FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL PHARMACOLOGY SUBCOMMITTEE

OF THE

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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Food and Drug Administration
Rockville, Maryland 20857

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C O N T E N T S

P R O C E E D I N G S

(8:28 a.m.)

DR. VENITZ: I'd like to call the meeting to order, please.

Welcome to the second day of the Clinical Pharmacology Subcommittee meeting. We have two agenda items to discuss today, but before we do that, I'd like to introduce all the individuals around the table, starting with Dr. Derendorf.

DR. DERENDORF: Hartmut Derendorf, University of Florida.

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

DR. FLOCKHART: Dave Flockhart from Indiana University.

DR. McLEOD: Howard McLeod from Washington University.

DR. SWADENER: Marc Swadener, Boulder, Colorado.

MS. REEDY: Kathleen Reedy, advisory committee executive.

DR. VENITZ: Jurgen Venitz, Virginia Commonwealth University.

DR. JUSKO: William Jusko, University at Buffalo.

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

DR. SADEE: Wolfgang Sadee, Ohio State University.

DR. LESKO: Larry Lesko, FDA.

DR. LEE: Peter Lee from FDA.

DR. VENITZ: Thank you, everybody.

Kathleen Reedy, the Executive Secretary, will read the conflict of interest statement.

MS. REEDY: Acknowledgement related to general matters waivers, Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science, for April 23rd, 2003.

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 at this meeting.

The topics of this meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broad applicability involve many industrial sponsors and academic institutions.

All special government employees have been screened for their financial interests as they may apply to the general topics at hand. Because they have reported

interests in pharmaceutical companies, the Food and Drug Administration has granted general matters waivers to the following SGEs which permits them to participate in these discussions: Dr. Edmund Capparelli, Dr. William Jusko, Dr. Gregory Kearns, Dr. Howard McLeod, Dr. Wolfgang Sadee, Dr. Lewis Sheiner.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

In addition, Dr. Hartmut Derendorf, Dr. David Flockhart, Dr. Mary Relling, and Dr. Marc Swadener do not require general matters waivers because they do not have any personal or imputed financial interests in any pharmaceutical firms.

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

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

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the

participants' involvement and their exclusion will be noted for the record.

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

DR. VENITZ: Thank you, Kathleen.

As we did yesterday, we are going to have an introduction of today's topic by Dr. Larry Lesko. Larry.

DR. LESKO: Thank you and good morning, everyone.

Yesterday during my introductory comments, I had said that we would discuss today the topic of pharmacogenetics and more specifically how it applies to improving the existing therapies, and in fact we're going to do that.

Following my introduction to that topic and the subsequent discussion, we'll move into the second topic that I mentioned yesterday which would be metabolism and transporter-based drug interactions. We'll be discussing some aspects of that that we'd like the committee to weigh in on and to discuss as well. And that will be Dr. Shiew-Mei Huang.

Well, as I said, I'm going to discuss pharmacogenetics in the context of improving existing drug

treatments, and leading up to this discussion yesterday, I mentioned actually three agency-wide initiatives. I thought it pertinent to mention a fourth sort of initiative that has been recently announced in the last day or two and that was a new draft guidance that's been released by our Center for Devices that relates to pharmacogenetics. The draft guidance from CDRH is entitled Multiplex Tests for DNA Markers, Mutations, and Expression Patterns.

I think as we look to the future and as we look to the future possibility of companies developing genetic test kits for consideration by the agency for approval, this guidance has a significant impact on that. That, of course, then relates to how such test kits, depending on which genetic test they might be focused on, would impact the use of them in improving existing therapies. So I wanted to bring that to your attention before I move forward with today's presentation.

Well, I think it's interesting we are in the month of April and it's in April that is filled with milestones related to pharmacogenetics. We've been bombarded really by celebrations of the 50th anniversary of the discovery DNA's helical structure. While we were all at dinner last night, there was a terrific show, which I taped and can share with you, on the discovery of DNA on the Public Broadcast station, and I'm looking forward to

seeing that.

It's also the announcement from Dr. Francis Collins of the completion of the 10-year human genome project and what the next 10 years is going to hold. I think it's interesting that one of the emphases that he's placed on genomics is the translation of this information into medicine and therapeutic practice which is really the interest that the agency has as well.

Finally, a little known fact is it's the 50th anniversary of the revision of the Webster's New World College Dictionary, which is a milestone for that.

It caused one to reflect about DNA and dictionaries because in each case, there's a unique combination of letters that form texts and that text, in turn, informs us to become more knowledgeable. As the dictionary brings in its 50th anniversary new uses and meanings of words that we've commonly held our belief in, the genome with its commonly thought combination of letters and sequences is really by comparison only in its infancy and we have a lot to learn about what it all means.

Well, I want to bring everyone back to a discussion we had in October of 2002 at the first meeting of the advisory committee. We opened up the topic of improving existing therapies with pharmacogenetics picking on one example from the thiopurine family of drugs, that

being 6-mercaptopurine. I didn't show this data at the time in October, but I wanted to share with you today the increase in the number of prescriptions for 6-MP over the last six or seven years.

It's interesting, looking at this slide, you can see where the prescription use of the drug is in all indications or all off-label uses, where the growth is in the area of GI use and where 6-MP is used in terms of prescriptions in the area of oncology. You can see some trends clearly in the direction of increasing use over the years, and we don't quite know where that will end up.

So I guess the point of this that it's not a small issue to look at existing therapies and how they can be improved in terms of their impact on public health. However, everyone should recognize that the approved use for 6-MP is in the area of oncology and in contrast, thinking about that slide I just showed, much of the use of this drug is off-label for things like in the GI area, inflammatory bowel disease, and a whole series of autoimmune diseases ranging from rheumatoid arthritis to multiple sclerosis.

Well, last time we came together, we talked about the metabolism of 6-MP by thiopurine methyltransferase, TPMT. This enzyme is actually not well described in the label for this product. If you look in

the clinical pharmacology section, you would not recognize the information I have on this slide. What this slide illustrates at the top is all the newly diagnosed ALL patients, acute lymphatic leukemia patients, both adults and children that we have each year, and that number is 30,000. It's not a huge number. Obviously, there are other diseases that have greater prevalence in the population, but nevertheless you have to think about, in some ways, the off-label use of this drug and the number of prescriptions being used.

What we do know in the case of ALL patients is that there are three major genotypes, and the ones that are of concern and are at high risk for toxicity to this drug are the two on the left, the homozygotes which have none or low TPMT activity and in the middle the heterozygotes and intermediate activity. In that box, I've illustrated, based upon the 1 in 100 and the 10 or 11 percent of the population that fall into those boxes, the number of patients that one might anticipate each year that would fall into these boxes.

This is a well-established metabolic pathway and polymorphism in the metabolism. We know that three major SNPs -- this is a single gene variant -- define these mutant alleles, the common ones being *3A, *3C, and *2. The remaining allele, *3D is in linkage disequilibrium with

*3A and travel together so that capturing the major alleles for predicting or risk stratification is not a difficult task.

But I want to think beyond the 6-MP for a moment. We'll come back to it. But it brings us to think about other genetic tests and how we're going to deal with these as the science moves forward. I mentioned the guidance in my introductory remarks. There are other polymorphic enzymes that we might think about, not that they're similar to 6-MP, but they pose similar questions and similar issues as we move forward in trying to improve existing therapies.

One might think, for example, of cytochrome 2D6. 30 percent of prescription drugs are metabolized by this enzyme. Polymorphism is well known. There are both retrospective and prospective trials that indicate poor metabolizers, the so-called phenotype of 2D6, have a higher risk of adverse events, and I'll show some examples of that in recent labels.

So they move forward with at one extreme an example like TPMT, a relatively small target population, to the other extreme, a cytochrome 2D6 with a large number of drugs and millions of people taking these drugs. How do we advance the science to improve therapeutics with drugs that are affected, in terms of their exposure, by the

polymorphism in these enzymes?

That's broadly what I'd like this committee to think about, and at the end of the day -- not today, but at the end of thinking about this -- we'd like to develop at least a general approach to these polymorphisms, that we don't have to deal with them case by case necessarily but rather have a broad perspective on what is important in thinking about these enzymes, the polymorphism, and translating that into medicine. What's the paradigm? What's the structure that we can ask generally, as well as specifically, of these examples?

Well, I've put on a general paradigm here. Is this what we should be thinking about with TPMT and 2D6? The three important things in my mind might be analytic validity, the manufacturing, the instrumentation, the performance of the test. How accurate is it in identifying a DNA sequence?

The clinical validity. This might refer to the clinical effectiveness of the test. How accurate is it in producing a clinical outcome. The clinical outcome might be predicting the genotype.

The third criteria is clinical utility. What is the likelihood that this test is going to lead to improved health outcome. If I had information from the test, can I alter treatment in a way that would improve

therapeutics? We don't want approve here at FDA. We don't want to see tests in genetics in the marketplace that have no clinical value. And I think that's an important paradigm.

This looks simple, but what are the details that underpin this and what are the important things that we should be thinking about in assessing validity and utility and so on? It seems to me the analytical validity is relatively straightforward, but the validity and utility in a clinical context may not be. What is the evidence for that? Can it be retrospective, prospective, circumstantial? We have to think about these issues to advance it into, for example, product labels.

Now, going back, thinking of these general criteria, let's talk about the screening of the TPMT genotypes. As far as the test goes, it appears to be reliable and accurate. I won't present that data today, so I guess you'll have to rely on what I'm saying. But there's virtually no false positives or negatives that I can tell from a homozygous-deficient patient. We've spoken with people who perform these tests. We've looked at some data that they've provided, and this seems to be true.

Well, what about evidence of clinical validity and utility? Well, this is some data that might be representative of the type of information that would

support updating, for example, a product label. This talks to the clinical effectiveness of a test and its clinical utility. On the left-hand side is a chart that shows the cumulative incidence of 6-MP dose reduction due to toxicity, and what's impressive is that on the far left-hand side, with the mutant alleles v/v indicated, that 100 percent of patients would develop toxicity on the usual doses of 6-MP. That's evidence of clinical effectiveness.

As far as clinical utility goes, on the right-hand side, what do you do about it? Well, the right-hand side shows the average final weekly 6-MP dosage that would be appropriate for these patients. It shows the dose reduction. So I have a test that's clinically in identifying those patients who would develop toxicity. I have clinical utility because on the right I can reduce the dose if I have that information in hand. So I see a thought process there, and maybe this is the way that we need to think about this in general.

Of course, there are other issues associated with this example. I indicate in the box interrupting therapy is an important issue in terms of recovering from toxicity. That lessens the intensity of treatment which seems to relate to event-free survival in these patients. And also the reduction of the 6-MP dose in the face of a poor metabolizing genotype allows for full dosages of the

other chemotherapy.

Well, this is very clear for the homozygous patient. The data on the heterozygous appears to be important, but there are some questions that remain and we have to address those as we move forward.

This is further evidence of clinical validity and utility, at least in my mind, and it shows the percent of weeks that full doses that were tolerated by patients. Again, you can see color-coded on the left is the homozygous mutant allele that has no activity of TPMT, and the toleration in terms of number of weeks is relatively few. That's an issue, of course, in terms of maintaining the intensity of therapy.

So these are data from the literature, and it might cause one to think about, for example, with other enzymes of 2D6, is the data in the literature sufficient to to provide evidence that would warrant its use in improving existing therapies.

At the October meeting, we did discuss this issue. We probably didn't give it enough time in terms of what we had. But as far as screening goes, we talked about the test very briefly. Today I've shown some data on the utility and validity, and this might represent the type of evidence that we think about going forward.

What we did talk about in October as well was

to reflect upon the current label for this product and just imagine how a label might be improved with the integration of new information about genotyping. I presented a proposal, an example for people to think about as to how this information could be incorporated into the clinical pharmacology section of the label. To appreciate the difference, one would have to have side by side the current label, which I said is deficient in its description of the role of TPMT. And I showed this section, clinical pharmacology. I showed something that might conceivably represent an effective dosage and administration section for such a label.

I think the important part of this label, not the exact words per se, but it conveys to the prescriber and to the patient two important things. It conveys, number one, a prevalence. It tells me that this is more than a rare -- I don't know what "rare" means in a label, but it tells me how frequently I might encounter this problem in using the drug. It also gives me some idea about what to do about it if I identify such a patient. I think that's the hallmark of an effective label. It completes the information package for the user.

I went back to the transcript to remind myself what the committee --

DR. SADEE: Is this for prescribers or for

patients?

DR. LESKO: This was a proposal as an example of label language, but I'm assuming it's not only for prescribers, but it's also for patients.

DR. SADEE: One may want to have simpler language I think.

DR. LESKO: That's certainly another topic.

Going back to our committee meeting, I did want to remind what the committee discussed at that time. They said for TPMT and 6-MP, there's considerable enthusiasm -- this was the summary part of our meeting -- and considerable use for having genetic tests -- we were talking about the label -- although there are some scientific and clinical issues remaining.

With regard to what I had just shown you, the proposed labeling seems to be a very logical positioning of the information, as well as the type of information.

We did discuss relatively briefly the issue of screening and intervention. This wasn't necessarily a specific question to the committee, but it was intended, using this example, to begin our discussion of how you position genetic testing in labels for drug dosing purposes.

For example, one option is to say all patients prior to receiving 6-MP would receive a test that would

identify the genotype, and then a priori a lower starting dose would be used. A product that falls into this category a little bit different than this one is herceptin. A test is done for HER-2 overexpression before the drug is prescribed.

A second option is to think about a test that might be used not a priori but either concurrent with or following the initiation of therapy. A test might be used in the case of reason, overt signs of toxicity, and the issue there is what's causing it, and is this, in fact, something I can do something about in terms of drug dosing or is it perhaps another drug in the regimen.

We discussed these two issues relatively briefly, and with regard to that, the committee summarized that by saying mandatory testing in the absence of clear pharmacoeconomic analysis is too early.

Interestingly, there have been two articles on the pharmacoeconomic analysis of TPMT testing in the literature. I believe one of the two came after our October meeting, and that might be worth looking at in a future meeting.

Further, the committee said that the test for TPMT increases awareness that there is a problem and that something can be done about it. As one member said, I don't think that's too much to ask. I think there's enough

data to support that sort of thing.

In terms of trying to generalize this type of consideration, it seems very likely that it would be done on a case-by-case basis. That's probably very true. But while we think about this on a case-by-case basis, can we also think about it in a broad paradigm of questions that we would ask of a genotype of a genetic test for the purposes of drug dosing and then segue down into the specific case?

So I'm looking to sort of get input on a broad paradigm and then what would be important on a specific case-by-case basis, taking into account obviously the risk-benefit considerations for the drug, the types of efficacy and toxicity, not unlike what we talked about in yesterday morning's session dealing with different dosing strategies to optimize therapeutics.

Well, I want to bring you back then to the relevance of this topic, and it relates to the FDA initiative that I presented yesterday, Dr. McClellan. Well, he's talked about this further, and in the Washington Drug Letter, reporting on one of his recent presentations on April 13th, he said that new therapies will be developed with genetic or phenotypic tests that can identify these populations and detect patients who need different doses or are prone to certain toxic effects.

We have been conducting informal discovery research of the FDA database, and this is an example of some of the results of the genotyping or phenotyping that we've uncovered in our IND and NDA database. The trend here doesn't necessarily indicate increasing usage of genotyping or phenotyping, but what it does indicate is our increasing discovery of submissions to the agency that contain this type of information. And you can see, as of August, it's not a small number. We have a fair amount of INDs and NDAs that have mentioned genotyping or phenotyping.

When you look at how that breaks down, something really jumps off the page here, and that is most of what we've seen in the submissions are related to 2D6. Almost three-fourths of the genotyping or phenotyping is related to 2D6, but not to exclude other applications which are on the bottom in smaller percentages, and how this will continue to play out in the future might be very interesting.

Keeping 2D6 in mind, let's look at a recent example of pharmacogenetic information in a product label. I've selected for the example a drug for attention deficit disorder. It's atomoxetine, or Straterra. This was approved recently by the agency. It is a substrate for 2D6 and based on the evidence that we had, the label reflects

how we've linked 2D6 genotypes with various aspects of the product label. For example, a fraction of populations are PM resulting, and you can check the label yourself, but I wanted to give you a sense of where the information appears. So it appears in the human pharmacokinetic section of the label. It appears in the drug-drug interaction section of the label. We've included information on the adverse reactions related to poor metabolizers and extensive metabolizers, and finally there's information in the laboratory tests section. So relatively speaking, it's a genotypically rich label that hopefully will allow for optimal use of this particular therapeutic agent.

But it brings me around to the central question that I have. That was a new drug with new evidence, a new submission. But how can existing therapies, drugs we've approved in the past 20-30 years, be improved with the new knowledge that genetics provides us?

So existing therapies. I've defined the therapy. Why is this important? Well, it's important because of the problem of adverse drug reactions. I'm not sure if you've seen in the recent edition of the New England Journal of Medicine a new report that indicates 1 out of 4 patients have a side effect to drugs. 10 percent of those are serious. 39 percent were avoided, and a

certain percent, which I can't remember but relatively high, was related to too high a dose.

We have a problem of variability in drug toxicity in the population and it raises the question is some of this attributable to pharmacogenetics, and if it is, it seems like we have in our hands a tool to apply towards reducing this problem, not only in terms of human suffering, but also in terms of pharmacoeconomics of public health care.

We have some evidence that pharmacogenetics is important. This was from a study in JAMA that looked at 27 drugs frequently cited in the adverse drug reaction literature. I think what was important here is that 59 percent, or 16, of these drugs were metabolized by at least one enzyme with an allele that causes poor metabolism. Thinking about the database at the agency, similarly 69 percent are metabolized by a specific enzyme, 2D6. And in contrast, we took a randomly selected number of drugs. Only 7 to 22 percent of those were metabolized. So the circumstantial evidence points towards pharmacogenetics being a factor, not the only factor, but a factor that perhaps we can think about doing something about.

Well, how are things working in translating genetic science into bedside medicine? I don't know, but I did search the new version of the PDR recently, and I

wanted to address the issue of how many labels in the PDR include pharmacogenetic information. Think about the history that we have behind us, 20 years since we've identified some significant polymorphisms. What I found was that 51 labels out of several thousand contained information on genomics. When you do see this information in the label, for the most part it's not translatable into the bedside practice of medicine.

There are challenges moving forward, and as we talk about including genetic information in the label for the purposes of drug dosing, in the discussion and debate of that, frequently people will ask what is the evidence. I think the evidence for including information in labels for older products is something we have to think very clearly about.

Will we need, for example, well designed and well conducted prospective investigations of analytic validity and clinical utility? That would be a challenge in terms of previously approved medication. Who would do that research?

How about a systematic assessment of evidence-based research in peer-reviewed journals? Would that be a standard of evidence to think about in terms of including information in product labels?

What about opinions and evaluations

professional associations and consensus groups? Is that evidence that could be considered in integrating genetics into therapeutics?

Premarket searches for pharmacogenetic factors influencing risk-benefit. We do that now with currently submitted NDAs. We probably did not ask the question as much as we do now, say, five years ago.

And we've begun to look at the FDA post-marketing reports of adverse events for selected drugs that are candidates for improved therapeutics by the integration of genetic information.

So this is a body of evidence, and it's not going to, obviously, apply to everything, but it's going to apply in different cases, and we might want to ask you to think about this evidence. What are the standards that we ought to be defining for improving existing therapies using genetics?

Well, that gets me around to some of the topics for discussion. What's next? I tried to present the current situation as best I can with regard to the genetic area for drug dosing? "What's next" means what is the systematic way of thinking about this question and what are the issues as we move forward in thinking about substrates for these polymorphic enzymes and starting to look for evidence that would help us decide whether this information

would be or would not be helpful for drug dosing and improving therapeutics in public health.

The second question might be what level of detail of genomic data should be included in the label. Is it enough to simply say poor metabolizers? Poor metabolizers are simply a phenotype. Would the data be more informative recognizing that many people read product labels, not just physicians and not just patients, but people that want to apply information in many other ways.

So I've indicated there are a couple of options. Is phenotype enough? Should we be more specific in the alleles that were investigated, say, within a clinical trial? Should we talk about enzyme activity, a percentage of activity that might be associated with a wild type situation? What about the PK information? Is it knowledgeable or informative to link alleles with area under curve, say, in a table, allele frequency, mutation? These are different depths of information about the genotype that we've begun to think about as being appropriate for a package insert, and we might like your opinion on that.

The third question relates to where you might think this information should be contained in the package insert. Where would its location be effective? We already know that location is important, like in real estate. If

it's buried somewhere in certain sections of the label, it's not very apparent to people and practitioners. So where should this information appear to have the impact that it's intended to have in improving drug dosing?

So these are the questions for the committee, and I look forward to your input and advice on these. Thanks.

DR. VENITZ: Thank you, Larry.

Any comments by committee members?

DR. SADEE: I think you really have defined the problem very well. I am concerned -- or not concerned. I think we have to consider that P450 is not the typical example. So in the case of P450s we have accumulation of non-mutations in the human population that on top of it directly affect drug metabolism or drugs in a way that is obvious. I think this is the most unusual case.

So if we take 2D6 as the star example that we then expand to other examples, I think we may actually be in trouble. The majority of genetic variations will be quantitative. The majority will likely be in regulatory regions where you get a little more or a little less enzyme or receptor or signaling molecule. So I think that would be an important consideration to begin with that. If we start out with 2D6, this may not be the template for the whole field.

DR. FLOCKHART: I guess I'd make two comments. First of all, in terms of translating the pharmacogenetic science into bedside medicine. And this gets to this central issue of its application in clinical practice, which I think we're very close to. I mean we're going it a little in research centers and a little connected to a number of small companies around the country, but we're on the edge of a much wider application that has really important implications for public health, and I think we need to think about this very seriously.

There are two general observations I'd make. One is that I'm very concerned as a clinician that the standard of evidence being applied here for the requirement for a test may well actually be much, much higher, almost a quantum higher, than is applied to many of the normal tests that clinicians use in everyday practice. I point out as a doctor a vast amount of the information one gets as a physician is gray information. It's not black and white. It's not an absolutely clear mandate to do this or to do that. It's something that you integrate into all the other things about an individual patient, the patient's size, the patient's gender, the patient's disease status, the patient's other drugs that they're taking. These are things that you integrate into a larger picture, and that's what medical practice is.

If we try and generate tests that are so pristinely studied and so carefully economically worked out, A, it's going to cost so much that it's going to be impractical to do that with all tests. And B, at the end of it, you're not going to end up with a test that really has any greater impact on the practice of medicine. There are many tests, like for example, the PSA which is a test of prostate specific antigen which is widely used by cancer physicians around the world, but which has relatively low specificity, relatively low sensitivity. The potential benefit of some of the pharmacogenetic tests we're talking about for patients is very remarkable when compared to tests put in the same ball park like the PSA or, indeed, the BRCA testing that we use for a small minority of patients with breast cancer.

So my first concern is that the committee set a series of standards that are not only practically but economically and clinically unattainable. So we need to set standards for these tests in the context of standards for other tests that are applied.

Now, that gets me directly to the question of what specific information should be included in the label, because it gets to the quality of the testing. I think that there are two separate processes here. There are going to be FDA-approved tests that are not FDA-approved

tests at the moment, but in the description of those tests, it would seem to be incumbent upon the companies and the research centers involved to describe the alleles that they're testing for and to communicate that information.

Personally I think the location in the label of specific allelic information and very specific genetic information that relates really to how the test is done, what alleles are tested for and so on, would be overkill. And that partly derives from my concern, the concern we all have, about there being too much information in labels. And I'm cognizant of the fact that people are working on that and that we're moving towards labels where there will be a specific section that is very clearly, in appropriate language, aimed at patient information.

In that section, there should be something that talks about the availability of pharmacogenetic tests I think, and there should be something that talks about the phenotypes. Personally I don't think it should get into allelic detail and that should be information that's provided in terms of a description of the test.

The second concern that I have -- and I want to just put this on the table for discussion -- is in relation to pharmacogenetic counseling. Do we say anything in the label about a pharmacogenetic test is available? You should consult or there are people available to provide

this kind of counseling. This derives in part from a major concern that I have because I think in the gross picture here, what's going to happen is there are going to be a relatively large number of people, relatively suddenly in the history of things, wanting and using these tests.

Now, if you think about it, what you need to provide counseling -- I'm talking as someone who has tried to do this -- to a patient for a pharmacogenetic test is you basically need a lot of information about the drugs. You need to know the side effects of the drug you're dealing with. You need to know the effects of the drugs you're dealing with. You need to be familiar with the trials involving that drug. You need to be very familiar with the drug interactions involved. And it is not simply enough to be a genetic counselor. You can't do this without a lot of information about drugs.

So there's a separate discussion I think that needs to take place about how that needs to be done, and that should not be part of the FDA's concern or something that we would mention in the label I think. But it is a concern that I have that suddenly we're going to have a large number of patients needing this, and there frankly are not enough people, by a long shot, to explain this kind of information clearly to patients.

DR. McLEOD: Going back to some of the general

framework that is needed for this, I think there are two specific issues that we need to come up with some kind of general language for.

First of all, in my mind the most critical component to any of these tests, whether they're genetic or otherwise, is in genetic parlance the penetrance. In other words, how often does this variant really result in the predicted outcome? So, in other words, with TPMT homozygous mutations -- how often does that result in a severe or life-threatening toxicity from standard doses of mercaptopurine? In that particular example, it's nearly 100 percent.

But for many of the other examples, it will not be that. There will be other components that come into play. As a matter of fact, I think many of us who are involved with TPMT and other examples have come across people who were prescribed thiopurines and had a homozygous variant genotype but did not have toxicity for issues related to things such as drug adherence. So they weren't taking the medicine, therefore they didn't get toxicity even though they were genetically predisposed to get the toxicity, reflecting that there is an environmental component, i.e., actually taking the medicine, that contributes to that. So it's not just bad genes. It's bad genes with the wrong drug that lead to the outcome. So

that knowledge needs to be there.

That's a framework that can be for any genotype, pharmacogenetic or otherwise. Certainly with the genetic testing for familial disease, that's a big issue, as to how often does this gene really cause the phenotype. So that needs to be sorted through.

The other part is that I think we need to define -- I don't know the language we should use -- the goal much more realistically. The goal in my mind should be we need tests that allow us to do better, and that isn't very quantitative. It's also not very objective. But it really is where we should be going. So right now, if you're prescribed mercaptopurine, you have testing performed on you. It happens to be a liver function test, a panel that is performed, in order to decide whether to go forward. Liver function tests are usually ordered prior to purine prescription.

So there's already testing being performed in order to decide on dosage to some level and also whether the drug is going to be used at all. So the concept of using testing for thiopurines is old. Just in this case, TPMT offers a lot greater precision than something as nonspecific as liver function tests.

So in my mind simplistically TPMT testing, as an example, is much more precise and useful than liver

function testing because it gives you a more quantitative endpoint, something you can actually do with the results, rather than a qualitative endpoint such as liver function tests. If they're high, you don't give it, that sort of thing.

So if we could somehow, as a committee, come up with that sort of framework whereby we can decide whether a test really advances the precision, that is a good thing. The goal of getting 100 percent predictability every time for every test in my mind is unrealistic because we're talking about polygenic diseases, polygenic metabolic and transport pathways, and also we're in a world where genes aren't everything. There's plenty of environmental components that will have no genetic basis. So I think 100 percent predictive testing is not our goal, but rather doing better than we're currently doing should always be the goal.

DR. RELLING: I'd just like to congratulate Larry because I think he did an outstanding job of summarizing these issues. In fact, he addressed the issues that you're talking about with penetrance and clinical utility in his slide where he talked about separating out analytical validity, clinical validity, and clinical utility. So I didn't hear any requests that the tests be 100 percent predictive of the phenotype, and in fact,

including information about just how much of the clinical variability you think might be accounted for by genetic testing was exactly what he presented. So it sounds to me like the FDA is already considering all of the issues that you brought up, and I don't see those as any kind of problem whatsoever. That's how penetrance would be accounted for by any sort of --

DR. McLEOD: The testing community, though, has the desire of 100 percent sensitivity, 100 percent specificity. To me that is unrealistic in the context. If we know that someone has a 6-fold risk of toxicity, that often is a test that has maybe only a 60 percent selectivity and specificity. But if we know that someone has 6 times the risk, which is more than TPMT brings, then we would alter the therapy. I think that's what I meant. I totally agree with you that what Larry has summarized hits it.

But if we can be very clear on some suggestions on the goal. The goal is not the usual lab medicine specificity/sensitivity issues, but rather better guidelines on how to actually use this stuff. So often people look at genetic tests and look at it in the old lab medicine way and say, oh, it's not sensitive or specific enough. Well, it's still useful. It's better than we currently are doing, and our goal should be to do better

and not to meet certain minimum guidelines for a device. That's the point I was trying to make.

DR. RELLING: I see. I agree with that statement.

I think that the issues of separating out how well does a genotypic test predict observed phenotypes and then how well does the genotypic test predict the larger clinical outcome question both are the kind of data that would be useful to have in the label, if available.

I thought that the examples that you gave of where the label information was were all useful places. Like you say, for a clinician trying to get at it, having things cross-referenced under multiple sections is good. The other place where it might be useful to have pharmacogenetic information would be, I think, under warnings and under the dosage, especially where there's data to indicate the dosage could be individualized or at least thought to be individualized based on genotype.

You talked about how to get information for changing labels based on existing pharmacogenetic data, and I thought those were all good places and good things. Looking at the peer-reviewed literature, talking to professional associations, and getting consensus guidelines, asking specifically as new drugs come to market, whether genetic predictors have been evaluated and

whether there are known polymorphisms in the targets and the transporters and drug metabolizing enzymes I think would be helpful.

The last thing that you mentioned, the thorough evaluation of FDA post-marketing reports of adverse events, I would have more concern that the lack of information about post-marketing adverse events should not be taken as evidence that there's a lack of a problem because in many, many cases these things are so well known in the scientific literature that clinicians don't consider them to be reportable events anymore. I know that that happened in the case of TPMT, that those events may not have been reported to the manufacturer or the FDA, but they were well known in the literature and by clinicians.

And at the end, you mentioned where in the label should genomic data related to drug metabolism be included. Like Dr. Sadee said, I would just be careful about -- I think many of the genetic polymorphisms that we may end up needing to refer to in labels are not going to be just drug metabolism. So let's not limit ourselves to that because I think there will be examples with transporters and receptors. There already are examples of targets and receptors that could probably benefit by being included in labeling, for example, the thymidylate synthase and the methylene tetrahydrofolate reductase polymorphisms.

Then on the issue of whether TPMT testing should be something that takes place preventatively prior to patients receiving the first dose or a posteriori after a patient has exhibited toxicity, I think really depends on the details of the particular treatment protocol. As an ALL therapist, I could give you examples of that.

If you were going to give 6-mercaptopurine the first time in a relatively mild and uncomplicated two-drug regimen, you might be willing to observe the patient, see if there's toxicity, and then do TPMT testing to see whether it's 6-mercaptopurine or the other drug. But many ALL regimens will have the first time the patient receives thiopurine in a very complex regimen with five or six or seven myelosuppressive agents and if a TPMT-deficient patient would receive those five, six, or seven agents, along with mercaptopurine, they might have very severe myelosuppression and it would be impossible to figure out what the cause of that myelosuppression was. It could be myelosuppression that lasts for weeks or even months, compromising the initiation of further therapy. So for that particular type of drug regimen, it might make more sense to test patients a priori. In other regimens, it might make sense to test them later.

So whether the FDA wants the labeling to get into that level of detail or not, I don't know, but I think

that's the reason that there's debate in the oncology community about whether to do this proactively or a posteriori, and it's because it really depends on the details of therapy.

But I think it's terrific that you're considering this agency-wide, and it looks to me like you're thinking about it in the right way.

DR. FLOCKHART: I have to really congratulate you also, Larry. I think putting this together -- and there's a lot of information you've provided us that is new. But I think it also indicates the level to which the agency is energized about this. The way you have organized the thinking about it, I totally agree with Mary in congratulating you in putting it together.

Just two little things to add to try and respond to your questions. I think that in the label, there has to be something that describes the size of the change, and this gets to the question -- it's relevant to Wolfgang's first comment I think. And I wouldn't agree with you in that sense that 2D6 is not a good paradigm to go forward with because the 2D6 size of change is very remarkable, and in that sense, it is something that promotes a useful example for other drugs and other polymorphisms.

But the size of the change -- and this is for

thinking about all the prior drugs, not for new drugs, this huge problem, which ones do we consider revising the label. And I would say this. If there is not a clear polymorphic distribution -- in other words, not a skewed distribution, but a clear change -- then that's something that's really hard to start upon. It's not impossible, but that might be a way of separating out the drugs and polymorphism combinations that are worth going after.

Of course, the other way of thinking about that is where there are very significant clinically important adverse events or, for that matter, loss of efficacy that occur as a result.

I'll stop there.

DR. SADEE: I also wanted to say once more that I'm very excited about the prospect of having genetic information brought directly to the prescribers and to the patients. I think this opens an entirely new era, if you wish. So this is a very important step, and therefore, like you said, Larry, we have to be very careful as to exactly what goes into the labels and actually what does it open up for us.

I fully agree with you, David, about the need for genetic counseling because once you put a single piece of genetic information into a label, there are, the more you think about it, multiple implications. Let me give you

just an example. These implications are legal, economic, health outcomes, et cetera.

If we come back to 2D6 and an example that would be fairly clear, as far as I know, codeine is an allogenic drug that has to be activated by 2D6 or it won't work in patients who do not metabolize it through the active ingredient. That appears to be fairly clear. So here's an example that's nearly an all or none.

What would be important is if we were to include with codeine a description that if you do not respond, what are the implications? Well, now we have a situation where we might imply this is a poor metabolizer. Alternatively, if we would have known or we would have genotyped, this person doesn't have activity for 2D6, then automatically we are obliged to provide information that actually 20 percent of the drugs this person may have trouble with. And that's a pretty big implication right there.

In addition, if codeine doesn't work, oxycodone might not work because, to my knowledge, it's also activated by the same gene. Nevertheless, physicians will just go to oxycodone, prescribe it. It doesn't work either. The pain is going on and it's actually aggravating the situation.

So each single piece of information that we

introduce has a whole host of further implications that if we phrase it carefully, introduce it carefully, must then engender a much greater capability of doing genetic counseling because it will become very, very important very quickly.

There's one more aspect to that. The cytochrome enzymes, for instance, have associated with them disease susceptibility, and so the question is, is there a responsibility to extend this and to say, if you have this genotype, you may be at greater risk, for instance, when smoking and getting lung cancer? We have to have some kind of a clause that if we introduce the first genetic piece of information, there should be some kind of a clause in there saying, if there is this type of information, it's important in more ways than one and there may be some things in terms of genetic counseling.

DR. FLOCKHART: I'd just say that the word needs to be pharmacogenetic counseling because everything you said was really related to a drug. I will put it on the table. I don't think simple genetic counseling is enough for this, but again, it's not particularly on the subject.

I have a concern about putting the metabolism of multiple other drugs in as a consequence of a particular genetic phenotype for two reasons. One is that 2D6, 2C9,

and 2C19's experience have all shown us that the same genetic variant does not mean the same things for all drugs. For example, 2C19 which has a huge effect, a 10-fold effect, on the exposure to omeprazole is basically clinically irrelevant. It doesn't mean anything. It's not a useful piece of information. It helps a little bit in terms of treating Helicobacter, but it's not something that's become widely used, even though it's been carefully examined. But certainly for a patient taking omeprazole, they wouldn't notice any difference whether or not they're a 2C19 poor metabolizer.

On the other hand, it's very obvious to an individual patient who's taking diazepam and who's heavily dependent on 2C19. They get completely knocked out for a long period of time when there are genetic variants. So there are different consequences of an individual variant for different drugs.

So I think we have to be very cautious about making a statement in the label like, for example, because you're a 2D6 poor metabolizer or because you carry a TPMT poor metabolizer phenotype, it follows that you will have sensitivities to a large number of drugs. I think we need to have specific criteria for what those drugs would be, for obvious reasons. One is we're talking about cross labels here, just as you would in drug interactions. So if

you raise it with one label, you have to consider it with the other label. That makes the process considerably more complicated. But I think some criteria for what that list of drugs should be is something we ought to try and provide.

DR. SADEE: I don't think I really wanted to put something specific in other than to say that knowing this phenotype has broader implications than usual, discuss with your prescriber, to a patient. I think that would also bring the ball back into the court of people ought to know these things. There will not be clear enough examples. If it applies 100 percent to codeine, it may apply 50 percent to another drug and it may be irrelevant to a third one. But that's exactly the type of counseling that one would need. Some people are more sensitive to drugs. There must be a system behind this, and we're getting to the bottom of that system. So I think that's possible to include in some fashion.

DR. McLEOD: I think in terms of the field of applied pharmacogenetics, your comments are very true. I think in the context of the label, the precedent is that just because there is a variable that affects one drug, you don't have to mention everything else. So if you look at renal function, you can clearly indicate that impaired renal function is important for drug A, but you don't have

to say anything about the other 400 drugs that it also will influence. Now, behind that is the more readily available knowledge that impaired renal function will affect a lot of things. So I think that gets to what you're talking about, that there's an education issue that is dependent of the agency that needs to take place to try to sort some of this out.

If there's a clear drug-drug interaction or a clear basis whereby a genetic variant for drug A will be important for a drug that is commonly co-administered, then I think there's precedent to follow to try to develop that into a label. But otherwise, I think it's going into a very important clinical applied area but not necessarily an area that needs to be in the label.

DR. RELLING: I'd like to echo Dr. McLeod's comments. I completely agree. We should be careful not to treat pharmacogenetic information as completely different ancillary clinical laboratory information that we have in deciding how to individualize medicines for patients, and the renal function example is a really good one. It has broad implications, but it's not part of the label and it doesn't prevent us from putting that information in the label that all of the implications of having renal dysfunction, having liver dysfunction, having diabetes, having other comorbid conditions. The complexity and the

far-reaching consequences that having a genetic polymorphism might mean doesn't preclude us from using that information, and it shouldn't be held to a much different standard than any other laboratory information that goes into the label is.

DR. VENITZ: Just to follow up on that, I think we have to separate what the label for the drug of interest should say and what the label of the test should say. A lot of things that you were talking about I think should be in the label that goes along with the test because it tells me how to use the test and what the limitations are. I think that's where the information would go not only about false positives and false negatives, but also things like what's the positive and negative predictive value based on the prevalence of whatever you're testing for. So the kind of information that as clinicians we expect of all of our tests to be readily available.

Now, to go back then to your question, Larry, about what information should be in the drug label, because I think that's what we are to focus on, I'm not sure whether you need that specific information.

What I'd like to see is, number one, there is a polymorphic receptor drug-metabolizing enzyme or transporter involved in the kinetics of the drug, that there's evidence to suggest that.

Number two, that there's evidence to show that that has a consequence in terms of the side effect profile or the lack of efficacy and what those consequences are and that there is a way that you can test for the genotype of that particular enzyme, transporter, or receptor.

I think it's those three pieces of information that should be there, and I'm not sure whether you need to list specifically the alleles even if it has been studied as part of the clinical program or specifically the pharmacokinetic consequences quantitatively because I think then you're putting the burden of interpreting the results on combining that information with the test because it's the interaction of the two that leads one to change treatment if necessary.

DR. FLOCKHART: So you would go just with simply putting, as I was saying at the beginning, the phenotype.

DR. VENITZ: Yes.

DR. McLEOD: I do think that the frequency information brings a lot to it. It doesn't have to be the frequency of each individual genotype, but for the TPMT example or for the 2D6 example, knowing that it's 10 percent makes someone at least pay attention. There are many examples out there where if you look at the ultra-rapid metabolizer genotype for 2D6, it's 1 percent or so,

and a lot of people might just say, oh, well, if we ever come across one of those people, we'll do something about it. But it's such a low frequency, they won't bother. Now, if you're one of those people, it's a big deal. 10 percent. That's a fairly large amount of your practice. If that number is robust, then I think it would add something.

DR. VENITZ: I agree with that, but the reason why I would agree with you is because it has significant consequences. Lots of times, even knowing the prevalence, if the consequence is headache or whatever the side effect profile looks like, it may not be relevant. And I'm concerned that we are already overfeeding information into the label that is very difficult to interpret.

DR. DERENDORF: I think there should be two pieces of information, frequency and magnitude, so that one can assess the situation. How often does it happen, and if it happens, how bad is it?

DR. SADEE: If you bring frequency into play, then you might also have to bring into play ethnic differences there. Clearly they are so large in some cases between different ethnicities, that once you mention these frequencies, it may necessary to do that too. One would like to possibly avoid this. But it's an issue we need to consider.

DR. FLOCKHART: There is precedent for that in labels. Specifically in the label that's on the screen right now, what level of genomic data should be included in the label? I think if something is very common in African Americans like the 3A5*1 variant or is relatively rare in African Americans like the 2D6 variants, that's worth putting in. If that data is robust and there is a clinical consequence, it is worth putting in.

DR. McLEOD: I think having the range of frequency that is found in, in this case, the United States population, because this is the FDA for the U.S., is useful. Putting the specific ethnic groups I do not think is useful for two reasons. First of all, it gives someone an excuse to forget about it or try to put it out of their mind in certain groups. Oh, it's only 2 percent in African Americans; therefore, I won't even think about it.

Also, there are so few components of the U.S. population that have been evaluated that we could focus on the European American and African American groups, Chinese American or Asian American in general, which is a very heterogenous population often not evaluated, Hispanic Americans are usually not evaluated, and then the huge numbers of others. So if you have a range, if there is a robust range, then that's fine, but if you start actually pinpointing the ethnic groups, then you might as well list

the ones you haven't tested as well. Often the range that is seen with the more common ethnic groups in the U.S. does reflect the range that is there in general.

I guess my worry is people now are trying to figure out whether ethnicity should or should not be a component of medical decision making, and I think we all have our opinion. I don't know that including specific ethnic groups would be in a patient's best interest.

DR. SADEE: But that addresses also the cost-benefit issue. So there is a limit as where you say beyond a certain frequency, that's where it actually becomes cost effective through genotyping. So if you can define a range of frequencies very precisely that you can assign to an ethnicity, then yes, it could well be that in this case, let's say, for Mexican Americans, it may not be worthwhile to do it, but for Asian Americans, it may as a whole because it's cost effective. I think that needs to be considered too. So the cost effectiveness is one that will play a major role. You will only implement something that you get more out of, you get a real benefit compared to the cost you have to put in because the overall energies you can put into health care is limited, and you take away from something else.

DR. McLEOD: That's a test issue not a drug issue. PSA is only ordered for half of the population in

the U.S. Females don't get PSA testing. It turns out there's no reason to. So choices are being made on other endpoints. Currently only breast cancer has HER-2 evaluation because it's known to be more frequently amplified in breast cancer and therefore of more utility. So what you mentioned about having a distinct group, in that case a tumor type or a gender, is currently used in terms of decision making.

Even though you could test HER-2 for every tumor type and see if you find somebody that's amplified in lung cancer or whatever else, you don't because of the limited utility, like you mentioned. But that's a device issue rather than a drug issue. I mean, herceptin labeling doesn't indicate much about that, as far as I know. It's more the actual HER-2 test that reflects it.

DR. RELLING: Yes. I was just going to say I didn't hear it said that the FDA needs to consider cost effectiveness of testing in its decision of whether to mention the availability of pharmacogenetic testing for individual drugs. I can't see how that would really be appropriate for the drug label because those costs are constantly changing and the costs of the test may change a lot depending on how its used. So I agree that that might be part of a clinician's decision making, but I don't think that that's really relevant to the labeling.

The other thing I was just going to mention because I've heard HER-2/neu testing being used as an example of how patients are tested before it's decided whether to give them the specific drug, and that's analogous to what would be done, for example, for TPMT testing and the decision of whether to do that before giving 6-mercaptopurine. But there is a difference, and some of that genetic testing like HER-2/neu testing has implications as to whether the medication will work at all depending on the results of that genetic test. So you might save the patient inappropriate use of a medicine that wouldn't work by having information on negative expression of HER-2/neu.

Whereas, at least as far as we know, for TPMT testing and for lots of other pharmacogenetic testing, it wouldn't be a decision as to whether the drug has any utility at all with the exception of your example you gave of some narcotics and 2D6, but just a matter of how to dose the medicines. So I think that's why there can be a little gray area as to whether pharmacogenetic testing would have to be recommended prior to prescription of the drug at all versus a posteriori after seeing how the patient responds to the medicine.

DR. FLOCKHART: I think you have to think about what the label is for. The label is to guide prescribers

and to help patients. The label is about a drug. So I think that information about the incidence, as we said many times, is important. It makes a huge difference whether something is .1 percent frequent or something is 20 percent frequent.

Personally I think there are situations where the ethnic difference is so extreme, Howard, that I would disagree with you. There is such a marked difference that you can't just throw out race. You can't say it doesn't matter because in both the patient's and the physician's decision about that drug -- not about the test specifically, but about that drug -- it makes a difference whether they're African American or they're Asian or they're caucasian if the difference is sufficient. We need to talk about what sufficient is. It's not 1 percent. It would have to be a very notable difference I think. There are situations where ethnicity might be included in the label, and I think it's not useful to say, Howard, that we haven't studied every sub-ethnic population within the United States because what you would include would be information about where there is a large difference where it really would be useful in clinical practice. So if I'm looking at an African American, that's something -- let me make an extreme example. Something that was 30 percent incidence in African Americans and 1 percent in caucasians,

that's a different decision for a patient and a different decision for a prescriber.

DR. McLEOD: I agree with you, but what about other common groups that aren't evaluated? That's where it starts falling down. For example, 2D6, the ultra metabolizer genotype is much more common in populations from an East African heritage compared to a lot of the other populations. But maybe Indian and Pakistani populations also have that high frequency but just haven't been evaluated carefully. Maybe other groups.

So it's positive information, but I think guess what it's missing is there as well. Taking it and saying I'm only going to test African American subjects because they're the only ones that have the higher frequency is not useful. That's what I'm afraid of. If it's dictated too carefully, people will say, oh, that's the only time I need to look.

DR. FLOCKHART: That's a language question. You can put it in language that says other populations have not been carefully studied, but there's a positive here.

DR. SADEE: What policy you will be setting is going to lead into the future for a number of years. This is initiating a new trend.

I would like to bring up a consideration that actually technology will outrun what we're discussing right

now so that the prospect of having your computer chip embedded where all the relevant SNPs are available is not that far off. But in the area of drug metabolism or pharmacogenetics, within 3 years you will not have a single test. If you order a test, the cheapest way, this is only going to be one, two, or three years away. The test will include 20, 30, or 40 or 50 SNPs depending on how fast we do this, and that information will be instantaneously available to all those who prescribe and to the patient as well. It will be economically inefficient to do a single test because the controls around the test are such that just doing the test is extremely expensive, but adding 1 or 20 or 100 new SNPs will become trivial.

That's why I brought in the implications of once we add this in, there's a whole slew of new things that are coming our way. If we only talk about the label, of course, we won't include this, but we must be cognizant that this is coming very, very rapidly, and if we open Pandora's box and seeing the single piece of genetic information there, in three years this single piece will be a very complex piece of information provided to all. That needs to be safeguarded. That needs to be privatized in such a way it cannot be utilized elsewhere and so on. So all these issues. It's an enormous issue and it starts right here with setting the proper policy.

DR. RELLING: Well, this wouldn't be the initiation of genetic testing. There are genetic tests that are being done all the time for factor V Leiden, for MTHFR, for Gilbert's disease with UGT1A1, for G6PD deficiency. So this has been out there for a while. I don't want people to overreact to the idea that by just mentioning a few genetic polymorphisms in relevant drug labels, it's opening a flood gate to genetic information that hasn't been present for the last 10 or 20 years. There is precedence for having genetic information, using it in specific ways and specific clinical information, and providing clinicians with useful information for how they treat patients that's not going to have overnight overwhelming sea change in patient care related to genetic information if the FDA decides to have a more uniform policy on how to incorporate genetic testing into drug labels.

DR. SADEE: Well, I think it is a sea change for drug therapy. There are small pieces coming into play, but within the next few years, there will be a sea change. That's how I see it coming.

DR. RELLING: I will be delighted if in one or two or three years we have accurate genotyping information on tens or hundreds of SNPs. We're not finding that it's all that easy.

DR. FLOCKHART: This is something where I heartily agree with Mary actually. I'm very concerned about how rapidly we move here, and I think it has to be done very carefully. Again, I think Larry set out a very nice rubric for doing it. But because we're doing it carefully -- and I think a lot of the conceptual issues with genetic testing have been dealt with by things like G6PDH, even cholesterol. So it's not new conceptual things, and I'm nervous of calling it something big like a sea change.

Really, these are genetic tests. They're not new. They're laboratory tests. They're not new. They're tests that influence pharmacotherapy. They're not new. These things have been done before. It's an evolution to me rather than a sea change.

DR. LESKO: In the context of thinking about the broader paradigm that I mentioned in my slides, there's another element to this. It gets to perhaps prioritizing or thinking about the best clinical value for a test. I can think of two different types of drugs that are based on how they're used in therapeutics.

At one extreme we might have something like a thiopurine with a TPMT, where there's a clear distinction between the activity of the drug in the genotype.

Another example might be a drug like dilantin

or phenytoin. I believe it's a 2C19 substrate, but when you begin therapy with it, there's no immediate response, either efficacy or safety. There's some time that it takes to respond to that drug.

Contrast that maybe to a beta blocker, say, metoprolol where you're using it for hypertension. So you see an immediate antihypertensive response and can react to a dose adjustment based on an easily measured phenotype. Warfarin with 2C9 substrate, polymorphic, but I can use an INR.

So I guess my question sort of revolves around how to think about priorities for a genetic test improving drug therapy in the face of having or not having easily measured phenotypes that I can use as a titrator of dose. It's sort of trial and error, but it's trial and error in the context of being able to look at response readily.

This isn't a small question because I mentioned last week's New England Journal of Medicine or JAMA, one of the two, with the new report on adverse drug reactions. But again, like other reports similar at the top of the list in terms of frequency were the antidepressants and the beta blockers and drugs that are typically polymorphically metabolized.

So where do you think this vector of titrating a drug versus not titrating a drug in a sense, a dilantin

versus a beta blocker, come into play in the thinking about a genetic test improving therapy?

DR. FLOCKHART: I always seem to have an opinion about these things.

First of all, I think that the availability of a phenotypic test does not mean that a genetic test is useless. The phenotypic test often takes considerable effort and is often not perfect. One nice thing about pharmacogenetic tests is you do it once and hopefully if it's done well, you don't have to do it again.

I could go through the specific examples that you mentioned, but they're illustrative actually. In the case of phenytoin, the difficulty with phenytoin prescribing is as one gets to the therapeutic concentration, there's a risk that as you increase the dose, you saturate metabolism and you go off the proverbial therapeutic roof. And having seen this happen with a few patients, that is what it feels like. So there's an issue there of although you're often measuring phenytoin concentrations, you still get a big surprise when you change the dose, and that's listed as an adverse drug reaction and that can cost a lot of money.

I could make similar arguments with warfarin. You follow warfarin all the time, but the way we normally do warfarin is we test INR a few days after we make changes

because we know it takes a while.

And in real clinical practice, I think we have to put this in the environment of regular medical care in the United States. It's not easy for people to see a physician. It just isn't. And it's not easy often to just schedule an absolutely easily timed test for therapeutic drug monitoring be it by phenotypic kind of changes like INRs or be it by drug concentrations.

So I think more information available to physicians and prescribers in general -- and that would include pharmacists and psychologists and so on -- is only a positive thing in the prescribing process and an addendum. An addition of a genetic test on top of an available phenotypic test in general is not something I think contaminates the prescriber's efforts. It enhances it.

DR. SADEE: I would just like to raise one general issue as a cautionary note, and that is recently -- well, not just recently. There's a recognition that gene expression, regulation and so on is not necessarily related to a primary change in the DNA so that a SNP analysis will tell you whether there's even a change in regulatory agent. Most of those SNPs we don't even know. But there are many other phenomena that are epigenetic, gene silencing, histone acetylation, et cetera that could actually last

over many cell generations or in an individual. Now the first article has come out that this may actually override many of the genetic changes.

So I just wanted to have this on protocol that we're cognizant of the SNP analysis is just one of the many ways that one could assess phenotypic variation and evolution across a population or within the same individual as a function of environmental impact and so on.

DR. McLEOD: I think the framework that we're talking about will encompass genotype, haplotype, gene expression profile, if there is a profile A versus profile B, silencing, non-silencing, methylation, non-methylation. If we do it right, whatever the means, it will be useful.

I think it's already in place in a way. Going back to the renal function example, below a threshold -- and it's different for different drugs -- there are warnings about the implications for that. And it may be the same thing. It may be that there's a reason in the future that gene expression profile A patients are at higher risk of toxicity or lack of efficacy, and if that data is as robust as we're talking about, then it will be able to fit right into this framework because when it comes down to it, the utility of these tools, regardless of whether they're biochemical tests, a molecular test of any ilk, a protein-based assay, we have to be able to stick a

label on a person to then use it. If they're in cluster A -- that cluster may have 33,000 genes in it -- they are cluster A patient, therefore their risk is X.

So I think the same framework will be useful because you're right. We're talking about genotype today. We'll be talking about those other things tomorrow or in the future, to be more precise. So I think getting the framework right this time will then allow all the rest of it to just slide right through.

DR. VENITZ: Just two points to follow up your comments. In the very article that you mentioned, it is not apparent whether the genetic testing would have made any difference because they didn't really separate out drug-drug interactions, and the very drugs that you mentioned are also prone to drug-drug interactions.

The second thing, more importantly for the discussion that we're having, a lot of those studies that find an increased incidence of side effects, let's say, usually find as the main reason for that is that the information is available. It's not being translated in practice. So it's not like we don't know it. It's not like we don't have the genetic tests whether they're in the label or not. People don't know how to use it or they don't use it. So there are systemic flaws.

I think maybe at a later point in time, we

ought to discuss this. How do we communicate that information in a way that it makes a difference, not just in a way that it reflects the best science that we know of and all the uncertainties involved, but in a way that it actually makes sense to the prescribers that are not necessarily highly educated in those areas.

DR. LESKO: Those are both good points. We didn't talk much about it today or even in our October meeting, but we are working on a guidance that would encompass label language that at some point, when it's in a suitable form, we might bring to the committee to talk about representative language for including genetic tests in a label.

I did want to bring up another dimension because I think there are many small bridges that we have to cross as we progress and move forward. I don't think it would be appropriate to be thinking about cost effectiveness in terms of a genetic test if it's important to public health, although you can't ignore that and how it factors in the thinking. We have to acknowledge that it does in some ways.

But probably more important in the context of a label with a pharmacogenetic test is the test availability. It wouldn't make sense, for example, to put a test in a label that physicians can't access if they read the label

and then choose to use it in applying it to their patient. We are somewhat in a bit of transition in the sense that none of the pharmacogenetic tests have been submitted or approved by the agency. So we're dealing with a community of testing laboratories that I'm not quite sure what the availability of testing is, let's say, for cytochrome 2D6, and if the sites are widely available for physicians to access, what the quality of that report is from that laboratory. I wondered if people had any thoughts on that aspect of what we're talking about today.

DR. RELLING: I mean, you're right. It is an issue. I guess I don't quite understand what is the percentage of specialized tests that are done in health care or even non-specialized tests that are FDA-approved. Is that something that is the vast, vast majority of laboratory tests that are used? I don't think that it is. So the fact that there aren't pharmacogenetic tests that are yet FDA-approved shouldn't be something that would prevent clinicians from utilizing them.

I guess the Internet helps a lot because now it is relatively easy for any of us to type in CYP2D6 genetic testing and probably come up with a list of companies that are doing that. Maybe not as many clinicians as need to know do know that they should look for things like CLIA approval or CAP approval for the test that they're going to

use as some sort of external imprimatur that there's some basic quality control.

But making that information available to both clinicians and to patients is a challenge, and I don't know whether the FDA wants to take responsibility for that or not. But those of us in this field deal with it daily, that physicians and clinicians and patients want to know about how they get genetic testing done and it's still at the point where it's not easily ordered by any clinician anywhere they're practicing and taken care of by the therapeutic drug monitoring lab or the pathology lab that handles processing orders.

So although that is definitely a hurdle that needs to be overcome, in the case of TPMT testing and CYP2D6 testing, at least for now, it looks like those tests are probably here to stay and widely enough available that they should be available to clinicians if they are mentioned in package labeling.

DR. FLOCKHART: I do not have an opinion about this, what I'm about to say, one way or the other, but I just want to put it on the table. It's whether it's appropriate for the agency to talk about actually counseling in a label or not in the sense of we haven't don't this with G6PDH, we haven't done it with other things. Is the smell of this beast sufficiently different

that we would want to do something like that?

I have concerns about the availability of tests without counseling. I know this has been carefully dealt with in the HIV area. So I would welcome a little bit more discussion at some point about that.

DR. LESKO: I was thinking about another aspect of product labels, and I recently searched the PDR for indications of therapeutic ranges for drugs, how many labels indicate that and what we say about that. There's actually a fair amount of drugs for which we recommend blood level monitoring, and not much is said in the label itself about interpreting blood levels other than this might be the therapeutic range. There's no counseling component in labels with respect to that.

It sort of brings you around to the question about genotyping which actually has some implications for third party reimbursement, and that is, what do you call it? Therapeutic drug monitoring is looking at a blood level and then adjusting dose and trying to get a patient in a therapeutic range where the probability of good things happening is higher and the probability of bad things happening is lower. It doesn't strike me that it's necessarily screening to measure a blood level of theophylline. It strikes me that's more monitoring. And if there's an opinion on this I don't know, but how would

you think about genotyping? Is this therapeutic drug monitoring? Is it screening? What is the appropriate terminology that would be applied to this activity?

DR. FLOCKHART: I think that's easy. It's case dependent. In the majority of situations, I think it's like therapeutic drug monitoring. You do it after you've started on a specific drug. There are very few situations possibly including 6-mercaptopurine -- I'd welcome Howard's and Mary's opinions about that -- where there might be a case for screening before.

DR. SADEE: HIV therapy should maybe set an example because it's already done. In 50 percent of the cases of high intensive therapy of HIV, you have genotyping. In this case it's genotyping of the virus, but it's the same idea. And that is being reimbursed. So I do not know who is doing the tests and what are the quality controls and who's regulating that, if at all, and how then the third parties decide to reimburse this on the basis of what criteria. That may be a good example because it's in practice.

DR. CAPPARELLI: At least in terms of the HIV genotyping situation, a lot of it is actually done after therapy. In a sense the wild type is not the issue or the sensitivity of the wild type. It's the sensitivity of patients who've already had therapy. So I think it gets

maybe again more towards the model of after therapy is initiated. In clinical trials, that's a different issue, that there is some up front discovery work being done, but I think for the great majority of this, it's really again being applied after the initial exposure to the drug classes.

DR. SADEE: There's continued therapy and so maybe initially you assume that it's not cost effective to do it right away, but while you go along, resistance is acquired, so it becomes necessary at one point.

DR. CAPPARELLI: No. It is a necessary component, but it also changes. It's a bit of a different animal than genotyping the patient where we're linking it to what we expect is an exposure pattern that we expect to be relatively constant over time.

DR. RELLING: I don't know what difference it makes for third party reimbursement, but it does seem that pharmacogenetic testing should be more closely linked with therapeutic drug monitoring labs just because the results are definitely interpreted by the people who are monitoring and adjusting therapy and they may be very closely linked to a posteriori tests of blood levels of the medications themselves.

And TPMT is a great example. We have a very detailed algorithm for how we do genetic testing, activity

phenotyping, and sometimes drug metabolite level monitoring, and all three of those things are used in conjunction with each other in really assessing what the patient's status is. Certainly having all of those tests interpreted by the same clinicians in a therapeutic drug monitoring laboratory makes sense I think.

There may be some examples where there are genetic tests performed that have implications not only for drug prescribing but for other health risks or other interventions, and some of those prothrombotic genetic risk factors are an example of that where it may be a bit of overlap between how much is patient monitoring outside the context of drug therapy and how much is patient monitoring within the context of drug therapy. So some of those details are probably going to have to be worked out over time.

DR. McLEOD: I think therapeutic drug monitoring is a good example of the spectrum of what we're going to see because you have situations like Mary described where you have very thoughtful linkage between the assay and the interpretation, and then you have the other extremes whereby a lab medicine department will measure something and put it onto the results, and it stops there. Then it's up to the individual clinical team to interpret what it means.

I think that's what's going to happen with pharmacogenetics. You're going to have situations where you have the whole package where the patient gets very thoughtful interpretation, and then you're going to have just labs that measure stuff and report a result and then good luck to you.

We see some of that now with direct-to-consumer marketing of pharmacogenetics which thankfully isn't widespread but is occurring whereby patients are encouraged to send a chunk of tissue in to the lab where they can measure some stuff and send results back and then take it to your physician for interpretation, which currently is not very useful. We wouldn't want to encourage that as the industry standard by any means, but I think it is and will continue to happen.

DR. SADEE: I think it's important that if there were a label on the drug that says there is genetic variability, then the first important piece there is not that one should go ahead and do genotyping, but it alerts the prescriber and the patient to say there is a chance I will have a very unusual reaction.

That was the same what happened to drug level monitoring initially. One would want to measure as many drugs as possible and then one could see the variation across the population. Then people like Lew Sheiner would

come in and say how can we, with that knowledge, apply it to a population, minimize the risk by just looking at all the factors that we do know and then suggest a dose which did mean that in many cases we dropped measuring normal levels because it wasn't necessary. The benefit was not sufficient. The error was so large that it was not worthwhile doing it.

So just by having a genetic label doesn't mean that we're necessarily locked into actually doing the genotyping, but rather that it alerts you that there could be problems and here is one of the reasons for the problem with that particular drug. That's step number one, and that's all education. That's all in the counseling area.

Then somebody needs to decide whether genotyping is appropriate. In a few cases, one may decide that a priori this drug should only be given if there's genotyping, and this will be a small minority of cases at the present time.

DR. VENITZ: Any final comments before we break?

(No response.)

DR. VENITZ: Then I suggest we take our scheduled break and reconvene at 10:30 for our last topic.

(Recess.)

DR. VENITZ: Let's get started, please.

Our last topic deals with transporters and drug metabolizing enzymes, and Dr. Shiew-Mei Huang, the Deputy Director of the Office of Clinical Pharmacology and Biopharmaceutics, will be giving us our final presentation. Shiew-Mei.

DR. HUANG: Thanks, Jurgen.

What I'd like to talk about right now, the last topic, is some of the recent issues and challenges in the evaluation and labeling of drug interaction potentials of new molecular entities. I'd like to start to review with you some of the recently withdrawn drugs from the U.S. market due to safety reasons, and I also added two drugs that were not approved in the respective year.

You can see that many of these drugs that were withdrawn had serious drug-drug interactions. Terfenadine, mibefradil, astemizole, drug X, cisapride, and more recently cervistatin, and drug Y. Many of these were associated with serious effects. For example, we have seen cases of torsade de pointes for drugs that were approved and were on the market before the approval and also for drugs that are being reviewed. We have seen QT prolongation. Some of the other drugs the toxicity involved hepatotoxicity, acute liver failure, bromphenac and troglitazone, and others such as alosetron, ischemic colitis, serious constipation, rhabdomyolysis,

bronchospasm, and other effects. Drug Y is an inducer that's affecting the metabolism of other drugs. So you can see that drug interaction is very involved in the drugs that were withdrawn recently.

What about the drugs that are on the market? As we have discussed earlier this morning, there's a tremendous number of adverse events every year. There are about 2 million based on these reports, about 100,000 deaths that are adverse drug reaction related, and it ranks about 4 to 6 of the cause of death in the U.S.. Not only is there harm for the patients, there's economic and health issues related to this ADR.

So why are there so many ADRs? In the recent study showing that one of the reasons could be because there's a lot of use of drugs or patients are given polypharmacy. Here this is the total use of individuals. This use is any use that's prescription drugs, vitamins, herbs, dietary supplements. And here is the breakdown between men and women.

If you look at the most susceptible group, elderly women over age 65, you can see that more than 50 percent was taking more than five drugs at one time, and about more than 10 percent were taking 10 drugs at one time.

In a recent study in '95, it shows that drug

interactions represent 3 to 5 percent of preventable ADRs, and they are an important contributor to emergency room visits and hospital admissions.

Earlier this month, a JAMA article has done a population-based evaluation of three co-administration, and they found that -- this is a study in Canada in an Ontario population. They showed that elderly patients with digoxin toxicity, that they are 12 times more likely to be given clarithromycin. In the paper this contributed to an interaction that's based on P-gp. Earlier reports have shown that this could be also because of a macrolide that's inhibiting bacteria lenton. That's a microorganism that's contributed to the metabolism of digoxin to dihydrometabolites.

In the same article, it has other combinations indicating, for example, pharmacodynamic interactions, patients that are given ACE inhibitors with hyperkalemia, and they are 20-fold more likely to have been given potassium-sparing diuretics. And other one is related to a pharmacokinetic interaction in patients with glyburide with the hypoglycemic effect, 6-fold more likely to be given with an inhibitor of 2C9 such as cotrimoxazole.

There are some recent studies showing that this could be related also to an interaction that's OATP based. That's organic anion transporting polypeptide. So you can

see there are a lot of interactions based on cytochrome P450 enzymes or transporters.

What's interesting in this article is they also monitor these patients and see their prescription. They're assuming if the doctors know there is an interaction, then perhaps they would modify the regimen. However, most of the patients discontinued. So perhaps the doctors do not know about the interactions, even many of these were stated in the labeling. For example, clarithromycin. This was stated in the labeling. Even it didn't say P-gp, it mentioned microorganism interaction. So they have postulated it's very likely because either the information was not updated for some other cases or because there is so much information overload. In the labeling there is so much trivial interactions that will pop up in the computer systems that the hospital used, that the operator just overrides anytime you see interaction.

So I think it's very important that we put the information properly in the labeling. I think this is related to our discussion earlier this morning. Also our discussion today about a classification system for CYP3A inhibitors is related also to address the issue and proper labeling.

In our Office of Clinical Pharmacology and Biopharmaceutics, our good review practice and quality

review, as far as drug interaction is concerned, we ask several questions. We must evaluate drug interactions well, especially in the cytochrome P450 area. So much is known and we are expecting that this be evaluated.

And as discussed yesterday, many of the interactions were pharmacokinetic based. So how do we interpret the clinical significance of the drug interactions, such as 100 percent increase in AUC, a 2-fold increase in Cmax? What's their clinical significance? I think we need to evaluate the safety/efficacy database and explore the exposure-response relationship, and many of the quantitative approaches that were proposed yesterday were discussed with this committee.

The drugs that are withdrawn from the market that I showed you earlier. We found that the Dr. Doctor letters that were sent out later may not be as effective as we would like them to be.

We think that it's important that you use prominent labeling when the drug is introduced to the market, and we also would like to project a level of risk in drug interactions. And later on we'll address what approach that we can take.

In addition, earlier on, the committee members already mentioned that the labeling, even the information is accurate, it's important but it may not be efficient.

So I think we need to continue to develop better means of communicating dosing information to practitioners and patients. Larry mentioned yesterday about a labeling initiative that the agency is taking where you highlight important interactions or information in labeling or we give an additional medication guide to patients. There are many other ways that we need to do. However, the starting point is still the labeling. So I think today what we're going to talk about is really focused on labeling.

So what is the optimal information for an NDA submission? Because so much is known about cytochrome P450, we think it's very important, and this is our guidance document that we have communicated to our sponsors. We must elucidate metabolic pathways well, the contribution of key cytochrome P450 enzymes, the fraction that's metabolized by those particular pathways so that we will be able to properly evaluate the effect of other drugs on the new molecular entities.

In addition, we need to evaluate enzyme modulating potential. The drugs that were withdrawn from the market or not approved -- the one that I mentioned. There are two drugs. Their main interactions is because of this modulating effect. One is a strong inhibitor of cytochrome P450 and P-gp. The other one is an inducer. So it is important to evaluate the effect so that we will be

able to understand the effect of this new molecular entity on the other drugs.

We have several guidance documents that have been published over the years. With '97, we have an in vitro interaction guidance talking about using in vitro metabolic methodology. In '99 we published an in vivo interaction guidance, and some of the committee members have been involved in the evaluation of this guidance. And using the population PK approach has been addressed by some speakers yesterday to address drug interaction issues.

And this is important. We have a so-called MAPP. This is like a reviewer's guidance. It's a Manual for Policy and Procedures where we instruct the reviewers, when you have a new molecular entity that we're going to contraindicate this drug with the other drug or that will result in a dose change of the other drug, that the review team needs to talk to each other if they're from different divisions so that eventually the sponsor of the interacting drug will be informed, and if there's a labeling change, they will be informed to submit supplements to effect the change in the labeling.

We have the good review practice, which Dr. Lesko has discussed at the FDA Science Board a week ago, which talks about what key questions that we must ask in our NDA review, and that included drug interaction as an

important issue.

The CDER working group right now is working on an in vitro metabolism because so much has evolved since '97, and we are having recommendation of a standardized approach to look at cytochrome P450 enzymes. We're also developing a guidance to look at phase II of metabolizing enzymes and other transporters such as P-gp. Part of this is being published in our intranet for reviewers, and we are still developing other portions.

Again, in order to interpret the interaction outcome, the exposure-response relationship is very important to explore, and this is an guidance which Dr. Lesko mentioned yesterday.

I'll just briefly mention our office's good review practice. This is one paradigm that we have recommended for our reviewers when we review the interaction data. We say initially we could look at a new molecular entity and use in vitro method using human tissues or expressed enzyme for key cytochrome P450 such as 1A2, 2C9, 2C19, 2D6. For each of these enzymes, we ask the question, is it a substrate or is it an inhibitor or inducer?

This question is no different than what we asked in '97 except at that time we thought the method is only available for substrate and inhibitor. Now I think we

believe the in vitro technology has developed so that we will be able to also evaluate using human hepatocytes, the in vitro induction effect.

So if we ask this question based on the in vitro method, if the answer is no, it's not an inhibitor or inducer, then we could stop and we do a general labeling that that particular cytochrome P450 is not involved. It's not being modulated by this new molecular entity. We would supplement this with population PK to look at in the patient population whether there is an interaction that we have missed. Are there other transporters not screened by this particular method that we might detect using that approach?

If the information is not available or we said it is an inhibitor or inducer, then we recommend in our '99 guidance that we use the most sensitive substrates, for example, for CYP3A you could use midazolam or some of the statins or buspirone, the one that's shown to be very sensitive and very large-fold changes when you give an inhibitor. And if the result is negative, then we could stop there and we can label it. If the result is positive, then we can continue with less potent inhibitors or use the drugs that are more commonly co-administered. And I'll address how do we define most sensitive substrates.

So if the drug is found to be a substrate or

not to be a substrate, that's another determining factor. If based on in vitro information we say it's not, then we could stop and give a general labeling again and then use supplemental with the population PK information.

If it is a substrate or the information is not known, then we continue this pathway and ask another question. Is this pathway major? If even this drug is a 3A pathway, if it's metabolized by 3A but the renal clearance is the major clearance pathway, then again we say you don't need to evaluate. You can do a general labeling and again use population PK to pick up unexpected findings.

However, with the event of pharmacogenetics, I think we need to be careful or be mindful about this approach. For example, if you say this drug is not a 3A substrate, it's a 2D6 substrate, however 3A may become important in the poor metabolizer. I think recently we've seen some studies on tolterodine that it's a 2D6 substrate, but in poor metabolizers we found ketoconazole has inhibited its metabolism and increased the AUC by more than 2-fold.

So again, if the pathway is major or we don't know -- we don't have the in vitro information -- then we recommended in our '99 guidance that we use the most potent inhibitor or inducer to study its effect. Again, if the result is negative, because a lot of times we don't know

the percent contribution of the pathway, then we could stop there and label. However, if the result is positive, then we continue the path and use a less potent inhibitor or inducer.

We just show this as one of the paradigms. It's not the only way to do it. However, we think with this approach, we can obviate certain in vivo interaction studies and only focus on the cytochrome P450 that's more important in the metabolism or in the modulating effect.

I want to talk about here, when we say most sensitive substrate and most potent inhibitor and relate it to a document which PhRMA has just published this month in the Journal of Clinical Pharmacology where PhRMA has proposed a classification system for 3A. I just want to mention. This is related to our approach as well, but it's an extension of that approach.

In the PhRMA paper, actually PhRMA has -- we have started a discussion when they had first prepared this early last year. They propose to use midazolam as a probe substrate. This one has about 40 percent bioavailability and it has both intestinal and liver high extraction. If we use it as a probe substrate and we look at the AUC ratio with the inhibitor versus without the inhibitor, given alone -- and these are the various inhibitors -- you can see they have different degrees of inhibition as manifested

in the fold change in AUC of midazolam and the use of boundaries of 200 percent and 500 percent.

So if a drug, an inhibitor, increased midazolam more than 500 percent or the fold change was 5, then we call that a potent inhibitor or strong inhibitor. If it's between 2- and 5-fold, then it's moderate. If it's less than 2, it's mild. And with our '99 guidance, we actually also have one that says there's not an inhibitor if the ratio is between 80 and 125 percent.

So this classification and what is potential use -- what I want to say is this has been used to guide in vivo studies. For example, if a drug is found to be a substrate of 3A, we have been recommending using the most potent one, and I think this has been commonly done. Again, it's ketoconazole or itraconazole. Most of the time we see ketoconazole as an inhibitor. However, if the result is positive and the extent of change is so that you may wonder whether safety data would support that or not, then you want to continue to study the less potent one to see what's the extent of change. So this has been used. Even we don't have a formal classification system in our review in our discussion with industry, this approach has been used.

Initially PhRMA has recommended that this system also be used in the labeling, although in the

eventual published paper, it only recommends that discussion with the regulatory agency on its use in the label.

But since the discussion, we have thought about this use in the labeling for inhibitor and substrates, and I will show two examples later on how this could be applied.

In our various discussions, there are concerns raised by individuals in the working group, individuals in scientific rounds where we have internal discussion and also with external experts like yourselves. Some of the concerns that inhibitors may modulate a lot of other pathways, other cytochrome P450 enzymes, other transporters. And if a compound was labeled as a potent inhibitor, you're expecting a large change with midazolam or some other substrates.

However, this potent inhibitor may affect other pathways and which may have opposing effect, may end up with no interaction. One example could be ritonavir which with alprazolam is a 3A substrate, but yet it may also affect the glucuronidation induction such that eventually after multiple doses, you don't see an effect. But most of the other cytochrome 3A substrates, you're seeing a large-fold change even after multiple dosing.

Similarly substrates are not just substrates of

one enzyme. Midazolam is a good example. It's a cytochrome P450 3A substrate. It's not a P-gp substrate. But a lot of other 3A substrates are also substrates of P-gp. So it's depending on how this interaction -- the classification may not precisely give us the output of what we would imagine based on the classification system.

Again, there are multiple drugs being prescribed and we have shown that elderly women, more than 50 percent, are taking 5 drugs at one time. If we label a drug as a moderate inhibitor and if this person is taking five moderate inhibitors, would that affect as potent inhibitors and we may not catch this if we only look at the potent inhibitors.

In order for the system to work, we need to classify drugs according to the system. With ketoconazole the data that I showed you, 16-fold change is only from one of the studies, and there are many studies in the literature, and the fold change ranges from 5 to 16. So depending on the study design, the dose, the dosing regimen, so we have to be very careful when we put the drugs -- to classify to the system. I think there are a lot of other concerns. And there are also genetic concerns on CYP3A, whether the same inhibition for CYP3A4 substrates versus the 3A5 substrates.

So with these concerns, we have several

discussions since PhRMA has the white paper. We have scientific rounds discussion within CDER. And we have talked about this at professional meetings and open forum at the American Association of Pharmaceutical Science meeting last year in Toronto and more recently at the American Society of Clinical Pharmacology and Therapeutics annual meeting. And Dr. Flockhart was on the panel and Dr. Vega in attendance also participated in that discussion.

I'd like to bring it up again with this committee to see what other factors we need to consider in implementing this. To facilitate our discussion, I'll have two cases that came from our NDA data but the data have been altered so that we can discuss publicly. Some of the labeling recommendations have also been changed since our first discussion based on the input from the scientific rounds discussion internally.

So there are two cases I'd like to talk about. First is the new molecular entity as a substrate. As I mentioned earlier, based on our good review practices, we need to ask three important questions. Are drug interactions evaluated? What are the data? And what's the clinical significance based on the exposure-response relationship? And how do we label these interactions?

We look at this chart. This compound is a substrate; pathways, major. And we will get an in vivo

with the most potent inhibitor. So if you look at CYP3A substrate -- and this is drug A. It's given with ketoconazole. That's the most potent inhibitor based on the classification system. AUCs increase 6-fold and Cmax 4-fold. And if you look at the other two which has been classified as moderate inhibitors based on the classification system, the AUC increased 4-fold and the Cmax about 3-fold.

For this drug and the particular clinical response that we're looking at, we thought Cmax was more appropriate. So we look at the Cmax. And ketoconazole is a 4-fold increase and erythromycin and verapamil about 3-fold.

There is exposure-response data looking at one of the important clinical responses, and there was some response relationship. We have not really modeled it, but if you look at the clinical database, initially the proposed clinical doses were 15, 30, and 60. And all of those three doses, the data do support that they are safe and effective. We proposed to approve 15 and 30 because of the drug interaction concern. The drug is a linear kinetic, so you can see that there are 4-fold exposure that we are comfortable with. When we approved 15 and 30, so you know if people are given 30, there's a 2-fold possibility change and it's still safe. If they're given

15, there's still a 4-fold increase in exposure that would still have data to support its safety.

So how do we label those interactions? The potential labeling language based on this data is not to take this drug with potent or strong 3A inhibitors because you could increase 4-fold or more, and that's outside our safety database.

What are the potent, strong inhibitors? And we have some list developed up to this point. We're still debating what information supporting to remain on the list or what other drugs that we need to include in this list. But these are some of them in the PhRMA paper, some of them based on our current labeling with ketoconazole and itraconazole, and so on.

We said we propose that we use lower doses with moderate inhibitors, which means give 15. And we do have data with 60, so you can increase up to 4-fold without any problem. And the moderate inhibitors so far showing a 3-fold increase in exposure. So they're still within the safety range.

What are the moderate 3A inhibitors? And based on some in the PhRMA paper some of our internal information, they could be erythromycin, verapamil, diltiazem, and so on.

The second case is new molecular entity as an

inhibitor. Again, we ask the three questions. The drug interaction is evaluated. What about the clinical significance of the substrates? Since now we're talking about the new molecular entity as a modulator, as an inhibitor of others -- the exposure-response information that we would like to have is for the other drugs, other co-administered drugs -- how do we label this? This is the case where it's an inhibitor. We want to study with more sensitive substrates.

The sponsor did follow this approach. So this is drug Y. The study with midazolam, the most sensitive 3A substrate. Here you show 6-fold increase in AUC, 3-fold in Cmax. Here we're going to use AUC as a parameter that we look at when we determine clinical significance.

For simvastatin, 8-fold, 5-fold increase in Cmax. Cisapride is 3-fold increase, 2-fold in Cmax. The drug is not an inhibitor for 1A2 and the other pathway, 2C9. The sponsor did the study and showed no interaction with theophylline or warfarin.

So based on the information with midazolam, 6-fold increase in AUC. If you look at this table, the drug appeared to be a potent or strong 3A inhibitor. So based on our understanding of the other substrates, the sensitive substrate or substrate with a narrow therapeutic index, which are 3A substrates, we look at some of the labeling

language in our existing where the strong inhibitors are contraindicated.

So we look at two cases. One is sensitive substrates. The drug is metabolized mainly by 3A, and the other one that was narrow therapeutic range. They're softly defined because of their QTc prolongation effect.

So here those are not underlined. We consider they're sensitive substrates: midazolam, triazolam, simvastatin, lovastatin, atorvastatin. These are some of the drugs that are named in our '99 guidance as suitable for study as sensitive substrates because of contribution of the 3A to the clearance.

And the ones that are underlined, some of them are not on the market anymore. Some of them are still under IND use. We do have pimozide. These are drugs that cause QTc prolongation and they're also major contributors for drugs withdrawn from the market in the last five years. So we're still compiling a list to see which are sensitive substrates, which are substrates with narrow therapeutic index. And drug A, the case one that I mentioned, may also make this list.

So how do we label this? Since this drug is a strong inhibitor, we think in the labeling we do want to say that the use of this drug is a strong 3A inhibitor. We actually say in the labeling. Currently we have not

consistently done so. A lot of strong inhibitors in the labeling -- we only said that it's an inhibitor. We do not mention anything about strong or moderate. So we thought if we say the use of drug B is a strong 3A inhibitor is contraindicated with some of the narrow therapeutic index drugs or sensitive substrates or the co-administration needs to be monitored such as midazolam or other drugs, sildenafil, budesonide -- for those substrates that we currently have in ketoconazole, itraconazole labeling, and we're still compiling the list. And this is what the working group is looking at. So if we have a strong inhibitor, what do we put in the labeling? This may facilitate this information to be used in the computer system that's used in the hospital.

I just want to mention some of the concerns that we discussed, these two cases. I have discussed these two cases internally in our scientific rounds and also in ASCPT meeting. In general, I think the feedback -- then you can comment later -- is this is an effective way to label an interaction by indicating that the drug, if it's an inhibitor, whether it's a strong inhibitor or moderate or mild or not an inhibitor. And when we approve a drug which is a sensitive substrate, that we know what drugs to put in the labeling to contraindicate or to put in precaution.

There are several concerns in that inhibitors may also affect other enzymes or transporters such as UGT or P-gp transporter.

I just want to talk very briefly on P-gp -- especially we have seen the report on clarithromycin and digoxin interaction in this April JAMA article -- before we go back to questions for the committee.

The P-gp based interactions. How important it is and how that affects our evaluation of drug interactions. We know this is an important interaction based on the various reports.

If we are going to evaluate a drug, whether it's an inhibitor or modulator of P-gp, knowing that there are a lot of inhibitors of 3A also inhibit P-gp, such as ketoconazole, initially we take comfort that any drug that's a 3A substrate, the sponsor will conduct a study with ketoconazole. So if it's a P-gp substrate, you might see some effect. So we may be covered in that area.

But what about as a inhibitor? This is the in vitro study showing that there's still some differentiation of inhibitors that inhibit both 3A and P-gp, but depending on the IC50 ratios, you can see the range from less than 1 to more than 120 where you can see here's the 3A inhibition effect much higher here compared to PSC833. This may help us to determine what can we use for in vitro system in the

evaluation of whether this drug is a P-gp substrate.

If we look in the literature, most of the studies evaluating P-gp substrate use fexofenadine and digoxin as a substrate. And some of the literature data or the first two examples are based on PDR labeling that ketoconazole and erythromycin -- its effect on fexofenadine which has minimal metabolism and yet it increased the AUC and Cmax.

With itraconazole is shown a similar effect.

With verapamil, this is a recent study that was just presented at the ASCPT meeting just a couple weeks ago, and this is Steve Hall's data from Indiana, showing that verapamil perhaps inhibited and induced P-gp. So depending on the time of administration, initially you might inhibit the P-gp transport. So you have higher levels on day 1 and day 10, but on day 38, the two interactions canceled out and you did not see a change in day 38. I'm interested in seeing more data coming out of this, but this is something that's of interest showing the P-gp effect on verapamil or other transporters.

On the other hand, we have seen also fexofenadine used to evaluate an induction effect by rifampin, which you see AUC ratio decreased, or St. John's wort. The data are a combination of various studies and they're a comparison of multiple dose versus single dose,

or this is with different preparations, showing that St. John's wort, given acutely, might have inhibited the P-gp, but given chronically as St. John's was given to treat depression, that it actually induced the P-gp.

What's interesting again, this was some data published by George Dresser and Richard Kim and presented again in the April meeting where grapefruit juice is an inhibitor of 3A and P-gp here is actually showing a decrease in fexofenadine levels. One of the possible mechanisms that it's inhibiting OATP, the organic anion transporter polypeptide, which is an intake transporter. So by inhibiting it, you reduce the absorption and therefore a reduction in the level. So this put in a question of how fexofenadine would be an effective P-gp substrate to study, if, as we can see more and more drugs may affect OATP, whether this is a still a suitable substrate to study.

The other one is digoxin that's often used by the sponsors in their study. In some of the literature data, these go back 18-20 years on quinidine and verapamil would increase some of the plasma levels. This may not be at steady state, but at day 7 or various days after treatment. I know this verapamil data is not 38-day treatment, so this is still an increase in the plasma concentration.

And recently with -- this is a Merck publication with this drug as shown, using digoxin to show that it has no effect on P-gp. Again, it's the substrate that's been used to study induction, and rifampin has shown a decrease in AUC and Cmax, St. John's wort also showing a decrease in plasma levels, and a grapefruit juice study showing that it's a small increase, a 9 percent increase.

I wanted to share with you some of our surveys. Right now we don't have a guidance that said every new molecular entity must be evaluated to see if they're a substrate or inhibitor, inducers of P-gp unlike the cytochrome P450. However, we're seeing a lot of digoxin data. You can see based on some of the surveys -- this was done in '96 and up to '97 -- that cimetidine and digoxin are the two most often studied drugs in drug interactions. Cimetidine was in the past because it was used as a general, nonspecific inhibitor, and digoxin mostly because the likelihood of co-administration as a narrow therapeutic drug. So the sponsors tend to study it. So we do have a lot of digoxin data, except our explanation of interactions may be different now. It may not be change in tissue binding distribution. Instead it may be the P-gp involvement.

So digoxin has continued to be studied, especially if a sponsor is developing cardio-renal

products, antiviral products, but not necessary in all therapeutic areas. So we have digoxin data even we don't have in vitro data. So my question later on is with the interplay of cytochrome P450 3A and P-gp, OATP, are we ready to recommend that P-gp as a standard approach or is it sufficient that this still continue to be studied because of the likelihood of co-administration. We do have a MAPP for our reviewers to see if P-gp is going to evaluated, what are the concerns that we need to look at when we evaluate in vitro data and in vivo data.

So our next steps -- that's what we're doing right now -- is to revise our guidance. This is the '99 guidance looking at drug metabolism and drug interaction. There are several issues that we would like to address in our addendum or the revision.

One is to look at the classification system and to talk about it in our guidance. The feedback we got from the PhRMA proposal, classification system, has been positive, although in the Toronto meeting, there were other suggestions of different systems, maybe just strong versus weak, just two instead of three. And this is further being deliberated in our working group.

We also need to generate the list of strong inhibitors and moderate inhibitors and looking at literature data very carefully to see where would they fit,

understanding the concerns of the interplay of the other metabolizing enzymes and P-gp.

We also want to say something about P-gp-based interaction. That's what we're doing right now.

We do have a cross-labeling manual of policy and procedures. We'd like to finalize it. Again, we have worked on half of the components of this manual where we look at CYP induction, inhibition, P-gp, and the phase II metabolizing enzymes, and we'd also like to finalize it.

So the questions for the panel based on my presentation. In addition to the three questions that were in the agenda, what we discussed at our internal meeting. What are the factors to consider in implementing the classification system for CYP3A inhibitors in the labeling now that you know what's our present thinking?

And do we need to define the sensitive substrates? Because we do need the list of the substrates where we could properly put it in the labeling so that when we're approving a strong inhibitor, we know what to place, what drugs to be put into precaution or maybe contraindication.

And if you agree with the classification system, should we now -- important to consider application of a classification system to inhibitors of other CYP enzymes. We have heard that the adverse events -- a lot of

them are related to antidepressants, calcium channel blockers. These are 2D6 substrates. Do we want to consider that and include that in the labeling so we can talk about strong inhibitors as the substrates?

What about inducers? We have informally indicated that rifampin is a strong inducer. Rifabutin, rifapentine are moderate based on our study design. When we talked to the sponsor, if rifampin induced the metabolism to such an extent that we have to contraindicate, then the next step is to study rifabutin to see if the alternate co-administration is proper. So we have done it informally. Is it important to put the classification system in the labeling to facilitate computer system in generating possible pairs or combinations of interaction?

What about transporter-based interaction? Let me give you a limited update on this. We probably can talk about, in subsequent meetings, whether we should recommend routine evaluation at this point based on what we know.

So I'll pause right here.

DR. VENITZ: Okay, thank you, Shiew-Mei.

Any questions about her presentation and/or comments in regards to those three questions?

DR. DERENDORF: Yes. You mentioned several times, rightfully so, that all interactions have to be seen

in the light of the response, that the exposure by itself really is not the clinical relevance, but it's what it does to the patient later on. But yet, in your classification system, you focus on exposure. You know, the weak, moderate, strong focuses on the AUC, independent of what it really means clinically. And I think there's an inconsistency.

Also, the language. A 4-fold increase in AUC -- to call that moderate, it may be not relevant, but I don't think you would ever call a 4-fold increase in dose a moderate dose increase. So this language I think becomes very important, how this is seen by people who are not that involved in the details.

DR. HUANG: Yes. On your first point, if I show you on our case 1, which is a substrate, and we've shown that there's a 4-fold increase with ketoconazole and then a 3-fold increase with the moderate. So based on that information, coupled with exposure response, where we feel that a 4-fold increase we're comfortable. I mean, more than 4-fold, we are not comfortable and that determined our language. So if you have a different data set where you say 2-fold increase I'm not comfortable, then we would have contraindicated the moderate inhibitors as well. Again, it still comes back to what exposure-response data we have, and based on the information we have, we're only