DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

CLINICAL PHARMACOLOGY SUBCOMMITTEE

Tuesday, November 18, 2003

8:30 a.m.

Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Jurgen Venitz, M.D., Ph.D., Chair
Hilda F. Scharen, M.S., Executive Secretary

MEMBERS

David D'Argenio, Ph.D.
Marie Davidian, Ph.D.
Hartmut Derendorf, Ph.D.
David Flockhart, M.D., Ph.D.
William J. Jusko, Ph.D.
Gregory L. Kearns, Pharm. D., Ph.D.
Howard L. McCleod, Pharm.D.
Mary V. Relling, Pharm.D.
Wolfgang Sadee, Ph.D.
Lewis B. Sheiner, M.D.
Marc Swadener, Ed.D.

GUESTS AND GUEST SPEAKERS (NON-VOTING)

Acting Industry Representative:
Efraim Shek, Ph.D.

Guest Speakers:
Richard Hockett, M.D.
Pertti Neuvonen, M.D.

FDA

Shiew-Mei Huang, Ph.D.
Peter Lee, Ph.D.
Lawrence Lesko, Ph.D.

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1 P R O C E E D I N G S

2 Call to Order

3 DR. VENITZ: Good morning and welcome

4 everyone to the second day of the Clinical

5 Pharmacology Subcommittee Meeting. This is the

6 continuation of yesterday's topic area. My name is

7 Jurgen Venitz and I am the Chair. I would like to

8 start by introducing all the members of the

9 committee and invited guests around the table.

10 Introduction of the Committee

11 DR. D'ARGENIO: David D'Argenio from the

12 University of Southern California.

13 DR. FLOCKHART: Dave Flockhart from

14 Indiana University.

15 DR. SHEINER: Lewis Sheiner, University of

16 California, San Francisco.

17 DR. SWADENER: Mark Swadener, Boulder,

18 Colorado.

19 DR. JUSKO: William Jusko, University of

20 Buffalo.

21 MS. SCHAREN: Hilda Scharen, FDA, Center

22 for Drugs, Executive Secretary.

23 DR. KEARNS: Greg Kearns, University of

24 Missouri.

25 DR. DERENDORF: Hartmut Derendorf,

1 University of Florida.
2 DR. DAVIDIAN: Marie Davidian, North
3 Carolina State University.
4 DR. SHEK: Efraim Shek, Abbott
5 Laboratories.
6 DR. McCLEOD: Howard McCleod, Washington
7 University.
8 DR. RELLING: Mary Relling, St. Jude
9 Children's Research Hospital, Memphis.
10 DR. SADEE: Wolfgang Sadee, Ohio State
11 University.
12 DR. LEE: Peter Lee, COPB, FDA.
13 DR. HUANG: Shiew-Mei Huang, Center for
14 Drugs, Office of Clinical Pharmacology and
15 Biopharmaceutics.
16 DR. LESKO: Larry Lesko from FDA, Office
17 of Clinical Pharmacology and Biopharmaceutics.
18 DR. NEUVONEN: Pertti Neuvonen from the
19 University of Helsinki, Finland.
20 DR. HOCKETT: Rick Hockett, Eli Lilly.
21 DR. VENITZ: Thank you, everyone. Let me
22 turn over the microphone to Ms. Hilda Scharen. She
23 is going to read the conflict-of-interest
24 statement.
25 Conflict of Interest Statement

1 MS. SCHAREN: The following announcement
2 addresses the issue of conflict of interest with
3 respect to this meeting and is made a part of the
4 record to preclude even the appearance of such at
5 this meeting.
6 The topics of today's meeting are issues
7 of particular matters of broad applicability.
8 Unlike issues before a committee in which a
9 particular product is discussed, issues of
10 particular matters of broad applicability involve
11 many industrial sponsors and academic institutions.
12 All special government employees have been
13 screened for their financial interests as they may
14 apply to the general topics at hand. Because they
15 have reported interests in pharmaceutical
16 companies, the Food and Drug Administration has
17 granted general-matters waivers of broad
18 applicability to the following SGEs which permits
19 them to participate in today's discussion; Dr.
20 David D'Argenio, Dr. Marie Davidian, Dr. Hartmut
21 Derendorf, Dr. David Flockhart, Dr. William Jusko,
22 Dr. Gregory Kearns, Dr. Howard McCleod, Dr. Mary
23 Relling, Dr. Wolfgang Sadee, Dr. Jurgen Venitz.
24 A copy of the waiver statements may be
25 obtained by submitting a written request to the

1 agency's Freedom of Information Office, Room 12A30,
2 of the Parklawn Building. Because general topics
3 could involve so many firms and institutions, it is
4 not prudent to recite all potential conflicts of
5 interest but, because of the general nature of
6 today's discussion, these potential conflicts are
7 mitigated.
8 We would also like to note for the record
9 that Dr. Efraim Shek is participating in today's
10 meeting as an acting, non-voting, industry
11 representative.
12 In the event that the discussions involve
13 any other products or firms not already on the
14 agenda for which FDA participants have a financial
15 interest, the participants' involvement and their
16 exclusion will be noted for the record.
17 With respect to all other participants, we
18 ask, in the interest of fairness, that they address
19 any current or previous financial involvement with
20 any firm whose product they may wish to comment
21 upon.
22 Thank you.
23 DR. VENITZ: Thank you, Hilda.
24 Two housekeeping issues before we get
25 started. You may have noticed in the original

1 agenda for the second, we had a topic on Pediatric
2 Population PK Template. Due to time constraints,
3 that topic had to be deferred to our next meeting
4 or one of our next meetings.
5 Open Public Hearing
6 I have also been informed that we won't
7 have any presenters at the open public hearing
8 today so we might be able to get an early
9 adjournment.
10 Having said that, I would like to ask Dr.
11 Lesko to introduce the topics for today and give us
12 our charge.
13 Introduction
14 DR. LESKO: Thank you, Jurgen. I am not
15 going to do much with the first topic, cytochrome.
16 I will Dr. Shiew-Mei Huang do that and then, after
17 that, I will introduce the pharmacogenetic topic.
18 So let me turn it over to Shiew-Mei.
19 DRUG INTERACTIONS
20 Introduction
21 DR. HUANG: Good morning.
22 [Slide.]
23 The first topic this morning, we will talk
24 about CYP2B6 and CYP2C8 drug interactions.
25 [Slide.]

1 Recall, at the last April meeting of this
2 committee I have discussed that the CDER Drug
3 Interaction Working Group is revising the guidance,
4 the In Vivo Drug Interactions Guidance, which was
5 published in 1999. Because of the emerging
6 technologies and tools, available, we have
7 additional information which prompted us to update
8 this guidance which is about three-years old.
9 We are going to use information that is
10 obtained from various workshops cosponsored by the
11 agency or the information that was published in the
12 PhRMA Position Paper or from internal research from
13 the reviewers about industry practices and
14 literature data.
15 As I discussed last time, we would like to
16 propose to include the information on
17 classification of CYP3A inhibitors in this revised
18 draft guidance which will be published for public
19 comment again so that when we have drugs that are
20 substrates of 3A, we will be able to prioritize our
21 study and we will be able to label drugs that are
22 strong or moderate inhibitors in the labeling to
23 facilitate the priorities of the interaction or
24 clinical significance of interactions in the drug
25 label.

1 We also discussed that we are seeing
2 increasing submissions that interactions are based
3 on P-glycoprotein. Based on our discussion in
4 April, the majority of the committee members agree
5 that the digoxin is a good substrate for
6 P-glycoprotein although it is also a substrate for
7 other transporters such as organic
8 anion-transporting peptide. Still, right now, it
9 is probably the best substrate to study because the
10 clinical significance of the interaction outcome.
11 In addition, in this '99 guidance, we will
12 also include in vitro evaluation technologies
13 discussing various substrates, inhibitors, inducers
14 for key cytochrome P450 enzymes. I will discuss
15 that a little bit more. In keeping with the
16 impending publication of the Final Rule of
17 Physician Labeling, we will also discuss case
18 examples indicating certain drug interactions that
19 may be put into the Highlights Section of the new
20 Physician Labeling in addition to an additional
21 section of drug interaction in the labeling.
22 [Slide.]
23 I just want to briefly discuss the current
24 practices on cytochrome-P450-based interactions.
25 In the in vitro evaluation, our reviewers have been

1 recommending and industry has been consistently
2 performing the evaluation of these key enzymes;
3 cytochrome P450-1A2, 2C9, 2C19, 2D6 and 3A, both
4 for reaction phenotyping, determining the metabolic
5 pathway of the new molecular entities. In
6 addition, these other enzymes, 2A6, 2B6, 2C8, 2E1
7 often are also evaluated.
8 For enzyme-modulating effects for
9 inhibition; again those five key enzymes have been
10 most consistently evaluated--if not, our reviewers
11 would provide feedback--also, for induction, since
12 2D6 has not been shown to be induced. These are
13 the four enzymes, plus some of the 2B6, 2C8
14 increasingly have been studied in this in vitro
15 evaluation.
16 As far as in vivo or clinical human
17 interaction studies, again, our reviewers have
18 communicated and the sponsor has been conducting
19 the studies to evaluate other drug effects on the
20 new molecular entity and the drug's effect on
21 others. They are often prioritized based on the in
22 vitro evaluation of cytochrome P450.
23 For example, if the reaction phenotyping
24 is indicating 3A as a major enzyme, there is
25 usually a study involving a strong inhibitor of 3A.

1 If this compound is shown to be inhibiting certain
2 enzymes, then the effect on others with appropriate
3 probe drugs are often conducting. Increasingly, we
4 have seen both in vitro and in vivo evaluation of
5 P-glycoprotein-based interactions using various
6 substrates in vitro, with digoxin, or in vivo with
7 digoxin, fexofenadine, as a substrate.
8 Depending on the drugs or previously known
9 similar compounds, other pathways such as phase-II
10 metabolizing enzymes or sudden peptide transport or
11 if it is renally secreted, certain compounds that
12 are inhibiting renal active secretion have also
13 been evaluated in various submissions.
14 [Slide.]
15 So why do we want to discuss CYP2C8 today?
16 The various cases of rhabdomyolosis involving
17 gemfibrozil in statins; there are data to show that
18 monotherapy of gemfibrozil and statins, on their
19 own, they have shown some dose or
20 concentration-related increase in the incidence of
21 myopathy or rhabdomyolosis. So this could be a
22 pharmacodynamic interaction. However, we are
23 seeing reports in the pharmacokinetics of statins
24 that have been changed because of coadministration
25 of gemfibrozil--I show cases there--since

1 gemfibrozil does not appear to interact with these
2 statins, via CYP3A, even some of the statins with
3 3A substrates.
4 There is a possibility of other enzymes or
5 transporters that are being affected by gemfibrozil
6 such as CYP2C8, 2C9, UGT, glucuronosyltransferases
7 or organic anion-transporting peptides.
8 [Slide.]
9 For example, just look at the sample of
10 literature data. Many of these were published by
11 Dr. Neuvonen and, later on, he will elaborate on
12 each study results more in detail. You can see
13 here the examples from statins such as fluvastatin,
14 a 2C9 substrate here. It didn't show an
15 interaction with gemfibrozil.
16 Rosuvastatin, as shown yesterday by one of
17 our presenters, there is a two-fold increase.
18 Simvastatin acid, lovastatin acid and cerivastatin,
19 there are various degrees of increase in area under
20 the curve when gemfibrozil was given together.
21 These were in healthy volunteers. Another,
22 rosiglitazone, a 2C8 substrate, repaglinide, also
23 as 2C8 substrate also so a different degree of
24 interaction. Here, with repaglinide, it is up to
25 more than an eight-fold increase when gemfibrozil

1 is given.
2 As a comparison, trimethoprim, which, in
3 the literature is also shown to be affecting 2C8,
4 has a relatively smaller effect on rosiglitazone.
5 [Slide.]
6 In our submissions, we have seen recently
7 compounds such as Drug A which has been shown to be
8 metabolized by CYP2C8. The major cytochrome P450s,
9 3A, 2C9, 2C19, 2D6, may not appear to affect this
10 metabolism. So what do we do if we would like to
11 know its interaction potential with this drug.
12 Especially as we discussed yesterday, certain
13 safety biomarkers such as QT prolongation have been
14 increasing evaluated when drugs are submitted for
15 approval.
16 If we need to evaluate QT prolongation, we
17 either use supertherapeutic dose or we try to
18 stress the system using enzyme-inhibitors to
19 increase the exposure and try to anticipate the
20 worst-case scenario. In that case, what can we do
21 to increase the exposure to see what is the maximum
22 exposure that will happen, assuming this is the
23 case, what inhibitors are available for us to
24 evaluate.
25 Or in another case, Drug B, which has been

1 shown to inhibit CYP2C8 in vitro, what are the
2 ideal or probe substrates of 2C8 that we can
3 evaluate this drug's effect on other drugs? So
4 this is about 2C8.
5 [Slide.]
6 So why are we interested in CYP2B6 which
7 we are discussing today? There are recent studies
8 on efavirens and bupropion which have shown that
9 2B6 is the key or the principal enzyme responsible
10 for efavirens metabolism and one of the key
11 pathways for bupropion. There are recent data on
12 inducers of 2B6 such as some HIV protease
13 inhibitors, dietary supplements such as St. John's
14 wort.
15 Our submission with Drug C is sometimes
16 metabolized by 2B6 in vitro. So, again, we would
17 like to see the clinical significance of other
18 drugs' effects on it, what kind of inhibitors are
19 available there for us to evaluate their clinical
20 significance.
21 [Slide.]
22 Today, we have invited two experts in the
23 field; Dr. David Flockhart to talk about CYP2B6
24 and drug interactions. Dr. Flockhart and his
25 colleagues at Indiana University have recently

1 published research data on efavirenz metabolism and
2 will give us a review in this field.
3 We also have Dr. Pertti Neuvonen from
4 University of Helsinki. Dr. Neuvonen and his
5 colleagues have published numerous articles
6 characterizing strong inhibitors such as
7 ketoconazole, itraconazole, on various probe
8 substrates of 3A to estimate their extent of
9 interaction. He has published a lot of
10 grapefruit-juice-related interaction and, more
11 recently, he has published various gemfibrozil and
12 statin interaction data, and also in vitro
13 evaluation of various substrates and inhibitors and
14 inducers.
15 [Slide.]
16 The issues for them to discuss and for the
17 committee to consider are what is the clinical
18 significance of 2B6- and 2C8-based interactions and
19 are there tools available, are there pro-inhibitors
20 for the clinical evaluation of 2B6- or 2C8-based
21 interaction, or do we have substrates that their
22 interactions are mostly based on 2C8.
23 Some of the examples that may be shown
24 later may have a lot of possible transporters
25 involved and we would like to know whether there

1 are good inhibitors and substrates that will be
2 able to provide us useful information particular to
3 these two enzymes. Also, maybe there are other
4 areas that we need to focus on based on this
5 particular evaluation.
6 [Slide.]
7 These enzymes are felt to be important
8 from our working-group discussion and this is just
9 to show you the big group of our Interaction
10 Working Group members from our Office of Clinical
11 Pharmacology and Biopharmaceutics, members from the
12 Office of Pharmaceutical Science, members
13 from--used to be from CBER, Center for Biologics,
14 and also from Office of the Commissioner who wants
15 to see what our current evaluation is and the
16 labeling impact, whether these are consistent with
17 the new proposed rule and how would this facilitate
18 the healthcare providers and patients to use the
19 labeling depending on how we will address the
20 interaction issues in the label.
21 With that, I would like to introduce Dr.
22 David Flockhart to discuss 2B6-related
23 interactions.
24 Evaluation of CYP2B6-Based Interactions
25 DR. FLOCKHART: Thank you, Shiew-Mei. It

1 is a great pleasure to be here this morning,
2 particularly, I must say, on the same podium as Dr.
3 Neuvonen whose work I have followed for a long
4 time. We have actually published together and
5 collaborated but we have never met until yesterday
6 evening.
7 [Slide.]
8 I am going to talk about cytochrome P450
9 2B6. Those of you who know me will know that I
10 really don't know much about this. But it is a
11 subject of a great deal of interest in our Division
12 of Clinical Pharmacology at Indiana and the work in
13 2B6 is led by Zeruesenay Desta. Dr. Desta has
14 currently a series of projects aimed at defining
15 probes and inhibitors of this important enzyme. So
16 I am going to talk a little bit about our thinking
17 about new ways of evaluating it.
18 [Slide.]
19 I am going to talk about some data on
20 expression because that is historically important
21 in terms of understanding why we have not spent a
22 lot of time on this cytochrome up until now and
23 then talk about some potential substrates, both in
24 vitro substrates and substrates that might be used
25 in the clinic, and then talk about inhibitors in

1 the same kind of context, ones that might be used
2 in test tubes and ones that might be used in
3 people.
4 2B6 is a heavily inducible enzyme. I
5 think that is one thing that is really obvious from
6 its study at this point. So interest in inducers
7 of it is as important, and there may be a large
8 number, actually, of important, clinically
9 important, interactions with this enzyme that
10 result in low concentrations, particularly of HIV
11 medications, that we, as yet, are--well, we are not
12 unaware of but we, as yet, don't understand in
13 terms of the mechanism.
14 [Slide.]
15 I think the main reason, as is the case
16 with many isoforms, and this would have been the
17 case in the past even for the two Cs, all of them,
18 2C9, 2C19 and 2C8, is that the early antibodies
19 that we always talk about, and I am referring in
20 particular to the classic paper published by
21 Shimada and Guengerich ten or fifteen years ago now
22 which first documented by Western Blot the amount
23 of different P450s in the liver.
24 On that, the amount of 2B6 expression was
25 very low. It actually isn't shown in their

1 diagrams but was estimated in the test to be a
2 minor component and less than 1 percent of the
3 total P450. Therefore, and as recently as two or
4 three years ago, in conversations with Grant
5 Wilkinson at Vanderbilt, he was absolutely
6 convinced that it played a tiny role in human drug
7 metabolism.
8 [Slide.]
9 This was why Grant thought that. This is
10 taken from a review article that Dr. Desta and I
11 have put together, but if you look just at the
12 detection percent on the left here, from a series
13 of studies published in the late 1990s--well, I
14 guess throughout the 1990s--there is a relatively
15 small n in the studies. So these are all
16 individual livers but, in a significant number, you
17 can't even pick up the enzyme at all.
18 If you just recall, you will see the rough
19 numbers here. So, 1 to 2 picamoles per milligram
20 of protein, which is not a lot of P450, in the
21 liver was detected except in one study, this one
22 from Japan, in which 19 picamoles were picked up.
23 This has a lot to do with the specificity
24 and sensitivity of the antibodies we were using at
25 the time. But the number of studies indicates the

1 potential interest in this isoform.
2 More recently, and you will notice that
3 the dates of these references on the right are
4 later--this is up until the present--in every liver
5 tested, or most livers tested in these studies, you
6 can actually pick up the enzyme. Not all, though.
7 And this may relate to genetic polymorphisms that
8 have been described but not terribly well
9 characterized to this point.
10 But you will notice, on the last slide, I
11 talked about 1 to 2 picamoles being present. The
12 average, in these studies--I haven't gone through
13 the somewhat disingenuous exercise of trying to
14 average all these things, but you see that it is
15 significantly higher, probably a lot higher, with
16 the newer antibodies and there are some that are
17 significantly higher.
18 Also, I think now people in the field
19 would agree there is a consensus that we have a
20 specific antibody. When you study using these
21 antibodies, the variability--there is a huge
22 variability in protein expression but also in RNA
23 expression. The RNA expression data is currently
24 confusing because Aaron Schutz and other people at
25 Mary Relling's institution have shown quite nicely

1 there are multiple splice variants of this enzyme
2 that might contribute to variations in its
3 activity. So we have yet to sort out really
4 confidence assays for the RNA. But, suffice it to
5 say, the amount is considerably more than we
6 thought it was originally.
7 [Slide.]
8 So new mono and polyclonal antibodies of
9 higher sensitivity and specificity have made it
10 clear that there is a greater frequency of
11 detection. I think, in all the livers we have ever
12 tested now, the enzyme is there, and there is more
13 of it and it looks rather less than 0.1 percent.
14 It averages about 6 percent of the total liver with
15 absolute maximum amounts that are really quite
16 significant, presumably in livers that are turned
17 on or people that are turned on for one reason or
18 another, up to 25 to 44 percent.
19 [Slide.]
20 This is taken from the paper that
21 Shiew-Mei referred to which is our in vitro study
22 of efavirenz metabolism. A couple of points about
23 this. Pharmacologists always have to put up
24 diagrams, structures, but there is an important
25 unusual group on this, this triethylene planar

1 group, monoplanar, group, out here which is common
2 to a number of substrates of cytochrome P450 2B6.
3 I am going to show you data that basically show
4 that this is the dominant route, this is the main
5 route, by which efavirenz is metabolized in people.
6 A minor route here we have recently shown
7 is mainly cytochrome P450 3A, but this, in people,
8 is about one-hundredth this route. So this route
9 is the dominant means of clearing this drug from
10 the body. It is an 8-hydroxylation in the 8
11 position down here whereas the 3A-mediated
12 metabolism is A7. It catalyzes the 7-hydroxylation
13 right here. You count from this side, so this is
14 7. This is 8 down here.
15 There is also metabolism of this, of the
16 metabolite, of the metabolite, although less
17 quickly to the 8,14-dihydroxy.
18 [Slide.]
19 Let me just show you some of the data that
20 supports this. These are data simply showing the
21 clearance of efavirenz, itself, from an in vitro
22 incubation. So this is the disappearance of the
23 parent. They might have parent left, if you like,
24 and you see the only one isoform under these
25 conditions which is 1 micromolar efavirenz,

1 approximately the concentration reached at steady
2 state during normal dosing of about 600 milligrams
3 a day. Only one isoform reduced it.
4 So these are the data that initially got
5 us interested in it. This is fairly comprehensive.
6 It does include 2C8, both 3A isoforms. There is a
7 difference between 3A4 and 3A5 out here which has
8 held up in subsequent studies. 3A5 seems to be a
9 more efficient catalyst of efavirenz metabolism
10 than 3A4.
11 [Slide.]
12 Our very first clinical data--this is the
13 first time I have shown this--phase I and phase II
14 here; phase I is in the absence of rifampin and
15 phase II is after 10 days of rifampin treatment.
16 You do see a decrease in bioavailability and an
17 increase in the rate of metabolism of efavirenz in
18 vivo.
19 This is something that you see with
20 cytochrome P450 2B6 but you also see it, obviously,
21 with cytochrome P450 3A, 2C9, 2C19, a number of
22 other isoforms.
23 We are currently conducting a study of
24 about 100 people in which we are trying to
25 determine at what point in this curve it would be

1 intelligent to conduct a phenotyping study; in
2 other words, one that might allow us to do a single
3 point determination to study a large number of
4 people in order to get some sense of the clinical
5 variability of this enzyme in vivo. That might be,
6 and we don't know the answer to this yet, a urinary
7 ratio of efficacy to 8-hydroxyefavirenz or it might
8 be a serum ratio. But we don't have those data yet
9 and I can't talk about it.
10 [Slide.]
11 This is a similar drug. This was
12 published in January of this year. It is a drug
13 with a number, DPC963 but you will notice a similar
14 structure up here. I am simply putting up this
15 complicated slide to make the point that 2B6
16 catalyzes metabolism of an efavirenz analogue as
17 well.
18 You will note that this drug also is
19 metabolized notably by 3A as well. But, again, the
20 dominant route to metabolism is by 2B6. All this
21 is saying, really, is that there are a number of
22 related drugs that are metabolized by the same
23 pathway.
24 [Slide.]
25 2B6 is also a low-affinity catalyst of

1 S-mephenytoin metabolism to Nirvanol. This is from
2 a paper published in 1996 that we became interested
3 in. I say low affinity because mephenytoin, which
4 we can't use without and IND anymore--it is off the
5 market in the United States, unfortunately. It is
6 a valuable probe drug, obviously, for cytochrome
7 P450 2C19, but, in this study, the metabolism of
8 mephenytoin not to is 4-hydroxy metabolite, which
9 is 2C19-mediated reaction, but to Nirvanol which is
10 the demethylation reaction of mephenytoin which was
11 studied. These authors showed that only one
12 isoform did this.
13 This was the only data in this paper, but
14 we became interested in this idea because we had
15 been interested in 2C9 team and actually had done a
16 study which we published in 1992 showing that
17 S-mephenytoin and omeprazole could be used as
18 probes for that.
19 So, what we wanted to do at the time, was
20 to take this large 200-person study, take their
21 urine and see if we could actually do 2B6
22 phenotyping from the same urine. Unfortunately,
23 that turned out not to be the case.
24 [Slide.]
25 This is largely because of work done by a

1 very smart Korean post-doc, Jim Ko, who showed at
2 the time, before we actually got into wasting these
3 valuable urine samples, that this same reaction,
4 the N-demethylation of mephenytoin at this
5 concentration can be carried out by two isoforms,
6 2B6, but also 2C9.
7 He went on to show in subsequent studies
8 that the high-affinity catalyst was 2C9 and not
9 2B6. So it remains unclear at the moment whether
10 or not one can use mephenytoin as a probe for 2B6.
11 Personally, I think it is rather compromised.
12 [Slide.]
13 I am going to skip this. This basically
14 just shows the metabolism of mephenytoin.
15 [Slide.]
16 These are our data suggesting the
17 R-mephenytoin might be a substrate probe for 2B6.
18 Certainly, in vitro, possibly, in the future as one
19 isoform that does it again. These data are rather
20 thin in the sense that they only are recombinant
21 enzyme data. We haven't done careful studies
22 because, at the time--this is 1996--we didn't have
23 any confident in vitro inhibitors of 2B6 that were
24 specific and only recently have we been able to
25 have those.

1 [Slide.]

2 Now, there are a number of inhibitors that
3 are now published clear and obvious. Not all of
4 them, unfortunately, are specific. It is very
5 clear that both paroxetine and sertraline can
6 inhibit this isoform using in particular bupropion
7 as a probe, the hydroxylation of bupropion as a
8 probe.

9 Antiretrovirals including nelfinavir and
10 ritonavir are potent inhibitors. Both ticlopidine
11 and clopidogrel have been shown by our group to
12 inhibit 2C8. Clopidogrel is metabolized primarily
13 by it. We and others have shown also that
14 thioTEPA, the chemotherapy agent, is an inhibitor
15 of cytochrome P450 2B6. We are pretty confident
16 that that happens in vivo and we have some data to
17 indicate that it is fairly specific in vitro.

18 [Slide.]

19 These are some of those data suggesting
20 that this is a specific P450 inhibitor in vitro.
21 This is just a percent of control activity with a
22 series of cytochrome P450 isoforms with a series of
23 different probes. This is 100 percent so
24 everything should be here. But when you coincubate
25 thioTEPA, I believe at 1 micromolar in this

1 experiment, you see a decrease principally in 2B6
2 although there is a little inhibition of 1A2 as
3 well.
4 When you look at this carefully, and you
5 do a dose-response to thioTEPA, and these are data
6 that we published, I think, three years ago now,
7 you see that 2B6 is preferentially inhibited
8 compared to the others. There are decreases in all
9 of these but the potent inhibition with an IC50 or
10 5 micromolar which is well below, actually, the
11 concentration that this drug reached in vivo, it is
12 here.
13 So, because of these data, we believe that
14 thioTEPA can be used as an in vitro inhibitor if
15 the conditions are done right and this low
16 concentration can be used as a specific in vitro
17 inhibitor of this enzyme. That is an important
18 tool to allow us to study it further.
19 It is the case, obviously, that the
20 thioTEPA is a chemotherapeutic agent and you can't
21 just give thioTEPA to normal volunteers. So it is
22 not something that we are going to be able to use
23 in vivo.
24 [Slide.]
25 This just shows the potency. We used

1 S-mephenytoin metabolism at high concentrations,
2 relatively high concentrations, to be inhibited by
3 thioTEPA. These are just Dixon plots indicating
4 that you see linear kinetics and potent inhibition.
5 [Slide.]
6 Cyclophosphamide has also been described
7 to be metabolized by this enzyme and it was first
8 described really carefully by a series of nice
9 studies done by Irv Wainer and his group at
10 Georgetown University and in Montreal when Irv was
11 there. This is the structure of cyclophosphamide.
12 Its metabolism to its principal active metabolite
13 which is 4-hydroxycyclophosphamide is carried out
14 primarily by 2B6--that is why it is in the red--but
15 also by these isoforms. A number of groups
16 including David Waxman's group and a number of
17 others have contributed to these studies as has
18 John Slattery's group at Seattle.
19 [Slide.]
20 So the difficult position we are in is we
21 have these in vitro data. It is not really--it
22 wasn't really clear, how much of this actually
23 occurs via 2B6 in vivo. But we have noted a study
24 from Holland by Huitema in 2000. What this is is a
25 study of a sequential treatment in cancer patients

1 with cyclophosphamide and thioTEPA.
2 In this situation here, what you are
3 looking at is concentration of drug against time in
4 two different sequences. So first, in this
5 situation, cyclophosphamide is given prior to
6 thioTEPA and you see the normal kinetics that you
7 would expect of cyclophosphamide. I just want to
8 point out that the concentration of the parent drug
9 is notably higher than that of the metabolite which
10 is in the squares below.
11 On the other hand, if you coadminister
12 thioTEPA, you give it I.V. at the same time, you
13 see a notable decrease in the red in the parent
14 concentration and a notable increase in the
15 metabolite concentration. So--I'm sorry; I got
16 that the completely wrong way around. This is the
17 parent here, which goes up, and the metabolite goes
18 down. So this is an inhibition of cyclophosphamide
19 metabolism, not an induction.
20 So we think, because of these data, that
21 thioTEPA is acting to inhibit 2B6 in vivo and
22 resulting in a change in cyclophosphamide
23 pharmacokinetics.
24 [Slide.]
25 As I indicated a moment ago, there are a

1 lot of inducers of this enzyme. In fact, many of
2 the substrates of this enzyme, we have not yet
3 found one that doesn't seem to auto-induce its own
4 metabolism. Rifampin, hyperforin, phenobarb,
5 ritonavir, phenytoin, carbamazepine, all induce.
6 We are familiar with these as ligands for PXR and
7 sometimes CAR.
8 The HMG-CoA reductase inhibitors,
9 interestingly, have been shown in some situations
10 to induce 2B6 metabolism as have nevirapine induces
11 its own metabolism as does efavirenz. Clotrimazole
12 has been shown in vitro to as well and there is
13 recently a clinical study indicating that
14 artemisinin induces the metabolism of bupropion.
15 [Slide.]
16 So, overall, 2B6 is a significant
17 contributor to hepatic CYP expression. The number
18 of substrates is growing and I anticipate that the
19 number of submissions to the agency will grow
20 although Shiew-Mei tells me that there are a lot
21 more substrates coming over the FDA's desk that are
22 2C8 than there are 2B6.
23 Efavirenz and bupropion, we believe, are
24 specific in vitro probes. I haven't spent much
25 time talking about bupropion because we haven't

1 studied it much ourselves. But there is a reason
2 we haven't studied it and that is because we felt
3 early on that it was pretty clear that its dominant
4 route of metabolism is via 3A and not through 2B6.
5 Although it does have a fairly specific 2B6 route
6 of metabolism, the hydroxylation, most bupropion is
7 via another route. So this compromises its utility
8 as a probe.
9 ThioTEPA is a specific inhibitor of 2B6,
10 we believe. There is clearly no evaluable specific
11 inhibitor yet of 2B6 in vivo that we can use and we
12 really need one, you know, to be able to prove for
13 sure that a lot of reactions are occurring via this
14 enzyme in vivo.
15 Lastly, we do think efavirenz is a
16 potentially valuable in vivo probe for the activity
17 of more currently evaluating that.
18 Thanks for your attention. I would be
19 glad to take a couple of questions.
20 DR. VENITZ: Thank you, David.
21 Any specific questions for David?
22 Shiew-Mei?
23 DR. HUANG: You listed ritonavir as a 2B6
24 inhibitor and later on as an inducer. This is
25 similar to the situation with ritonavir with 3A.

1 DR. FLOCKHART: Yes.
2 DR. HUANG: Ritonavir is shown to
3 self-induce. It is an inducer for 3A. It is an
4 inhibitor of 3A. Although the 10-day or 14-day
5 study, most of the studies with ritonavir have
6 shown an inhibition effect.
7 DR. FLOCKHART: Yes.
8 DR. HUANG: That is the basis for
9 ritonavir and nelfinavir.
10 DR. FLOCKHART: The nelfinavir with
11 ritonavir is inhibition.
12 DR. HUANG: Right. I wonder if, for 2B6,
13 do we know about what is the net effect?
14 DR. FLOCKHART: No. It is clearly in
15 vitro. Several groups now--I think three groups
16 have shown that it is an inducer in vitro. In our
17 hands, it is a good inhibitor in vitro but we don't
18 know in vivo. I guess, with ritonavir, you have to
19 be a little careful about that to net. After about
20 ten days or two weeks, it is clearly an inhibitor
21 but there are periods in between when it would be a
22 net inducer.
23 DR. SADEE: David, I assume that this is
24 all hepatic activity.
25 DR. FLOCKHART: The data that I am

1 presenting is hepatic activity. It is clearly
2 present. I cut out a slide showing some of our
3 work and the work from Mikael Akoban's group and
4 Aaron Schutz' work indicating that it present in a
5 lot of tissues. It is not just an hepatic enzyme.
6 DR. SADEE: Because that could also make a
7 big difference in terms of inducibility. If there
8 is also a lot of extrahepatic activity, the
9 inducibility will--
10 DR. FLOCKHART: Absolutely. Notably, in
11 my business, it is present in the breast. It is
12 present in muscle. It is present in CNS. It is a
13 very widely distributed isoform which may have all
14 kinds of interesting implications. It is also an
15 effective catalyst of a lot of endogenous things
16 like testosterone, estradiol and so on.
17 DR. SADEE: It could be present in tumor
18 as well.
19 DR. FLOCKHART: It is present in some
20 tumors. That has been shown, active in tumors, RNA
21 protein and activity.
22 DR. SADEE: Another question. The
23 variability; is this caused by maybe
24 pathophysiology? Is there anything known about
25 particular states of liver disease?

1 DR. FLOCKHART: I would really be going
2 out on the edge to suggest that, Wolfgang, at the
3 moment. But it clearly a very inducible enzyme.
4 You can turn it on very easily. It seems to be
5 less inhibitable, at least in our hands. It is
6 something that is very sensitive to the PXR and
7 CAR-inducing mechanisms and maybe others.
8 DR. SADEE: One more comment, and it is
9 semantics, basically. I always feel very
10 uncomfortable about specific inhibitors.
11 DR. FLOCKHART: Yes; you never know until
12 you have studied for infinity.
13 DR. SADEE: That is why it is so--just for
14 official use, I would strongly recommend using
15 "selective."
16 DR. FLOCKHART: Selective; okay. I have
17 tried to use the term "relatively specific."
18 DR. LESKO: David, what do we know about
19 the distribution of 2B6 activity in the population
20 and what is the range of expression or activity,
21 say, from low to high? Is it like 3A4, for
22 example, or is it like something else?
23 DR. FLOCKHART: The problem is we don't
24 really have a good probe at the moment in vivo, so
25 I think we are conducting a study right now that

1 should give us a handle on that using efavirenz.
2 There are studies that have been done by Ed Lecluse
3 and others indicating there is a fair amount of
4 variability, ten- to twenty-fold variability, in
5 bupropion hydroxylation in people.
6 But my problem with that is that some of
7 that could be influenced by 3A activity in
8 alternative routes. So, in this particular
9 setting, 2B6 variability, I think we really don't
10 have the data yet, Larry. I would be reluctant to
11 extrapolate the in vitro variability in livers
12 although, of course, that is about the variability
13 you see in 3A.
14 DR. HUANG: We can elaborate on the
15 discussion later on but I just want to follow on
16 Wolfgang's discussion on nonselective inhibitors.
17 Recently, we have been discussing drug interactions
18 whereby you want to use two drugs to inhibit two
19 major, equally major, pathways in order to create a
20 worst-case scenario.
21 DR. FLOCKHART: A really bad thing, to
22 create a really bad thing.
23 DR. HUANG: A really bad case. So it may
24 not be a bad idea to use a nonspecific inhibitors
25 where you could inhibit one major pathway and the

1 other one that you are also concerned with.

2 Here, you have listed several that are not

3 specific. For example, ritonavir has various

4 pathways.

5 DR. FLOCKHART: Right.

6 DR. HUANG: But if you know this drug is

7 not metabolized by all the other pathways, and we

8 know that when it is a strong inhibitor--

9 DR. FLOCKHART: That is a very, very good

10 point. So Bob Temple has, many times, and I am

11 sure both you and Larry have made the point that,

12 if you want to study the worst possible interaction

13 with 3A, you have got to kill the thing with

14 ketoconazole. So one could make the case, if

15 something is metabolized, both by 3A and 3B6, that

16 you could coadminister a drug that inhibits both,

17 like Ticlid, like ticlopidine, which is a fairly

18 effective inhibitor of both drugs.

19 Ketoconazole, actually, interestingly, at

20 high concentrations, you have to use a fair amount

21 of ketokonazole but it seems to kill 2B6 as well if

22 you go high enough.

23 DR. HUANG: Just to clarify; for

24 ticlodipine, is it the parent drug that is active

25 for both, or is the metabolite.

1 DR. FLOCKHART: The parent drug is the
2 inhibitor.
3 DR. HUANG: For both; okay.
4 DR. FLOCKHART: Yes.
5 DR. HUANG: Thanks.
6 DR. SADEE: I have one more question,
7 David. If the variability of 2B6 is as high as it
8 appears to be and the variability in 3A4, for
9 instance, also, so you would have a substrate for
10 both. Then, in one person, there would be a 3A4
11 substrate. In another person, it may be the 2B6
12 substrate and the other enzyme may play no role.
13 So I am just wondering about labeling this or
14 presenting the information that this is a substrate
15 for both enzymes and, in reality, in individuals,
16 there may be other--
17 DR. FLOCKHART: I guess that might be the
18 case. I don't have data yet, Wolfgang. I think
19 that generically I would agree with you. I think
20 there may be people for whom there is very little
21 3A activity and 2B6 would be the dominant route.
22 My bias, at the moment, and it is a bias based on
23 not much data, but I will share the data, is that
24 2B6 is really dominantly the enzyme for efavirenz.
25 Even when you turn on with rifampin, you

1 don't see a lot of 3A contribution. The basis for
2 that is the big difference in affinity between the
3 two isoforms for efavirenz and the fact in the
4 urine of the patient that I showed you that was
5 induced, we see the 2B6 hydroxylation, the
6 8-hydroxylation route, really turned on. There is
7 a lot of that metabolite in the urine and very
8 little of the 7-hydroxymetabolite although that is
9 increased as well.
10 So I think, in that situation, when it is
11 really turned on, there is more 3A. But it is
12 still a dominantly a 2B6 drug.
13 DR. VENITZ: Any further questions? Thank
14 you, David.
15 Our next speaker is Dr. Neuvonen. He is
16 going to share with us his experiences with 2C8.
17 Evaluation of CYP2C8-Based Interaction
18 DR. NEUVONEN: Thank you, Mr. Chairman,
19 dear colleagues and committee members.
20 [Slide.]
21 In my talk about CYP2C8 and drug
22 interactions, I will review substrates, inhibitors
23 and inducers of 2C8, some in vivo interaction
24 studies and finally present some suggestions for in
25 vitro and in vivo studies.

1 [Slide.]

2 CYP2C8 is highly expressed in the liver.
3 The protein content of 2C8 is on the same level as
4 that of 2C9 and clearly than that 2C19. There is
5 lots of interindividual variation in the protein
6 content of 2C8 and 2C8 seems not to be detectable
7 in the intestine.

8 [Slide.]

9 Many drugs are substrates for 2C8. In
10 vitro studies, paclitaxel, amodiaquine and
11 torsemide have been used. 6-alpha-hydroxy
12 paclitaxel is a 2C8-mediated reaction and
13 amodiaquine is metabolized mainly by 2C8.
14 Torsemide is metabolized both by 2C9 and 2C8 but,
15 in some conditions, this can be used as a marker
16 substrate.

17 In vivo studies, cerivastatin, repaglinide
18 and rosiglitazone have been used as substrates.
19 Also many other compounds are substrates for 2C8.
20 For example, many of the substrates of CYP3A4 are
21 also substrates for 2C8. But the relative
22 contribution of different CYP enzymes may depend on
23 the substrate concentration used, for example, in
24 in vitro studies.

25 [Slide.]

1 This slide shows the relationship between
2 amodiaquine metabolism and paclitaxel,
3 6-alpha-hydroxylase activity. As can be seen,
4 amodiaquine clearance and formation of
5 N-desethyl-amodiaquine correlate very well with the
6 activity of paclitaxel 6-alpha-hydroxylase. This
7 was a study where microsomes from ten human livers
8 were used.
9 [Slide.]
10 Trimethoprim is a competitive of 2C8. It
11 has a Ki value of about 32 micromolar and it is
12 relatively selective up to 100 micromolar
13 concentration.
14 [Slide.]
15 As can be seen here, the inhibition of
16 other CYP enzymes is very little, up to the
17 concentration of 100 micromolar.
18 [Slide.]
19 However, when higher concentrations are
20 used, and here are shown 250 and 500 micromolar
21 concentrations, trimethoprim inhibits, for example,
22 2D6, 3A4, 2C19, 2C9, 1A2 enzymes.
23 [Slide.]
24 Quercetin is a competitive and potent
25 inhibitor of 2C8. It has a Ki value of about 2

1 micromolar but quercetin is also a potent inhibitor
2 of 1A2. So it is a nonselective inhibitor of 2C8.
3 Glitazones are potent inhibitors of 2C8.
4 Gemfibrozil is nonselective but it seems to work
5 both in vitro and in vivo. There are also many
6 other nonselective inhibitors; for example, many
7 substrates of 3A4 seem to be inhibitors of 2C8.
8 [Slide.]
9 Here are shown Ki values of some
10 glitazones. Rosiglitazone and pioglitazone are
11 relatively selective for 2C8 whereas trogliazone
12 inhibits more 2C9.
13 [Slide.]
14 Some of the so-called selective probe
15 inhibitors used as a diagnostic inhibitors in in
16 vitro studies are also inhibitors of 2C8 at the
17 concentrations generally used. For example,
18 ketoconazole at the concentration of 1 micromolar
19 considerably inhibits activity of 2C8.
20 Ketoconazole is a noncompetitive inhibitor with an
21 apparent Ki value of 2.5 micromolar.
22 So data regarding ketoconazole--let's say
23 that the inhibition data where it has been used as
24 an inhibitor of CYP2A isoforms may include also
25 inhibition of 2C9. Also DDC is a significant

1 inhibitor of 2C8.

2 [Slide.]

3 2C8 is clearly inducible. In vitro

4 rifampin is a more potent inducer of 2C8 than of

5 2C19 or 2C9 and rifampin is more potent as an

6 inducer of 2C8 than, for example, phenobarbital or

7 dexamethasone. In in vivo studies, rifampin

8 clearly decreases, for example, the AUC of

9 repaglinide which is a substrate of 2C8. It

10 decreases the AUC roughly by 60 percent. Of

11 course, here, maybe the induction of 3A4

12 contributes to the finding, but probably it is best

13 to measure extent to induction of 2C8.

14 [Slide.]

15 In the following, I will present some in

16 vivo interaction studies where gemfibrozil and some

17 statins or oral antidiabetics have been

18 administered. All these studies are randomized

19 crossover studies in healthy volunteers where

20 gemfibrozil or placebo or a comparator have been

21 given for three to four days. Then, on Day 3, a

22 single dose of either cerivastatin, simvastatin,

23 lovastatin, repaglinide or rosiglitazone has been

24 administered.

25 [Slide.]

1 Here are data on the effect of the
2 gemfibrozil on cerivastatin. As can be seen here,
3 gemfibrozil greatly increases the AUC of unchanged
4 cerivastatin. The AUC was increased on average
5 five or sixfold and in 110 healthy subjects the
6 increase was tenfold. Also, the concentrations of
7 cerivastatin, lactone or M1 metabolite, which is
8 formed by CYP3A4, are greatly increased by
9 gemfibrozil whereas the concentration of M23
10 metabolite is drastically decreased. This M23
11 metabolite is formed by CYP2C8.
12 I think that this pharmacokinetic
13 interaction greatly contributes to this toxicity of
14 the gemfibrozil/cerivastatin combination which has
15 been previously found.
16 [Slide.]
17 Gemfibrozil inhibits cerivastatin
18 metabolism also in vitro, the formation of 23
19 metabolite is clearly reduced by gemfibrozil.
20 [Slide.]
21 Here are shown the effect of gemfibrozil
22 of the pharmacokinetics of simvastatin or
23 simvastatin acid. Gemfibrozil increased AUC of
24 simvastatin acid about two, threefold, whereas the
25 AUC of the parent simvastatin was unchanged.

1 [Slide.]

2 Here is shown the role of CYP enzymes in
3 simvastatin metabolism and it can be seen that
4 simvastatin acid is metabolized by CYP3A4 but also
5 partially by 2C8. It seems that gemfibrozil could
6 inhibit this 2C8-mediated partway. Of course,
7 there are also some alternative explanations for
8 the finding.

9 [Slide.]

10 Gemfibrozil also increases the AUC of
11 lovastatin acid whereas the AUC of parent
12 lovastatin remains unchanged. Bezafibrate had no
13 effect.

14 [Slide.]

15 Here are shown the effect of gemfibrozil,
16 itraconazole and their combination on the
17 concentrations of repaglinide and its M1
18 metabolite. Repaglinide is a short-acting oral
19 hypoglycemic agent. Plasma concentrations of
20 unchanged repaglinide were increased greatly by
21 gemfibrozil whereas itraconazole had only a minor
22 effect on plasma concentrations of repaglinide.
23 The combination of gemfibrozil and itraconazole
24 drastically increased plasma concentrations of
25 repaglinide.

1 Gemfibrozil increased greatly the
2 concentration in one metabolite which is formed
3 mainly by CYP3A4 and, as expected, itraconazole
4 greatly reduced it.
5 [Slide.]
6 Here are shown the effect of two CYP3A4
7 inhibitors and gemfibrozil on the AUC of
8 repaglinide. The data regarding clarithromycin are
9 derived from another study. Clarithromycin and
10 itraconazole both increased the AUC roughly 40
11 percent. Gemfibrozil increased it on average
12 eight-fold and the combination of the gemfibrozil
13 and itraconazole about twenty-fold. Of course, the
14 flat glucose-lowering effect was clearly increased
15 along with these increased concentrations.
16 [Slide.]
17 Here are shown the effect of gemfibrozil
18 of rosiglitazone. The AUC of rosiglitazone was
19 about two, three-fold--increased two, three-fold,
20 by gemfibrozil and both the Cmax and half-life were
21 increased.
22 [Slide.]
23 In the final two figures, I will suggest
24 some possibilities for in vitro and in vivo
25 interaction studies, in vitro human liver

1 microsomes or recombinant human 2C8 enzymes can be
2 used. Paclitaxel and amodiaquine seem to be well
3 suitable substrates. Torsemide is useful only with
4 recombinant 2C8 because also 2C9 is metabolizing
5 torsemide and forming just the same metabolites.
6 Trimethoprim, quercetin and pioglitazone
7 or rosiglitazone can be used as inhibitors and
8 rifampin is useful as an inducer.
9 [Slide.]
10 For in vivo studies, repaglinide can be
11 used as a probe compound, probe substrate. Also,
12 rosiglitazone is useful. Cerivastatin would be
13 also useful but, of course, it may be difficult to
14 get for in vivo studies. Amodiaquine is probably
15 too toxic to be used in interaction studies.
16 Gemfibrozil can be used as an inhibitor.
17 Of course, one should remember that it is
18 nonselective. It inhibits, for example, 2C9 and
19 also some transporters, at least OATP2.
20 Trimethoprim is more selective but it is not very
21 potent. By now, there have been only very few in
22 vivo data about trimethoprim as an inhibitor of
23 2C8.
24 Pioglitazone and rosiglitazone could also
25 be possible inhibitors. Rifampin is a useful

1 inducer but, in conclusion, further studies are
2 needed to find optimal probe substrates and probe
3 inhibitors, particularly for in vivo interaction
4 studies with 2C8.
5 Thank you.
6 DR. VENITZ: Thank you, Dr. Neuvonen.
7 Any questions? Mary?
8 DR. RELLING: So some of those
9 interactions that you described at the end with
10 gemfibrozil were remarkably potent interactions.
11 So do you suspect that there are other mechanisms
12 involved besides just CYP2C8, with gemfibrozil, for
13 example? That was a 1900 percent effect on AUC.
14 DR. NEUVONEN: I agree that there may be
15 also other possibilities. For example, the role of
16 OATP2 inhibition should be clarified in these
17 interactions. But surprisingly all substrates of
18 2C8 we have studied by now together with
19 gemfibrozil, there has been a significant
20 interaction with gemfibrozil and those substrates.
21 DR. RELLING: That is in proportion to
22 their relative KM's or Ki's roughly.
23 DR. NEUVONEN: Not very well. So it is
24 not sure if it is a parent gemfibrozil or some of
25 its metabolites, for example. Of course, we are

1 not aware of the liver concentration of
2 gemfibrozil.
3 DR. HUANG: I was just going to add to it.
4 I guess many of these drugs that you study as a
5 substrate, with gemfibrozil as a 2C8 substrate, the
6 concentration of 2C8 may vary among these drugs and
7 so KM may not be the only determining factor.
8 But I want to comment on do we know
9 anything about gemfibrozil dose and the effect on
10 some of the statins? Do we know any dose effect.
11 DR. NEUVONEN: We have used the standard
12 dose, 1200 milligrams per day and we have not
13 studied possible dose-effect correlation. So I
14 have no answer to that at this time.
15 DR. HUANG: I was wondering, is there an
16 interaction between itraconazole and gemfibrozil?
17 DR. NEUVONEN: Between itraconazole and--
18 DR. HUANG: Itraconazole and gemfibrozil.
19 DR. NEUVONEN: I am not aware of it. We
20 have not studied it.
21 DR. HUANG: Okay, because the
22 nineteen-fold increase was only when itraconazole
23 was added.
24 DR. NEUVONEN: Actually, I would like to
25 correct my previous answer. Of course, we measured

1 the concentration of itraconazole too in these
2 studies. If I remember correctly, it was, perhaps,
3 that plasma concentrations of gemfibrozil were
4 decreased.
5 DR. HUANG: Decreased.
6 DR. NEUVONEN: Yes. It has been reported
7 in the publication. If I remember correctly; yes.
8 We thought that it could be a displacement from
9 protein binding or something like that, but we have
10 no final--
11 DR. HUANG: I was just wondering, the
12 higher effects of gemfibrozil on repaglinide when
13 itraconazole was additionally added to the regimen,
14 was it due to its effect of gemfibrozil or just
15 added other mechanisms of interaction because
16 itraconazole, itself, doesn't really affect
17 repaglinide.
18 DR. NEUVONEN: In the case of repaglinide,
19 I guess, or at least one explanation could be, that
20 repaglinide is metabolized by 2C8 and 3A4. If both
21 of these metabolic enzymes will be blocked, then
22 this could explain more than the additive
23 interaction observed with these compounds.
24 DR. VENITZ: Dr. Derendorf?
25 DR. DERENDORF: You mentioned quercitin as

1 a potent inhibitor. I would assume that data comes
2 from in vitro studies. When you give quercitin,
3 you hardly find any in the blood. It gets
4 converted to the conjugate. So is there any
5 information on the quercitin conjugates or any in
6 vivo interaction data.
7 DR. NEUVONEN: Actually, we have no
8 experience of our own with quercitin. These data
9 are based only on the literature. So I have not
10 seen any in vivo studies with it.
11 DR. VENITZ: Larry?
12 DR. LESKO: What is the nature of the
13 relationship between the in vitro data and the in
14 vivo data on the substrates and inhibitors? In
15 other words, is there a qualitative rank order
16 that, if I have a sensitive substrate in vitro, I
17 would see the same sensitivity in vivo in the
18 comparative sense, or, conversely, if I had a weak
19 inhibitor in vitro, would it serve as a weak
20 inhibitor in an in vivo situation for the same
21 substrate.
22 DR. NEUVONEN: You mean, basically, now
23 with 2C8 enzyme?
24 DR. LESKO: With 2C8.
25 DR. NEUVONEN: Actually, our data with

1 trimethoprim--well, based on our in vitro data, we
2 calculated, if I remember correctly, that in vivo
3 it should inhibit roughly 20/70 percent 2C8
4 activity. I think that the in vivo data, actually,
5 we have in press in line with these findings. So
6 trimethoprim increases the AUC of
7 of repaglinide but not as much as gemfibrozil.
8 DR. VENITZ: David?
9 DR. FLOCKHART: Two things. I think I
10 would like to congratulate you for just doing the
11 experiment with both itraconazole and gemfibrozil.
12 As Mary points out, it is a big effect. But I
13 think this is relevant to the kind of evolution of
14 the guidances about drug interactions. We have all
15 been talking about multiple drug interactions. I
16 think many of us have been saying for many years
17 that, while the real world is people are taking
18 many, many different drugs, we have been studying
19 one-on-one drug interactions.
20 So I would just like to emphasize the
21 point that we need to move into a mode, and I know
22 Larry is aware of this problem, of studying more
23 multiple-drug interactions. There has been data,
24 really, for twenty-five years indicating that, in
25 the elderly, they really get into bad adverse drug

1 reactions once they are over five or six
2 medications, at least in the V.A. system. I think
3 that is important.
4 I would also--since you are here and in
5 this country, I would like to thank you again for
6 coming and for the large contribution that your
7 group has made to our understanding of these things
8 over many years. Many, many times we, in the U.S.,
9 have talked around doing studies, thinking of doing
10 things. Your group has actually been the one that
11 has actually done it.
12 DR. NEUVONEN: Thank you. Actually, one
13 point I would like to add is that we should not
14 look too much at the mean increases but just to
15 look at the interindividual variation in the extent
16 of interaction because I guess that just those
17 adverse effects are coming from those patients who
18 are most sensitive and, therefore, the variability
19 in the extent of interaction should be
20 overreported.
21 For example, in the case of cerivastatin,
22 there were, even in the material of ten homogeneous
23 students, an increase of 10 in 1, so what is the
24 variation in a typical population.
25 DR. KEARNS: I think you just answered the

1 question I was going to ask. It is remarkable.
2 Not only have you come a long way, but you have
3 managed to at least read my mind a bit. But, my
4 point is from a regulatory perspective. To me, and
5 maybe this is just a very simple way of thinking
6 about it, but it is the constitutive expression of
7 the enzyme in a patient that will determine the
8 extent of the interaction.
9 So, from a regulatory standpoint, when you
10 are contemplating putting in labeling about an
11 interaction and you may be basing that on mean
12 data, how do you reconcile that with respect to a
13 prudent warning. If it is a drug that has a huge
14 therapeutic index, it makes no difference. But if
15 it is a drug that is used to treat cancer or other
16 narrow-therapeutic-index drugs, it is a big issue.
17 So, to my friends at FDA, how are you
18 going to deal with that?
19 DR. LEE: May I answer that? In the last
20 two advisory meetings, we actually proposed a
21 method to look at the probability of an adverse
22 event due to the drug-drug interaction. So we
23 would look at the PK safety relationship and
24 calculate, based on the distribution of PK
25 change--and calculate what will be the probably of

1 an adverse event.

2 So we would not only look at the mean

3 value but also look at the patients who are on the

4 extreme.

5 DR. SHEINER: That's the right thing to do

6 except that now your data requirements go way up

7 because you are now talking about estimating sort

8 of tails of the distribution, not that they are not

9 the most important. They are because we are

10 concerned about 1 in 100, 1 in 1000, events. There

11 are a series of things. But the amount of data you

12 need to actually get a confident estimate of

13 something like the tail area is really, really

14 nasty. It is not just like twice as much.

15 Have I got that right?

16 DR. HUANG: Just to add to that, I think

17 at the last advisory committee meeting we presented

18 a case where we are estimating the percent

19 population that may have QT prolongation more than

20 30 milliseconds due to drug interactions or due to

21 renal disease because that particular example, the

22 drug is both metabolized and renally excreted. So,

23 actually, the assimilation also shown was a

24 percentage of population which would result in QT

25 prolongation more than 30 milliseconds where you

1 have both renal failure, a certain
2 creatinine-clearance range, and having
3 ketoconazole. So we are approach that
4 quantitative approach. We haven't done the multi
5 drugs yet but we are doing two different conditions
6 to estimate that. We have not applied widely but
7 we are starting to.
8 DR. KEARNS: I understand that. That is
9 laudable. But, again, and I hate to go back to the
10 QT discussion because it is always painful for me,
11 but ketoconazole is an IKR-channel inhibitor.
12 Until you can factor in the intrinsic ability of
13 that interacting substrate to have its own
14 pharmacologic effect that may produce an adverse
15 effect, then the kinetic piece is just part of it.
16 As Dr. Sheiner just mentioned, then the n
17 goes up way big to factor out maybe the
18 pharmacodynamic piece of it.
19 DR. HUANG: Yes; our reviewers take note
20 of that and actually this was in the consideration
21 when we look at the data on some of the inhibitors
22 that we would recommend in order to increase the
23 exposure of drugs that we are evaluating for QT
24 prolongation.
25 DR. KEARNS: Still on the point that Greg

1 raised, I don't know if you had something in mind
2 as an alternative but, yes, in fact, averages are
3 used, or mean values are used, along with some
4 other considerations, I suppose, in making
5 recommendations in the label. Is what you are
6 asking related to the way this information is
7 expressed in the label?
8 For example, is it leading to expression
9 of ranges of let's say area-under-the-curve
10 increases? How else can you do it, I guess, is
11 what I am sort of trying to get to. What are some
12 alternatives to the way it is done currently?
13 DR. KEARNS: I wish I knew. But what is
14 troubling me sitting here as a pediatric
15 pharmacology person is that, if we look at
16 developmental expression, activity of the enzymes
17 changes over time. There are not a lot of
18 drug-interaction studies in children to see, at
19 three months of age, if you look at the P450-based
20 interaction and the extent of it, how far do you
21 move it kinetically, compared to when the enzyme is
22 fully expressed.
23 Again, it boils down to the therapeutic
24 range so there is this clinical need for people to
25 generalize and to put interactions on tables and

1 charts or to memorize the important ones. I think,
2 at some level, that is good. It is like a warning.
3 But, at another level, if the pharmacist refuses to
4 fill the prescription because there is a drug
5 interaction in the label, then patients can be
6 deprived of therapy where the interaction for a
7 given person may not exist in a meaningful way.
8 So I don't know the answer, but it is a
9 problem.
10 DR. HUANG: That is why at least one of
11 the approaches that we are taking is to warn about
12 the most significant interaction. That is why we
13 are trying to put in the labeling that you are
14 dealing with a drug with a strong inhibitor or, if
15 this drug is given with a strong inhibitor what you
16 should do.
17 Hopefully, this will be caught up in the
18 computer system where you can search for only
19 strong inhibitors and that is where you put maybe
20 three flags instead of one to make a difference
21 between all these interactions that will come up as
22 a warning when patients are--I think that is the
23 first step. At least that is what we are trying to
24 do to minimize the trivial interactions and flag
25 the important ones.

1 DR. SHEINER: Not to dwell too much on the
2 technical side, but means are bad descriptors for
3 distributions that are highly skewed. This is
4 probably what you have got here. It depends on
5 which way you look at it. If you look at AUC
6 increase and it goes up twenty-fold, that is a huge
7 skew to that side.
8 If you just flip it upside down and say
9 you are looking at the amount of active enzyme or
10 something like that, then that is going towards
11 zero and that actually compresses the thing.
12 So there usually is some reasonable
13 transformation, whether reciprocal or square root
14 or whatever, that will allow you to get a more
15 symmetrical distribution and then allow you to
16 maybe make a little bit more confident statement
17 about what fraction of people are beyond a certain
18 limit. That is sort of a very simple type of a
19 thing.
20 The other point is progress can be made
21 here because these are really population issues.
22 In other words, we study the population and if we
23 can know what the distribution of various isoforms
24 of the enzymes and so on are, and we can know what
25 the distribution--perhaps this is a little bit

1 tougher--of the sensitivity of individuals if it
2 varies.
3 If it doesn't vary, if it is just a matter
4 of this particular enzyme has this particular
5 inhibition potential from that drug, then maybe we
6 can get a lot from sort of these pooling data
7 across multiple sources rather than having every
8 manufacturer have to go out and get his panel of
9 people and go and do the same thing over and over
10 again.
11 DR. HUANG: Just to add another point. We
12 are starting to--at least for extreme cases, we
13 have started to put it in labeling; for example,
14 Strattera, which was talked about yesterday, or
15 last week, actually. In the labeling, we actually
16 talk about CYP2D6 inhibitors effects on an
17 extensive metabolizer versus a poor metabolizer.
18 So I guess, in the past, we just
19 mentioned, it is a D26 substrate and with a 2D6
20 inhibitor, you may need to be aware of the adverse
21 events and--we didn't say dose adjustment. But, in
22 poor metabolizers, we do not expect to have an
23 interaction. So I think this needs to be taken
24 into consideration. We have started to put this
25 information on the labeling so, at least in the

1 extreme cases, where we know that a poor
2 metabolizer, you don't expect an interaction. That
3 we are putting in.
4 The subjects with intermediate metabolized
5 activity, then you may see variable interaction,
6 extent of interaction. I think we are starting to
7 see this and I think this may be discussed more in
8 the later session. But at least we try to address
9 one aspect.
10 DR. LEE: Just to follow up Dr. Sheiner's
11 suggestion. Are you suggesting that if we see a
12 sort of increase of AUC or PK due to an inhibitor
13 we can verify the distribution of the increase to a
14 population PK type of analysis using the pooled
15 data?
16 DR. SHEINER: No; I wasn't saying that. I
17 am not exactly sure how you could verify anything.
18 I was just saying that when you think about how you
19 describe--let's say even in the label, how you
20 describe what you are likely to run into. I am
21 saying if you have a very skewed distribution, the
22 mean is not a good descriptor of what is going on.
23 It is sort of like we saw yesterday with
24 the QT interval. We can't get at the individual
25 parts of the heart and their conduction and their

1 repolarization but the mean there is really
2 insensitive to the fact that you have got
3 heterogeneity which is what the issue there is.
4 It is the same thing here. You have got
5 heterogeneity in the population as to how much
6 enzyme they have got. So X amount of drug will be
7 a lot of problem for somebody but not much for
8 someone else. You want to find some way of A,
9 estimating what is important, and B, expressing it
10 in such a way that people can understand it. All I
11 am saying is taking the average may not be what you
12 want to do.
13 DR. VENITZ: I think you have got a lot of
14 general comments back on drug-drug interaction.
15 Let me get back to what you guys what us to talk
16 about which is 2B6 and 2C8.
17 Committee Discussion
18 DR. VENITZ: The question put in front of
19 the committee is what our recommendations would be,
20 as to committee support, given the state of the
21 art in our knowledge on 2B6 and 2C8. I think you
22 are primarily interested in in vitro substrates, in
23 vitro inhibitors and in vivo substrates and in vivo
24 inhibitors.
25 What is the committee's feedback or

1 response to that question?

2 David, do you want to summarize?

3 DR. FLOCKHART: Just for 2B6, I think we

4 have a decent couple of substrates in vitro. We

5 have got efavirenz and we have bupropion. I think

6 in some settings, mephenytoin is a reasonable

7 substrate probe as well. As inhibitors, the only

8 specific in vitro one, selective in vitro

9 one--excuse me--is thioTEPA that I am aware of. I

10 don't think we have specific inducers and I don't

11 think we have validated in vivo probes.

12 DR. VENITZ: That was my conclusion, too,

13 listening to David. Any additional comments on

14 2B6? I am looking at Dr. Neuvonen. Maybe you want

15 to summarize what your recommendations would be

16 with respect to 2C8 in vitro inhibitors, in vitro

17 substrates, in vivo inhibitors and in vivo

18 substrates.

19 DR. NEUVONEN: In vivo assay substrate, I

20 would recommend repaglinide because it seems to the

21 most sensitive of those compounds which are easily

22 available. Of course, rosiglitazone can also be

23 used, but it may be not so sensitive a marker.

24 As inhibitors, I would like to use

25 gemfibrozil even with great reservations regarding

1 its mechanism of action because it seems to be so
2 potent. But trimethoprim is more selective and
3 actually I have no data regarding pioglitazone and
4 rosiglitazone. They may be in the future more
5 useful but actually further data are needed.
6 DR. VENITZ: Any additional comments by
7 anyone on the committee?
8 DR. SHEINER: How do you usually sort of
9 probe for these things? We have seen some
10 exquisite experiments in which you have done area
11 under the curve and things like that which you
12 can't argue with that. But, in a typical situation
13 where you are trying to--I am thinking again about
14 gathering information on populations; what do you
15 do to decide whether somebody has or has not got a
16 given enzyme or some drug does or doesn't inhibit
17 another one in a sort of a survey sense.
18 You can't do intensive PK studies,
19 crossover studies, in that many people. So what
20 are the techniques you try to use to decide what
21 these distributions are?
22 DR. FLOCKHART: I think there are
23 techniques, but they haven't been used a huge
24 amount, Lew. There are a number of not necessarily
25 recent, but there are a number of studies over the

1 years where people have looked in large databases
2 to look for well-known interactions. I am thinking
3 of things like interactions between ACE inhibitors
4 and potassium, those kinds of things, the things
5 that are fairly well documented, and looking in
6 large populations to see how real they really are.
7 DR. SHEINER: How would you know?
8 DR. FLOCKHART: If you have the mechanism
9 biologically understood, you can go into a large
10 database like the Reagan Strafe Institute database
11 at Indiana and look at the number of people who
12 actually coprescribe those two things who actually
13 get hyperkalemia.
14 That kind of activity is valuable, I
15 think. We haven't done enough of it. But
16 increasingly, as we move towards being able to use
17 databases like that more--for two reasons. One is
18 there are more of them. Two is the data in them is
19 becoming more reliable. Three, I guess, is they
20 are becoming more accessible. So I think those
21 kinds of estimates are things that are not
22 something that we talk about or use widely,
23 certainly in medical practice, at the moment but it
24 is the kind of data that really ought to be
25 integrated into a doctor's thinking about

1 coprescribing drugs.
2 DR. VENITZ: Shiew-Mei?
3 DR. HUANG: Just a clarifying question.
4 Dr. Neuvonen, you mentioned, during your talk, that
5 there are quite a few CYP3A substrates, that they
6 are also CYP2C8 inhibitors. Are you talking about
7 some of the 2C8 inhibitors or just some of the
8 substrates that we have not evaluated as
9 inhibitors?
10 DR. NEUVONEN: If I remember correctly,
11 there was a study published in British Journal of
12 Clinical Pharmacology some two or three years ago
13 where they showed that many of the typical
14 substrates of 3A4 were inhibitors of 2C8 so that
15 when they are used in vitro, concentrations which
16 were roughly five times the KM volumes, regarding
17 the 3A4 enzyme, these compounds caused nearly total
18 inhibitor of 2C8. I guess it was a paper by Ung et
19 al. I can't remember exactly.
20 DR. HUANG: Thanks.
21 DR. SADEE: I just have a general
22 question. When preclinical data are being
23 submitted, are all these P450s covered in the
24 preclinical data that are submitted to the FDA or
25 is it mandatory now? What is the status?

1 DR. HUANG: I guess you meant nonclinical
2 human microsomal data.
3 DR. SADEE: Right.
4 DR. HUANG: For reaction phenotyping, for
5 metabolic pathway, in addition to the five critical
6 enzymes, 1A2, 2C9, 2C19, 2D6 and 3A, most of the
7 time, for reaction phenotyping, we also see 2A6,
8 2B6, 2C8 and 2E1 data. For inhibitors, the five
9 are the ones that we most consistently see.
10 Sometimes, we also see 2B6 and 2C8.
11 For induction, it is 3A is the majority
12 that we look at. In addition, some of the 2C9 and
13 2C19. Increasingly we are seeing 2B6 and 2C8 in
14 addition to 1A2.
15 DR. SADEE: So there is no guideline as to
16 what preferably would have to be presented?
17 DR. HUANG: In the past, we have stressed
18 those five that I mentioned earlier because it
19 constitutes 90 percent of the metabolism of most
20 drugs as metabolized by CYP enzyme. But,
21 increasingly, the tools are available as we
22 discussed today when we have more specific probes
23 and we have inhibitors in vitro available. We are
24 going to include those in our guidance on what
25 substrates, conditions, were studies so that the

1 study will be valid to be able to be evaluated.

2 However, in vivo, based on today's

3 discussion, we are probably not ready to make a

4 strong recommendation until we have a better idea.

5 I guess some of the substrates, we might be able to

6 recommend, and some of the inhibitors, especially

7 in light of possibly inhibiting multiple pathways.

8 So, ever if they are nonspecific enzymes, they

9 might be able to be useful in certain conditions.

10 DR. SHEINER: I have got to get back to

11 Greg's question. How is that going to translate in

12 labeling? What are you going to say when you find

13 that there is a possibility that lots of different

14 drugs taken together could make a big difference in

15 the metabolism of something else.

16 DR. FLOCKHART: I don't think you are

17 going to do that. It is going to be guided. So,

18 for example, at the moment, pick a drug, Versed,

19 midazolam. We have in the label that you see a big

20 change with ketoconazole, erythromycin,

21 clarithromycin. That is totally appropriate. It

22 is the main metabolic route.

23 But what we are seeing here, really, is

24 that increasingly companies, for good reason, are

25 coming up with drugs that avoid one isoform for

1 genetic reasons and for drug-interaction reasons.
2 That is to everyone's benefit, probably, because
3 they have alternative routes when one is cut down.
4 But I think the next level of sophistication here
5 is really to be able to say, okay, I know this drug
6 is a 3A, 2D6 drug and what happens if I put in
7 ritonavir, which kills both enzymes. That is the
8 logical sequel to Bob Temple's saying the worst
9 interaction would be keto. Well, for that drug,
10 the worse interaction may be ritonavir, something
11 that kills both.
12 DR. HUANG: I just want to add that
13 looking at these interactions, some of them are
14 multiple interactions, some of them are specific to
15 drug interaction. The utility is at least twofold.
16 One is to help us in designing our study and to
17 evaluate the safety database. For example, as
18 shown yesterday, we look at the most stressed
19 system where the exposure would increase because of
20 multiple--right now, we are talking about one at a
21 time--multiple drug interaction.
22 So what kind of exposure do we need to
23 evaluate? So that is what these interactions can
24 provide us, and the other one is the labeling that
25 has been discussed where we have different degrees

1 of labeling depending on the severity of
2 interactions. Sometimes, we contraindicate or
3 sometimes we modify the dose or dosing interval to
4 accommodate a certain drug interaction.
5 We have not given specific instructions
6 when multiple drugs are given together. Right now,
7 it is still individual drugs.
8 DR. VENITZ: Any final comments on the
9 metabolic drug interactions? Mary?
10 DR. RELLING: Just that, based on what Lew
11 is saying, the most important thing is to carefully
12 describe what has been done to determine which
13 enzymes are involved in the disposition of the
14 drug. We can't predict five years from now what
15 potent 3A inhibitors or PGP inhibitors or 2C8
16 inhibitors may come on the market that we don't
17 know about and we have to trust pharmacists and
18 physicians to keep educating themselves, to keep
19 providing public sources of what those inhibitors
20 and inducers are. But you can't expect the
21 manufacturer to list all the drug interacting
22 agents at the time the drug is approved. But you
23 can expect them to carefully list what has been
24 tested and what hasn't and give a guesstimate of
25 KMs or affinities so somebody can come up with--a

1 knowledgeable person can come up with
2 recommendations of how to avoid or modify drugs.
3 DR. SHEINER: I really like that. So the
4 dossier, so to speak, is about your drug.
5 DR. RELLING: Yes.
6 DR. SHEINER: And not about all the other
7 ones.
8 DR. RELLING: You are responsible for your
9 drug.
10 DR. SHEINER: Right.
11 DR. NEUVONEN: I would like to add to the
12 previous, that when studying the contribution of
13 different CYP enzymes in vitro, I hope that the
14 substrate concentration used is as close to that in
15 vivo as possible because the contribution of
16 different enzymes may be quite different at
17 different concentrations. I think there have been
18 some artificial data previously based on those
19 kinds of errors.
20 DR. VENITZ: Final words on drug
21 interactions? Thank you.
22 We are moving to our next topic and our
23 last topic for today, pharmacogenetics. I am going
24 to ask Larry to give us the introduction.
25 Pharmacogenetics: Integration into

1 New Drug Development

2 DR. LESKO: Thank you.

3 [Slide.]

4 We are in the home stretch talking about a
5 related topic but still somewhat different. I want
6 to introduce the topic of pharmacogenetics and
7 integration into new drug development. This is
8 actually the first public advisory committee in
9 which these issues, I think, have been discussed in
10 a general way, although we have had other meetings
11 that have discussed specific pharmacogenetic
12 issues.

13 This is really the beginning of a
14 discussion on this topic. I anticipate we will
15 have many more of them within this committee and,
16 perhaps, some others. So today is really a
17 starting point to open up the discussion of where
18 we ought to be going with pharmacogenetics as it
19 matures in the context of drug development.

20 I think of drug development as not only
21 what a sponsor does during the research phase in
22 getting an NDA put together but drug development
23 also includes the regulatory decision stage as well
24 so a lot of what we are talking about encompasses
25 that entire scope.

1 [Slide.]

2 I mentioned yesterday that
3 pharmacogenomics is one of the key areas in the
4 FDA's new strategic plan that came out in August.
5 As part of that strategic plan, there are some
6 target goals for the development of guidances
7 related to this topic for the purpose of advancing
8 pharmacogenomics in drug development and its use in
9 public health.

10 We had a workshop last week on the first
11 of these guidances that was released on November 1.
12 It was called Genomic Data Submissions. This DIA
13 workshop was intended to gather public comment on
14 this draft guidance and also to raise issues
15 related to the integration of this information in
16 drug development and how it might be submitted to
17 the FDA in one of various pathways depending on the
18 criteria that define it.

19 Dr. McClellan opened up the conference,
20 and this quote is taken from his presentation which
21 reflects the strategic plan and the interest that
22 he has as well as our Center Director and that is
23 we need to speed up the use of genomics to help
24 make our medicines safer and more effective.

25 Part of speeding that up is to provide

1 guidance to the industry, particularly in an area
2 that is evolving where there is a lot of
3 uncertainty as to how the FDA views this data and
4 how it is going to use it. So this was the first
5 of several guidances which are targeted for the
6 genomics area. Two more are targeted for 2004.
7 One of them is a general pharmacogenomics guidance
8 which will touch upon the issues I will introduce
9 today.
10 [Slide.]
11 Pharmacogenomics, or pharmacogenetics, is
12 a broad area so I want to try to narrow the
13 discussion a little bit and thus I will define
14 pharmacogenomics as a tool, a tool to segment
15 phenotypes based on genotypes. Pharmacogenomics,
16 in and of itself, doesn't necessarily cause bad
17 things to happen or good things, but it is a way of
18 finding out information about patients. What we do
19 with that information is, of course, what we want
20 to discuss.
21 The focus is on interindividual
22 variability in pharmacokinetics. We can also talk
23 about pharmacodynamics but not for today. The
24 problem is basically one dose given to many genomes
25 results in different degrees of variability and

1 different degrees of exposure; that is, the
2 patients.
3 For the purposes of today, let's define
4 phenotype as an exposure metric--for example, area
5 under the curve--or pharmacokinetic parameters such
6 as intrinsic clearance, and let's define genotype
7 as some inherited variation in drug-metabolizing
8 enzymes.
9 [Slide.]
10 The problem is interindividual
11 variability. This is a major obstacle for
12 effective therapeutics, as we all know. This
13 variability predisposes people to risk. We give
14 the same dose to many patients. We have some that
15 react fine, some that have adverse events and some
16 that don't react at all. So there is a wide
17 spectrum of patients. Part of that is thought to
18 be related to the genetic characteristics that
19 affect the metabolic activity.
20 It has become quite common in clinical
21 pharmacology to conduct studies routinely during
22 drug development to focus on the so-called
23 intrinsic and extrinsic factors that affect PK.
24 These include the well-known ones of demographics
25 such as age, gender, ethnicity and race, the

1 diseases, hepatic and renal, and, as we just
2 discussed, the whole spectrum of drug interactions.
3 What we do with the information is look at
4 the potential need for dose adjustments based on
5 changes in exposure, usually, sometimes changes in
6 exposure and response. Then, based on that change
7 in exposure under the special-population situation,
8 we recommend adjusted doses that we think will
9 provide exposure that is considered safe and
10 effective.
11 Where we have come to is that genotypes
12 have become known to influence exposure and these
13 influences are as large, if not greater than, the
14 factors that we routinely consider in the clinical
15 pharmacology area of drug development. I am
16 talking about the factors that relate to the
17 alleles of the common enzymes that have polymorphic
18 aspects of the drug metabolism.
19 [Slide.]
20 This is not necessarily new. Everyone
21 here is familiar with the well-known polymorphisms
22 and drug metabolism. We discussed TPMT extensively
23 in our first two meetings and 2D6 is well known,
24 responsible for a high percentage of the drugs in
25 the marketplace and 2C9, less drugs, but some

1 significant drugs with a high incidence of adverse
2 events such as a warfarin.
3 So the evidence is growing. There is more
4 and more information appearing in the literature on
5 the importance of genetic factors, both
6 retrospective analysis and prospective studies.
7 While all this is not new, what has changed in the
8 landscape recently is the potential that we have to
9 deal with the variability.
10 [Slide.]
11 Tests for the cytochrome P450 genotypes
12 have become more widely available, potentially, in
13 the future, FDA approved, and, if available, and if
14 sensitive and specific enough, these tests can be
15 used as an adjunct tool, not much different than
16 blood levels of drugs for individualizing doses of
17 drugs that are substrates for these enzymes. The
18 value of this type of information is that, unlike
19 therapeutic drug monitoring, this can be done in
20 advance of giving the drug as opposed to after
21 administration of the drug.
22 Likewise, the evidence of clinical utility
23 of these tests is increasing both in the published
24 literature. Oftentimes, years back, it was
25 retrospective but, more recently, in prospective

1 literature. This is not equivocal evidence,
2 necessarily, and there is a lot of debate about
3 what level of evidence underpins the clinical
4 utility. This is another area that is still
5 evolving.
6 [Slide.]
7 Related to regulations, we have labeling
8 regulations that talk about evidence that is
9 necessary to support the safe and effective use of
10 the drug. This includes dosing adjustments in
11 selected subgroups of the larger population. In
12 any case, that labeling should describe this
13 evidence and identify tests or actions that are
14 needed for the selection and monitoring of patients
15 who need the drug.
16 This, if we interpret it in the context of
17 pharmacogenetics, would also lead one to conclude
18 that a genetic test, if suitably validated
19 analytically and clinically, would be a valuable
20 adjunct for label information.
21 [Slide.]
22 So the problem that we have to solve, not
23 today but in the next coming year, let's say, is I
24 think we need a systematic way of thinking about
25 pharmacogenomics in drug development; for example,

1 a type of decision tree. When are pharmacogenomic
2 studies important based on some prior in vitro
3 studies, let's say, of drug metabolism? What
4 phases of development might this information be
5 efficiently and effectively gathered?
6 What types of studies ought to be designed
7 and conducted? How should these results be
8 interpreted and, probably most importantly, at the
9 end of the day, how do we put these results in the
10 label and translate it for the benefit of
11 practitioners and patients?
12 [Slide.]
13 One example of a possible strategy, just
14 to start somewhere; let's say we had in vitro data
15 that indicated a pathway of drug metabolism was the
16 major pathway for clearance of the drug and that
17 pathway has known polymorphisms. One might think
18 about determining the differences in
19 pharmacokinetics in the important genotypes in
20 phase I healthy volunteers and then, taking that
21 pharmacokinetic information and assessing its
22 significance in terms of differences using some
23 exposure-response relationships involving
24 biomarkers or clinical endpoints.
25 That may be where things stop. Maybe

1 there is some significance, but one might think
2 about including complete or partial DNA collection
3 in phase II trials and/or phase III trials in
4 patients. One could design this collection as a
5 prospective sparse-sample strategy with formal
6 population PK analysis looking at genotype as a
7 covariate as we have done before with other
8 covariates in the area of, for example, age or race
9 or ethnicity.
10 One can also look at retrospective
11 analysis of genotype associations with clinical and
12 safety endpoints and then, from this data,
13 collectively conclude that this is or isn't an
14 important variable in the drug-concentration
15 response relationship. There may be other ways to
16 gather this information but that is the purposes of
17 opening up this discussion. But this is one
18 starting point.
19 Lastly, labeling products with the
20 information; conceptually, it seems like it would
21 be similar to other special populations defined by
22 other factors.
23 [Slide.]
24 Then, finally, there are the questions
25 that we want to put on the table for the committee.

1 The way we planned this session is basically to
2 begin to hear what the issues are and, thus, we
3 have asked the presenters to look at this issue
4 from three different perspectives.
5 Dr. Flockhart will look at it from his
6 experience in academic research, significantly in
7 the area of 2D6 and some other areas. We have
8 asked Dr. Hockett to come from his experience with
9 developing atomoxetine and what the issues were in
10 that program in terms of what we know about that.
11 And then, thirdly, we asked Dr. Relling to present
12 a clinical view as a clinician--a new drug came on
13 the market that is a substrate for one of these
14 enzymes; in the future, what would you like to know
15 about it.
16 With those three perspectives, then, we
17 hope we get the issues on the table for discussion
18 and the two questions that we have here, are the
19 approaches presented to study the influence of
20 pharmacogenetics on exposure response sufficient
21 and appropriate. It may actually be a premature
22 question because we don't really have a lot of
23 approaches and it is okay with me if we end up just
24 discussing the issues that might lead us to answer
25 that question in the future.

1 I think the second question is important;
2 are there criteria or approaches that the agency
3 should consider recommending to sponsors. Again,
4 this may be premature but I think, overall, if we
5 have a good discussion on the issues surrounding
6 the question and the problem we are trying to
7 solve, I think it would be very beneficial to our
8 thinking and, perhaps, we can come back to these
9 questions at a later time for more specific
10 recommendations.
11 DR. VENITZ: Thank you, Larry.
12 Let me ask David to come back and take the
13 podium and give us the academician's perspective.
14 Academic Perspectives
15 DR. FLOCKHART: I am going to talk about
16 two things, really.
17 [Slide.]
18 One is a large picture of how we might
19 approach this process and the second thing is
20 Shiew-Mei asked me specifically to talk about--this
21 is pretty funny--2D6 while I was here. What I
22 heard on the phone was 2B6. So I spent a lot of
23 tie developing my 2B6 presentation before and I
24 didn't realize she also wanted me to talk about
25 2D6.

1 So, can you clean up your accent a little bit.
2 The other thing that Larry has not talked
3 about and I think he does deserve a fair amount of
4 credit for, and the Office, in general, does, and
5 that is for what I think is a real kind of series
6 of acts of leadership that led to the labeling
7 changes for the TPMT enzymes. That is something we
8 have known about for a long time, but the recent
9 Committee on Pediatric Oncology basic approval of
10 what this committee would have recommended, I
11 think, is a real step forward.
12 Now I think we have to approach other
13 things and so 2D6 came up logically as a next
14 subject. I like to think about big decisions like
15 this in diagrams and some of you are aware of this,
16 pyramids and other things. I have tried to be a
17 little bit more organized this time and presented
18 this way of making decisions as a target, a
19 circular target.
20 The idea here is that you go from the
21 middle out towards the wider world of healthcare
22 professionals prescribing and patients being
23 treated. You start in the middle with a valid
24 genetic test which is really the basis after you
25 have decided that there is a real distinction, of

1 course, that that test can make.

2 And then I think you could argue that we

3 may even need a guidance on this. I think there

4 are a lot of things about a genetic test that we

5 assume but which are not written down in code and

6 there is a fair amount of confusion about. Howard,

7 among others, has educated many of us about how

8 many snips in the human genome are wrong and how

9 many we haven't picked up.

10 I think the characteristics of a genetic

11 test and the series of hoops such as genetic tests

12 might have to jump through from a regulatory point

13 of view are important things that might be the

14 subject of a guidance.

15 Outside that, once you have that, there is

16 obviously the correlation between that and

17 phenotype. Larry just really alluded to this

18 series of discussions. How do you do that? There

19 are lots of ways of doing it. You can do it

20 retrospectively. You can do it prospectively in a

21 very highly expensive and organized way or you can

22 do it using random sampling. There are lots of

23 efficient ways to do this. But which are the ones

24 we trust and which are the ones we think we should

25 seal with you like the imprimatur of the FDA in

1 terms of a good way for a company to do a test like
2 this. That might also be a subject for a guidance.
3 Then, beyond a simple correlation of
4 genotype and phenotype, there is the real world,
5 the real dirty world, of drug interactions,
6 diseases, races, genders and really large clinical
7 trials. The genetic tests that we come up with
8 must be robust enough to survive in that
9 environment. I think one might come up with
10 recommendations for how to do that as well.
11 I am not sure this last one needs to be
12 here. This is economic assessment. But it is
13 something that is in people's mind all the time.
14 It has been done for TPMT. It has been done
15 recently, several times, including I just saw an
16 article this morning, yet another article, about
17 2C19 and Helicobacter pylori, Greg, demonstrating
18 its economic effectiveness.
19 But I think this is important to the
20 people who are doing the testing. It is important
21 to healthcare professionals and it is certainly
22 important, I think, to pharmaceutical companies,
23 what is the value of these tests in the larger
24 picture. That is also potentially a subject at
25 least for discussion.

1 [Slide.]
2 A way of thinking about this is--and this
3 is an old diagram that I have just reorganized a
4 little bit. If you think about the population
5 treated with a drug--and here I have just got the Y
6 axis, really. This could be a unidimensional. But
7 this is a schematic representation of a population
8 treated, an average drug, where about a third of
9 people don't have a response. So this is no
10 response and this is a response on the upper side.
11 What we are really doing here is coming up
12 with a genetic variant that would divide these
13 people up one way or another.
14 [Slide.]
15 In an absolutely ideal situation, you
16 would have this, an ideal parameter separation
17 where the relative risk between the two things is
18 huge. Unfortunately, there may be situations where
19 this is the case. I am thinking potentially of
20 hemochromatosis and a number of other situations
21 like that.
22 [Slide.]
23 But, in fact, in reality, in my
24 experience, anyway, there is hardly ever--maybe I
25 should never say never, but this hardly ever

1 happens and you are nearly always dealing with a
2 messy situation like this. So it becomes important
3 to have a parameter that makes this distinction,
4 that separates these two things.
5 I think, myself, this is probably a
6 disease-specific parameter. I say a disease rather
7 than a drug or a population because, for many, many
8 diseases, there are separators already. I work in
9 breast cancer. You can predict a person's response
10 to therapy for breast cancer with a large number of
11 things; the stage of the tumor, the grade of the
12 tumor, the number of lymph nodes, the age of the
13 woman. We routinely put this into regular clinical
14 decision making in terms of what we are going to do
15 with women who have breast cancer.
16 A genetic test that is going to improve on
17 that has to survive in that decision-making matrix.
18 It has to be something that will improve it. I
19 think it is not enough to say it would just
20 survive. It has got to improve it.
21 So what do we do here? I am really just
22 putting this up for a matter of discussion It is
23 one thing to call it just statistically
24 significant. The clinicians amongst us would say
25 you need to do more than that. It has got to be

1 clinically as well as statistically significant.
2 But we spend a huge amount of our time just testing
3 for the p-value and really not thinking enough
4 about more clinically relevant statistics like the
5 relative risk or, in fact, the absolute risk
6 between these two things.
7 As clinicians, certainly as someone who
8 teaches clinical pharmacology, I try and encourage
9 our residents and interns and medical students to
10 think in terms of absolute risk because it is a
11 more valuable thing in many contexts and, indeed,
12 to think about the number needed to test or the
13 number needed to treat. So the number of patients
14 you would need to treat, to come up with a
15 significant outcome, or, in this case, the number
16 of patients you would need to test in order to come
17 up with someone who really had a significant
18 difference on one side or the other; what is the
19 parameter we should use?
20 I am not standing here saying we should
21 use one or the other. I am saying we should have
22 an intelligent and informed discussion about how we
23 do this. I, personally, am biased towards thinking
24 this is a disease-specific thing and that, in
25 breast cancer, I could give you the relative risk

1 caused by four lymph nodes. I could give you the
2 relative risk brought about by a woman being
3 aged--having a stage 3 tumor.
4 I know those numbers. Therefore, if I had
5 an equivalent change caused by a genetic test, I
6 would think that might be something valuable.
7 Something that was less than that would not be as
8 useful.
9 [Slide.]
10 I am going to change tracks completely.
11 That ends my general statements because Shiew-Mei
12 asked me to talk about 2B6--I mean, 2D6. The
13 specific question that Shiew-Mei asked me to
14 address was the question of distinction between the
15 extremes. So, I guess, in some ways, it is related
16 to the same thing.
17 [Slide.]
18 Just to summarize very quickly about 2D6,
19 we know it is absent in 7 percent of Caucasians.
20 Fascinatingly and interestingly, it is hyperactive
21 in 30 percent of East Africans including Ethiopian
22 and Saudi Arabians and a number of people in Spain.
23 It ketolyses the primary metabolism of a large
24 number of drugs which is why we are talking about
25 it, really, and is potently inhibited by a large

1 number of equally interesting drugs.

2 [Slide.]

3 This is frozen? This slide didn't come

4 out in the handout? It is a big figure.

5 [Slide.]

6 Just to make some points about this.

7 These are old data from the Swedish group.

8 Debrisoquine is a probe for 2D6 activity. This is

9 the number of subjects. We can clearly distinguish

10 these people because they are two logs different

11 from the mean over here. So poor metabolizers are,

12 in general, a completely separate phenotypic group.

13 There is a cutoff here. There is also a cutoff up

14 here and, for the very fast people, these are

15 actually, I am increasingly coming to believe, very

16 distinguishable as well.

17 We had someone recently who destroyed

18 codeine at a rate, really, that was almost 100

19 times someone in the middle here. So there are

20 unusual people at the extremes out here but it is

21 not really, if we are honest about it--like, there

22 is nobody in here. This is something like a

23 thousand subjects. So, inevitably, if you increase

24 this to a million subjects, there would be people

25 in here who it is hard to distinguish.

1 If you are talking about 2D6, this is 7
2 percent of the population. But this is much more
3 of the population. This is well over 30, 40
4 percent of the population. There are people who
5 are intermediate metabolizers of one kind or
6 another. So the difficult question for a company
7 is what do you do about these people. Do you make
8 any kind of dosing recommendation at all or do you
9 just leave that there.
10 Now, the case for making any
11 recommendation would be that there would be, if
12 there is a difference in pharmacokinetics that is
13 real in this group, and secondly that there is a
14 large number of people in that group. What I am
15 going to say is two things. I am going to say that
16 the answer to this is really sometimes it is worth
17 it but not always.
18 [Slide.]
19 This is from Michael Eichelbaum's data in
20 a paper published with Esmeier and a number of
21 others in 1997. It is a very bad slide, I'm
22 afraid, but it basically shows that this is
23 ultrarapid metabolizers and poor metabolizers by
24 genotype here. You can see that there are a group
25 of people who you genotypically predict to be in

1 the middle but, nearly always, they overlap with
2 these people over here. So, for this given
3 genotype here, which is a star-1-star-1
4 genotype--this is the old nomenclature; I'm
5 sorry--it overlaps over here whereas this also
6 overlaps.
7 There are a group of people, the star-10s
8 here, who are intermediate. But, certainly, when
9 this was published, six or seven years ago, there
10 weren't clear ways of distinguishing this group.
11 Since this was published, and I am missing
12 the allele slide that I had, we have really
13 relatively ethnic-specific alleles, the star-10
14 allele among Asians--I say relatively, because it
15 is not absolutely. You can pick up star-10 in
16 Caucasians and you can pick up star-10 in Africans,
17 but it is a relatively Asian allele.
18 Star-17 is an African allele. Andrea
19 Guideker and Greg Kearns' group has shown the
20 importance of star-29 in African-Americans as well.
21 So it is possible that it is able to define
22 people--it is possible now to define people more
23 who are in this group and we can discuss that a
24 little bit.
25 [Slide.]

1 Now here is the difficulty. These are
2 also data from the Swedish group. So this is the
3 number of functional alleles against nortriptyline
4 concentration. You are simply looking at
5 concentration on a normal, not a log, scale against
6 time. So this is the number of functional alleles.
7 A poor metabolizer would have a rate and a
8 half-life like this.
9 But you notice that, if one allele is
10 deficient--so if this would be a star-4
11 heterozygote, for example, someone who had one
12 knocked-out allele, one completely dead,
13 nonfunctional, completely inactive half of the DNA
14 and the other is perfectly active, and that person
15 has a very slightly different pharmacokinetic
16 profile from this person, but a very notably
17 different pharmacokinetic profile from someone who
18 has two alleles knocked out.
19 This is true for a number of drugs but not
20 all. So this is a situation where, if you change
21 from two active alleles to one, you see a
22 significant change. This is a substrate-specific
23 thing, I believe, and there are substrates where,
24 if you go from two to one, you don't see much
25 change.

1 [Slide.]
2 But we, and others, have modeled these
3 kinds of data. So, if you look at the number of
4 functional alleles at a low dose, 25 milligrams,
5 you see people come into the therapeutic range and,
6 at a middling dose, you see people exceed the
7 therapeutic range and, at the 75 milligrams TID
8 dose, you see people go way above the therapeutic
9 range and people who have two or three functional
10 alleles fall nicely in the therapeutic range.
11 [Slide.]
12 Now, these kinds of data have been used by
13 the Europeans to come up with dosage guidelines.
14 This is just a diagram from the omega document on
15 dosing nortriptyline. So this is doses of
16 nortriptyline recommended for different 2D6
17 phenotypes and genotypes in Europe. So this,
18 again, is the same debrisoquine diagram that I
19 showed you, number of subjects, rate of metabolism
20 in the inverse. The poor metabolizers are over
21 here.
22 The genetic variants are indicated in
23 these cartoon forms. The X is a knocked-out
24 allele, so that would be here and here, and the
25 multiple-copy alleles are over here. And the doses

1 predicted from the model by the European group--I
2 am trying not to designate any particular person
3 because there were so many people involved in doing
4 this--were a 500-milligram dose, 100 to
5 150-milligram dose, or 10 to 20-milligram dose. So
6 this is a ten-fold difference, a fifty-fold
7 difference, from one end to the other of
8 nortriptyline dose according to the phenotype and
9 genotype.
10 Obviously, what these people have done
11 here is they have made a recommendation in the
12 middle, even though I showed you a moment ago that
13 there is not a huge difference between the
14 pharmacokinetics of nortriptyline in a heterozygote
15 compared with someone over here. But they have
16 gone ahead and done it anyway because this
17 variation is so large.
18 So the important question, I think, for
19 us, is are there substrates where we should do a
20 similar thing.
21 [Slide.]
22 I am just putting these questions out. So
23 two recommendations. These are really both
24 recommendations for discussion. In the long-term,
25 over the next several meetings, we should define

1 and make clear a disease-specific parameter that is
2 a target for useful pharmacokinetic tests and,
3 secondly, for these three isoforms, at least, and I
4 would recommend that these be the first addressed,
5 we recommend a genotype and phenotypic test that
6 defines this. We, at least, can get into this
7 discussion.
8 Personally, I am not here yet. I haven't
9 got this really clear in my mind and I am not sure
10 how we would recommend doing this but it is an
11 important thing that is worth discussing.
12 So I will stop there and I think I might
13 sit down as well. If there are any
14 points-of-information questions that people have, I
15 would be glad to deal with that.
16 DR. VENITZ: Are there any information
17 questions for David before we get into our
18 discussion?
19 DR. SADEE: With the heterozygotes, it is
20 not clear why they would be, necessarily, closer to
21 the homozygous null carriers.
22 DR. FLOCKHART: You are right. It is not
23 clear. It is an observation.
24 DR. SADEE: So, most likely, the ones that
25 one finds to have this, the other allele has

1 something wrong with it, too, that may be less well
2 expressed.
3 DR. FLOCKHART: You mean, it is not a
4 knock-out? The other allele is--
5 DR. SADEE: No; one is a null allele and
6 the other one would be less well expressed in some
7 fashion.
8 DR. FLOCKHART: Conceivably an interaction
9 because of the absence of one allele, you mean.
10 DR. SADEE: Yes; or the ones that you find
11 have relatively poor metabolism. It is just there
12 is another genotype that affects this that we don't
13 know about.
14 DR. FLOCKHART: What you are talking about
15 is, in this situation, where one allele is dead.
16 DR. SADEE: Right.
17 DR. FLOCKHART: And this situation is
18 where both alleles are dead.
19 DR. SADEE: Yes.
20 DR. FLOCKHART: So what--
21 DR. SADEE: Then the gene, the allele that
22 is not dead, is somehow impaired and that may be a
23 polymorphism that is not described.
24 DR. FLOCKHART: Oh; I see what you meant.
25 I'm sorry. We might be missing one here in this

1 particular setting. That is possible there; yes.
2 DR. HOCKETT: If you get more than a few
3 patients, that can't be the explanation because
4 there aren't that many alleles that decrease
5 function a little bit that would give you that
6 picture. So it is going to depend how many
7 patients went into the formation of this graph.
8 DR. FLOCKHART: And how many alleles,
9 actually, because we have done so much on 2D6. I
10 mean, we are still beating up new alleles. We have
11 43, 44 new alleles. Really, if all of them were
12 tested here, and I don't know that they were, but
13 the vast majority--these are people who know what
14 they are doing, I think, in general, Sweden--the
15 vast majority would have been tested here so it is
16 possible that the average--that if this were one
17 patient, which it is, that that could be the case.
18 But if this were a population average, and I think
19 you could plot a population average like this, it
20 would be hard to explain it that way.
21 DR. VENITZ: Any other questions? Thank
22 you, David.
23 Then our next speaker is Dr. Hockett. He
24 is going to give us the industry perspective
25 discussing a recently approved drug.

1 Industry Perspective
2 DR. HOCKETT: Good morning.
3 [Slide.]
4 I appreciate the chance to address the
5 committee with an industry perspective but I
6 caution you, there is no way I can give you an
7 overall industry perspective so you have to take
8 this in light of what this would be consideration
9 of one person at Eli Lilly.
10 [Slide.]
11 Like David, I am going to start off with a
12 few general comment. I am actually going to get on
13 my soapbox for a couple of slides. I think there
14 have been a couple of difficulties for the field in
15 pharmacogenomics and I will go through those.
16 The title is a case study of Strattera. I
17 will talk a little bit about Strattera because that
18 is the most recent example of where a genetic test
19 has been put in the label, at least a mention of
20 one. Then I will talk, again, about some more
21 generalized thing about pharmacogenomics and how we
22 think they are going to apply and what I think,
23 from my perspective, would be nice to see as far as
24 CYP2D6 if it would have been required in the
25 Strattera label.

1 The first problem that I think the
2 industry has had and, thankfully, it is getting
3 less and less as we progress, is illustrated on
4 this slide where there are far too many definitions
5 of what we are talking about; pharmacogenomic,
6 pharmacogenetic, applied genetics, applied
7 genomics. I reminds me a little of the
8 "po-tay-to"/"po-tah-to" argument as to how you
9 pronounce this.
10 I have seen the slide of David's that now
11 says that pharmacogenomic and pharmacogenetic are
12 actually just a two-snip change of the same
13 terminology. I didn't steal that from him but he
14 has done that. In fact, you can see several
15 groups. EMEA, which is the FDA equivalent in
16 Europe, has got a very broad definition. The PWG,
17 which is a loose consortium of pharmaceutical
18 companies and biotech groups called the
19 Pharmacogenomic Working Group, actually has split
20 the definition. Why they have chosen, and I am
21 with this group, to split hairs is still unknown to
22 me. It is not very helpful. Even at Lilly, we
23 have subdivided this. In pharmacogenomics, we have
24 a little bit narrower view. It really means we
25 want to understand the genetic influences of how

1 people respond to drugs.
2 None of those are right or wrong, but you
3 can say it leads to confusion in the field.
4 [Slide.]
5 The second problem that we have had is
6 pharmacogenomics has been hyped, I think, an
7 overamount in the field. We are not going to have
8 a choice. We are actually going to have to do
9 this. The field, pharmaceutical companies, will be
10 dragged, kicking and screaming if we don't help
11 lead the way.
12 I illustrate this from this U.S. News and
13 World Report that actually fell on my doorstep in
14 January of this year where the cover of this said,
15 "This drug is for you." There have been several
16 magazines that do this. Interestingly, if you open
17 up this and look at the article, the gist of this
18 was that we are all going to run around with our
19 human genetic sequence on a card about the size of
20 a credit card. That will allow physicians to
21 figure out which diseases you are going to get,
22 which drugs he can give you to prevent those
23 diseases you are susceptible to and, if you get a
24 disease that wasn't predicted, what drug.
25 Boy, that may happen. But it isn't going

1 to happen anytime soon. There are multiple
2 problems, not the least of which, how much is it
3 going to cost me to sequence a single person. The
4 first time we did it was several billion. We are
5 probably a log-fold or two less than that now, but,
6 even if it was a million dollars, how many of us
7 are actually going to have the sequence done.
8 Second off, even if I could sequence
9 everybody in this room, I don't know how to
10 interpret all the variation yet. There is not
11 enough data for me to understand disease
12 susceptibility versus drugs.
13 In fact, I have put a collection of my
14 favorite hyped sayings for pharmacogenomics here.
15 I am not going to go through those, but some are
16 rather interesting such as, "Applying
17 pharmacogenomics to drug development will cut cycle
18 times to 1.5 to 2 years." I don't see that ever
19 happening. I just think that is not going to be
20 true and I think we are deluding ourselves.
21 [Slide.]
22 What this combination has done is what I
23 would like to illustrate on this slide. This is,
24 in applying new technologies, you have this
25 gentleman with the telescope and let's equate that

1 with pharmacogenomics. He hasn't got his eye on
2 the prize. He is looking in the wrong place. I
3 think this has deflected what we should be talking
4 about in pharmacogenomics, when he has missed the
5 comet over here in the sky.
6 This comet, I think, for pharmacogenomics,
7 is developing new genetic biomarkers that will
8 allow us to predict how people are going to respond
9 to drugs, not we are going to change cycle times,
10 not that I am going to be able to predict
11 everything. But, in certain instances, we are
12 going to develop specific biomarkers that are going
13 to help us do it.
14 [Slide.]
15 Now I say this because at Lilly I sat down
16 with my colleagues and we developed a list of how
17 we are to apply genetics to drug development. We
18 really apply that in three areas; in the discovery
19 arena, in preclinical toxicology, where we give
20 these drugs to animals and try to make sure that
21 they don't destroy a whole bunch of organs when
22 they then go into humans, and then in the clinical
23 side.
24 You can see there are lots of different
25 things but, in reality, we have two key activities

1 and two key activities only. The first one of
2 these is to identify and understand targets. We
3 want to use genetics to try to figure out where
4 there is the next available drug target for an
5 unmet medical need. Then the second one is to
6 develop human biomarkers where I can actually
7 predict, then, who should be on a particular drug,
8 either for a positive reason--they are going to
9 have efficacy--or a negative reason--to avoid
10 toxicity or adverse events. That is what we are
11 going to talk about.
12 [Slide.]
13 What I have listed here, then, are the
14 broad categories where genetics is going to be
15 applied in medicine currently. We have two big
16 areas called disease-susceptibility biomarkers and
17 drug-activity biomarkers.
18 Now, the disease-susceptibility ones are
19 those that would predict you are going to come down
20 with a genetic disease. You are familiar with
21 several of these, especially under the single
22 disease genes of Mendelian inheritance. This is
23 where I think I would differ with David when he
24 said the absolute distance between a genetic event
25 and a response never happens. It actually does in

1 the Mendelian inheritance like sickle-cell anemia.
2 If you get two copies of the disease, you
3 have the disease and, if you don't, you don't.
4 But, other than that, he and I agree precisely.
5 However, in complex diseases, that is much less the
6 way it is. If you take Alzhemier's disease and
7 Apo4, it has got a fairly large relative risk but
8 it does not separate the population at all, and we
9 will come back to that.
10 Then the drug-activity biomarkers which
11 some would call the true pharmacogenomic
12 biomarkers. This is where I think, as a drug
13 company, we need to spend all our time. I have put
14 the one in green that we are talking about today
15 those things that happen when you have defects or
16 variants in metabolic enzymes and that leads to
17 changes in PK profiles and can lead sometimes to
18 profound toxicities.
19 [Slide.]
20 I have put a list of things on here where
21 we, as a drug company, would choose to include
22 genetics in drug development. Contrary to some
23 prevailing opinions in at least the lay press, we
24 don't like to give drugs to people who are going to
25 respond badly. It is not very cost effective for

1 us to have adverse events and severe toxicities.
2 So we are very much in favor of trying to identify
3 those individuals and keeping them off our drugs.
4 We may get into the discussion are we
5 willing to subdivide our market, et cetera. That
6 is actually an entirely different topic. But you
7 can see we are planning to apply this very early in
8 discovery and all through clinical development;
9 phase I studies of a particular type, mainly in the
10 PK variety, Phase II and III if we can use to
11 figure out who is going to respond either
12 positively or negatively to our drugs.
13 [Slide.]
14 For Strattera, it is primarily metabolized
15 by CYP2D6. You can see there are profound
16 differences in the plasma clearance, a ten-fold
17 difference if you are poor metabolizer. In fact,
18 the AUC has got a ten-fold difference, ten-fold
19 higher in this case, if you are a poor metabolizer
20 and the half-life is significantly extended.
21 Obviously, we were interested and
22 concerned about this. Did this lead to safety
23 concerns or just did it have tolerability or
24 efficacy issues. That, obviously, the interplay
25 between those things, would have profound

1 implications for the label. So, if it developed a
2 very severe toxicity, it may become a label
3 requirement. If it is simply a tolerance issue, it
4 might not be. And you will see that is, indeed,
5 what happened.
6 [Slide.]
7 When you look at the clearance of
8 Strattera, and this is the number of patients, and
9 the plasma clearance here, this very much looks
10 like the metabolizer status that Dave showed on one
11 slide and I am going to show in just a minute where
12 you have got the poor metabolizers down here in
13 black. You have got the extensive metabolizers
14 here or the wild-type variants and then the
15 ultrametabolizers here. It looks very much the
16 same for Strattera as it does for any kind of drug.
17 [Slide.]
18 I am going to show you just one slide of
19 data. It came from a single study. It is the best
20 data that I think illustrates the point. We did
21 some initial clinical pharmacology studies to look
22 at what the maximum dose was. We looked at some
23 CYP2D6 genotypes obtained under double-blind
24 conditions. Therefore, the clinicians are now
25 going to start patients on a dose of the drug not

1 knowing what their genotype is. Then are then
2 going to adjust the dose based on toxicity,
3 tolerability and efficacy.
4 In the end, then, we are going to compare
5 EMs to PMs and see where they ended up and where
6 there are large changes in the ultimate dose they
7 were given for efficacy, toxicity and tolerability
8 and were there any differences between EMs and PMs.
9 [Slide.]
10 So that is what happened. It is
11 illustrated on this slide where you can see the
12 extensive metabolizers are in green, the poor
13 metabolizers are in purple. The bottom is weeks of
14 therapy and the Y axis is the mean dose in
15 milligrams per kilogram per day. You can see the
16 comparison between EMs and PMs is essentially there
17 is no difference.
18 So, without understanding EM to PM
19 differences in prescribing these drugs, they
20 actually ended up on the same dose which means we
21 haven't got a profound toxicity problem with PMs in
22 Strattera.
23 [Slide.]
24 To summarize several different kinds of
25 studies on this slide, there were some

1 adverse-event discontinuations in all studies. In
2 fact, poor metabolizers had a slightly higher level
3 than extensive metabolizers except they were based
4 on insomnia and irritability not on profound
5 toxicity. So, in the end, what we really had was a
6 tolerability question and not a safety question.
7 There was a slight hint of efficacy
8 increase in PMs especially on an ADHDH response
9 scale compared to EMs, but we didn't have enough
10 patients in there to make that terribly profound
11 and, obviously, there weren't enough patients to
12 affect the label.
13 [Slide.]
14 So, in negotiations with the FDA, CYP2D6
15 was put in the label. In fact, it occurs seven
16 times in the Strattera label in the
17 Pharmacokinetics Section, Adverse Events Sections,
18 Drug-Drug Interaction Sections and the Laboratory
19 Testing Section. But it is not a requirement
20 because there is no profound safety issue dealing
21 with CYP2D6 in Strattera.
22 Here is one of the verbatim quotes.
23 Actually, this has been mentioned already today
24 where it talks about the incidence of poor
25 metabolizers, et cetera, as well as having to pay

1 attention to the alternate drugs that may induce a
2 poor metabolizer status.
3 [Slide.]
4 Obviously, as far as Lilly was concerned,
5 that is almost a non-event in pharmacogenomics. It
6 is in our label. We were happy to have it
7 mentioned in the label. For medical reasons, we
8 don't mind people testing. But it didn't make any
9 sense to require it because there wasn't a toxicity
10 issue and we agreed and we came to terms.
11 Obviously, that doesn't give you a whole
12 lot to talk about and so I am going to expand this
13 a little bit in how do you define PM status and how
14 actually, if you do have one that is required,
15 would you put it in the label.
16 For some of the P450s, it is actually
17 pretty easy because there are a couple of alleles.
18 Dave has already alluded to CYP2D6. It is more
19 problematic. There are actually 44 alleles
20 defined, as he already said. This is a typo.
21 Actually, there are 21 alleles that have been
22 defined that have absent activity. The vast
23 majority of those are at such low frequency that
24 they probably shouldn't be routinely ordered and we
25 will come back to that in just a second.

1 There are at least two that are classified
2 as decreased or intermediate alleles, star-10,
3 star-29, star-17 and then a duplication exists in
4 this where you can have more than two copies of the
5 gene, et cetera.
6 [Slide.]
7 All of that leads to some problems. In
8 fact, as Dave has already alluded--and he and I
9 didn't talk about our presentations beforehand and
10 they ended up being remarkably similar--you have
11 vast differences in ethnic groups.
12 Here are Caucasians that have a 5 to 7
13 percent incidence of poor metabolizers. You have
14 Asians where the poor metabolizers are actually
15 less than 1 percent. But then they have a
16 significant number of intermediate metabolizers.
17 In fact, there can even be differences among Asian
18 groups.
19 And then there are a bunch of ethnic
20 groups that we don't have any data, or at least
21 there is no published data, on what this means.
22 What this is going to come down is you are probably
23 going to have different recommendations based on
24 different ethnic groups and different alleles that
25 need to be ordered if you are talking about a

1 different ethnic population.

2 [Slide.]

3 Just like Dave, here is my requisite

4 phenotype/genotype slide. It is rather complicated

5 but I think there are about three or four important

6 points to make on this slide. On the bottom, here,

7 is the metabolic ratio which, in this case, is a

8 dextromethorphan/dextrorphan ratio. On the Y axis

9 is the genotype under the star allele nomenclature.

10 Here, there are three, or the amplified status,

11 two, one and no functional alleles.

12 Then you have got the designations here of

13 where the ratio is in relation to the genotype.

14 The first important point, as Dave has already

15 pointed out, there seems to be relatively good

16 separation of poor metabolizers. I have seen at

17 least a dozen or eighteen different studies that

18 show the same kind of thing. It is relatively easy

19 and there is a decent phenotype/genotype

20 correlation for poor metabolizers.

21 For the rest of these, there actually

22 isn't, in my mind, a very good separation, in fact,

23 if you have got one allele. There is a huge

24 overlap if you have got two functional alleles, at

25 least for dextromethorphan. Obviously, this kind

1 of decision has to be data driven and, if you get
2 additional data, especially with different drugs
3 that separate them, that is true.
4 Even if you look in places where they have
5 only one functional star-10 allele, which, in this
6 case, is this star-4, star-10, where they have
7 three patients here, those people are clearly not
8 over here in the intermediate. They are well
9 within the extensive-metabolizer status for this
10 drug.
11 So I would agree with Dave. It is not
12 very clear. Then, if you look under the
13 ultrametabolizers up here, I think, for this case,
14 they have such an overlap that it is not useful to
15 distinguish between those two.
16 [Slide.]
17 Obviously, then, you have a decision; are
18 you going to require a phenotype or a genotype. I
19 have put just a few things up here. It is not
20 exhaustive. There are some advantages to going to
21 either side. From a drug-development perspective,
22 I would prefer a genotype. The reason for that is
23 I can measure it at once, as Dave said, before I
24 give any drug and I can actually measure a bunch of
25 alleles at a time and get more than one drug, or

1 more than one metabolic status for one particular
2 enzyme out of this.
3 In fact, we are developing a chip at Lilly
4 where I am going to be able to look at 120
5 different genes all at one time for a relatively
6 inexpensive cost and, obviously, then, we are going
7 to prefer to do that kind of thing.
8 [Slide.]
9 I have just a couple more slides and then
10 I will end because I think I am getting close.
11 There are, then, a bunch of other considerations
12 that come into play when you decide to do a genetic
13 test. I can't do justice to this topic. It is
14 probably worth an hour's presentation in and of
15 itself.
16 But I am going to touch on two of them,
17 and those are the first two on the list here. The
18 ethical, legal and social implications of this can
19 be rather profound. It really has to do with the
20 population's reticence at doing genetic testing and
21 their fear that something bad is going to happen to
22 them, like insurance is revoked or they are going
23 to be labeled in some way if they do a genetic
24 test.
25 For this reason, I am in favor of having

1 something like a metabolic enzyme be one of the
2 first tests that are propagated here because it
3 doesn't have the disease-association status that
4 some other things such as complex disease would
5 have and will potentially be swallowed by our
6 public much easier than a different kind of test.
7 [Slide.]
8 Obviously, that is a profound thing that
9 we have to get over. We also have to make sure
10 that we educate them properly and try to get rid of
11 the hype for what this can do and talk more about
12 what it actually is going to be practical to do on
13 that kind of scheme.
14 [Slide.]
15 Then the last one is the utility of the
16 information and biomarker. Once again, these are
17 very similar to the slides that Dave already
18 showed. This is the best case; if I have got a
19 genotypic variation and a response, I get absolute
20 discrimination between the two. I agree, that
21 almost never happens.
22 We will be lucky if we can get them that
23 have this kind of separation. This would probably
24 be acceptable. If they are like this, I don't
25 think they are even going to be instituted or

1 accepted. The example we have, I think, the best
2 example we have for where it is a poor separation
3 is the Apo-E4 variant that causes at least 50
4 percent of Alzheimer's disease in the Caucasian
5 population. But it has such poor separation
6 between those that are going to get Alzheimer's
7 disease and those that are not, that I don't know
8 what to tell the patient if they come down with an
9 E4; you are at slight increased risk to get
10 Alzheimer's but certainly not guaranteed. That
11 kind of test, obviously, is not going to be very
12 widely accepted.
13 [Slide.]
14 The last slide I have is CYP2D6
15 recommendations. I think the PM genotype predicts
16 the PM phenotype in roughly 99 percent of cases.
17 That is at least shown very well in two very large
18 studies that have been published. Since there are
19 21 alleles that actually cause a null phenotype,
20 you would think that is very challenging but, if
21 you look at these very large studies, they do it
22 with only about five or six. Those are the most
23 frequent ones that are found in these populations.
24 Here is the listing of these more frequent alleles
25 that pick up about 99 percent of this.

1 I think, to avoid confusion, the FDA
2 should specify that you can do both phenotype and
3 genotype as acceptable methods for defining this PM
4 status, but I think this should include a
5 recommendation for what is minimal genotyping, a
6 minimal number of alleles that would be acceptable
7 for that kind of genotyping, similar to the list
8 that is supported in the literature.
9 I don't think the genotypic designations
10 of UM, IM and EM have--they have distinguishable
11 phenotypes on a population basis but not on an
12 individual patient basis and, therefore, I am not
13 actually in favor of indicating them by current
14 data. The important point here is current data.
15 If we generate specific instances where you have a
16 separation between the two, obviously, it has to be
17 a data-driven decision.
18 Then, recapitulating what has happened
19 with the Strattera label, genotyping for these
20 mutants is warranted only when a compound's margin
21 of safety is exceeded in poor metabolizers and, if
22 it is, then I fully am in support of it actually
23 being a requirement in the label.
24 [Slide.]
25 The last one of these things I just have

1 is we are all in favor of getting the right
2 targets, the right drugs, into the right patients.
3 Within our education program, though, we have to
4 make sure we convey what we think is the
5 appropriate time line for this. Unfortunately, my
6 guess for this appropriate time line is after I am
7 done, actually, practicing in this field. I think
8 it is going to be dozens of years before we get to
9 that ubiquitous type.
10 With that, I will stop, take general
11 questions, if you like, but I think there is going
12 to be a discussion in the end.
13 DR. VENITZ: Thank you, Dr. Hockett.
14 Any specific questions, informational
15 questions, about his presentation?
16 DR. FLOCKHART: Just one question, Rick,
17 within an excellent presentation. But the graph
18 you showed of Strattera, the
19 population-distribution graph, you had shaded the
20 UMs, the ultra-rapid metabolizers.
21 DR. HOCKETT: Yes.
22 DR. FLOCKHART: How had you defined them?
23 There was a big overlap, but how did you define
24 them?
25 DR. HOCKETT: Whether they had three or

1 more copies of a functional allele which had been
2 the star-2 allele. That is how they were defined.
3 I have seen descriptions of thirteen copies, but we
4 never saw anybody over four copies. It was always
5 three or four.
6 DR. FLOCKHART: That is one family in
7 Sweden.
8 DR. HOCKETT: Yes; right. Exactly.
9 Generally, I don't see that number. It is usually
10 just three or four, it appears.
11 DR. KEARNS: Rick, when you did your
12 presentation, you had a slide that suggested when
13 Lilly might include pharmacogenetics in--did you
14 find, in the PK data for Strattera, that having 2D6
15 genotype was useful in examining your PK data?
16 DR. HOCKETT: Yes. It clearly helped
17 distinguish who was--we had a very high correlation
18 between the genotype/phenotype. So when there was
19 a poor metabolizer by PK, it came up poor
20 metabolizer by genotype as well.
21 DR. KEARNS: So do you think it is
22 reasonable and, I guess, where I am going here is
23 in pediatric studies, in particular, where the
24 numbers of subjects in a PK study may be smaller
25 then in an adult phase I or phase II, that, when

1 there is a drug that is metabolized by a
2 polymorphically expressed enzyme, having that
3 genotype data, assuming it does correlate with
4 phenotype, can be useful in separating out,
5 perhaps, is there an age effect on the disposition
6 of the drug.
7 DR. HOCKETT: Let me answer that, or
8 respond to that, in two ways. We are developing a
9 program at Lilly where we are going to be doing
10 metabolic-enzyme and transporter testing out of
11 every phase I patient who comes through our
12 clinical trials. That will include pediatrics
13 because we think it will help us understand the PK.
14 The only hesitation I would have is in
15 definition of what useful means. I think there is
16 going to be a scientific useful and a
17 drug-development useful. Generally, we don't have
18 enough patients with enough PK outliers to know
19 precisely what is going on and say, with absolute
20 certainty, that it is due to a particular genotype.
21 We don't necessarily need that to
22 understand if we have to worry about it in phase II
23 and phase III. So if you allow me that distinction
24 between absolutely scientifically proving and then
25 figuring out what we have to follow in phase II and

1 phase III, then I would agree that it will be
2 useful for us to understand and have the genotypes
3 on these individuals.
4 DR. SHEINER: I am not questioning the
5 conclusions you drew about the drug you spoke about
6 where you found that this difference in metabolism
7 didn't reflect in the difference in outcome, but I
8 do want to discourage the use of the design wherein
9 you conclude that some genetic difference or
10 anything else is not important because you find
11 that physicians ultimately don't wind up adjusting
12 doses differently in the two groups.
13 The medical profession has a long and
14 glorious history, not only of not noticing what
15 harms they do but actively promoting harmful
16 therapies. So I don't think that is a sensitive
17 way to design a study although I am sympathetic
18 with the notion of saying, what are the practical
19 consequences as opposed to the sort of theoretical
20 ones. But I think we can probably come up with a
21 better design to try to see whether something
22 actually makes a difference than that one.
23 DR. HOCKETT: Point taken.
24 DR. HUANG: Either you are going to do a
25 prospective study or retrospective genotyping if

1 you are going to have another 2D6 drug with what we
2 know about, the more alleles that we know are null
3 alleles, which the assay may not be available
4 before. What would be your minimum alleles that
5 you would like to test in order to conclude that
6 the genotype may not have an effect on your adverse
7 events.
8 DR. HOCKETT: Do you mean in 2D6? I would
9 put it at six or seven, which is what we typically
10 measure, although, by the middle of next year, I
11 think it will be a moot point. The chip we are
12 going to build is going to test 40 or 42 alleles
13 for 2D6 and we won't have to worry about that.
14 DR. HUANG: Even those that are available,
15 because I just wanted--because not all chips have
16 all the alleles. What are the essential ones on
17 based on, in your opinion, expert opinion?
18 DR. HOCKETT: Which is available? The
19 ones that were listed--
20 DR. HUANG: It doesn't matter, available
21 or not. What are the key ones?
22 DR. HOCKETT: The key ones are the ones
23 that are most frequent that you are going to see.
24 So, in 2D6, it will be three, four, five, six, nine
25 and you might add a couple of others like 16 or 15.

1 But it is really a frequency question. So we
2 typically do about six or seven. Those are the
3 ones that I would continue to really look at.
4 DR. HUANG: Because you cited two large
5 studies. I assume they are mostly a Caucasian
6 population.
7 DR. HOCKETT: Yes. The poor metabolizer
8 status in things like Asians and African-Americans,
9 we will add one or two alleles depending on those
10 although, for CYP2D6, right now, I don't think an
11 intermediate status is--and the poor metabolizers
12 for Asians are basically the same alleles as
13 Caucasians but just less frequent.
14 So that is why I say it is six or seven.
15 We would add a 17 or a 21 for African Americans or
16 Japanese and then those are the ones that we
17 frequently look at. We are still running about a
18 99 percent genotype/phenotype correlation in
19 everything we have seen.
20 DR. FLOCKHART: Could I just amplify that
21 a little bit because this is an important point.
22 We routinely add, on the basis of ethnicity--we
23 don't have your chip yet, so we conserve our
24 resources by looking for star-10 in Asians and
25 star-17 and 29 in Africans.

1 There is a problem with that in thinking
2 about this because we can't really separate those
3 phenotypes yet. So a star-17/star-17 homozygote
4 strictly is not distinguishable in most studies of
5 most drugs from an extensive metabolizer.
6 Key in this decision-making algorithm is
7 whether there is a gene-dose effect. If there is a
8 really clear intermediate group, and I think there
9 probably are drugs where that is the case.
10 Tamoxifin is one of them where you do see that.
11 But, in general, I think that is going to be a
12 really hard thing. Whether we actually recommend
13 it, I think, depends on whether there is a
14 phenotypic difference.
15 So I think, in general, I would agree
16 completely with Rick. You need relatively small,
17 five or six, to do it. But I would also agree with
18 Rick in that the point is going to be moot in a
19 couple of years when we will have lots of ways of
20 doing it.
21 DR. VENITZ: Wolfgang?
22 DR. SADEE: I do come back to the issue of
23 the heterozygous, even the patients with two
24 "normal" alleles. The spread is so large that it
25 is, in some cases, convenient to say they are poor

1 metabolizers and intermediate metabolizers. But
2 half of the intermediate metabolizers are very
3 close to the poor metabolizers and the ratios that
4 you can see here in the genotype and phenotype
5 plots are such that one would worry about a fairly
6 large percentage of the patients having a very slow
7 metabolism even though they are not classified as
8 poor metabolizers.
9 So, again, it would appear that there are
10 yet unrecognized polymorphisms probably in the
11 promoter regions and other regions that contribute
12 to this or whatever else factors contribute to
13 that. So, in some cases, it may be useful to just
14 say, here is the group of poor metabolizers and
15 those are going to be the only ones who are at
16 risk. But that may be few cases because the
17 intermediate metabolizers may have such a poor
18 metabolism that they are also at risk.
19 So how do we deal with that?
20 DR. HOCKETT: The one thing that is not
21 contained in the genotype/phenotype graph I showed
22 you was a reproducibility among a series of
23 individuals. So you are dealing with a single
24 determination here. I would have bet that there is
25 a fair amount of variability within the group that

1 you can swap them from one position to another
2 within their own distribution graph.
3 Therefore, I don't know how to interpret
4 those that are close to poor metabolizer status as
5 to whether or not, if you measured them repeatedly,
6 they are always in that position. I would bet they
7 are not, but Dave might be able to answer that
8 question because I have never seen that kind of
9 data.
10 DR. SADEE: I think that is a key question
11 because, if they are just in the same position,
12 then this is some intrinsic factor. If that is
13 extremely variable, then all bets are off.
14 DR. HOCKETT: As long as the variability
15 doesn't flip them over to the poor metabolizer on
16 the other side of the ratio.
17 DR. VENITZ: Larry?
18 DR. LESKO: Rick, I wanted to ask about
19 the early study in the clin-pharm area. Was this
20 study done by enrolling X number of subjects and
21 then retrospectively looking at their genotype to
22 figure out the difference in pharmacokinetics or
23 was it prospectively enrolled to get suitable
24 numbers in each of the genotypes that you were
25 interested in.

1 DR. HOCKETT: No. Every study that was
2 done with Strattera for genotyping was done
3 retrospectively. We did collect some things
4 prospectively, but we kept them double-blinded to
5 try to answer the question in a different way. I
6 should say that there were a couple of late phase
7 III trials where they separated the individuals
8 based on poor metabolizer status, but the early
9 stuff was all done retrospectively.
10 DR. LESKO: Do you think that is the most
11 efficient way to do it?
12 DR. HOCKETT: No, but that was our first
13 foray into one of these drugs that was going to be
14 necessary. I think we have learned a fair amount.
15 I think we would change our approach slightly.
16 DR. LESKO: What do you think would be
17 more efficient?
18 DR. HOCKETT: This is going to open up
19 another can of worms. I think, prospectively, it
20 would be, especially if we find that there is a
21 toxicity that we have to identify or deal with with
22 poor metabolizers. Then we have to gear up to make
23 sure we get an FDA-approved test when our drug is
24 released, is the most efficient, because, for us to
25 be able to sell a drug that requires a test, at

1 least my understanding is you are going to require
2 at least a fair amount of work going down the road
3 to an FDA-approvable assay for that to happen.
4 That has, then, got to be done in parallel.
5 Otherwise, I can't sell my drug.
6 DR. LESKO: I was sort of coming from
7 another standpoint, the increased cost of screening
8 people to get suitable numbers of genotypes versus
9 just sort of increasing the enrollment in a study
10 and hoping that the breakout occurs--
11 DR. HOCKETT: Yes; it is far most
12 cost-effective to screen people even if it is $300
13 or $400 than to enroll them. The average cost in
14 most clinical trials is about, what, $10,000 a
15 patient to carry them through a clinical trial. So
16 if I can screen a bunch to keep that number down, I
17 am much better off.
18 DR. VENITZ: Thank you, again.
19 Our last presentation for this meeting is
20 Dr. Relling. She is going to give us the
21 practitioner's perspective for pharmacogenetic
22 testing.
23 Practitioner Perspectives
24 DR. RELLING: Good morning.
25 [Slide.]

1 I think it has been implicit in what we
2 have all been saying that obviously there are some
3 drugs where the therapeutic range is so wide we
4 don't need to know anything about how to prescribe
5 them and we are willing to give a very high
6 population dose to everybody in order to achieve a
7 high probability of efficacy and a low probability
8 of toxicity, and that it is for drugs with narrow
9 therapeutic ranges.
10 Of course, anticancer drugs definitely
11 fall in this range where the dose that one needs to
12 achieve a reasonable probability of efficacy is so
13 close to the dose that achieves serious toxicity
14 that anything that we can do to help us to
15 individual doses in any given patient is something
16 that we would try to have.
17 [Slide.]
18 So let's go ahead and make the assumption
19 that getting the right dose of the drug for the
20 disease being treated is important. Of course,
21 sometimes, that can be true, but there may be other
22 approaches to titrating the dosage besides doing
23 something like genetic testing.
24 So, in cases where that might be
25 problematic is, of course, the probability of

1 response and the adverse effects should be related
2 in some way to drug exposure and titrating dose may
3 not be optimal. Either the disease would be too
4 serious to risk a period of undertreatment, and I
5 think the this we just heard about, for example,
6 ADHD, might be a disease where it is not so serious
7 if the patient goes a few weeks with a suboptimally
8 controlled disease whereas there are other diseases
9 where spending even a few weeks at suboptimal
10 control could compromise overall long-term outcome,
11 that the adverse effects are so serious that it is
12 not ethical to risk then and that you are really
13 bound to do whatever you can to adjust the dose as
14 accurately as possible from Day 1 or that the
15 response or the adverse effects are delayed to too
16 difficult to monitor.
17 Too difficult to monitor, for example,
18 might be something extremely expensive or extremely
19 invasive, Swann-Ganz catheters or some implantable
20 device that just wouldn't be reasonable for
21 following patients long-term or that, really, there
22 is nothing that you can monitor while you are
23 seeing the patient week after week or month after
24 month to give you a clue as to what might be going
25 on with long-term adverse effects.

1 Again, we have, in cancer, got examples of
2 that that comes from our association between the
3 cumulative incidence of a very late adverse effect,
4 the development of irradiation-induced brain tumors
5 whose onset didn't occur until five years after the
6 start of radiotherapy, so that was over six years
7 after the start of treatment for acute
8 lymphoblastic leukemia that was related to a single
9 genetic polymorphism and a single gene, this TPMP
10 or thiopurine methyltransferase gene.
11 So, obviously, there is nothing that would
12 could monitor during this period of therapy when
13 patients were receiving their thiopurine daily for
14 two-and-a-half to three years that would give us
15 any clue that the patient would ultimately develop
16 a life-threatening secondary brain tumor. So that
17 is an example of a late effect that we need
18 something earlier to monitor to figure out how to
19 adjust doses.
20 [Slide.]
21 In the diseases that we treat at St. Jude,
22 the most common pediatric tumor is acute
23 lymphoblastic leukemia. I think some of the
24 phenotypes that we monitor in this disease are
25 illustrative of how we have to go about monitoring

1 therapy. So ALL is treated with, as I said,
2 two-and-a-half to three years of almost daily
3 chemotherapy with anywhere from five to eight drugs
4 almost all of which cause myelosuppression and
5 those patients are monitored weekly for their blood
6 counts. Myelosuppression is something that we can
7 monitor and sometimes make dose adjustments in
8 therapy to prevent that myelosuppression, at least
9 in the following week or ten days.
10 Vincristine-induced peripheral neuropathy
11 is another example that has a relatively short
12 onset adverse effect. It is possible to adjust the
13 doses of vincristine to try and avoid that adverse
14 effect as patients are being treated. As we start
15 going out, the onset starts getting longer and the
16 relationship to therapy more complicated. So the
17 use of glucocorticoids like prednisone and
18 dexamethasone have been associated with the
19 development of avascular necrosis but exactly when
20 it happens, what its onset is, what the best way to
21 prevent it is, is not clear so that now we are
22 left, when a patient has symptoms or MRI imaging
23 indicating vascular necrosis, we cut the dose or we
24 stop the dose but we have no idea if it is right
25 thing to do in terms of long-term overall outcome

1 of that disease and cure.

2 Methotrexate neurotoxicity can be quite

3 delayed. Sterility, long-term obesity might be

4 five, six, ten, fifteen years after the start of

5 therapy. Ultimately, whether the patient is cured

6 is a decision that can't be made until you are at

7 least five years from the diagnosis of the disease

8 and the development of secondary tumors is also one

9 that is three, four, five, six, seven years out.

10 So monitoring therapy during the period of

11 treatment isn't feasible in this case and having

12 anything to help us adjust doses prospectively

13 would be worthwhile.

14 [Slide.]

15 Also, to make the point we are all making,

16 that we recognize this has to be made in the

17 context of other factors that we know affect drug

18 pharmacokinetics and pharmacodynamics. So, as

19 there are some drugs for which renal function might

20 really be the most important determinant of

21 exposure and it is likely that there are not strong

22 polymorphisms, for example, in drug-metabolizing

23 enzymes that could be important but whatever the

24 environmental or nongenetic influence on drug

25 disposition, it does have to all interact with the

1 patient's constitutive genetic state.

2 [Slide.]

3 What I have been struck with is the

4 conversations we have just been having is we are

5 focusing where the light is shining. We are

6 focusing on the polymorphisms that we already know

7 are important, like CYP2D6 and TPMT. But I guess I

8 am a strong believer that I do think we will

9 discover additional genetic polymorphisms in the

10 next ten, twenty, thirty years that we currently

11 have no idea are important, so that to make

12 decisions about drug development based on phase I

13 studies doesn't seem to me to be an option. There

14 has to be DNA collection throughout all phases of

15 drug therapy.

16 I have been told that Dr. Sheiner is

17 someone that likes us to think in a sort of

18 organized way about decision-making so I am trying

19 to use this as a little bit of a platform for what

20 do I want to know, how sure do I need to be and

21 what am I willing to assume as a clinician who

22 wants to have prescribing information for

23 pharmacogenetics.

24 [Slide.]

25 I want to know whether specific genetic

1 polymorphisms influence the probability of response
2 or adverse effects. Whereas there can be twin
3 studies or family studies that indicate a genetic
4 component in drug response, I think we are talking
5 about wanted to identify individual genetic defects
6 that may be problematic. So we are talking about
7 specific proposal polymorphisms.
8 [Slide.]
9 And we want to have some idea of how the
10 polymorphisms affect drug response, by interfering
11 with protein products involved in absorption,
12 distribution, metabolism, excretion or the response
13 or pharmacodynamics to the drugs. That is because
14 of the point we made earlier that, in order to have
15 an idea of how to put this in the context of drug
16 interactions and diseases, we have to have an idea
17 of what the underlying mechanism is involved.
18 So if it is a genetic polymorphism and a
19 drug-metabolizing enzyme, then I should have
20 heightened sensitivity to the administration of any
21 other drugs that are substrates for those same
22 enzymes and that providing this information in the
23 context of all that information, the nongenetic
24 information, is important.
25 [Slide.]

1 Also, to give me a little bit of
2 information in the labeling about what doses or
3 routes of the drugs were tested when
4 pharmacogenetic information was collected so that,
5 in situations where doses are relatively low or
6 exposures are long, a 24-hour infusion instead of a
7 two-minute I.V. push, the effect of the drug
8 saturating an enzyme or a protein product could be
9 quite different.
10 So let me understand a little bit about
11 how the studies were done. And the same would be
12 true in terms of predicting how relevant
13 polymorphisms and hepatic metabolism would be
14 helpful to know if there is oral or prolonged
15 exposure versus very short acute exposures.
16 [Slide.]
17 What am I willing to assume? We have kind
18 of been talking about this all morning. The in
19 vitro data and preclinical data can be helpful so
20 even if the clinical information isn't strongly
21 supportive of an effect, having the basic
22 information about what enzymes are involved in the
23 metabolism or the handling of a medical is helpful
24 if only for doing things like predicting three and
25 four drug interactions. As we heard about this

1 morning, three and four drugs is a whole lot
2 different than just two drugs interacting, to help
3 the prescribers use the information that we know
4 about the effects of polymorphisms from other drugs
5 on the drug of interest.
6 Again, by using basic principles of
7 pharmacology, the clinician may be able to make a
8 more sophisticated decision about how to use the
9 medication by providing that information.
10 [Slide.]
11 This is what I think was mentioned earlier
12 also, this European group has tried to get together
13 and come up with some dosage recommendations that
14 would be reasonable to put into place now for some
15 drugs that are substrates for 2C9, 2C19 and CYP2D6.
16 They have come up with recommended starting doses
17 for a number of drugs in poor metabolizers and
18 extensive metabolizers, and, in once case, where
19 there were sufficient data, in the ultrarapid
20 metabolizes.
21 Having this kind of information, again,
22 although the clinician would have to be careful, by
23 knowing about how the medication is handled, how
24 the drug us dosed relative to the concentrations
25 that are likely to saturate these protein products,

1 you might willing to state that an ultrarapid
2 metabolizer receiving another drug in this class
3 might be deserving of a higher dose even though
4 there might not be clinical data specifically
5 testing that drug at those higher doses in those
6 genotypes.
7 [Slide.]
8 What do I want to know? I do want to know
9 the frequency of the specific genotypes in at least
10 the three largest ethnic racial groups,
11 understanding that Hispanics are, in many cases, a
12 larger ethnic group but that they are going to be
13 somewhere in between these three groups in terms of
14 allele frequencies, in general.
15 You basically want to know the frequency
16 of the common homozygous genotype, heterozygotes
17 and those that are homozygous variant or defective.
18 [Slide.]
19 Giving allele frequencies is another
20 possibility that I think most clinicians are not
21 really comfortable going through Hardy-Weinberg
22 calculations. So I think clinicians are going to
23 be more comfortable with knowing the frequency of
24 the genotypes rather than allele frequencies.
25 [Slide.]

1 We have talked about the difference
2 between phenotype and genotype. While it is true
3 that phenotype is the bottom line, phenotype can be
4 influenced by concurrent drugs, by diet, by
5 disease. This information could be important to
6 put in the label as long as it is clear to the
7 clinician that that is the truth whereas, of
8 course, the patient's germ-line DNA is the
9 patient's germ-line DNA with the possible exception
10 of stem-cell-transplant survivors whose blood DNA
11 is not going to be their germ-line DNA.
12 It has the advantage that it must only be
13 studied once, although, again, with the caveat that
14 the technology could improve so that genotype might
15 need to be repeated in the future as technology
16 improves. It has already been mentioned that
17 genotype is probably more susceptible to false
18 negatives than phenotype is just by virtue of the
19 fact that probably no genotyping test is going to
20 capture all inactivating alleles or mutations.
21 [Slide.]
22 Some concepts about genotyping tests that
23 I think we have to educate ourselves about, that
24 there are multiple types of variant and wild-type
25 alleles for every gene. We have already heard

1 about those. We have already talked about false
2 negatives, and that the number of false negatives
3 really depends on the proportion of the
4 inactivating variants that a genetic test is going
5 to account for.
6 I think, in my mind, this is going to be
7 the responsibility of the person providing the test
8 results to indication what variants they test for
9 and, given current data, what proportion of
10 inactivating variants their test covers, and that
11 putting that in a label is probably not feasible
12 because that is a piece of biology that is going to
13 change rapidly over time. So I don't think we
14 should hold manufacturers of individual drugs to
15 that standard.
16 [Slide.]
17 That patients can be heterozygotes.
18 Clinicians are going to get back results that will
19 indicate more than one mutation in some cases.
20 Again, the better the interpretation of the test,
21 the less information has to go in the label and the
22 less we have to worry about clinicians being able
23 to understand this. I do think, again, this is
24 going to be the responsibility of the people
25 providing genetic tests to say, here is what the

1 raw genetic results are. We are willing to
2 interpret the haplotype likelihoods this way and so
3 there is a 95 percent chance that this result means
4 that the patient is a heterozygote and there is 1
5 in 100 chance it means that this patient is
6 homozygous-deficient.
7 [Slide.]
8 Again, some knowledge of genetics and
9 molecular biology will be helpful as
10 pharmacogenetics gets incorporated into labels. We
11 have heard people debating about the role of
12 assessing heterozygotes but I do think, in most of
13 these cases, is it going to be a reasonable
14 assumption that heterozygote phenotypes are usually
15 in between the two homozygous genotypes and that,
16 although there may not be strong clinical data for
17 that particular drug indicating a different dose is
18 indicated in heterozygotes versus homozygotes of
19 one genotype or the other, given a patient has
20 other concurrent drugs, given a patient might have
21 other altered routes of metabolism or excretion, it
22 is reasonable for the clinician to make some
23 assumptions about heterozygotes and so provide the
24 clinician with that information.
25 We have already talked a lot about gene

1 duplications and how a gene-duplicated allele along
2 with a heterozygote variant allele could confound
3 interpretation. Again, I would put more of that
4 responsibility on the provider of the test result
5 and not that kind of detailed information being
6 requested in the label, necessarily.
7 [Slide.]
8 Again, the more information the clinician
9 has about how they understand how these different
10 mechanisms of genetic variants might affect the
11 expression of a protein product will be better if
12 the clinician understands that a gene deletion
13 obviously means the gene can't be expressed at all.
14 There is no controversy, that an early stop codon
15 means there absolutely can't be any protein, that
16 gene duplication means there might be more active
17 protein and that things like conserved amino-acid
18 substitutions or promoter polymorphisms are likely
19 to have a less significant effect, that will be
20 helpful but, again, interpretation of the genetic
21 results should take care of most of these
22 relatively complicated decisions.
23 [Slide.]
24 As I am writing all this down, I am
25 thinking, is this too much to expect of clinicians?

1 It may be, but I do think that there are plenty of
2 examples where we expect a high degree of
3 sophistication in clinicians in being able to
4 prescribe drugs. Now, with the availability of
5 ematinib, the 922 translocation in peripheral blood
6 or bone marrow really needs to be followed to see
7 how it is progressing within a patient.
8 That can be assessed several different
9 ways, by cytogenetic tests, by FISH, by RT-PCR, and
10 there may be a lot of clinicians who don't
11 understand the subtleties between the way that
12 those tests work. But that doesn't mean that we
13 don't expect them to have some idea of how to
14 follow diseases in these patients.
15 There are many drugs for which G6PD
16 deficiency is either a warning or a
17 contraindication and most clinicians don't
18 understand how those tests are done. They don't
19 know whether they are phenotype or they are
20 genotype, that we are expecting them to try to get
21 them, to try to utilize them, to try to prevent
22 adverse effects for patients prescribed some of
23 those drugs in some cases.
24 I noticed in the Hepatic Dosing FDA
25 Guidelines, the Child-Pugh score is used repeatedly

1 to describe how to interpret the liver dysfunction
2 in patients. I would wager to guess that there are
3 many clinicians using drugs for which the
4 Child-Pugh score is described in the label but they
5 don't understand exactly how to calculate that or
6 what those numbers mean, and we can go on and on.
7 So I do think it is a lot to expect of
8 clinicians but I don't think that that means it
9 shouldn't be done.
10 [Slide.]
11 What else do I want to know? I don't want
12 to know a lot of the details about phenotype but at
13 least tell me whether it is a blood test or a urine
14 test, give me a little idea of the direction of the
15 phenotype, so that could be AUC, that could be
16 enzyme activity, and how, at least, directionally,
17 it relates to the genotype and give me some idea of
18 what interferes with the phenotyping test so I know
19 whether it is reasonable to try on the patient.
20 For genotyping, we have already mentioned
21 at least an idea of the number of inactivating
22 variants, their approximate frequencies and it
23 would be helpful--again, this could be provided by
24 the person providing the genotyping test to
25 understand what proportion of inactivating variants

1 their genotyping test accounts for in at least the
2 major racial ethnic groups.
3 [Slide.]
4 Also, that negative results can be very
5 helpful, so just understanding that a drug has been
6 tested to see whether it is a substrate for
7 different genetically regulated polymorphism gene
8 products and knowing that it is negative may be
9 helpful and that that information should be
10 included where possible.
11 [Slide.]
12 How sure do I need to be? I think it is
13 helpful to just provide examples of real data and I
14 guess I would prefer that we leave the option
15 somewhat open as to exactly what kinds of data are
16 presented. Knowing the average or standard
17 deviation or the median plus-or-minus the
18 confidence interval for the dose in three
19 genotypes, homozygote, wild-type, heterozygote and
20 homozygous variant at some specific doses.
21 For example, given here are some doses.
22 That can be helpful. Understanding the frequency
23 of a serious toxicity like QT widening along with
24 confidence intervals in patients of different
25 genotypes. Given a dose, a fixed dose, what

1 proportion of patients displayed evidence of
2 response or what proportion of patients displayed
3 evidence of toxicity?
4 [Slide.]
5 The literature is filled with these kinds
6 of examples that I think would be helpful in the
7 labeling.
8 [Slide.]
9 This is an example of the frequency of the
10 median and confidence intervals for severity of
11 mucositis in patients who are homozygous CC,
12 heterozygote or homozygous TT for an enzyme
13 involved in folate metabolism who are given
14 methotrexate as transplant preparative regime.
15 [Slide.]
16 This is an example of the warfarin
17 milligram-per-day dose in patients who were
18 titrated to achieve a target INR. One can see the
19 degree of overlap among the genotpyes, see that
20 there is overlap but that there will be differences
21 in the median and range of doses tolerated by
22 patients in those various genotypes.
23 This is the proportion of patients cured
24 based on their 2C19 genotype in the wild type
25 versus heterozygote versus homozygous variant

1 genotypes treated with a standard dose of
2 omeprazole.
3 [Slide.]
4 So our favorite gene polymorphism TPMT;
5 this shows the difference in enzyme activity of
6 frequency distribution and the mean tolerated
7 weekly dose of 6 mercaptopurine in the 1 percent of
8 patients who are homozygote mutant, the 10 percent
9 who are variant heterozygote and the 90 percent who
10 are homozygous wild-type, the same polymorphism,
11 the cumulative incidence of requiring a dosage
12 decrease based on myelosuppression in the
13 homozygous variant, heterozygote and wild-type
14 patients along with confidence intervals for that
15 cumulative incidence.
16 I think any of that kind of information is
17 information that clinicians can interpret if they
18 want to understand how to best prescribe
19 medications in their patients.
20 [Slide.]
21 In terms of the labeling sections that may
22 be relevant for clinicians, I think that we have
23 heard about most of these today, that the Clinical
24 Pharmacology Section is very important to provide
25 general background information, a little bit of

1 information about what doses of drug were used,
2 what concentrations were used in in vitro studies,
3 a little bit about how the studies were done, where
4 relevant to put information in the Warnings,
5 Precautions and Adverse Reactions and Overdosage
6 Section, and to provide some information on dosage
7 and administration, especially given that what is
8 right there right now includes information on
9 dosage adjustments, given degrees of renal
10 dysfunction and hepatic dysfunction which often
11 have far less ability to discriminate doses that
12 have been true for many pharmacogenetic
13 polymorphisms that have been associated with
14 different doses and adding information on what has
15 been observed in different genotypes for dose of a
16 drug, I think, in that section is important.
17 [Slide.]
18 The other principle that I think has been
19 illustrated already in a couple of labels that have
20 been approved by the FDA, having just cross
21 references among sections I think is a good idea.
22 So, if there is something about genetic
23 polymorphisms in clinical pharmacology, it can
24 state, "Please see the Adverse Reaction Section for
25 additional information on dosing of these drugs."

1 [Slide.]

2 A couple of miscellaneous items in terms
3 of terminology that I think should be considered,
4 that it should be allowed to use colloquial terms
5 where it is relevant and people may be familiar, so
6 extensive and poor metabolizers, fast and slow
7 acetylators, that is fine to use if they are
8 already out there in the medical literature. To
9 try to avoid the word "mutant" if possible. Most
10 people don't like to hear themselves referred to as
11 mutants-- although I don't mind at all, and I am
12 homozygous variant for all kinds of things--that
13 the terms variant and defective are more neutral
14 and probably descriptive.

15 Avoid the word "normal" if possible and
16 use wild-type or describe what the effect is on the
17 phenotype, high activity, normal expression. All
18 of these star HUGO nomenclature designations that
19 those of us in the field throw around are not going
20 to be very interesting to most clinicians.

21 If they can be easily mapped to the
22 wild-type, common or variant-defective allele in
23 the label or at least in the genetic test, I think
24 that will be helpful to prescribers, but we are
25 going to have to deal with the fact that this is

1 confusing, that there may be several HUGO
2 designations for a wild-type allele and lots for
3 defective or variant alleles.
4 [Slide.]
5 I apologize because I have still got a
6 couple of typos in here. In terms of a
7 decision-tree, it is really nothing other than what
8 we have been talking about. If the ability to
9 titrate the dose intraindividually is apparent
10 without compromising the patient, that, just based
11 on response, then I don't think we really have to
12 look very much further on how to prescribe the drug
13 intelligently.
14 But, if not, and if the drug is
15 complicated by late effects or invasive monitoring
16 or, as I mentioned, very serious diseases where
17 under or overtreatment is not an option, then are
18 there other simple lab tests that can be used or,
19 like Bill Evans used to say, "If you can use shoe
20 size, you use shoe size." You use what works.
21 If that is not an option, and
22 pharmacogenetic tests are available and an option,
23 then, yes; they should be used and I don't really
24 think we have to decide on phenotype versus
25 genotype. I think both kinds of information should

1 be provided to prescribers.
2 So I will stop there and be happy to take
3 questions.
4 DR. VENITZ: Thank you, Mary.
5 Any questions for Mary? Let's get started
6 on the discussion,
7 Committee Discussion
8 DR. VENITZ: You all have the questions
9 that Larry and the FDA are asking us; are the
10 approaches presented to study the influence of
11 pharmacogenetics on exposure response sufficient
12 and appropriate and a follow up question, are there
13 any other criteria or approaches that FDA should
14 consider recommending to sponsors?
15 So I will open the floor for general
16 discussion as well as any questions that you might
17 have for Mary's presentation.
18 DR. SHEINER: Mary, can you just flash up
19 the one slide again? Is that possible, or is it
20 gone? Has it disappeared? I think it was maybe
21 the first or second one.
22 That's it. I just wanted to say, Mary,
23 that I knew that anti-cancer drugs were dangerous
24 but I didn't know that you could get more than 100
25 percent toxicity at a high dose.

1 DR. McCLEOD: It is more than one
2 toxicity.
3 DR. SHEINER: I wanted to say I am pleased
4 that you used the three questions that I have
5 asked, but that was actually more in the line of,
6 if you are going to do an investigation, sort of a
7 learning study or a confirming study, because when
8 you get to decisions things get a bit more
9 complicated and you need utility functions and
10 stuff like that, sort of like that, sort of that
11 how certain you need to be becomes what is it worth
12 to you. So life gets a lot more complicated.
13 But I did want to say I really like the
14 way you sort of put it all together there. The
15 problem is you had an awful lot of, "What do I want
16 to know?" We have got to do some kind of
17 distillation. Maybe some people can handle it and,
18 as you say, the expectation is the people in the
19 field taking care of people will have to be able to
20 respond to these things, but we have got to distill
21 it down. That was a lot of, "What do you want to
22 know?"
23 And you went so far as saying, "And I want
24 to see some real data." I know that is you and I
25 know that is us, but it is a big demand and, you

1 make the label huge that way, you may find that you
2 get an unintended consequence which is nobody pays
3 attention to it, which is already a problem with
4 labels. They go on and on.
5 The other point I just wanted to make
6 about your last slide when you said, if you can
7 titrate, then maybe you just should titrate. One
8 of the things we shouldn't lose sight of is, even
9 though therapeutic drug monitoring is not as good
10 as effect, if the issue is a pharmacokinetic
11 change, and if you are worried about this drug is
12 inducing and that drug is blocking, and so on, in
13 the end it comes down to what is the drug level.
14 It may be the easiest thing to do is just to find
15 out and not have to worry about all those details.
16 DR. RELLING: Yes. I put drug levels as
17 phenotype.
18 DR. SHEK: Again, looking at this decision
19 tree and looking at the adjusted dose, with regard
20 to practicality, I would assume, for injectables it
21 might be easy but how practical is it with the
22 dosage that industry is putting that you can adjust
23 the dose. Do we have also to look at more
24 flexibility there which might have its own economic
25 impact where you have more variability in the

1 dosage, strains that a supplier, a manufacturer,
2 will come up with to enable you to do it.
3 Although maybe drugs, they wouldn't have
4 the toxicity, but I believe that side effects might
5 have an impact on compliance and might have an
6 impact on efficacy, people are not complying
7 because of the side effects. I don't know how much
8 flexibility is there, whether the industry has to
9 respond and come up with more dosage flexibilities.
10 DR. RELLING: As somebody in pediatrics,
11 we deal with this all the time. I mean, we just
12 have to come up with different dosages based on
13 formulations. But there are examples where I am
14 sure there is pressure on the industry to come up
15 with more formulations.
16 Again, I don't think we can let the fact
17 that different doses may be required in different
18 patients be the reason not to have individualized
19 doses. We have got to figure out a way to do it.
20 DR. HUANG: Going back to your decision
21 tree, and your question whether we can titrate to
22 the response and, if so, then you adjust dose
23 accordingly. All the examples that you have shown,
24 which one do you think the clinician will not
25 answer, "I can adjust the dose?" For example, some

1 of the warfarin and this whole list of tricyclics
2 where the physician was saying, "No; I cannot
3 adjust and I am going to go to the left," or the
4 majority would go to the right, where they say, "We
5 could adjust according to the response."
6 DR. RELLING: I will let somebody else
7 handle tricyclics. My impression is that
8 under-treatment of psychiatric disorders is a major
9 problem, the fact that there is this assumption
10 that there is a huge proportion of the population
11 that just intrinsically don't respond and nobody
12 knows why and it is only a trial-and-error period
13 of six to eight weeks. I think that causes
14 unbelievable morbidity in this country right now.
15 There might be a lot clinicians who say
16 they can do that, but having better information
17 about how to come up with a good starting dose, I
18 would think would be critical in that area. Almost
19 every anti-cancer drug is a drug that can't be
20 titrated based on response accurately or reliably.
21 I don't know--let everybody else put in their
22 favorite compounds. I guess there are others where
23 it is not problematic. Insulin is one where you
24 can titrate to response.
25 DR. McCLEOD: I think the warfarin example

1 is a good example of why you can titrate to
2 response but it is not good enough. The cohort
3 data that David Veenstra and others have published
4 identify that the people with the homozygous
5 variant genotype were able to be titrated to a good
6 INR. It took an average of 94 days and we all
7 know, in the area, that is the first 70 days that
8 are most critical for preventing clot post
9 arthritic--or hip replacement or in the case of
10 atrial fibrillation.
11 So it can be done, just not in a timely
12 enough manner to prevent some events. How many of
13 those events is arguable. In other situations, it
14 is not as big a deal. If you have a mild
15 rheumatoid arthritis and you want to get the
16 methotrexate dose right, you have a few weeks to
17 get it wrong. It is inconvenient and patients
18 don't like it, but it is not life-threatening or
19 associated with high morbidity.
20 So I think maybe that decision tree needs
21 to go how soon you need to get it right because, if
22 you need to get it right quickly, then it may be
23 that a lab test will be more appropriate and can be
24 done, as Rick mentioned, before you ever give the
25 drug as opposed to having to wait and respond.

1 DR. SADEE: I think, looking at all the
2 data, there is a fundamental problem in that we
3 have a few polymorphisms in the P450s that are
4 clear. They abrogate the function of a protein and
5 that is useful in a fraction of the patients. But
6 then there is additional variation that is really
7 very, very large. So you cannot say we cannot
8 titrate the dose on the basis of genotypic
9 information because it may only take care of a very
10 small fraction of the problem.
11 Maybe it is useful to just think about the
12 fact that the cytochromes that are highly
13 polymorphic are a very unusual example in that it
14 hardly ever happens in any other gene that
15 nonmutations, mutations such as abrogate the
16 function altogether of a protein, accumulate to
17 such high levels, let's say 30, 40 percent of
18 allele frequencies in some cases. So that is a
19 very unusual situation.
20 If you do a genomewide study and those
21 studies have been published now, then polymorphisms
22 in promoter regions, polymorphisms affect the
23 stability of mRNA processing, splicing, et cetera,
24 are probably five times as prevalent or maybe even
25 ten times as prevalent as those that affect protein

1 function. That is where most of the research has
2 been going.
3 So I agree with Mary's statement that
4 anything we do should make sure that the
5 polymorphisms that we put into any labeling are
6 seen as just maybe the ones that we know right now,
7 that there is room for additional polymorphisms
8 that can be 100 KB upstream of a gene, nobody has
9 ever looked at it and they are extremely important,
10 could affect the expression tenfold, easily.
11 So these polymorphisms may appear over the
12 next few years. So whatever we do needs to be
13 predicated by the sense that we actually only know
14 a very small portion. Lew, you said we have to
15 distill it down, and that is correct. But we can
16 only distill down if we know from where we are
17 distilling down.
18 And I think we are still, even in the
19 cases of 2D6, quite a way from knowing all the
20 important variations that occur, not even to talk
21 about epistasis, compart heterozygosity, haplotype
22 information, you name it. All those are
23 complicating factors that you definitely want to
24 touch after having distilled down, but you have to
25 know it ahead of time. There is no good method to

1 determine whether two functionally important
2 polymorphisms are on the same allele or on the
3 opposite allele except for maybe the methods you
4 are using now, and they work pretty well. But
5 nobody is using it.
6 So there is a lot of uncertainty and that
7 is the difficulty of what we are dealing with, to
8 distill down from an entirely incomplete piece of
9 information to something that then is supposed to
10 educate us how to use dosages. That will be rather
11 difficult.
12 DR. VENITZ: Let me add something and
13 maybe reiterate something that Lew had mentioned
14 early on and this goes back to my favorite utility
15 function implicit in both of your presentations.
16 If I look at Strattera, the reason why you
17 ultimately didn't care about the phenotype is
18 because you were worried about insomnia. The
19 reason why Mary cares about it is because her
20 toxicities are life-threatening, at least
21 potentially.
22 If you had to pick the perfect
23 pharmacogenetic test or the perfect scenario where
24 it might be useful, you want to pick something
25 where the stakes are very high. Either the stakes

1 may be the consequences of toxicity or the
2 consequences of lack of efficacy. That is why I
3 think oncology is a perfect area for that because
4 the stakes are very high.
5 A lot of other diseases or indications you
6 may find, yes, there are relevant genotypic
7 differences that are reflected and genotypic
8 differences that you can measure in terms of
9 exposure of response, but the consequences,
10 clinically speaking, are insignificant. Those are
11 the ones where there is very little at stake and it
12 is very difficult to convince practitioners that
13 are already having a tough time translating all the
14 nice research that we are doing into practice. It
15 is very difficult for us to convince them to
16 actually change anything.
17 So, in terms of strategic planning on the
18 FDA side, I would focus on the scenarios where
19 there is lots at stake as opposed to picking the
20 ones we know a lot about but clinically the
21 relevance is limited at best.
22 DR. SHEINER: There is also an interesting
23 signal-noise issue. It is right that we focus on
24 the poster children, the big effects and so on,
25 sort of to get people's consciousness up about what

1 is going on. But I remember, and maybe I am
2 showing my age too much here--I remember 30 years
3 ago digoxin. This was the classic drug to adjust
4 for renal function.
5 Yet, when we looked at a huge number of
6 patients receiving digoxin, they were mostly old
7 and their creatinines were around 2 because they
8 were old and their kidneys were not working as well
9 as young people. But the number of people with
10 renal disease in a random population in a hospital
11 ward was rather small and, if you just did the sort
12 of standard statistical test and asked, did renal
13 function help when you put it into the regression.
14 Very little information about how you ought to dose
15 that drug in practice was conferred by knowing the
16 creatinine.
17 Now, that is not true. The person with a
18 creatinine of 10, obviously, you learned a lot.
19 But they were very, very rare so you couldn't get
20 it to show up. Now, does that mean we should be
21 sort of segregating out the outliers and saying,
22 "But that is who we really care about," or does it
23 mean we really want to talk about average behavior.
24 These are all issues that don't really
25 come up as scientists because you are trying to

1 push the knowledge forward but do come up very much
2 in a regulatory agency. How much do you hold
3 people's feet to the fire? How much do you put in
4 the label? How much do you prevent things from
5 happening. It is very tough to answer because,
6 again, you need population data. You need somebody
7 is going to be realistic about the way they
8 evaluate it rather than somebody who has got a flag
9 to wave or an ax to grind.
10 It is just starting here. You found a
11 couple--I think it was brilliant of Larry to limit
12 this discussion to metabolic enzymes of a certain
13 type. But this is opening a Pandora's box of
14 thousands of possible genetic variants and their
15 implications for pharmacodynamics,
16 pharmacokinetics, lord knows what else and just the
17 thought of how you were going to deal with in some
18 way in which you do pay attention to the important
19 ones and not to the unimportant ones is really
20 almost daunting.
21 DR. SADEE: I think focussing on the ones
22 where it really makes a difference, the dosing, and
23 you mentioned tricyclics, but also the treatment of
24 psychosis, of first-case psychosis, is a real
25 problem because, if it is not treated properly, it

1 may cause damage for the rest of the life of that
2 particular patient.
3 And yet you do not know whether a drug is
4 effective until maybe six or eight weeks. At least
5 that is the conventional wisdom. There may be
6 better techniques. So if you underdose because
7 there is a high metabolizer, for instance, you
8 wouldn't know about this and these patients would
9 be damaged for life. So I think that is another
10 situation where it is extremely critical to get the
11 dosage right.
12 With respect to all these multiple
13 polymorphisms and unknown factors that we are
14 talking about, I think we must be aware of also the
15 increasing knowledge about epigenetic changes and
16 accommodate of the modeling which is exploding into
17 our face. There may be absolutely no polymorphism
18 and it still may be epigenetic; that is to say,
19 there is a stable genetic change in the gene that
20 you may not see by the normal genotyping where the
21 gene is silenced or where the comatin is remodeled.
22 That appears to be malleable even though
23 it was thought to be once a gene is silenced, that
24 will be for life but it can be reversed. So these
25 are epigenetic changes we do not even touch upon

1 and they may be also huge in their effect.
2 DR. LESKO: Just to elaborate a little bit
3 on "the stakes are high issue." The current let's
4 call it "model" in drug development is to look at
5 covariates that affect pharmacokinetics early on
6 and then react to that in one form or another in
7 terms of drug dosing.
8 I guess I am trying to get to maybe a
9 better understanding of why the issue of stakes are
10 high would be any different in a genetic or
11 genotype-defined population than the stakes are
12 high for any drug in which we study routinely
13 hepatic disease, renal disease, and so on.
14 I understand it is only interpretation but
15 how does it differ as a cofactor that might become
16 something that is a routine factor to study in drug
17 development with the decision about what to do
18 about it later on. It almost sounds like, "I don't
19 want to study this cofactor unless the stakes are
20 really high."
21 But it is part of understanding the basic
22 informational content of the clinical pharmacology
23 of the drug, so I sort of want to pursue that
24 thinking a little bit.
25 DR. VENITZ: Fundamentally, I don't think

1 it makes any difference. What I was referring to
2 is how you can translate that into actually
3 changing the practice. If you pick the low-hanging
4 fruits, you have a better chance of convincing
5 people that this is actually important. Otherwise,
6 we are going to swamp labels with pharmacogenetic
7 information that, in reality, is not going to be
8 used.
9 You heard what Lew was saying about
10 distilling information. I am talking about
11 information may not even be relevant so distilling
12 it to the point that it doesn't even appear on the
13 label.
14 DR. SHEINER: I think it is very
15 different. The difference is that how many
16 drug-eliminating organs are there. There is the
17 kidney, the lungs and the liver and that is about
18 it. So there are only a few things you need to
19 look at. We lump all hepatic diseases together.
20 Maybe we shouldn't, but we do.
21 So it was doable. We are now entering a
22 realm where the number of possible things you could
23 have to look at just keeps on multiplying. Not
24 only does that produce terrible problems in false
25 positives and the ability to extract from

1 100-people's worth of data when you have got a
2 thousand covariates which one makes a difference.
3 We have got to be much more intelligent about this.
4 A drug that is excreted unchanged, you
5 have got to look at the kidneys. Basically, it is
6 how well do they work. It doesn't matter what
7 disease has caused them to not work so well. It is
8 a doable containable problem. This is not. So
9 that is the difference. There is no conceptual
10 difference but the difference is we are in a very
11 different universe. We are in a
12 thousand-dimensional universe. And everything
13 changes.
14 DR. LESKO: So what do we do about it. It
15 gets to another question I was thinking about and
16 it is that when studies like this would be
17 conducted, they might be conducted, for example, in
18 a phase I healthy volunteer population. Typically,
19 that information, whether it is drug interactions
20 or anything else is extrapolated to many other
21 populations for the purposes of adjusting doses
22 without a lot of consideration of issues other than
23 the differences in exposure.
24 So I guess what I was wondering is, as we
25 have gone through, actually two days and maybe,

1 Greg, you touched upon this is if you had a
2 genotypic difference demonstrated in a test
3 population which would be a phase I
4 healthy-volunteer population, as you extrapolate
5 that knowledge to other populations, where would it
6 become more important or less important?
7 For example, in the elderly where you have
8 maybe in an extensive metabolizing group slower
9 metabolism so the differences become closer,
10 genotype doesn't make much difference. In young
11 kids, maybe the development process doesn't make
12 much difference.
13 Does genotype interact with other
14 covariates that are out there in that little circle
15 that Mary showed? What do we know about those
16 sorts of issues?
17 DR. RELLING: I think that the Strattera
18 example is interesting. I would like to know a lot
19 more information. Where you see this incredible
20 bimodal distribution, in some estimate of I think
21 it was a parent oral clearance, I don't know where
22 those doses that were tested were relative to the
23 doses that were actually used in the chronic dosing
24 over weeks that you showed us where it ended up
25 that there was no difference in the delivered dose.

1 I don't know what was titrated week by
2 week in order to decide whether to go up or down on
3 the dose. But, yes; presumably those other
4 nongenetic factors--it may just include simple
5 things like what dose you are working at, which is
6 the other way of saying what AUC are you working
7 at, which is kind of what Larry just said. If you
8 are very, very old and everybody has lousy
9 clearance, you may wipe out the importance of a
10 polymorphism. If you are very, very young and
11 everybody has beautiful clearance, you may wipe out
12 the effect of a polymorphism.
13 So that is why I am afraid, even though I
14 know that that was a lot of slides of information
15 that I want, I think to really use the information
16 smartly, you are going to need to have a fair
17 amount of information and you are going to need to
18 assume a pretty high level of functioning about
19 understanding of pharmacology and pharmacokinetics
20 to use the information optimally.
21 Anything you do to make it real simple so
22 it looks like the package inserts we have now is
23 going to wipe out so much of the complexity that
24 really helps clarify the information that it will
25 be misleading. I have thought about why does the

1 label have to be manageable? Nobody reads it
2 anyway. It is all on the Web. Why not make it
3 huge. Why not make it fully referenced, fully
4 graphicized? Put a lot of information there. Make
5 it the world's best review article on the drug.
6 Now that is all electronic, what does it
7 matter how big it is? And then put in everything
8 that affects it including drugs and age and renal
9 function and liver function and put in tons of
10 information.
11 DR. VENITZ: Any other comments or
12 recommendations? Larry, do you want to wrap things
13 up?
14 Concluding Remarks
15 DR. LESKO: I think we are getting near
16 the end and getting pretty tired. I think we have
17 been overwhelmed by information from the last two
18 days and it has been extremely valuable to us to
19 get the comments and input that we have.
20 As usual, we have to distill a lot of what
21 we heard over the last two days and try to take
22 each of the four, five different projects we
23 brought to this committee and move them forward to
24 the next level.
25 I guess I will just close by expressing my

1 thanks and appreciation to the committee for their
2 input into the topics. I would express thanks to
3 the guest presenters that we had. They added a lot
4 to the meeting. Appreciate that. And thanks to
5 all of the FDA presenters that were able to put on
6 the presentations during the course of the last two
7 days.
8 So, as always, it has been a very good
9 experience and a learning experience. Thank you.
10 DR. VENITZ: Let me add my thanks to the
11 invited guests for coming that far, to the
12 committee members for freeing their time and for
13 the FDA staff for organizing it. Let's adjourn the
14 meeting. Have a safe trip home.
15 [Whereupon, at 12:00 p.m., the meeting was
16 adjourned.]
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