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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE
CLINICAL PHARMACOLOGY SUBCOMMITTEE

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

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A T T E N D E E S:

Wednesday, October 18, 2006
Members- voting

Meryl H. Karol, Ph.D.
Jurgen Venitz, M.D., Ph.D.

Special Government Employees (SGE)-non voting

Jeffrey Barrett, Ph.D. FCP
Edmond V. Capparelli, Pharm.D
David Z. D'Argenio, Ph.D
Marie Davidian, Ph.D
Kathleen Giacomini, Ph.D.

William J. Jusko, Ph.D

Howard L. McLeod, Pharm. D.
Joanne Mortimer, M.D.

Mary V. Relling, Pharm.D.

Paul Watkins, MD

FDA (CDER) Participants- non voting

Shiew-Mei Huang, Ph.D.
Lawrence Lesko, Ph.D.
Richard Pazdur, M.D.

Atiqur Rahman, Ph.D.
Sally Yasuda, Pharm.D.

Guest Speakers- non voting
Matthew Goetz, M.D.
David Greenblatt, M.D.
Mitchell Taub, Ph.D.

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AFTERNOON SESSION

Topic 2: Evaluation of transporter-based drug interactions

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Mitch Taub, Ph.D.
Boehringer Ingelheim Pharmaceuticals

Clinical Significant Transporter-Based Interactions

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David Greenblatt, M.D.
Tufts University

Clinical Significant Interactions of OATP1B1 and Their Transporter-Based Interactions
Kathleen Giacomini, Ph.D
University of California, San Francisco

Committee Discussion and Questions

Adjournment

P R O C E E D I N G S

October 18, 2006

CALL TO ORDER

CHAIRMAN VENITZ: Can everybody take their seats, please?

Good morning, everyone, and welcome to the Clinical Pharmacology Subcommittee Meeting. My name is Jurgen Venitz, and I'm chairing this committee for the next day and

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a half.

I'd like to begin our proceedings by going around the table and have everyone, including the invited guests and the FDA staff, to introduce themselves. And maybe we start with Atigur Rahman.

DR. RAHMAN: I am Atigur Rahman, Director of the Division of Clinical Pharmacology V in the Office of Chemical Pharmacology.

DR. HUANG: Shiew-Mei Huang, Deputy Director for Science, Office of Clinical Pharmacology.

DR. LESKO: I'm Larry Lesko, Director of the Office of Clinical Pharmacology.
DR. PAZDUR: I am Richard Pazdur, Office Director, Office of Oncology Drug Products.
DR. YASUDA: I'm Sally Yasuda, Senior Reviewer in the Office of Clinical Pharmacology.
DR. JUSKO: I'm William Jusko, a committee member from the University at Buffalo.
DR. CAPPARELLI: Edmund Capparelli from the University of California, San Diego.
DR. DAVIDIAN: Marie Davidian from the North Carolina State University.

CHAIRMAN VENITZ: Jurgen Venitz, Clinical Pharmacologist, Virginia Commonwealth University.
DR. PHAN: Mimi Phan, designated federal officer.
DR. KAROL: Meryl Karol, Professor Emeritus from the University of Pittsburgh.
DR. BARRETT: Jeff Barrett, the University of Pennsylvania and the Children's Hospital, Philadelphia.
DR. GIACOMINI: I'm Kathy Giacomini, the University of California at San Francisco.
DR. MCLEOD: Howard McLeod, University of North Carolina at Chapel Hill.
DR. MORTIMER: Joanne Mortimer, University of California, San Diego.
DR. D'ARGENIO: David D'Argenio, University of Southern California.
DR. RELLING: Mary Relling, St. Jude Children's Research Hospital, Memphis.
DR. WATKINS: Paul Watkins, University of North Carolina at Chapel Hill.

CONFLICT OF INTEREST STATEMENT

CHAIRMAN VENITZ: Thank you, everyone. As you can tell by looking at the agenda, we've got a pretty long

morning ahead of us, so let's get started by reading the conflict of interest statement. Mimi.
DR. PHAN: Good morning. The Conflict of Interest for Meeting of Clinical Pharmacology Subcommittee Meeting of the Advisory Committee for Pharmaceutical Science.
Today is October 18, 2006. This is the conflict of interest for the Clinical Pharmacology subcommittee update and introduction.
The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.
This meeting is being held by the Center for Drug Evaluation and Research. The Clinical Pharmacology Subcommittee Meeting of the Advisory Committee for Pharmaceutical Science will hear an update on previous Clinical Pharmacology Subcommittee Meeting recommendations and will receive an introduction to the three new topics of this meeting.
Unlike issues before a committee, in which a particular product is discussed, the issue of broader applicability, such as the topic of today's meeting involves

many industrial sponsor and academic institutions.

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

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

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

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

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

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

In the event that the discussion involves any other product or a firm that is 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 interests of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

CHAIRMAN VENITZ: Thank you, Mimi.

UPDATE ON PREVIOUS CPSC MEETING RECOMMENDATIONS

INTRODUCTION TO THE MEETING TOPICS

Our first speaker is going to be Dr. Larry Lesko, who is going to summarize the results from the previous meeting and give us an introduction of the three topics that we're going to discuss for the next day and a half. Larry.

DR. LESKO: Moving that mouse is like ice skates.

Good morning, and thanks, Jurgen.

I'm probably going to do more introduction of the topic today than reviewing some of our past meetings, mainly because I notice that I cut myself to 15 minutes instead of the usual 30 minutes on the agenda.

But that's okay, because I think today and tomorrow, we have some very important topics to discuss, and I was sort of reflecting on actually the last four years of this Committee, and we met for the first time to talk about pharmacogenetics in 2003. And we had a meeting in 2004, 2005 and 2006, all of which dealt with pharmacogenetics on one hand or another.

And I felt compelled to compliment and congratulate the committee on the work and the deliberations that they've

done over the last three or four years, because we've heard a lot about personalized medicine from Secretary Leavitt, from our Acting Commissioner, Dr. Von Eschenbach, from Dr. Woodcock, and if you Google any one of those three, you'll find that many of their recent presentations have highlighted the importance of personalized medicine as an FDA priority.

This morning I was getting coffee over in the Parklawn Cafeteria, and I noticed the guy next to me getting coffee, and I said, oh, that's the Acting Commissioner, and I said, Andy, by the way, we're talking about Tamoxifen today and 2D6 and its influence on outcome, and he says, great; go for it.

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Not that that should influence your decision and discussions today.

But some of the things you don't know about our committee meetings, and it's what happens behind the scenes a bit, and I was also thinking about last year's meeting where we discussed Warfarin and 2C9B4C1 and its influence on dosing.

And it was amazing over the past year what that meeting has stimulated. It's stimulated studies to be done in terms of clinical outcome. It's stimulated tests to be developed by diagnostic companies. It's stimulated databases to be formed, and hopefully it's stimulated the utilization of tests in clinical practice, for, ultimately, the reason we're discussing all these topics is for the benefit of patients.

Today, we're going to start off with a discussion of the efficacy and pharmacogenetics of Tamoxifen.

Tamoxifen is an old drug, as everyone knows. It's a drug of high importance for patients with breast cancer, in particular patients with post-menopausal breast cancer where choices of treatments are available to them.

I want to emphasize that we're talking about efficacy

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pharmacogenetics. This is the first time in the four years we've been talking about pharmacogenetics that we focused on efficacy.

We have, in the past, focused on safety for 6-mercaptopurine, irinotecan, and Warfarin, and we have a drug that's well known. We've discovered a lot more about it recently, as you'll hear today.

We have a gene, 2D6, which is probably the most studied and the most well understood gene of all the cytochrome enzymes.

And finally, we do have at least one approved test for 2D6 and possibly more.

Now, one of the ways we've tried to frame our discussion of pharmacogenetics and it gets around to one-size-fits-all, and I selected an article that's a little bit dated now from Lazereaux [ph.] where they pointed out that drugs are effective, ineffective, or, in some cases, cause serious adverse events, as I've shown on that pie chart.

If I was a little quicker in getting my slides

together, I might have picked the article that appeared in JAMA this week that basically illustrated the same thing,

with the old work horses, as they said, causing most of the adverse events in the country, including Warfarin that we discussed at the last meeting.

But I think this kind of data has come out repeatedly over the last 10 years, and it's somewhat stimulated I think industry, regulatory agencies around the world, physicians, and patients to want to have a better understanding of which patients should receive which drugs; and then once that decision is made clinically, to understand what patient should receive which dose.

In the past we talked about primarily dosing. We talked about 6MP, reducing the dose; Irinotecan reducing the dose; and Warfarin, reducing the dose in the appropriate individuals with gene variance.

Today, we're going to be talking about something a little bit different. It's whether to give the drug or not, and it's not a dosing question, and you'll hear a lot more about that.

Critical to understanding pharmacogenetics in the context we've been discussing it is the concept of exposure. And this is really the first principle of clinical pharmacology and underpins the selection of both drugs and

doses.

We know from history that dose is a poor predictor of response, and mainly because there's a huge variability in dose exposure. For Warfarin, it was at least 30-fold; for 6-mercaptopurine, it was a hundred-fold.

So what we try to do about that is individualize dose based on age, sex, body weight, drug interactions, renal function, liver function, and we all know those are rather crude estimates of changes in exposure based on pharmacogenetics.

Nevertheless, they're the key to labeling. In many of our labels if you look at dosing adjustments, the initial choice of a drug and the dosing regimen is determined by estimating the exposure and PK properties of the drug, usually from special population studies that companies do. So

changes in exposure drive dosing.

In the case of Tamoxifen, changes in exposure in certain subsets of the population drives exposure in the sense that the exposure isn't there, so that individuals like this may want to go through some other choices.

If the situation leads to higher or lower exposures,

product labels recommend dose reductions. And the interesting thing to me over the past three or four years is that we found genetic variance in cytochrome enzymes can result in anywhere from a ten- to a hundred-fold difference in exposure compared to non-genetic factors, and yet we worried about, to a large degree non-genetic factors much more than we worry about genetic factors, but perhaps that's

changing with technology and education.

Now, this being the fourth time we've come before the committee in terms of pharmacogenetics, I thought it would be good to remind about the framework that we've used to decide which drugs we've talked about and how we think about re-labeling.

These are sort of the criteria or framework. We need to have a clear definition of phenotype. When we talked about irinotecan, it was very clear we were talking about grade four neutropenia [ph.]. That was the phenotype that we were trying to reduce the risk of.

The phenotype is serious and relatively common, and in each of the drugs, we had relatively common issues, even with 6MP, where one in 300, which is fairly high, had problems with phenotype.

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We looked for a strong genotype-phenotype relationship. We looked for studies with sufficient sample size to identify the relevant variance, although not all of them.

And one of the most important things we've tried to do is look at plausible mechanistic or biological hypotheses to explain the genotype and phenotype relationship.

And the reason we looked for that mechanism is because the evidence of the association is usually not from prospective randomized control trials.

So, by and large, in pharmacogenetics, we had to rely upon -- and I'm not saying this is bad because good observational studies are good evidence in my opinion, but we've relied upon retrospective observational, case-controlled studies. The advantage of these is they do reflect data from real world practice, usually from studies that involve a standard of care.

We do look at the analytical validation of the genotype, and we try to identify potential bias introduced by unmeasured factors, which is characteristic of observational studies.

But most importantly, in all the drugs we've brought

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before the Committee, we tried to look for consistency in a direction of change across studies and across demographics.

And we've seen that with 6-mercaptopurine. We've seen it with irinotecan. We've seen it with Warfarin, where studies come worldwide, all pointing in the same direction. And we've seen it now and are beginning to see it with Tamoxifen as well. So this is how we decide that it's the right time to talk about pharmacogenetics and a drug.

You've seen this slide before. Almost every time I speak before the Committee, I present it to remind that we have a regulatory statute, 21 CFR 21.7. Some of that indicates that labeling with the tests is entirely appropriate based on the evidence at hand.

This is a summary of our prior meetings, where I've listed the drug, the polymorphic enzyme, the dates of the Committee, and action taken, and the consequence of the genotype in terms of toxicity, and again reminding that today we're going to be talking about risk and lack of

efficacy.

Now, I want to update a little bit on the drug we talked about last year, because, as you can see, I've indicated the label as being updated.

Well, the label has been updated. If you remember last year, the Committee voted almost unanimously to recommend updating the Warfarin label with the 2C9 and B4 information.

And on October 6th, 2006, we did update the label for Warfarin, and it's a black box warning to bring to the attention of prescribers and patients the serious bleeding risks that occur with Warfarin.

You'll also note that in the black box, there's no pharmacogenetic information, and you can read the announcement of the black box warning on the Web sites I've listed below.

And this was an action that was in progress at the time. We talked about adding pharmacogenetics, and this came out at a time when we are still negotiating the label language with the sponsor and with the medical division.

So where we are at with the 2C9B4 critical information is we are at the final stage of negotiating label language to include the genetic information on the label, as recommended by this Committee a year ago.

Our timetable to do that is hopefully within the next three months. There's obviously factors that influence that

timetable, so that's why I say we hope.

As I mentioned, numerous clinical trials have been planned or launched to validate dosing algorithms and study clinical outcomes.

I noted in my copy of Clinical Pharmacology and Therapeutics that came in the mail this week, there was another study pointing out that these two enzymes -- or excuse me the 2C9 and B-COR -- along with some demographic factors -- account for 60 percent of the variability of dose response in an Asian population.

So I think that validates in many ways what we believed to be true a year ago.

Several diagnostic companies have launched 2C9 and B4 tests. They are not all FDA-approved. I'm not sure we have any FDA-approved tests for this combination, but certainly there's a lot of activity going on.

The other thing that's occurred in the case of Warfarin and basically all the drugs we've talked about in pharmacogenetics is to try to think about how we can design an effective risk communications strategy for pharmacogenetics.

We all know it's relatively new. We all know the

challenge of changing clinical practice.

We're trying to find a way internally by discussions to figure out what's the most effective way for communicating issue-specific risks to patients and health care providers, whether the issue-specific thing is a drug or a genetic factor.

So we've been working with various offices within FDA to explore focused risk communication strategies, and one of the examples of these strategies, which is not a done deal by any means, is to think about the possibility of information sheets for health care providers that contain information on pharmacogenetics that are useful to both the provider and the patient.

This is a work in progress. I'm anticipating that we may want to bring this in front of the Committee to discuss one of these risk communications strategies, given the background that you have in pharmacogenetics, and we'll put that in the parking lot for a possible future topic.

So that's topic number one.

If you look at your agenda, you'll see that we're going to really provide you the background in terms of the mechanistic aspects of Tamoxifen pharmacogenetics and

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clinical outcome data, and then hopefully we'll move onto to our discussion.

The second topic for today will be this afternoon. That's drug transporter interactions.

And this is sort of motivated by the fact that really over the last 10 years, we've developed the ability to predict drug-drug interactions at the CYP [ph.] level as a risk management strategy. And, of course, that has a huge impact on labeling.

This has facilitated drug development and regulatory decision making. We've had guidances out for the industry for quite a long time.

In the footnote, I've indicated a new version of our drug interaction guidance that was just published about a month ago, and the Web site.

And one of the open questions that we wanted to discuss within the draft guidance and within the Committee discussion this afternoon is looking at the paradigm for enzymes.

NME is an inhibitor of substrate for CYP enzymes. We know that. In the old days, with CYP enzymes, we decided that an in vivo study is needed enough for labeling

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purposes, and if a study is necessary what substrate should be given.

So this is what we've all worked out with the cytochrome enzymes, and that's contained within the guidance as an update.

Transporters is a different story, and that's why we're bringing it to the Committee. Knowledge of our transporters in major organs and tissues and their role has dramatically increased.

It presents challenges for doing molecular entity development, and the questions are similar to where we were with enzymes years ago: which transporters are important and should be studied? Do transporter and enzyme interactions coexist? Can drugs interact through multiple transporters? Can in vitro studies obviate the need for in vivo studies as we currently do with the cytochrome enzymes and reduce some in vivo studies? What are the best

transporter substrate inhibitors?

What's interesting in the context of this topic is that several previously unexplained clinically important drug-drug interactions, which were surprises, if you think mechanistically on the CYP enzyme basis, can now be

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explained by transporter mechanisms. And I think the context is do we wait to be surprised and can we predict those better with in vitro methodologies and in vivo studies.

Finally, topic number three is one that's been before the Committee in the past. It's drug disease placebo models.

And as a little background here, you may not remember this, but back in 2003, we released a concept paper that we called the end of phase 2A, and we published that on October 16, 2003.

Interestingly, the concept paper is still on our Web site that I've indicated there. There was a concept paper and we're anticipating developing that as a full guidance in the upcoming 12 months.

Anyway, back in 2003, we discussed a two-year pilot project with up to 24 end of phase 2A meetings between sponsors and FDA. We asked the Committee what they thought about the value of these meetings, and the kind of things that would be discussed.

And in the concept paper and before the Committee, we talked about what a data package and analysis would look

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like for an end of phase 2A meeting. And we talked about exposure response analysis for efficacy and safety, putting that into the package insert.

We talked about modeling and simulation of clinical trials as a way to improve the productivity of drug development. And we finally talked about the analysis of disease progression as opposed to symptomatic treatment of disease.

Now, we've had since then about 10 or 12 end of phase 2A meetings. We could have had a lot more had it not been for resource constraints. We actually have slowed down on our 2A meeting requests until we get more resources.

But what they did do while we were having them up until probably July of this year is motivated for us and companies the development of drug disease models, and here some different diseases.

These models are not complete. They're in the process of development. Some have been used in 2A meetings but they've proved to be extremely valuable.

So what you're going to hear is a session of our meeting on disease progression models. As everyone knows, many of our traditional drug approvals are based on either

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partial or full relief of disease symptoms. But we're beginning to find as we have a better understanding of disease pathophysiology that both new drugs and old drugs can modify disease processes that cause the clinical phenotypes.

Sometimes we don't know the mechanisms at all. Sometimes we have a semi-understanding of the mechanisms.

But the question that will be on the table is can we look at slowing and halting disease progression using disease models.

So what you'll hear is a section that deals with the question how can disease models be built and data analyzed to document evidence of effect on disease progression.

It will be a huge breakthrough for many chronic diseases, such as Alzheimer's and Parkinson's and others, if we can, in fact, show that and use that as an evidence basis for improvement.

To do that is complex. We need placebo-response data. We need different time points of measuring clinical outcome than we're used to. We need different mathematical and statistical approaches to analyze longitudinal changes in biomarkers of clinical outcomes, but you're going to see the

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progress that we're making and some of the questions that the group will have tomorrow.

And we'll be using a prototype for the purposes of discussion. We're going to be presenting several models, but in particular the Parkinson's disease model that we've been working on, which has been a joint project of pharm and biostatistics, and the question that will be on the table as you hear that model tomorrow is how can one detect and analyze changes in the typical, clinical efficacy outcome, which is the NPDRS telesmart [ph.], as evidence of slowing or halting disease progression.

The current way of analyzing that kind of data doesn't do the job. What you'll hear tomorrow is the new ways of analysis that may do the job, and we anticipate that this topic, as it's discussed tomorrow, will be a preview of another advisory committee that we'll be having next spring with the medical group that deals with Parkinson drugs and neuropharmacology, so this will be a good dry run, an Off Broadway show, if you will.

That's my introduction, but before I leave the podium, I want to mention one other thing that's new and I don't want you to be confused by it.

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It has nothing to do with the topics we're going to be discussing today, but it does have to do with the voting that we conduct at this meeting.

It has come to our attention that this being the Subcommittee, it's called Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Sciences. It is not officially, if I'm using the right term, authorized to vote. In other words, the vote that is taken -- am I correct, Mimi -- is not an official vote.

We learned this after our last advisory committee, and we put in a request to take this committee to the full advisory committee status, and that request is under deliberation for today's meeting. Unfortunately, it didn't happen.

On the other hand, we will be asking you to vote I think from Dr. Venitz, when he gets to the topic. And I

think what's important here is not whether the vote is official or not. What's important is the input we get from the committee, and I hope that -- you keep that in mind as we go around the table and signal what your interest is, and the questions that we're going to pose to you.

Thanks.

CHAIRMAN VENITZ: Thank you, Larry. Any quick questions by the Committee?

As Larry indicated, I was just informed half an hour ago that we cannot officially vote, but we will vote. It just won't be recorded in the minutes.

Okay. Any questions for Larry? Thank you, Larry.

Then before we start with our first topic, Mimi is going to give us another COI update.

DR. PHAN: And official votes. This is the conflict of interest for the first topic, the Tamoxifen, which is Scientific and Clinical Evidence Related to Cytochrome P2D6 Polymorophisms and Response to Tamoxifen Therapy.

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

This meeting is being held by the Center for Drug Evaluation and Research. The Clinical Pharmacology Subcommittee Meeting of the Advisory Committee for Pharmaceutical Science will discuss and provide comments on the first new topic, the scope and strength of evidence to support the inclusion of pharmacogenetic information at Cytochrome P2D6 Polymorphism in the revision of the label

for Tamoxifen to improve the benefits/risks of the drug.

In accordance with 18 USC 208 B.3, full waivers have been granted for the following participants: Dr. Edmund Capparelli for unrelated data and safety monitoring for activities for a competitor which he received less than $10,001 per year; Dr. Kathleen Giacomini for her spouse as unrelated speaker bureau activity for a competitor in which they received less than $10,001 per year; Dr. Paul Watkins for unrelated consulting for a competitor which he has not consulted or received any fees in the last 12 months.

Waivers documents are available at FDA's docket Web site. Specific instruction as to how to access the Web page are available outside today's meeting room at the FDA information table.

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

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

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

CHAIRMAN VENITZ: Thank you, Mimi. And that gets us into our first topic, the Scientific and Clinical Evidence Related to CYP2D6 Polymorphism and Response to Tamoxifen Therapy.

Our first speaker is Dr. Pazdur. He is the Director of the Office of Oncology Drug Products, and he's going to review the importance of pharmacogenetics in oncology.

SCIENTIFIC AND CLINICAL EVIDENCE RELATED TO CYP2D6 POLYMORPHISM AND RESPONSE TO TAMOXIFEN THERAPY

DR. PAZDUR: Thank you very much for the introduction.

It's kind of interesting that we're talking about Tamoxifen. This was probably one of the first drugs I used as a medical oncologist, and to show my age, this was an experimental drug, an investigational drug, when I first met it as a beginning medical oncologist in the 1970s.

And at that time, there was a great deal of debate as far as what should be the dose of Tamoxifen that should be

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used. Should it be 10 milligrams bid? 20 milligrams bid? 30 milligrams bid?

And it's interesting now, you know, 40 years later almost, we're beginning to understand really kind of the scientific principles that govern or make up or, i.e. dose selection of the drug.

I wanted to begin some of the topics that I'm going to discuss, and some of this will be a duplication of what Larry has introduced, and I'll try to minimize when there is some duplication of Larry's previously presented material.

But integrating pharmacogenetics into therapeutics is really an agency-wide initiative. It's part of the critical pathway program that many of you have heard about. In addition to that, each in the divisions I think is committed to really look at the available information, both on existing drugs that have been approved and also on new molecular entities that can come -- that do come into the various offices to try to really better define populations that are more likely to benefit or be it more likely be exposed to certain toxicities.

And Janet Woodcock, who is the Deputy Commissioner, or one of the Deputy Commissioners, mentioned this in one of

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our publications. For the first time, physicians will have a chance to treat people as individuals, not as members of a "population."

We will also be able to treat patients based on the actual biology of the disease, not just according to their symptoms.

I think in oncology this is particularly a very important area, because it's clear to us that what we call a certain disease, such as breast cancer or colon cancer or lung cancer, probably are many, many diseases. Breast cancer probably has many manifestations. Some of these manifestations on the genetic level may be related to other tumors; and, hence, our adherence just to looking at a histological diagnosis may be somewhat outdated and will probably, with time, need to be revised and how we study

patients' oncology will also be -- have to undergo certain scrutiny.

I think it's important that we keep an open mind or that the disease itself and our definition of disease may change, but those that the agency interacts with also may have to basically change. We have traditionally had our major interactions with the pharmaceutical industry.

However, the pharmaceutical industry obviously is not geared toward disease redefinition. They're more into drug development.

And I think one of the areas that this whole pharmacogenomics area is bringing up, especially in oncology, is how to we better redefine disease, and this will really cause a more -- an interaction between multiple stakeholders, not only the FDA and industry and regulated industry, but also with academics and other stakeholders, such as patient groups and basic scientists.

Larry had already mentioned and shown this slide. I just want to reiterate the importance of product labeling.

Product labeling is something different to many people, and has many, many implications here. It is one of our chief ways of communicating with the outside world, the FDA's way of communicating to our stakeholders.

Secondly, it's a patient information guide.

Thirdly, it's a physicians' information guide.

And one of the areas that we in the FDA take quite of a course is that it is a licensing agreement between the Federal Government and the holder of the license for a particular indication.

It is where many of the advertising claims are derived; and, hence, the review staff takes a look at the product label with a great deal of scrutiny, looking at exactly what claims are being made here; are comparative claims being made to another drug which would require a different level of evidence, for example.

So it's a very complicated area, because I think product labeling means something different to different stakeholders here.

Nevertheless, we want to make sure that there is a scientific basis and a strong scientific basis for what goes into product labeling. And that may change, okay, depending on what type of information we're talking about.

Generally, we have been used to, as far as the review staff, of looking at submissions from pharmaceutical companies where we do randomized trials these are prospective trials -- done as supplements or for new indications of the drug or for the initial new indication of the drug.

But here, especially in the past examples that we have made in oncology, we're looking at older drugs; for example, the drug today, Tamoxifen; irinotecan that we discussed at

previous Committee meetings; and also 6MP. So there probably has to be an acceptance of probably a different level of -- or I should say a different type of information

that review staff will have to look at and have comfort with in really looking at product labels.

Our eventual goals is, is the information going to be of benefit to the treating physician and the patient that eventually receives that medication.

Today, I'd just like to touch on really four, briefly four, areas: Why do we need to optimize benefit and risk in cancer therapy? How can pharmacogenomics or pharmacogenetics help to optimize the benefit-risk in oncology? What have we done so far in oncology? And how can we promote individualized benefit in oncology treatment?

I think it's obvious for most people in the room that our medical oncologists or have a familiarity with oncology is that there is really -- if any subspecialty had the need to optimize the risk-benefit relationship, it is in the area of oncology.

We have marginal efficacy, and serious and life threatening toxicities.

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For the most part, the reasons why oncology drugs do not get approved in the United States or by other regulatory authorities is the efficacy question. It's efficacy, efficacy, efficacy.

The toxicities, which are serious and life threatening, as a discipline, we have generally accepted a high degree of toxicity, and we have framed this in the context that well, this is a serious life threatening disease, so patients should or may experience greater toxicities.

I'd like to question that, though; okay? And I think we should question it always, because I'm not quite sure if we have an ethical mandate to say that people with life threatening diseases should experience life threatening toxicities or have "the right to experience" these life threatening toxicities.

And I think if you really take a look at the field of oncology, and here I'm going back to the 1960s, the reason why we've accepted life threatening toxicities and a higher degree of toxicities is an historical reason. If you take a look at the older drugs, such as the nitrosureas or nitrogen mustard, we felt that basically we didn't know how

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to give these drugs. We didn't know what the correct dose is, and perhaps more is better, so we really didn't have a good idea of what the dose of the drug is.

But here again, I want to question and leave in your mind that really serious toxicities, although we in oncology have accepted serious toxicities and our risk-benefit relationship is obviously different from other therapeutic areas, that is always open to some debate, and we really as a discipline need to take a closer look at trying to minimize the toxicities to these patients.

Well, how can pharmacogenomics or genetics help to optimize this risk-benefit in oncology?

Well, various reasons, and I don't probably list them all, but there are four here. We could have candidate drug

selection based on genetic biomarkers and have a more thorough understanding perhaps of how our drugs work.

We can use PG relationships to develop dose concentration response relationships more accurately, and Larry already commented on the importance of this critical hallmark of the genomics of the dose response relationship.

Most -- well, I think one of the areas that are most important is patient selection in clinical trials, and I

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mean rational selection of patients in clinical trials.

As you all are aware, over the past five years, there's been a great ballyhoo of targeted therapies in medical oncology. And I assert to you unless we can clinically identify with appropriate tests which patients are more likely to benefit from a particular therapy, this whole concept of targeted therapy is not a reality. It is merely a myth of unless one is able to to really suggest and utilize this in a really I should say suggest -- but utilize a marker to identify the population either more likely to respond to a particular therapy or at greater risk for a toxicity.

And as we've seen before in our earlier discussions with this Committee, we can use PG relationships to basically select doses for various sub-populations to try to modify the toxicity or, in the case of Tamoxifen, perhaps to enhance its efficacy.

The other question I wanted to pose to you is how can pharmacogenomics help to optimize the benefit-risk in oncology?

Obviously, we can provide evidence for effectiveness and safety in the drug label, if you tailor drugs for a

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specific population, as I mentioned before, and recommend monitoring for safety in a particular sub-population

What have we done so far in the field of oncology? This is a list of drugs and biologics that have been approved in oncology for specific indications. Please note that the sub-populations have been identified during the development of their drug and may include, for example, the Philadelphia Chromosome Positive Population Gleevic, the unique receptor for Herceptin, the epithelial growth factor for both Erbitux and Panitumumab that was recently approved, and Rituxan in a specific population

Of interest all of these specific populations were pre-specified in the entry criteria for the populations that were to be studied at the very introduction of the drug into the clinical trial, and I think that this has ramifications not only for its clinical usage, but also for reimbursement purposes.

Many of these have, although they have been included in how we use the drugs, many people are questioning at that time because some of these drugs have not been adequately studied in marker negative populations; specifically, does Erbitux only work in EGFR receptor positive patients or is

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there activity in EGFR negative populations.

Unfortunately, when the drug was studied, the drug was

only utilized in patients for only really entered that had EGFR positive tumors.

What have we done in oncology so far? Well, let's take a look at where we looked at dose modification for several genotypes. And these are drugs that were also discussed by this Committee, one a pediatric drug for the treatment of ALL, 6-mercaptopurine, and the other drug irinotecan for the treatment of colorectal carcinoma, again looking at pharmacogenomic and pharmacogenetic issues with dose modifications of these drugs.

It's interesting with both of these drugs and I kind of question my colleagues that are out on the field, although we put this information in the product label, how much of it is utilized by the practicing physician, and it's quite variable; okay?

And I think one of our goals really for medical oncology as a discipline is willing to try after the drug is approved to change clinical practice and that is primarily done I think by implementing these testing procedures in prospective clinical trials that are done either

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commercially or in conjunction with the NCI.

The product label can only do so much. And here, again, because people have a great deal of familiarity, physicians have a great deal of familiarity with the two drugs and how to use them in sub-populations, I think there has been some reluctance in the universal adoption of these.

Here again, these are old drugs. These are not new drugs and to change and to teach kind of an old dog new tricks is sometimes very difficult.

Well, what do we need to do for personalized medicine in oncology treatment?

Listed here are just some of the areas that I think are somewhat obvious -- develop potential targets and biomarkers. We have a relationship with our sister center, the Center for Devices and Radiology for co-development of drugs and tests and an upcoming guidance on that as well as several working groups, and meeting with them when it comes to a specific application.

We could take a look at personalized medicine in the diagnosis of staging to help us identify patients that are more likely to respond and really to communicate to the

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practicing physician and patientd and other stakeholders the pharmacogenomic and genetic information in package inserts.

Well, lastly, I'd like to end with a comment that Dr. Von Eschenbach mentioned that we are discovering so much about disease, such as cancer, at the molecular level. And this was in response of how the FDA would help quickly and identify targeted therapies to sub-populations.

I think this is a great deal of interest to the review division, but here, again, the information and the discussion here should center on what is actually known about these sub-populations and the testing procedures that are done, and then how would this impact the practicing physician and the patients that are ultimately being

treated. Thank you.
CHAIRMAN VENITZ: Thank you very much.
Any questions by any of the Committee members?
Let me ask you a follow-up question just to make sure that I get the gist of what you were trying to discuss.
You mentioned that the labeling itself doesn't change practice?
DR. PADZUR: Well, no, I can't comment. It may change practice; okay? But in many cases, you know, it's hard to

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make universal suggestions.
In areas where the drug has been out for a long time, such as 6MP, such as irinotecan that's been out for more than a decade, yes, we can change the label. We can communicate that, but many people have ingrained treatment -- I mean ingrained practice as to how they treat patients.

So it's really I think one of the motives that we would have and really to change practice is really to work with the NCI and try to promote the incorporation of these tests in prospective ongoing trials, because that's how most people change their practice: they see that the clinical trials are using a certain test and then would adapt them into a new clinical site.
CHAIRMAN VENITZ: That was my point, so you --
DR.PAZDUR: Okay.
CHAIRMAN VENITZ: -- so you think that the prospective clinical trial is really would change the --
DR. PAZDUR: Well, I think the fact that they are going to be used -- you know, I'm not saying that that would be mandated necessarily to change the labeling, however. But there's a difference between what's changing the

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labeling and what changes actual clinical practice. I think, you know, anybody that practices medicine, I can' see that people when we change the 6MP label that, you know, the whole treating community is going to just rush out to read that product label. You know, so there has to be alternative ways of communicating this, and we have tried to do that when we changed the product label by sending e-mails out to professional organizations, by publishing in cancer journals different changes in product label, et cetera.
CHAIRMAN VENITZ: And I agree with you. I just wanted to point out to the Committee our recommendation is obviously regarding the labeling language?
DR. PAZDUR: Correct.
CHAIRMAN VENITZ: The practices that might or might not change is subject to other things, such as prospective clinical trials, reimbursement rules and what have you.
DR. PAZDUR: Correct.
CHAIRMAN VENITZ: Any other questions?
DR. BARRETT: Along the same topic, you mentioned about the reluctance regarding some of the historical agents in which the pharmacogenetics have been part of the label, and you didn't mention utilization.

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I was wondering do you have access to quantitative

data that specifically addresses utilization. I know particularly with some of those agents you -- many hospitals are putting those kinds of things in place or at least on the in-patient side, 'cause some of the data may be available.

DR. PAZDUR: No, I don't have that information.

CHAIRMAN VENITZ: Any further questions? Thank you, again, Dr. Pazdur.

Then our next speaker and the person that is I think going to give us the framework for our discussion later on today is Dr. Atiqur Rahman. He's the Director of the Division of Clinical Pharmacology V, and he's going to talk about Tamoxifen Pharmacogenetics: The FDA Perspective.

Atiqur.

TAMOXIFEN PHARMACOGENETICS: THE FDA PERSPECTIVE.

DR. RAHMAN: Good morning. I'm Atiqur Rahman, Director of Clinical Pharmacology V.

My objective today is to present the FDA perspective on the pharmacogenetics of Tamoxifen.

I will give you an overview of the scientific and the clinical evidence that relates to CYP2D6 Polymorphism with

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the clinical outcome for Tamoxifen therapy in the adjuvant setting for breast cancer treatment.

This year in the United States approximately 250,000 women and men will be detected with breast cancer, and approximately 41,000 will die from this disease. This estimate does not include 62,000 patients will be diagnosed with Ductal Carcinoma in situ of the breast.

Breast cancer is the highest form of cancer in the female population.

Although the lifetime probability of developing cancer is higher for men, because of the relatively early age of onset of breast cancer, women have a slightly higher probability of developing cancer before the age of 60.

There is a notable improvement over time in the relative five-year survival rate for breast cancer. In the '70s, 75 percent of the breast cancer patients were expected to live through the fifth year after diagnosis and initial treatment of their cancer.

In the year 2001, the five-year survival rate was improved to 88 percent, with effective therapies that are currently available.

Although the overall survival rates are lower in the

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African American population, recent findings suggest that African Americans who receive similar treatments and medical care as Caucasians experience similar outcomes.

So we are here today dealing with the cancer that provides hope for a reasonable lifespan after initial diagnosis and the selection of initial treatment makes significant impact in the overall clinical outcome. Next slide.

Tamoxifen is a non-steroidal hormonal agent first approved in 1977 for the treatment of metastatic breast cancer in post-menopausal women.

Subsequently, Tamoxifen received approval for all

metastatic breast cancer and also for the adjuvant treatment for lymph node positive and negative breast cancers.

Recent approvals include two important indications: first is the reduction in the breast cancer incidence in the high-risk women; and, second is the treatment of Ductal Carcinoma in situ of the breast.

Therefore, a breast cancer patient is likely to be treated with Tamoxifen in the early or late stages of their disease.

Tamoxifen is an anti-estrogenic agent which, by

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binding to the estrogen receptors, prevents cell proliferation.

Aromatase Inhibitors are agents that block the enzyme Aromatase and prevents the production of estrogen, thereby, inhibiting tumor cell proliferation.

Currently, three Aromatase Inhibitors -- Letrozole, Anastrazole, and Exemestane -- are available for the adjuvant treatment of breast cancer. However, Tamoxifen is still the only agent approved for breast cancer risk reduction in high-risk women.

Tamoxifen is metabolized by a number of cytochrome P450 enzymes. 4-hydroxy Tamoxifen is armed [ph.] via CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A, and it was considered the active metabolite responsible for the major pharmacologic effect of Tamoxifen.

4-hydroxy Tamoxifen is 3,200 times more potent than Tamoxifen or N-desmethyl Tamoxifen.

Recently, 4-hydroxy Tamoxifen and desmethyl Tamoxifen, or Endoxifen, is considered a major entity responsible for Tamoxifen's anti-cancer activity.

Endoxifen has a similar potency as 4-hydroxy Tamoxifen; however, the circulating earmark of Endoxifen is

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five- to 10-fold higher than 4-hydroxy Tamoxifen.

Endoxifen is formed predominantly by CYP2D6 from N-desmethyl Tamoxifen. Therefore, CYP2D6 is an important enzyme that controls the level of Endoxifen in vivo.

CYP2D6 is a polymorphic gene located in Chromosome 22. There are four distinct phenotypes. Ultra rapid metabolizers have overactive enzyme activity due to gene duplication. Extensive metabolizers carry two alleles with normal enzyme activity. Intermediate metabolizers carry at least one allele with reduced enzyme activity, and the poor metabolizers carry two alleles with no enzyme activity.

Five to 10 percent of the Caucasian populations are poor metabolizers and 10 to 15 percent are intermediate metabolizers.

Notable that patients who are extensive or intermediate metabolizer genotype, but are on moderate to potent inhibitors of CYP2D6 may exhibit poor metabolizer phenotype.

This slide shows the distribution of alleles with reduced or null activity in various ethnic groups. The star four allele is the predominant variant allele in the Caucasian population; whereas, star 17 is the predominant

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variant allele in the African American population, and the star 10 is in the Japanese population.

Both star 10 and star 17 alleles are alleles with reduced enzyme activity; whereas star four, star five, and star six are alleles with no enzyme activity.

There are a number of publications that extensively investigated -- there are a number of publications that extensively investigated the metabolic pathways of Tamoxifen. Lien et. al. first reported Endoxifen as a human metabolite of Tamoxifen in 1989. Subsequently, others reported similar findings. The publication assessed the binding affinity of Tamoxifen, 4-hydroxy Tamoxifen, and Endoxifen in estrogen receptors, assess the suppression of estrogiles [ph.] stimulated cell proliferation, and assessed gene expression of 4-hydroxy Tamoxifen and Endoxifen.

These publications also investigated the pharmacogenetics of Tamoxifen and N-desmethyl Tamoxifen and determined exposure to various metabolites after administration of Tamoxifen in cancer patients.

Recent publications have demonstrated that patients who carry genetic variance with low or null CYP2D6 activity or who receive potent CYP2D6 inhibitors while on Tamoxifen

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have significantly lower exposure to Endoxifen.

In the next presentation, Dr. Sally Yasuda will present the scientific evidence relating the impact of CYP2D6 polymorphism on Tamoxifen metabolism and variation in Endoxifen exposure in detail.

There are a number of clinical studies that investigated Tamoxifen pharmacogenetics and clinical outcome. I will present an overview of the major studies in my next few slides.

The Swedish Breast Cancer Group had access to frozen tumor tissues from 226 patients treated with adjuvant chemo or radiotherapy with or without Tamoxifen.

The investigators determined the genotype of two polymorphic enzymes -- CYP2D6 and Sulfatransferase 1A1 in 112 Tamoxifen-treated patients. The distance recurrence-free survival was the clinical endpoint measured in the study.

Patients with at least one CYP2D6 star four allele had a relatively lower risk or recurrence when treated with Tamoxifen compared with patients not treated with Tamoxifen.

Similarly, patients with wild type Sulfatranferase 1A1

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gene had a better clinical outcome when treated with Tamoxifen.

The authors concluded that their results contradict the prior hypothesis that patients with variant alleles of CYP2D6 have a poorer clinical outcome in terms of recurrence rate and also concluded that these findings need to be conformed with a larger cohort.

From this study, we know that 40 milligrams of Tamoxifen was given for two years. Tamoxifen activity was tested against chemo and radiotherapy. Limited number of ER positive patients were enrolled in this trial, and the

number of ER positive and CYP2D6 star four homozygous patients in the Tamoxifen-treated and untreated arms were only four.

What we don't know from this study is the impact of five years of Tamoxifen treatment in ER positive patients without concurrent chemo or radiotherapy in the adjuvant setting.

We don't know the clinical outcome of patients with poor metabolizer phenotype based on variant alleles and use of CYP2D6 inhibitors who received Tamoxifen.

We also don't know the impact of concomitant

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medications, such as CYP2D6 inhibitors on the overall clinical outcome.

We don't have a reasonable mechanistic explanation of why patients with Sulfatranferase 1A1 normal alleles, which are likely to lower the levels of 4-hydroxy Tamoxifen and Endoxifen, have a better clinical outcome compared to patients with variant alleles.

Paraffin-embedded tissue samples from 165 patients who were treated with Tamoxifen in the adjuvant setting and 172 patients treated with chemo-radiation or a combination of chemo and radiotherapy at the Arkansas Cancer Research Center were used as a source of DNA for genotyping.

The genetic status of one phase 1 enzyme, Cytochrome B4502D6, and two phase two enzymes, Sulfatransferase 1A1 and UGT -- uridine-diphosphoglucuronosyl transferase 2D15, were determined in the patient population. Clinical outcome measures included overall survival and progression-free survival.

CYP2D6 genotype, which included any patient with at least one star four allele, showed no association between genotype and overall survival, whether treated with Tamoxifen or with chemoradiation.

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Also, CYP2D6 genotype had no association with progression re-survival.

On the other hand, patients with highly active UGT 2B15 alleles in normally Sulfatransferase 1A1 alleles had a poorer clinical outcome when treated with Tamoxifen.

What we know from this study results that the genetic variation of Sulfatransferase 1A1 and UGT2B15 may play a role in Tamoxifen clearance and clinical outcome.

However, this study lacks in evaluating the effect of Tamoxifen in poor metabolizer phenotypes as defined by patients who are homozygous for star four alleles and patients taking a strong CYP2D6 inhibitor for a reasonable length of time.

Again, we don't know the impact of chemo and radiation on the overall clinical outcome. The clinical outcome of patients who are homozygous for CYP2D6 allele and treated with Tamoxifen is not known from this study.

The study by Dr. Matthew Goetz and his colleagues, which will be presented later today, included 256 surgically-treated estrogen receptor positive breast cancer patients who were treated for five years with Tamoxifen in the adjuvant setting.

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No one received adjuvant chemotherapy. The genetic variations in CYP2D6 gene were assessed in 190 patients.

In a multi-variant analysis, women with CYP2D6 star four, star four genotype had worse relapse-free time and disease-free survival.

The exposure to Tamoxifen is affected by Cytochrome B4502D6 polymorphism and by concomitant use of drugs that are inhibitors of CYP2D6.

An updated analysis of the trial data showed that women with either variant allele of CYP2D6 or on moderate to potent inhibitors of CYP2D6 or a combination had significantly worse clinical outcome. This data will be presented by Dr. Goetz.

A recent report of the Italian Chemoprevention Trial in the Journal of Clinical Oncology supported the findings of a study by Dr. Goetz and his colleagues at the Mayo Clinic.

This study evaluated the frequency of Cytochrome B4502D6 star four, star four genotype in 46 patients who developed breast cancer and 136 control patients who did not develop breast cancer after treatment with Tamoxifen for five years.

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The frequency of CYP2D6 star four genotype was 8.7 percent in women with breast cancer versus 0.7 percent in women who are free of cancer. This difference was statistically significant.

I'd like to emphasize at this point the desire of the agency to bring forward any pharmacogenetic, pharmacogenomic data that is available in the public domain. That may help to tailor a dose for a specific population and move forward to the era of personalized medicine.

I will shift gears and touch upon the issue of the availability of a test to detect variant genes of CYP2D6. The AmpliChip CYP450 test is the first micro-array based genetic test that is approved by the FDA for detection of the variant alleles of two important Cytochrome B450 genes -- CYP2D6 and CYP2C19.

The test detects almost all of the important non-alleles of CYP2D6 known at this time and two variant alleles resulting in reduced enzyme activity of CYP2C19.

The assay is robust, with 99.9 percent correct call rate for seven CYP2D6 gene panel tested and 100 percent precision with test amplification and detection reagents.

The system failure rate for this AmpliChip or the

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micro-array is only one percent.

This slide lists a number of national laboratories, research centers, and other laboratory facilities that provide CYP2D6 genotype tests. These laboratories are CLIO [ph.] certified and regulated by the Center for Medicare and Medicaid Services.

Patients or physicians interested to find out the CYP2D6 genotype for any treatment purposes have access to this test.

For many years, in drug labels, empirical evidence has

supported dose adjustment based on age, renal and liver function, cardiac conditions, performance status, food intake, and use of concomitant medications.

These factors have somewhat balanced the benefit-risk of a therapy and individualized treatments, especially for narrow therapeutic agents.

In many situations, the evidence gained came from a small clinical study using blood levels of the active moiety as a surrogate for effectiveness and safety.

The studies that we will discuss today have mechanistic approach using Endoxifen levels as surrogate to relate to CYP2D6 polymorphism, along with direct

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relationship between CYP2D6 phenotype and clinical outcome.

The sample size of these studies are adequate enough to be larger than some of the effectiveness and safety trials conducted for cancer drug approvals.

So our objective today is to discuss the scientific and the clinical evidence that relates CYP2D6 polymorphism with Tamoxifen metabolism and demonstrates the impact of CYP2D6 polymorphisms on clinical outcomes in patients treated with Tamoxifen in the adjuvant setting.

We have four issues on which we would like to get the Committee's recommendation.

The first discussion issue is the scientific evidence on the metabolism of Tamoxifen demonstrates that CYP2D6 is an important pathway in the formation of Endoxifen.

The second discussion point is the pharmacologic and clinical evidence that are sufficient to demonstrate that Endoxifen significantly contributes to the pharmacologic, anti-estrogenic, effect of Tamoxifen.

We'd like to ask the Committee to give their unofficial vote on two questions. The first voting question is, does the clinical evidence demonstrate that

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post-menopausal women with ER positive breast cancer who are CYP2D6 poor metabolizers are at increased risk for breast cancer recurrence.

If the Committee's recommendation is yes, then we'd like the Committee to address, should the Tamoxifen label include information about increased risk for breast cancer recurrence in CYP2D6 poor metabolizers prescribed Tamoxifen.

If the recommendation to the question number three is no, then we'd like the Committee to address what additional types of clinical evidence will demonstrate that post-menopausal women with ER positive breast cancer who are CYP2D6 poor metabolizers may be at increased risk of breast cancer recurrence.

Based on the answer to the previous question, we'd like to ask the Committee to give their unofficial vote on this question: Is there scientific and clinical evidence to support revisions of the Tamoxifen label that recommends CYP2D6 genotype testing for post-menopausal patients before they are prescribed Tamoxifen for adjuvant treatments.

I appreciate that the Committee members keep these

issues and questions in mind as you hear the next two presentations. Thank you.

CHAIRMAN VENITZ: Thank you, Atiqur. Any questions for Dr. Rahman? Any clarification questions?

DR. RELLING: In the question number three, I guess I'm surprised at the wording. It seems like we should be asking, if not, what additional types of clinical evidence will demonstrate whether post-menopausal women with ER positive breast cancer who are 2D6 poor metabolizers are at increased risk for recurrence.

The question seems to presuppose that there is, in fact, this relationship and I assume based on the evidence that you just presented that it's quite possible that's an open question, so we should not presuppose what the outcome is.

And I guess the second part, which maybe is implied in question four, is whether there are -- the risk for 2D6 poor metabolizers of recurrence is still lower than it would be without Tamoxifen? Right?

I mean if the question would be whether to decide that 2D6 genotyping should be recommended before a decision is made about whether to prescribe Tamoxifen, the question has to be whether Tamoxifen is still better than nothing in CYP2D6 poor metabolizers, which was somewhat addressed by the first study that you presented, but I don't believe it was addressed by the other studies.

DR. RAHMAN: Yes, you're correct. And we can modify the language of the questions as we discuss. So based on how we proceed with our discussion, if we need to change the language of the questions, we can do that.

And you're right that we not should presuppose some of the assumptions that I'm presenting and the other presenters will present today.

DR. KAROL: I note that the Wegman paper used post-menopausal women as the study subject. Could you tell us about the Nowel study? What was the age of that population?

DR. RAHMAN: Those were a population that ranged -- they were post-menopausal also in the adjuvant setting, so I believe that the age group will be 50 and above or so. I'm not sure whether they included -- they might have also included pre-menopausal women.

So in that case, the age group will range from 50 to 60 and beyond.

DR. MCLEOD: I realize we can only make specific recommendations about the box of the package insert, but in terms of your review of the data, was there any data of CYP2D6 in the context Aromatase inhibitors, being that a likely decision that we made in practice will not be Tamoxifen versus nothing, but Tamoxifen versus an Aromatase inhibitor?

DR. RAHMAN: I think Dr. Matthew Goetz will be addressing some of those issues as he presents the clinical evidence that relates to all those issues that you just

mentioned.
I just kind of gave an overall summary of what you'll be hearing from the subsequent two presenters.
DR. MCLEOD: And do you have any data or maybe Matthew will present this on CYP2D6 genotype in breast cancer patients that received no therapy at all?
DR. RAHMAN: The Noel paper has an arm whether patients received chemo and radiation therapy, but no Tamoxifen, and they have not shown any association between 2D6 or SULT1A1 gene with clinical outcome.
But if you're saying no Tamoxifen, I don't think -- I at least am not aware of any data.
DR. MCLEOD: I don't have a hypothesis whereby CYP2D6

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will influence breast cancer biology, but there's a lot of reasons that biology's influence per scan, so it would be nice to see that data just to put it to rest.
DR. RAHMAN: I completely agree.
CHAIRMAN VENITZ: Any other questions? Okay. Thank you again.
Our next speaker is Dr. Yasuda. She's going to talk about Tamoxifen, Endoxifen, and CYP2D6 Polymorphism.

TAMOXIFEN, ENDOXIFEN, AND CYP2D6 POLYMORPHISM

DR. YASUDA: Good morning. I'm Sally Yasuda from the Office of Clinical Pharmacology. And I am going to talk about Tamoxifen and Endoxifen and our characterization in terms of pharmacology as well as in vitro and in vivo drug metabolism.
And before I get started, I just want to say this story is kind of a clinical pharmacologist's dream story, and it starts with a single observation at the bed side and goes back to the bench and back to the bed side again. And I'll tell the first part of it, and Matthew Goetz will tell the rest.
So I'm going to start by talking about the single case observation, followed by evaluation of exposure to Tamoxifen

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and its metabolites after administration of Tamoxifen in women with breast cancer.
Then we'll talk about the pharmacology of Tamoxifen, Endoxifen, and other metabolites. And then we'll switch and talk about CYP2D6 mediated metabolism of Tamoxifen and formation of Endoxifen in vitro, and then talk about the role of CYP2D6 in the formation of Endoxifen in vivo, focusing on patients with variant CYP2D6 genotype as well as patients taking strong inhibitors of CYP2D6.
And this begins with a case report that was communicated by David Flockhart, and this was a 45-year-old female who presented with intense intolerable hot flashes after being prescribed 20 milligrams of Tamoxifen per day for one week.
She was placed on 10 milligrams per day of Paroxitene for depression and this is a strong CYP2D6 inhibitor.
She had resolution of hot flashes within one week, and her hot flashes resumed when she was taken off of the strong CYP2D6 inhibitor.
At the time that this case was observed, the classic

understanding of Tamoxifen pharmacology relied on the active metabolite 4-hydroxy Tamoxifen, and it was known that this

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was formed from Tamoxifen by CYP2D6.

And 4-hydroxy Tamoxifen binds to the estrogen receptor in competition with estradiol and then prevents the binding of the estrogen receptor to the estrogen response element on DNA, thereby causing it antagonist effect as an anti-estrogen in the breast.

So based on the single case exposure and the knowledge of Tamoxifen pharmacology at the time, Dr. Flockhart and his colleagues proposed a hypothesis that CYP2D6 inhibition interferes with formation of 4-hydroxy Tamoxifen.

So in a pilot study, they looked at 12 women with a history of breast cancer receiving Tamoxifen 20 milligrams per day as adjuvant treatment for at least four weeks before starting the study.

The women had a history of troublesome hot flashes for which treatment with a non-hormonal agent was considered to be appropriate, and blood samples were collected before and after four weeks of co-administration of Tamoxifen with 10 milligrams per day of Paroxitene.

And in contrast to the investigators' hypothesis that the concentrations of 4-hydroxy Tamoxifen would change, they didn't see a change in 4-hydroxy, but what they did see was

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a peak that had been characterized or reported in the literature previously that they then characterized as 4-hydroxy N-desmethyl Tamoxifen, and called it Endoxifen. And if you look at the figure before administration of Paroxitene, you can see the peak of Endoxifen is about 10-fold higher than the peak of 4-hydroxy Tamoxifen.

And after exposure to Paroxitene, there was significantly less exposure to the Endoxifen peak.

And other things I wanted to point out on this slide were that the most prominent metabolite is the N-desmethyl Tamoxifen. It's about twice as high as exposure to Tamoxifen, and it's the most prevalent metabolite.

Endoxifen concentrations are about 10 times higher than the other active metabolite, 4-hydroxy Tamoxifen and about eight times less than the exposure to N-desmethyl Tamoxifen.

So in that study, it was noted that Paroxitene has no effect on plasma concentrations of Tamoxifen, N-desmethyl, or 4-hydroxy Tamoxifen. And just for an example, the levels of 4-hydroxy Tamoxifen are shown on the left-hand side, and you can see no change in the mean 4-hydroxy Tamoxifen concentrations before or after exposure to Paroxitene which is a

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strong 2D6 inhibitor.

But there was a significant effect on exposure to Endoxifen, and that's shown on the right-hand side of the slide. There was a significant decrease in Endoxifen levels after exposure to the strong CYP2D6 inhibitor Paroxitene, reporting the role of CYP2D6 in the formation of Endoxifen.

Also in this figure, the solid symbols represent patients who had two wild-type alleles for CYP2D6, so

they're extensive metabolizers for CYP2D6, and that's where you see the change in Endoxifen exposure in the presence of the CYP2D6 inhibitor.

The open red circles represent patients who had one variance allele for CYP2D6, so there was no effect on these patients after exposure to Paroxitene.

Next, the investigators looked at the relative pharmacologic activity of Endoxifen and Tamoxifen and its other metabolites. And it has been known and published in the literature for many years that Tamoxifen and N-desmethyl Tamoxifen have similar pharmacologic activity.

It's also been published previously that 4-hydroxy Tamoxifen is 30 to 100 times more potent as an anti-estrogen than Tamoxifen.

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And these investigators recently reported that Endoxifen is equipotent to 4-hydroxy Tamoxifen and remember it has five- to 10-fold higher plasma concentrations.

They have looked at the pharmacologic activity and Endoxifen in several different types of assays, but I'll describe two of them for you.

This figure shows decrease in polarization, which reflects displacement of a synthetic fluorescent estrogen probe from a recombinant estrogen receptor in the presence of increasing concentrations of Tamoxifen, which is shown in the triangles, compared to 4-hydroxy Tamoxifen and Endoxifen. And you can see that 4-hydroxy as well as Endoxifen are more potent than Tamoxifen in displacing this binding from the estrogen receptor. And also you can see that 4-hydroxy and Endoxifen have relatively the same potency at binding to the estrogen receptor.

The next type of study they did was more of a functional assay, looking at estrogen stimulated cell proliferation in MCS7 cells, and these are a breast cancer cell line.

If you look at the Y-axis on both of these graphs, absorbance reflects the number of cells. It's proportional

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to the number of cells in the cell proliferation assays.

So if you first look at the top graph, you can see cell proliferation at day four, seven, and 10. And the very top curve reflects estrogen-stimulated cell proliferation. And the very bottom of the curve in one of the open circles represents control, which is in the absence of estrogen, so there's no cell proliferation in that case.

The solid triangle represents Tamoxifen, and you can see some decrease in estrogen-stimulated cell proliferation in the presence of Tamoxifen. But what is really noticeable is Endoxifen and 4-hydroxy Tamoxifen, which have overlapping curves and overlap with the controls, so they completely inhibit the estrogen-stimulated cell proliferation at day seven and day 10.

The bottom figure just shows the dose response curve for Endoxifen and 4-hydroxy Tamoxifen in the cell proliferation assay, and you can see they're overlapping and equally potent as anti-estrogens.

Next, the investigators turned to in vitro studies to

characterize the formation of Endoxifen from Tamoxifen, and this work was published in 2004 by Dest et. al.

This figure shows the primary metabolism of Tamoxifen

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forms many, many metabolites and many isoforms of P450 are involved.

But the primary route of metabolism of Tamoxifen is via CYP3A to N-desmethyl Tamoxifen, and this is reflected in the exposures that you see in the plasma of patients taking Tamoxifen.

A minor pathway, as we also saw in the exposure, is to 4-hydroxy Tamoxifen and that is primarily mediated by CYP2D6, although you can see there are other P4540s involved as well.

The next thing the investigators did was to take the 4-hydroxy Tamoxifen and the N-desmethyl Tamoxifen and use them as substrates in in vitro assays to look at formation of Endoxifen as well as other metabolites. And I'm just focusing here on the formation of Endoxifen, and this figure looks at the formation of Endoxifen from the N-desmethyl Tamoxifen.

So if you look at the upper right-hand figure, you can see across a panel of human liver microsomes with differing CYP2D6 activity and the Y-axis shows the rate of formation of Endoxifen. And you can see a very nice correlation between the rate of Endoxifen formation and CYP2D6 activity.

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At the bottom right-hand part of the screen shows the results of three human liver microsomes that express different amounts of CYP2D6, and CYP2D6 activity is shown on the right. So the HG23 has the highest amount of CYP2D6 activity, and HG06 has practically no CYP2D6 activity.

And you can see here the correlation with intrinsic clearance for the formation of Endoxifen, which agrees with the amount of CYP2D6 activity present in these individual human liver microsomes.

They also looked at the CYP3A activity in these microsomes and found no correlation.

So this supports the role of CYP2D6 in the in vitro formation of Endoxifen from N-desmethyl Tamoxifen.

If you look at a figure on the upper left-hand part of the screen that's labeled "B," you see the results from recombinant expressed human P450s. And you can see that most of the activity for the formation of Endoxifen is accounted for by CYP2D6.

And then finally, at the lower left-hand part of the screen, you see results of specific chemical inhibitions on human liver microsomes. And almost all of the activity for

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formation of Endoxifen is inhibited the presence of Quinidine, which is a strong CYP2D6 inhibitor.

So all of these results support the important role of CYP2D6 in the formation of Endoxifen from N-desmethyl Tamoxifen.

The authors also looked at the formation of Endoxifen from 4-hydroxy Tamoxifen and in general most of those

results point towards CYP3A as the important pathway for the formation of Endoxifen from 4-hydroxy Tamoxifen.

So just to summarize those in vitro findings and this is a very simplistic view because you remember the primary metabolism of Tamoxifen formed many metabolites. But it's primarily metabolized via CYP3A to N-desmethyl Tamoxifen, and primarily that is metabolized to Endoxifen, although both 4-hydroxy and N-desmethyl Tamoxifen have several other metabolites.

I also want to point out that both 4-hydroxy Tamoxifen and Endoxifen undergo phase II conjugation with Sulfotransferases for glucuronidation, and you'll see that reflected in some of the clinical studies as well.

Now, I want to switch gears and start talking about the pharmacogenetics of CYP2D6 and the role of CYP2D6 in

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Endoxifen formation in vivo.

And just to remind you and to reflect on what Dr. Rahman mentioned previously, the pharmacogenetics of CYP2D6 is quite variable and in this figure it's reflected in a metabolic ratio, which shows the ratio of debrisoquine and for -- to its hydroxlylated metabolite, and we have quite a range of activity with the poor metabolizers with the highest ratio and intermediate and extensive metabolizers showing quite a bit of variability, and ultra rapid metabolizers at this end.

And we know that the CYP2D6 genotype reflects the CYP2D phenotype.

So based on the pilot study in 12 subjects, the investigators next looked at CYP2D6 genotype, CYP2D6 inhibitors, and Tamoxifen exposure in 80 pre- and post-menopausal women with newly diagnose breast cancer, starting Tamoxifen 20 milligrams per day as adjuvant therapy.

And they collected blood samples for determination of Tamoxifen and its metabolites in plasma.

And it's important here to note that the half-life of Tamoxifen and the N-desmethyl metabolite are very long. The

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half-life of Tamoxifen is one week and N-desmethyl is even longer.

So it takes at least four weeks for Tamoxifen itself to get to steady state, and so the investigators looked at sampling at one month and also four months, and saw that the exposure had gone up at four months.

So the data that I'm presenting here and it's presented in their paper is from the four-month data.

They also looked at genotype of functional and variant alleles of CYP3A5, CYP2D6, CYP2C9, and SULT1A1, because that's -- we have previously. These are involved, to some extent, in the metabolism of Tamoxifen.

And they found no statistically significant associations of candidate genotypes with Tamoxifen or metabolite exposure except for CYP2D6.

This figure is from their results from that paper, and it shows mean plasma Endoxifen concentrations according to genotype. So we have wild-type, wild-type, wild-type with

one variant allele, or the four metabolizers that have two variant alleles.

And you can see a gene dose effect with a significant decrease in mean Endoxifen plasma concentrations in the

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patients who were poor metabolizers and had no functional alleles at the 2D6.

But you can see here also that there is substantial variability, even when you can separate it by genotype for CYP2D6. And so next the investigators looked at what could account for some of that variability, and they looked at patients who were taking CYP2D6 inhibitors versus patients who were not.

And so this is the data from the same subjects. The solid bars show the patients who were not taking CYP2D6 inhibitors, and the open bar shows patients who were taking CYP2D6 inhibitors.

And the authors put all of the CYP2D6 inhibitors together as one class, but I would just like to point out they included strong CYP2D6 inhibitors that were Paroxitene and Fluoxitene; weak inhibitors Amiodarone, Sertralene, and Citalopram, and also Metaclopramide, which is shown to be an inhibitor in vitro, but it hasn't been evaluated in vivo yet.

So here you can see a significant difference even among the wild-type patients between an exposure to Endoxifen in patients who were not taking CYP2D6 inhibitors

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and patients who were taking CYP2D6 inhibitors, and this is a clinically significant -- I mean a statistically significant increase in Endoxifen exposure in the presence of CYP2D6.

Similarly, in the intermediate type patients, you see a decrease in Endoxifen exposure in the patients who were taking CYP2D6 inhibitors, although this didn't reach statistical significance, but you also have to remember that this included all types of CYP2D6 inhibitors, weak or strong.

So these data support an association between CYP2D6 genotype and Endoxifen exposure, and the role of strong CYP2D6 inhibitors also supports the role of CYP2D6 in the formation of Endoxifen.

The authors also looked in that study at commonly used anti-depressants, and the patients were allowed to take SSRIs when they were enrolled in the study. So this figure looks in that same group of patients according to genotype and SSRI that was taken versus serum Endoxifen concentrations.

And once again, you can see the highest exposure in either wild-type patients or wild-type who were taking drugs

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that don't significantly inhibit the 2D6. But the patients who were taking -- the wild-type patients taking the strong CYP2D6 inhibitor, Paroxitene, had substantially reduced Endoxifen exposure, which brings it down almost to the level of patients who were poor metabolizers.

So once again, there's a very important role for

CYP2D6 in Endoxifen exposure.

Next, the authors looked at a larger cohort of patients in the same study and looked more extensively at different CYP2D6 genotypes. And in this figure, you can see on the left-hand side, they looked at the ratio of Endoxifen to N-desmethyl Tamoxifen plasma concentrations, which decreased the variability in the measurement quite a bit more than looking at the Endoxifen plasma concentrations, which are shown on the right.

But what you see here is basically three groups of patients, and in the bottom third of the figure, the patients who are denoted by the solid diamond are the patients who are ultra rapid metabolizers and extensive metabolizers.

And this is all patients, even those who might have been taking CYP2D6 inhibitors.

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Here you can see quite a range again of exposure to Endoxifen, whether it's measured by Endoxifen alone or the ratio of Endoxifen to the N-desmethyl.

The second, or middle, group of patients, who are mostly denoted by the circles, are patients who had at least one functional allele of CYP2D6. And you can see in those patients it looked like they have a little bit lower exposure to Endoxifen to the N-desmethyl ratio.

And finally, in the upper third of the figure, where you see the patients in the triangle, those are patients who had no functional alleles, and so -- or no fully functional alleles, and that included patients with a partially functional allele or absent function. And these people had very little exposure to Endoxifen, as we had seen in the previous study.

Also, in this study, the investigators looked again at patients who were taking strong CYP2D6 inhibitors and again found that that reduced some of the variability in exposure in the wild-type patients.

So, once again, this supports an important role for CYP2D6 in the formation of Endoxifen.

Recently, there's been an abstract published from a

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Norwegian group that also looked at CYP2D6 genotype and Endoxifen exposure, and they found very similar results; that poor metabolizers have much lower exposure to Endoxifen.

So, in conclusion, Endoxifen is an active metabolite of Tamoxifen, and it's present in patients at five- to 10-times greater concentrations than the other active metabolite, 4-hydroxy Tamoxifen.

In vitro studies demonstrate the primary role of CYP2D6 in the formation of Endoxifen, and potent inhibitors of CYP2D6 reduce Endoxifen concentrations in patients taking Tamoxifen.

Finally, CYP2D6 genotype correlates with Endoxifen concentrations in patients taking Tamoxifen, and all of this supports the important role for CYP2D6 in the formation of Endoxifen.

And Matthew Goetz will follow up showing the clinical

relevance of this.
And I want to acknowledge the very helpful discussions I've had with people inside of the FDA as well as Todd Skar, Dave Flockhart, and Dr. Desta. Thank you.
CHAIRMAN VENITZ: Thank you, Sally. Any questions for Dr. Yasuda?
DR. MORTIMER: So what are the negative clinical trials is the Scandinavian trial, and the if hydroxy Tamoxifen's anti-estrogen effect is equivalent to Endoxifen, and we know -- I mean there are studies that look at 10 milligrams versus 20 milligrams of Tamoxifen being equivalent. The Scandinavian trial used 40 milligrams a day. So would that account for the difference? My thought process consisted here that if you double the dose, you increase the dose of hydroxy Tamoxifen and that would take away the effect of 2D6 and Endoxifen production and make a negative trial.
DR. YASUDA: Well, first that study I believe was the study that only had four poor metabolizers in it, so it would be very difficult to make a general conclusion about that. But it's probably unlikely that in patients who are -- it's unlikely that patients who are deficient in CYP2D6 or have no functional CYP2D6 could form Endoxifen by the N-desmethyl Tamoxifen route, and so it's hard to imagine that in patients who have one functional allele may be able to do it if you increase the dose, but that would have to be studied and I would think you would need an even higher dose than that.
DR. MORTIMER: But the tumor effect with hydroxy Tamoxifen is still there, and so you wouldn't be able to see it I guess is my question.
DR. YASUDA: I think what this really comes down to is we don't know what happened to the rest of the metabolic pathways when patients are missing CYP2D6, and it's probably likely due to a composite of activity of all of these active metabolites. And at this point, that hasn't been determined.
CHAIRMAN VENITZ: Dr. Capparelli?
DR. CAPPARELLI: Yes, in trying to assess the complex interaction between the two metabolites, is there any information on relative protein binding?
DR. YASUDA: I am not aware of any data on the protein binding.
DR. RELLY: I just want to follow up on the first question, 'cause that was mine also. So there are no data on whether increasing the dose in individuals who have at least one defective copy of 2D6 increases the Endoxifen concentration, that you know?
DR. YASUDA: I am not aware of that data. I've seen another study that I believe looked at genotype of lower doses, but I'm not aware of any.
DR. GIACOMINI: Yes, I'm just looking at the variation in the Endoxifen levels with CYP2D6 genotypes, and then you gave or somebody's study gave the inhibitors.

But I'm also wondering what are the other pathways Endoxifen -- how is it being eliminated? How is it being eliminated -- you know, how because the inhibitors could be affecting other, you know, pathways.

DR. YASUDA: So really beyond the level of Endoxifen in terms of any data on metabolism, I'm not aware of any studies looking at that. It is conjugated by Sulfotransferase and glucuronidases as well. And --

DR. GIACOMINI: I think people are just starting to look at that, and how it goes with transporters. Some of these compounds are transporters.

DR. YASUDA: I think Dr. Greenblatt looked at Tamoxifen and several metabolites. I don't recall if Endoxifen was included, but they were considered to be inhibitors of PGP, but not substrate.

CHAIRMAN VENITZ: Any other questions?

DR. LESKO: Just a clarifying question because it

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follows on two of the questions that were asked.

It was the question about overcoming the poor metabolizing by 2D6 with a higher dose. I don't think we've had any data to look at that question, but on the figure, it illustrates -- at least one of the later figures I guess from '03 -- that there was a connection between the 4-hydroxy and Endoxifen being a 3A4.

So in answering that question, does that mean that that can't happen with a higher dose, because converting a 4-hydroxy has many different enzymes. So even if 2D6 was a poor metabolizer, you could still be forming it from the other first order pathways there.

So the question would be why can't you form more Endoxifen from higher doses of Tamoxifen via that 3A4 pathway?

DR. YASUDA: I don't think we know that you can, and that hasn't been validated yet. I don't think that we know what the composite activity of all this is or what would happen.

We don't see an increase in the formation of 4-hydroxy Tamoxifen. I think we don't know.

DR. LESKO: Yeah, so there's no data on the -- so you

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showed us the Endoxifen and N-desmethyl ratios to sort of explain the shutdown of that process in genotypes, but there's no similar relationship between Endoxifen and 4-hydroxy Tamoxifen in different genotypes?

DR. YASUDA: I believe that's -- we will look at that information. The only other thing I can add is that in their 80-patient study, there were five patients on CYP3A inhibitors, and the only change was an increased response.

DR. LESKO: Now, I was just thinking about protein binding, because you haven't seen -- and that's probably out, because I haven't seen what that is, but at least on the hydroxylated or polar metabolite, you would expect relatively small protein binding.

CHAIRMAN VENITZ: Any other questions? Thank you again, Sally.

It looks like we're moving along quite rapidly. So

let's take our break now, and let's reconvene at 10:30 a.m., and we'll move everything up by 15 minutes.

TAMOXIFEN PHARMACOGENETICS AND PREDICTION OF BREAST CANCER RELAPSE AFTER ADMINISTRATION OF TAMOXIFEN

CHAIRMAN VENITZ: Our next speaker is Dr. Goetz. Dr. Goetz is Assistant Professor in Oncology at the Mayo Clinic,

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and he's going to talk about Tamoxifen Pharmacogenetics and Prediction of Breast Cancer Relapse After Administration of Tamoxifen. Dr. Goetz.

DR. GOETZ: All right. Thank you very much. My name is Matthew Goetz. I'm presenting from -- on behalf of our group at Mayo Clinic as well as in collaboration with David Flockhart's group, which is the Consortium of Breast Cancer Pharmacogenomics in the Pharmacogenomics Research Network.

I'm just going to spend a few moments again reviewing the clinical importance of Tamoxifen for estrogen receptor positive breast cancer.

This is already been reviewed by Dr. Rahman. Invasive breast cancer in the United States in 2006 is estimated there will be about 212,000 new cases. Ductal Carcinoma in situ, approximately 62,000 cases. And two-thirds of these are estrogen positive. So that means that they are candidates for hormonal therapy.

Tamoxifen arguably is the most important drug worldwide for hormone receptor positive breast cancer, and it's been approved by the FDA for the treatment of high-risk patients, DCIS pre- and post-menopausal breast cancer and metastatic disease as already been alluded to.

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It's also the most commonly used hormonal therapy in early and advance male breast cancer.

This particular timeline here gives you the indications ranging from 1977 post-menopausal metastatic to the adjuvant setting in 1986; pre-menopausal patients as well as in node negative. And you can see high-risk patients in Ductal Carcinoma in situ more recently.

So what do we know about Tamoxifen? Well, Tamoxifen is probably one of the most studied drugs in all of oncology, and we know that from a meta-analysis, and this is continually updated about every year or two, that Tamoxifen reduces the risk of recurrence significantly when women take Tamoxifen for five years.

And note that this particular timeline that the separation that occurs actually continue to happen, and despite the fact that Tamoxifen is stopped after five years, such that about your 15 for patients who receive control there is about a 454 percent risk of recurrence versus those who receive five years of Tamoxifen, and approximately 33 percent.

Well, Tamoxifen is not the only kid on the block anymore, and that really is the issue that we need to

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discuss today, because we're not talking about here a drug where we only -- excuse me -- a disease where we only have one drug. In fact, the real issue here is that we have other choices.

And these trials that I'm going to show you here really bring this out.

The first trial, which is on top, was the MA17 trial -- or it's listed as extended adjuvant therapy. And this is where women who had received five years of Tamoxifen and who actually were not -- and had not had a recurrence were randomized to placebo or an Aromatase inhibitor; in this case Letrozole.

And in this case, Letrozole reduced the risk of recurrence by almost 40 percent, and also led to a survival advantage as well.

Now, the next set of trials that were done were what we call switching trials where women took two to three years of Tamoxifen, and in these trials they had to have gotten through those first couple years.

So, in other words, people were -- most of these trials they were not randomized up front. They were randomized after they had been on Tamoxifen for two to three

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years.

And then the randomization was either to continue Tamoxifen so to complete what was the standard of care, five years of Tamoxifen, or an Aromatase inhibitor.

And you can see that in those trials, again, in probably over 20,000 women enrolled in these trials, in these switching trials, switching to an Aromatase inhibitor resulted in a significant reduction in the risk of a disease event.

So finally, more recently, we have the up-front studies where the -- and you see this for initial adjuvant therapy where women were randomized to either an Aromatase inhibitor or Tamoxifen. And in this case, the Aromatase inhibitors reduced the risk of event, although not as significantly -- and this was still statistically significant, around a 17 percent reduction.

So what I'm trying to show you here today is that we don't just have one drug available. We have multiple drugs that, in fact, what's happening out in clinical practice is that most people are actually using Aromatase inhibitors as first-line therapy.

There are some people that still use Tamoxifen for

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several years and then switch, and so this slide here indicates this. For pre-menopausal patients, we really only have Tamoxifen for five years. There are a number of studies that are looking at additional therapies, but those have not been completed.

But for post-menopausal women, our options and what's used most often at this point is Aromatase inhibitors for five years or to use Tamoxifen for two to three years, followed by an Aromatase inhibitor.

Now, notice here that I don't have Tamoxifen for five years, and it's really because no one uses Tamoxifen for five years, and that's because when women who have been on Tamoxifen for two years have been compared to completing five years or switching to an Aromatase inhibitor, there is definite superiority for switching to an Aromatase

inhibitor. So these are really the -- when I see a woman in the clinic today for breast cancer, these are the options that we discussed.

So this point here really brings up clinically what we actually -- the problem that we face when we see women in the clinic, and that is there is a difference at the two- to three-year mark, and this is at the 30-month mark, of about

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1.6 percent. So here you see that when Anastrazole was compared to Tamoxifen in the ATAC trial, and this has been published, and this over 6,000 women that the women who received Anastrazole had a significant reduction in the risk of recurrence, and that risk reduction was even at 30 months.

Now, the absolute difference is small. It's about 1.6 percent, so this is why many physicians out in the community will actually say I will not put a woman on Tamoxifen within those first two years because I am concerned about the risk of recurrence.

So really the clinical question that we were asking and have been asking for some time -- and other people are asking as well -- is there a better way to identify patients for whom Tamoxifen or Anastrazole would be the preferred drug for additional adjuvant therapy. And in this point today, we're focusing on the variability in Tamoxifen.

So when one looks at the Tamoxifen metabolic pathway -- and I'll be brief here, because we've discussed this -- I was taught during my training that 4-hydroxy Tamoxifen was the most important Tamoxifen metabolite. It has been alluded the reasons to that are obvious: because it is

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about a hundred-fold more potent in terms of its effect on NCO7 breast cancer cells. It's more potent in terms of its binding.

The problem, as Dr. Flockhart's group has shown and Dr. Desta, is that most Tamoxifen, over 90 percent of it, 95 percent, is immediately converted in N-desmethyl Tam. So if 4-hydroxy Tamoxifen is the most important metabolite, in reality, there's very little of it, and N-desmethyl Tamoxifen is the most abundant Tamoxifen metabolite.

So recently, as you've been told, there has been a number of studies that have been shown -- have shown that N-desmethyl Tamoxifen is converted to Endoxifen and this is under genetic control via the CYP2D6.

And just a review again, when you look at comparing Tamoxifen, the parent drug, with the metabolites 4-hydroxy Tamoxifen and Endoxifen, you can see that there are significant differences in terms of their effect as inhibitors of estrogen-stimulated cell proliferation, such that Tamoxifen is a weak anti-estrogen and its metabolites, 4-hydroxy Tamoxifen and Endoxifen, are potent anti-estrogens.

So this kind of summarizes this here. Endoxifen and

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4-hydroxy Tamoxifen, their potency in ER binding is the same. Their suppression of estrogen-dependent MCO7 proliferation is the same. The same in terms of global ER

response of gene expression.
Where they're different is that Endoxifen concentrations are up to 10-fold higher than 4-hydroxy Tamoxifen.
So what we have then is Tamoxifen, a weak anti-estrogen, and we have the metabolites, 4-hydroxy Tamoxifen and Endoxifen, which are potent anti-estrogens.
So, as it has been alluded to, Dr. Flockhart's group has already shown that patients -- that the metabolism of Tamoxifen to Endoxifen is under genetic control; that patients who have at least one reduced functional allele or two reduced functional alleles, such as the star four, star four, have significantly lower plasma Endoxifen concentrations than patients who are wild-type.
So this really brought up the clinical question that we initially asked, and that is, do patients who have, who are CYP2D6 poor metabolizers have a worse clinical outcome than patients with normal or perhaps increased CYP2D6 metabolism.

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And I would just make a point, and, as one of my mentors, Dick Wincherbaugh [ph.] once told me, he said the translation of pharmacogenomics or in this case any biomarker into the clinical setting is probably the most difficult step, and it's the most difficult step for a number of different reasons.
First of all, you have to have obviously a robust patient population. Secondly, you have to make sure that you're studying the right patient population. Thirdly, you're going to have to have good follow-up, and obviously, fourthly, you have to have DNA available to answer to question. So this has been really the issue with the translation of Tamoxifen pharmacogenomics and it's really, as I would point out, one of the difficulties with the studies that have been done. Literally up until the last five to 10 years, people have still been giving Tamoxifen for ER negative breast cancer.
So we know that Tamoxifen is ineffective in ER negative breast cancer.
So, for example, when you look at the studies that have been done today that have been alluded by Dr. Rahman, you have a patient population that has been composed of ER

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negative and ER positive breast cancer. So that's one issue.
The second issue is the endpoint. So, for example, we know that Tamoxifen not only reduces the risk of distant relapse, which is the endpoint that was studied in the Wegman paper, the Noel paper, but it also reduces the risk of local relapse and also contra-level breast cancer.
And notice that the FDA endpoint for adjuvant clinical trials is not distant relapse-free survival, it is what we call disease-free survival, which encompasses distant relapse, local relapse and also contra-level breast cancer.
So with that in mind, there are -- those to me really are the biggest issues with the studies that have been done to date.

So what we attempted to do was to look at the importance of CYP2D6 pharmacogenomics in this patient population. And this was a prospective clinical trial. It was a cooperative group trial. Jim Engle [ph.] was the principal investigator, and post-menopausal women and were randomized to either five years of Tamoxifen or five years of Tamoxifen plus esterone [ph.].

Important here is that all women were required to have

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estrogen receptor positive breast cancer.

The second thing of import was that the follow-up on these patients was the sort of follow-up that you would expect from a cooperative group trial.

So who are these patients? Well, they're surgically ressected stage one through three breast cancer patients. All tumors were estrogen receptor positive, and in order to get on the trial, you were required to have a greater than 10 fenti-mole per milligram cytozole protein by a charcoal binding assay or you were required to be positive by an immunohistochemical [ph.] assay.

No adjuvant chemotherapy was allowed. The median follow-up in this trial was 11 years. Accrual completed in April of 1995. And the primary endpoint of the trial, which was looking at the difference in those two arms; there was no difference in relapse-free survival or overall survival.

So we looked at the Tamoxifen monotherapy arm. Again, there was 256 patients that were enrolled in this. Formalin fixed paraffin embedded tumor blocks were available in 223 patients. And genotyping for CYP2D6 star four and also star six was performed. I am not including star six here, because there were -- no variants were seen.

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And you can see here that the frequency of the poor metabolizer phenotype was about what was to be expected in this predominantly Caucasian population, of around seven percent.

And here were the findings.

So this here endpoint that we looked at is relapse-free time. Now, the endpoint here is simply local, regional, or distant relapse or the development of contra-level breast cancer.

And you can see that patients who are CYP2D6 poor metabolizers had a significantly worse or time to -- shorter time to relapse than patients who were intermediate metabolizers or wild-type.

This is relapse-free survival, so this endpoint here looks at the endpoints of relapse, but it also looks at death as well. So relapse or death, and you can see here that CYP2D6 poor metabolizers had a significantly worse relapse-free survival compared to intermediate metabolizers or wild-type -- or otherwise extensive metabolizers.

The other thing that we looked at was we actually had information about hot flashes. Now, hot flashes are probably the most common side effect of women who take

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Tamoxifen receive. And what we noted was that patients who were CYP2D6 poor metabolizers by virtue of the star four

genotype that the incidence of moderate or severe hot flashes was zero percent.

Now, hot flashes are graded on this trial. This is a 1989 trial. In fact, at this time, there was no -- at the time this trial was developed, the grading of hot flashes was relatively I would say early in its development. Hot flashes were simply graded at zero or one, which is mild. Two is considered moderate or troublesome, and three is severe.

So when we looked at patients who had moderate or severe hot flashes, patients who were poor metabolizers did not develop that versus the incidence was approximately 20 percent in patients who were intermediate or extensive metabolizers.

So the final -- I would say the final point here is that we did a multivariate analysis, and this is, you know, very important to do. When you look at the effect of a particular genotype on outcome, you need to adjust for the most important factors that influence outcome, namely nodal is tumor size, tumor grade -- these sort of things.