PXR link, I

think.

DR. VENITZ: I think that would be a yes.

DR. WATKINS: Yes, that's a yes.

DR. VENITZ: Okay; I'll throw my yes in, and we have three abstains, one no, and eight yeses, okay?

Then, question number seven, Shiew-Mei?

DR. HUANG: Question number seven is early on clarified by Dr. LeCluyse. When we say that the in vitro induction, and here, we look at increase in enzyme activity, is more than 40 percent of the positive control, and the 40 percent could be any of the three with a preparation, so the mean value could be lower than 40 percent, but it's any one of them, because you need to have them all lower than 40 percent before you would declare it's negative.

So with that clarification, the question is is 40 percent the proper positive control?

DR. VENITZ: Okay; any questions or comments?

DR. SADEE: But if you have an inhibitor, ritonavir again, you get a decrease, so--

DR. HUANG: Yes, in our guidance, we actually have some provision. You need to look at the inhibition. If there's a mechanism-based inhibition, then, you look at mRNA and other parameters in addition to enzyme activity. So that would have taken care of this.

DR. GIACOMINI: Is this the human hepatocyte again for--

DR. HUANG: Yes.

DR. GIACOMINI: It absolutely is. So it sets it as a standard, then.

DR. HUANG: This is, yes.

DR. GIACOMINI: Like not a reporter or anything like that assay.

DR. HUANG: Here it's human hepatocyte.

DR. GIACOMINI: Okay.

DR. VENITZ: Hartmut?

DR. DERENDORF: It needs to be related to a concentration, as Dr. Jusko pointed out, some EC52P concentration term in there.

DR. HUANG: Yes, here in the appendix of the concept paper, we recommended if we know the

concentration that we expected using tenfold or up to 100-fold of concentration. So you have a spectrum of concentration because of sometime, you see an expected U-shaped or inverted-U effect, so we need to look at various concentrations. So we did have some detail in the concept paper about what concentration to use.

And right now, this question, we're looking at the maximum, maximum induction, and we did not take into account EC52, even as it was discussed. But this particular criterion was based on that.

DR. SADEE: But in the human hepatocytes, you then have to screen for those that have low basal activity in order to get a high percentage. Is that correct or--

DR. HUANG: Yes, our only recommendation is that you need to have positive control, and positive control needs to work. And we did put in a reference value in the guidance on what should we expect when certain concentrations of rifampin are incubated with this particular system. What should

we expect to see? And only when those values are valid, then, we will consider this next step.

DR. VENITZ: Any other comments?

Okay; then, I think, Dr. Watkins, you're the one to go first.

DR. WATKINS: Now, I'll say no.

You know, the implication here is that human hepatocytes have been widely standardized, and companies can sprout all up and come up with a reliable 40 percent estimate and a cost-effective way that will be like an Ames test and yes-no determining the subsequent development, and I have just not seen any data that supports that, so no.

DR. VENITZ: Dr. Sadee?

DR. SADEE: Yes.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: No.

DR. VENITZ: Dr. Jusko?

DR. JUSKO: No.

DR. VENITZ: Dr. Hall?

DR. HALL: I would like to say yes. I'm not sure about the 40 percent, and the details are

important, but in principle, yes.

DR. VENITZ: Okay; Dr. Giacomini?

DR. GIACOMINI: No.

DR. VENITZ: Dr. Derendorf?

DR. DERENDORF: No.

DR. VENITZ: Dr. Davidian?

DR. DAVIDIAN: Abstain.

DR. VENITZ: Dr. D'Argenio?

DR. D'ARGENIO: Abstain.

DR. VENITZ: Dr. Capparelli?

DR. CAPPARELLI: No.

DR. VENITZ: Dr. Blaschke?

DR. BLASCHKE: No.

DR. VENITZ: Dr. Barrett?

DR. BARRETT: Yes.

DR. VENITZ: And I throw my no in.

Seven noes, three yes, and two abstentions.

DR. HUANG: The last two questions: as related to the multiple inhibitor studies, and it's a long question. We say is it acceptable to recommend that under certain conditions, and in

particular, when we're evaluating QT prolongation effect, it's important to determine the maximum exposure of new molecular entities. Actually, these are in the ICH guidance on QT. It was the detail that we're asking for recommendation.

The maximum exposure, it's probably not what we should be discussing for this guidance. I mean, the comment should be for the other guidance. But with that guidance recommendation, how would we achieve the maximum exposure? We can do that with a single inhibitor or multiple inhibitor, so this would be the focus of discussion when there is more than one pathway or under multiple impaired conditions, such as renal impairment plus co-administration of an inhibitor.

DR. VENITZ: A couple of comments: I'm still not sure that you can't predict this based on the individual interactions that you know, and then, use modeling and simulations to predict what the maximum exposure would be.

Number two, you obviously would want to do this for drugs where the stakes are high, meaning

you're really worried about toxic effects. Well, those are probably the ones that you ethically couldn't do a study like this unless you reduce the dose. Well, if you reduce the dose, then, you have to have some idea about what to expect; in other words, you have to do modeling and simulations to figure out how to adjust your dose.

And the last thing is to do those kinds of studies logistically to me is a nightmare, and I'm not sure what you're gaining. Are you just making up for lack of dose finding in phase two or phase one where you didn't push the dose enough to achieve some toxicity that you can identify? So I don't see any purpose.

DR. HUANG: Is that the Committee recommendation?

DR. VENITZ: Only speaking for myself.

DR. WATKINS: Yes.

DR. VENITZ: Any other comments?

[No response.]

DR. VENITZ: Are you ready for the vote? Looks like it's late.

Okay; then, we're voting on question number nine, and I think we're starting with Dr. Barrett.

DR. BARRETT: No.

DR. VENITZ: Dr. Blaschke?

DR. BLASCHKE: No.

DR. VENITZ: Dr. Capparelli?

DR. CAPPARELLI: No.

DR. VENITZ: Dr. D'Argenio?

DR. D'ARGENIO: No.

DR. VENITZ: Dr. Davidian?

DR. DAVIDIAN: Abstain.

DR. VENITZ: Dr. Derendorf?

DR. DERENDORF: No.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: No.

DR. VENITZ: Dr. Hall?

DR. HALL: No.

DR. VENITZ: Dr. Jusko?

DR. JUSKO: No.

DR. VENITZ: Dr. McLeod?

DR. MCLEOD: No.

DR. VENITZ: Dr. Sadee?

DR. SADEE: No.

DR. VENITZ: Dr. Watkins?

DR. WATKINS: No.

DR. VENITZ: It looks like I'm speaking for the Committee, so I'm a no.

So we've got 12 noes and one abstention.

DR. HUANG: So we probably do not need to ask about question number 10.

Originally, we were asking whether should we consider individual factors first and then recommend a study or after the modeling and simulation. But since the answer is no, the only final question, is there any other issues that we should have been addressed in the concept paper? We have heard comments that transporter-related issues; we probably need an additional discussion before we have some more general discussion, more general recommendation or guidance.

But are there other areas where the science is mature that we have not included in our concept paper?

DR. VENITZ: Any suggestions, comments for Dr. Huang?

DR. HALL: I notice one thing: it's not so much something to add but maybe something to think about taking out. You mentioned stimulation several times, and to the best of my knowledge, there are no examples of clinical drug interactions due to stimulation. Maybe the guys at Merck have some more information on that, because they've worked on it, but that seems to be just an unnecessary burden, I think.

DR. DERENDORF: I hope that this guidance doesn't end up as a checklist with all kinds of studies that are required independent of if they're really needed or not from a response point of view.

I think each drug is different, and each interaction has a different significance, and that needs to be considered somewhere. And just to do a study to do a study isn't good enough. So there needs to be some flexibility based on the individual drug.

DR. VENITZ: And I'd like to recommend

that as far as the process is concerned that perhaps you could review with the Committee at a future meeting not just the guidance per se but the decision making process that is part of it, because part of the issues that I think most of us had wrestled with when you forced us to vote is to put those questions in perspective, and I think some of the votes may have gotten different results if we had seen how that fits into the overall scheme, such as recommendations for further process.

DR. JUSKO: Many years ago, Craig Brader did some very nice drug interaction studies looking at diuretics and their effects and found that it was the drug in the urine that best represented the biophase for the action of the diuretics and that drug interactions, when looked at from the viewpoint of plasma concentrations, were misleading in terms of the clinical relevance of such interactions.

So perhaps something could be added to the guidance about what may be the relevant biophase for the activity of the drug and include that in

the measurements in the context of drug interactions. The whole guidance speaks to drug interactions in the pharmacokinetic sense, and of course, probably in the next decade, you'll be getting to drug interactions and pharmacodynamics.

DR. VENITZ: Any further comments?

Then let me turn the podium over to Dr. Lesko, who is going to wrap up the meeting for today, right?

DR. LESKO: Thank you. I'll do that right from my seat here, and I'm sure I wouldn't be very popular if I take more than 30 seconds, given the hour of the day, to wrap up. So I'm going to be kind and thank the Committee that we don't need to ask for any recounts on any of the votes.

[Laughter.]

DR. LESKO: However, the discussion today was extremely helpful to us, and we really appreciate your thoughtfulness and the quality of your discussions and questions, and we left here, I think, achieving the goals that we set out for early this morning.

So I want to express your appreciation for today and the hard work that you've done and look forward to another exciting and high quality discussion tomorrow on our biomarker topic that we'll be bringing to the Committee.

DR. VENITZ: Thank you, and then, one last announcement: the Committee members, we are going to meet for dinner at 6:30 in the hotel restaurant right next door, so hopefully, we will see you all. If not, we will see you tomorrow, bright-eyed, bushy-tailed at 8:00 for the second part of this.

[Whereupon, at 5:33 p.m., the meeting was recessed, to reconvene on Thursday, November 4, 2004.]

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