

1 comfortable to increase up to 4-fold. So we
2 contraindicated in this case only the potent inhibitors,
3 but if the data are different, we could also contraindicate
4 moderate inhibitors as well.

5 DR. DERENDORF: I guess what I was trying to
6 say is if you have an inhibitor, it's not the inhibitor
7 that decides if it's moderate or strong, it's the other
8 partner.

9 DR. HUANG: Exactly.

10 DR. DERENDORF: You can have the same effect
11 that can be very relevant or not relevant at all.

12 DR. HUANG: Right, and that's why we say we
13 need to come up with a list of sensitive substrates. So if
14 it's a strong inhibitor -- there are a lot of sensitive
15 substrates out there, but we may not contraindicate all of
16 them. And you can see we have a differential -- we treat
17 midazolam as a very sensitive substrate, but yet we do not
18 contraindicate it for the second case because the drug can
19 be titrated based on -- there are other information you can
20 use. But for those drugs that prolong QT, we put it in the
21 contraindication because we're sensitized with a lot of
22 experience from the withdrawn drugs.

23 And coming back to your question about 4-fold,
24 whether it's moderate or not, this is something we're
25 discussing. In our open meeting, we actually had a lot of

1 | questions. How do you determine that 4.4-fold is a
2 | moderate, but yet 4.9-fold, which may be rounded to 5, is
3 | potent? How do you differentiate this to the only .9-fold
4 | difference?

5 | I've been thinking about this, and I think this
6 | could -- maybe you can equate to renal clearance where you
7 | said a patient was less than 30 or 20 mls per minute
8 | creatinine clearance is severely impaired. The moderate is
9 | between 30 to 50, 30 to 60. And you always have this
10 | patient at 32 versus 28, but they're in two different
11 | categories.

12 | I think the purpose of putting them into
13 | different systems is there would be precaution and we put
14 | it in the labeling. People will be aware of it. It's not
15 | that they are going to just give 15 and then not observe
16 | the patients at all. This is just to sensitize the
17 | prescribers, health care providers, or patients that we
18 | know.

19 | There is always this debate on the numbers.
20 | Should you put 4-fold? And then we debate 3.5 versus 4.5,
21 | or do we put in 5 and debate what is moderate?

22 | DR. CAPPARELLI: Well, I think the key issue
23 | that you addressed earlier is really the linkage to the
24 | substrate, at least in the first example. It's helpful to
25 | have these working definitions, and whether or not 4-fold

1 | would be considered moderate in a controlled environment
2 | where you're sort of maximizing the effects, I think that's
3 | something that will evolve.

4 | But I think your point as well in part is
5 | linking to the substrate that you're looking at the
6 | interaction, and that's where the importance comes. Taking
7 | it as a drug-by-drug basis, as you did there, I think is
8 | critical to the process.

9 | The one other question -- and it may be sort of
10 | a minor question -- relating to this is -- maybe two
11 | questions. One is that there may be some differences
12 | between PO and IV administration, especially with drugs
13 | like midazolam, for instance, where you're seeing a huge
14 | effect in one area, and when it's given IV for short
15 | instances, the effect is not nearly so great. At least in
16 | our working with the pediatric population in HIV, having a
17 | very strong recommendation or a global one that doesn't
18 | take that consideration into account really puts us in a
19 | bind of what we can use safely or at least what information
20 | is given to the practitioner and what can be used, where we
21 | don't see a problem with having a large interaction as long
22 | as we recognize the route of administration as well.

23 | DR. HUANG: Yes. The classification system
24 | right now is based on the oral midazolam to maximize the
25 | effect.

1 DR. JUSKO: Shiew-Mei, you've done a very
2 admirable job over the years of managing a very confusing
3 area of trying to make sense of drug interactions.
4 Sometimes they don't make complete sense. Like yesterday,
5 we saw an interaction where there was a 7-fold change with
6 grapefruit juice. I don't see that particular one
7 mentioned or part of this presentation. But my question is
8 really something else.

9 Many pharmaceutical companies have implemented
10 the in vitro screens for drug interactions, being able to
11 focus on particular cytochrome systems as a way of
12 anticipating whether to do in vivo studies or not. Have
13 you had an opportunity to do a retrospective on how well
14 that whole approach has been working?

15 And to follow up that, do you anticipate
16 similar possible success in being able to do in vitro
17 screens of transporters to anticipate which in vivo studies
18 to do or not do?

19 DR. HUANG: Yes. As far as the in vitro system
20 to predict in vivo, we did some cases that we looked at
21 where we have in vitro information and in vivo. We did
22 publish. This was early on in '99. And we did find cases
23 where there are inconsistencies, and fexofenadine is one of
24 the examples where you show no interaction, and yet when
25 you give it with ketoconazole, you found a 2-fold increase.

1 And later on we found this possible involvement of P-gp.
2 So there are a lot of exceptions. Many of them are because
3 of the P-gp involvement.

4 However, there are also other involvement as
5 far as I over Ki ratio. That's the one that we've been
6 using from in vitro data to project whether there is an
7 interaction or not. Right now we're just using the ratio
8 to say okay, based on this one, the number is so small we
9 don't think there will be an interaction. Or the sponsor
10 would have done the I over Ki. So you have a rank order of
11 different isozymes.

12 What we often observe is that even all of this
13 I over Ki are very small, the sponsor still went ahead and
14 did one study. And in that case actually that's used as a
15 reference point. Most often they pick the most sensitive
16 one, so the one with the highest I over Ki, and that one
17 shows no interaction. Then we're comfortable with the
18 others. And we have seen quite a few of those cases,
19 though not all of them.

20 There are also other cases where I over Ki
21 perhaps could not project the extent of interaction, but
22 that's in the area where there's a possible interaction.
23 Whether the in vitro system can accurately project, that's
24 really not our concern because in our guidance that we
25 provided to the sponsor, only when you don't see an

1 interaction, then you can stop right there.

2 But if you are projecting an interaction, then
3 we recommend an in vivo study to quantitate it. So even
4 there are discrepancies in the in vitro projection versus
5 the in vivo observation, that is okay because the in vivo
6 study always follows when you see there's a possible
7 interaction.

8 Whether there's not a precise correlation,
9 partly could be because the concentration in plasma may not
10 represent a concentration in the liver. So what we are
11 recommending in our reviewer guide is to use the most
12 conservative approach. We use the total concentration in
13 doing our projection. We don't use the free concentration.
14 So we are more concerned if you use a much higher I in our
15 calculation of I over K_i .

16 DR. FLOCKHART: I'd like to, first of all, to
17 take a 10,000-foot view of this. I think that both you,
18 Shiew-Mei, and the office in general and PhRMA have done a
19 sterling piece of work here in terms of coming up with a
20 classification scheme. In history I think we have this
21 huge problem with information overload about drug
22 interactions, and a classification scheme is going to help.

23 And I remember talking about this three or four
24 years ago and everybody just assumed this would be
25 absolutely impossible. It is to PhRMA's great credit that

1 | they managed to get together and put something together
2 | that wasn't terribly different from what the FDA came up
3 | with.

4 | Personally I think that three categories is
5 | appropriate because of the contraindication issue, but I
6 | wouldn't go down burning on that. I think some form of
7 | classification is important.

8 | To deal with the specific question of
9 | transporters, if I could, again looking from a fair height,
10 | the situation that we're in with cytochrome P450s in vitro
11 | is that we have pretty much all the important ones mapped
12 | and we have assays for them. We have specific substrates.
13 | We have specific inhibitors. We have genetic tests. This
14 | is absolutely not the case yet with transporters, and it's
15 | important because, as we're seeing with the fexofenadine
16 | example, we have good assays for P-gp in vitro. Nobody
17 | would debate that we can do that.

18 | What we don't have is the full picture. So
19 | it's almost like we have 3A but we don't have 2D6 and 2C19
20 | and all the others. So it's hard at the moment to
21 | recommend at the level of substrates a screening for
22 | transporters for drugs in the same way as we screen for
23 | cytochrome P450s. It's hard to recommend that at the
24 | moment because we --

25 | DR. HUANG: Are you talking about in vitro?

1 DR. FLOCKHART: I'm talking about in vitro.

2 DR. HUANG: Okay.

3 DR. FLOCKHART: On the other hand, at the level
4 of inhibition -- and Steve Hall and I reviewed this
5 recently for a review article -- outside digoxin it's very
6 hard to find something that we believe is a transporter-
7 based interaction that matters to anything. Now, we have
8 digoxin. We have quinidine/digoxin is an important thing.
9 We have clarithromycin/digoxin is an important thing. We
10 have verapamil/digoxin is probably an important thing.

11 So if a drug comes along that is a potent
12 inhibitor of P-gp, then if it's likely to be co-prescribed
13 with digoxin specifically at the moment, I think it's a no-
14 brainer to say that you ought to test in vitro, test for
15 the ability of a drug to inhibit P-gp. That's at a
16 minimum.

17 On the other hand, there may well be HIV-
18 related drugs, because of P-gp and lymphocytes, where this
19 is important also.

20 So I think the importance of measuring
21 inhibition of P-gp transport by drugs during development is
22 increasing. Screening for substrates of transporters in
23 general at the moment, I'm not there yet.

24 DR. HUANG: And as far as in vitro screening,
25 you don't think that digoxin transport A2B/B2A with various

1 | cell systems will be able to tell you whether it's a
2 | substrate?

3 | DR. FLOCKHART: Oh, no, absolutely. I think
4 | you can tell whether something is a P-gp substrate, but
5 | what you can't tell -- I'm sorry. I didn't elaborate the
6 | example of fexofenadine -- is what other transporters it
7 | might also be a substrate for. So you don't have a full
8 | picture. You might have a very narrow picture. In the
9 | case of fexofenadine, it's probably very significantly
10 | transported by OATP as well. So if you simply describe the
11 | P-gp story, you're going to get confused, and we have got
12 | confused. The grapefruit juice effect on fexofenadine
13 | comes from left field if you don't understand that there's
14 | more than transporter involved.

15 | DR. SADEE: Yes. I wanted to actually bring up
16 | the same point. We have just completed a survey of many
17 | tissues and measured the transport home, if you wish. So
18 | all genes that encode transporters -- and there are 48 ABC
19 | transporters, of which ABCB1 of P-gp is one. So we're
20 | looking at one out of 48, and there are several hundred SLC
21 | transporters. So the picture is relatively complex.

22 | Nevertheless, it would appear that P-gp does
23 | play a dominant role in many cases. The problem is that if
24 | one then relies on P-gp, sometimes it fits and it may just
25 | be fortuitous. It's because there are five other

1 | transporters that have similar substrate affinities and you
2 | get the answer with just measuring P-gp and you wouldn't
3 | know the difference. And that could be problematic because
4 | then you look at differences among individuals and you
5 | cannot explain them anymore. So there is a bit of caution.

6 | On the other hand, I would agree that focusing
7 | on P-gp at the present time is probably going to give you
8 | quite a bit of information in terms of what we have seen
9 | that each drug correlates. We not only have just looked at
10 | the expression of the transporters, but how does it relate
11 | to drug potency across the tissues. That gives you an
12 | ability to say, well, these and these and these
13 | transporters are relevant. Maybe I'll send you that paper,
14 | so you can have a look at it. But P-gp does play a
15 | prominent role.

16 | DR. HUANG: Thank you.

17 | DR. VENITZ: I'd like to echo what Dave said.
18 | I think with the 3A4 inhibition, I think you are there.

19 | The classification with three categories makes
20 | sense to me because of the consequences that you would
21 | attach, either contraindication, dose modification, or
22 | monitoring. And that's a gradation in consequences, so it
23 | makes sense to grade your degree of inhibition by the same
24 | token, provided that you have exposure-response information
25 | on the NME as you had in your first example.

1 As far as the induction is concerned in your
2 second question, I'm not sure whether we are there yet,
3 whether the science is there to allow us to compare
4 different inducers. One of the reasons why, for
5 inhibitors, I think it works, because we have this nice
6 midazolam ranking that allows us to rank all of them on
7 that scale. We don't have that for inducers, as far as I
8 know. So for inducers, I'd be very reluctant at this stage
9 to categorize them, to rank them unless you have data to
10 support for a known, very specific substrate what the
11 degree of induction is for a whole bunch of different
12 inducers.

13 As far as your last question is concerned,
14 P-gp, again other than digoxin, I don't know of a clinical
15 significant drug interaction. So even if you did have that
16 information in terms of inhibition is what I'm talking
17 about right now, I'm not sure what a clinician would do
18 with it. And the use of digoxin is going to go down, if
19 anything at all. So unless, as David was saying, it's
20 likely that digoxin is going to be co-administered with
21 that NME, well, then you may want to do a clinical study
22 anyway, and the in vitro study would be irrelevant. But I
23 don't think the science is there yet to say from an in
24 vitro P-gp substrate or inhibition experiment, that we know
25 what the consequences are clinically.

1 DR. HUANG: As far as just the inducer, there's
2 some data to show rifampin is more potent than rifabutin or
3 rifapentine as far as the data with ritonavir, and there
4 are several other ranking with ethinyl estradiol. That is
5 the only information I found and with St. John's wort.
6 Right now the labeling usually just says drugs that induce
7 certain enzymes, like rifampin, rifabutin, St. John's wort.
8 That's how we put it the labeling, "may affect" the drug
9 disposition. But we also did put in the contraindication
10 for rifampin in one case and say rifabutin can be used in
11 that case. But we just don't have a system to say it's a
12 potent inducer right now.

13 DR. VENITZ: And that's basically what I'm
14 saying. You don't have a study where midazolam is used as
15 a prodrug to compare different inducers, and until and
16 unless you have something like that, I don't think you can
17 categorize them other than on a case-by-case.

18 DR. CAPPARELLI: One other point, at least on
19 the transporter issues -- and I'm in agreement with, I
20 think, what's been said here in terms of need for clinical
21 information and the fact that we really have an incomplete
22 picture. The clinical information that we look at may be
23 qualitatively a bit different than what we have focused in
24 on on standard drug interaction studies because one of the
25 issues is it's not just systemic exposure that's going to

1 change, but it's also going to potentially be the change
2 between systemic exposure and exposure in various tissues.
3 So one area where you may see a lot of exposure is the
4 fexofenadine, and one of the reasons we don't have sedation
5 may have to do with some of these transporters. So when
6 you're dealing with interactions at those levels, the
7 studies really need to be designed not only from the
8 standard PK standpoint but really evaluating the dynamic
9 exposure-response relationship as well.

10 DR. HUANG: Yes. That's a good point because
11 it's about the brain penetration and for drugs that have
12 CNS toxicity, I think that's a very important issue.

13 DR. RELING: In your case 1, the new molecular
14 entity that -- you ended up saying, do not take with potent
15 CYP3A inhibitors. So was there life-threatening toxicity
16 from that new molecular entity, or was it simply the
17 potency of the inhibitors and the likelihood of a drug
18 interaction that made you say do not take instead of take
19 with caution or consider a dosage decrease?

20 DR. HUANG: There is severe but rare clinical
21 consequences. For that class of drug, we put it right in
22 front of information for patients. So there is significant
23 consequences, although that clinical endpoint was not
24 studied in the exposure response.

25 DR. RELING: Right, but that's your criteria

1 | for making a contraindication, is the clinical consequence
2 | of overdose. Is that correct? You never make it be that
3 | there is a contraindication or do not take simply based on
4 | the potency of the interaction?

5 | DR. HUANG: Well, for this one, we are
6 | particularly concerned with one clinical endpoint, and
7 | that's why the sponsor was asked to conduct an exposure
8 | response to see exactly how the concentration response will
9 | affect where we actually study the drug's concentration
10 | when you gave ketoconazole at that level. I was trying to
11 | tell you the endpoint without telling you what the drug is.
12 | I probably cannot do that. But it is severe enough that
13 | there's a concern.

14 | DR. RELING: I'm just trying to understand is
15 | that your general principle because I'm a little bit
16 | worried about some labeling coming out with very strong,
17 | what sound like contraindications. They're either labeled
18 | as contraindications or they say do not take. And I'm
19 | surprised that that would be the case unless there were a
20 | very life-threatening adverse event that would be possible
21 | like torsade de pointes or something like that because --

22 | DR. HUANG: Yes. We just say do not take.

23 | DR. RELING: I guess that was the only thing I
24 | was unclear about as you were going through your slides.
25 | It does seem to me it is informative to give prescribers an

1 | idea of the strength of the drug interaction, but I would
2 | be careful about translating that wording into
3 | contraindication or do not take. Treating childhood
4 | leukemia, there are only so many drugs we can use, and
5 | vincristine is going to be affected by every P-gp substrate
6 | and 3A substrate, but our alternative is not to say do not
7 | take vincristine. It is to use with caution or dose
8 | adjust.

9 | DR. HUANG: The decision was that the clinical
10 | outcome was such that we want to say do not take. But in
11 | some instances, we actually also put a time period there.
12 | We say do not take within this certain time.

13 | DR. RELING: Which also may not be helpful to
14 | the prescriber in some situations. So I would be cautious
15 | about putting in such strongly worded statements about not
16 | taking medications together when there may be few
17 | alternatives for the prescriber. And you accomplish your
18 | task in many cases just as well by just putting in the
19 | data. This is a very high likelihood of a very potent drug
20 | interaction that could have as much as a 6-fold or 8-fold
21 | or 10-fold effect on the exposure to the drug, and that
22 | gives the clinician an idea of how serious the drug
23 | interaction is.

24 | DR. HUANG: Yes. To go back to your question,
25 | we don't do it always this case. Sometimes we put in

1 precaution. For example, I think some of the grapefruit
2 juice interaction, we are not sure about the outcome. We
3 just say -- well, we did say do not take, but it's not in
4 the contraindication section. It's in the precaution
5 section.

6 Actually I was going to ask health care
7 providers, do you see a difference when you say do not take
8 or contraindicated? Do you see a difference? We do have
9 different labeling languages in our --

10 DR. RELING: We have had this come up in
11 recent submissions to our protocol review committee. It's
12 very confusing. No, there is not a significant difference
13 there. To the clinician, that means the same thing. So
14 it's confusing when something says there's no
15 contraindication, but another section says do not take. It
16 doesn't make sense.

17 DR. HUANG: To the sponsors, they make a
18 difference.

19 DR. LESKO: Just a comment on the general
20 question. I don't think we have a link between the potency
21 of the inhibition and what it says in the label. I think
22 that gets to what Hartmut asked earlier, and that is
23 there's a second step to making that decision, which is to
24 evaluate the potency or whether it's potent, moderate, or
25 weak in the context of the exposure-response relationship.

1 And then that actually drives where it goes in the label.

2 But in the specific example number 1, there's
3 also another consideration, and that is the area under
4 curve increase in exposure exceeded by far the exposure
5 that we had seen with the approved doses. So if people
6 were exposed to this exposure, there's no clinical
7 experience with it in terms of it being safe. It just
8 wasn't studied at a high enough dose in the clinical trials
9 to have safety information. I think that was in her
10 example. 30 milligrams was the upper dose, but the
11 exposure in the interaction may have been equivalent to 120
12 milligrams. And I think that drives where the information
13 goes in the label as well.

14 DR. RELING: But an alternative to saying do
15 not take or contraindication would be to suggest the
16 possibility for dose reductions in that situation. I'm
17 sure it depends on the overall utility of the new drug
18 entity to clinical care, but there are some drug entities
19 that are so critical that we use, it would not be helpful
20 if the labeling tied the hands of the prescriber to not
21 allow them to use a critical agent just because of a drug
22 interaction that might not be avoidable.

23 DR. HUANG: One of the things that we really
24 couldn't say because for this particular case, there are
25 only 15 and 30 available. If there's an 8 milligram or 7.5

1 milligram available, then we could say take the 7.5
2 milligram dose to start with. Sometimes we have the
3 choices, but the majority of the time we do not have that
4 choice. So we either have to make the dosing regimen
5 change, like instead of b.i.d., give q.d. if it's possible.
6 Occasionally we have that kind of recommendation. A lot of
7 times we don't.

8 DR. RELING: The idea that the dosage
9 formulations available would be what would tie your hands
10 sounds a little silly for people who work in pediatrics.
11 We never get to use the formulations that are available.
12 We always have to cut things down. So there are
13 alternatives.

14 DR. HUANG: That's a good point. These are for
15 adult use and we don't have the pediatric for that
16 particular case. I think that's a very good point.

17 DR. DERENDORF: I'd like to follow up what Ed
18 said earlier that we're focusing in the whole session on
19 systemic exposure really as the major piece of information.
20 But there's more to a drug interaction, and one area that
21 we're not talking about at all is pharmacodynamic
22 interactions. I know that the data situation is not very
23 good, but I think that's an area that needs to be explored
24 in the future much more.

25 DR. HUANG: A lot more population

1 | pharmacokinetic study -- we have more chances of seeing
2 | pharmacodynamic interaction that was evaluated in that way
3 | from the sponsor. So we do have cases where
4 | pharmacodynamic interaction was evaluated in that setting.
5 | And you are correct. 90 percent of the interactions are
6 | pharmacokinetic based.

7 | DR. FLOCKHART: Just two things which are
8 | really just filling in gaps. I think the cytochrome P450
9 | interactions -- I think we largely have it figured out. I
10 | think with P-gp or with transporters, we're slowly getting
11 | there.

12 | The reason we're not there with inducers I
13 | think relates to an important thing, and that is that these
14 | are pleiotropic. Nearly all of them have multiple effects.
15 | We don't have specific inducers. I happen to believe we
16 | don't have a lot of specific inhibitors either.

17 | Induction is really a big thing. So we
18 | published a paper a year or so ago showing that RNA levels
19 | are changed by rifampin for a whole bunch of transporters,
20 | 10 of the ABC transporters, a bunch of the SLC
21 | transporters, glutathione-S-transferase, UGTs,
22 | sulfotransferases, cytochrome P450s, a number of other
23 | enzymes, and also that you can't actually go into to an
24 | individual enzyme system and say rifampin is going to turn
25 | on all of these because it's specific within them.

1 So the inducers have very complex effects, and
2 it follows that something that is a potent inducer for 3A
3 like rifampin would turn on midazolam potently, but you
4 can't translate that to a bunch of other drugs very easily.
5 So saying broadly that it's a potent inducer unfortunately
6 is not an accurate statement. It has to be tempered in a
7 drug-specific way. That's inducers. So really there's not
8 a good system for inducers at all.

9 I think one last point, and this is something
10 that hasn't come up yet, but it's something that I did
11 bring up at the ASCPT meeting and have said multiple times,
12 and I know that a number of people disagree with me about
13 this. But I think in these studies, once we're beyond in
14 vitro and we're in the clinic doing drug interaction
15 studies, we're in an environment right now where the
16 availability of surrogates is blossoming, the availability
17 of proteomic surrogate markers, the availability of a large
18 number of possible surrogates. And while people are
19 resistant to including them in these kinds of studies, I'm
20 a strong advocate for including them absolutely whenever
21 possible because that makes the whole drug development
22 process actually I think a lot more efficient if you have
23 good information about the markers you're going to use in
24 phase III and beyond early on. A relatively small
25 investment for a lot of payback.

1 DR. VENITZ: One more thing that I'd like to
2 add that we didn't discuss either, and that's related to
3 all the discussion focused on changes in parent drug
4 exposure. One thing that obviously has to be kept in mind
5 is that by the time that you inhibit, you're going to
6 change the metabolic profile. By the time that you induce,
7 you're changing the metabolic profile of circulating
8 metabolites. That has to be considered when you make those
9 decisions because those metabolites may contribute to
10 safety and efficacy issues. Like in your first example,
11 you mentioned, well, we don't have any data at the 120
12 milligram dose. Well, giving a 120 milligram dose may not
13 be the same as giving a 30 milligram dose and a strong
14 inhibitor because your metabolic profile may be different,
15 which could have safety consequences.

16 So part of whatever the considerations are in
17 the review team has to focus on do we know what those
18 metabolites are, do we know what activity they may or may
19 not carry, and is it sufficient. Just to look at dose
20 limited toxicity from a phase I, is that the same as
21 inhibiting or inducing.

22 DR. DERENDORF: To follow up, the same is true
23 about the quantification of interaction with a simple 3-
24 fold, 4-fold, 6-fold. I think that's concentration-
25 dependent frequently on either partner. So it's dangerous

1 to come up with a constant number for that.

2 DR. LESKO: That's going to be a complication
3 because if you go to the second step of the assessment of
4 exposure response, we're really by default talking about
5 the parent compound exposure response being realistic
6 relationships between metabolite and response are going to
7 be, in most cases, not available.

8 DR. VENITZ: But as opposed to requiring the
9 company to give 120 milligram dose, you could tell them
10 give a 60 milligram dose and an inhibitor because then
11 you're mimicking what you're concerned about which is
12 inhibition, or the inhibition is going to push your
13 systemic exposure of the parent and change the metabolic
14 pattern. But just giving a higher dose, you're not going
15 to change the metabolic pattern. Yes, you're going to
16 achieve higher systemic exposure of the parent, but you
17 don't know what happened to the metabolites that you're
18 shutting off and the metabolites that are going to be
19 formed by --

20 DR. HUANG: Yes, that's a very good point.
21 There's a concept paper on QT evaluation, and we actually
22 talk about the drug, if it's a substrate of 3A, then it's
23 expected that you want to study it with ketoconazole, again
24 as a standard approach so that we can evaluate the highest
25 exposure that you may see when you give it with other drugs

1 and what would affect the QT. We have discussed that,
2 although we did discuss whether this is a better approach
3 than giving a higher dose. If we know ketoconazole is 4-
4 fold, is it better to study the 4-fold dose or just study
5 this drug with ketoconazole?

6 DR. VENITZ: In your first example, I would say
7 that it's better to study ketoconazole in a high dose
8 because that mimics what you're concerned about, not only
9 in terms of mimicking your exposures that you haven't seen
10 the response related to, but you're also going to look at
11 any change of metabolites it may impact on.

12 DR. HUANG: Just to get back to Dr. Jusko's
13 question. You mentioned about grapefruit juice. I guess
14 that's probably the only study that we see the highest
15 change, the one that was presented yesterday on drug A
16 where grapefruit juice increased AUC 7-fold. And you say
17 why we didn't include it in the potent inhibitors. Because
18 a lot of times the fold change, while we did see some fold
19 change of 20-fold with some of the statins, I think that's
20 a fluid statement on grapefruit juice. It depends on what
21 brand you use, how many times you dose it, did you dose it
22 2 hours before, at the same time, one-half hour, 2 hours.
23 So the results are going to be variable.

24 But I think we need to consider where to put
25 grapefruit juice, but understanding that it's very

1 variable. I think once we put a precaution in the
2 labeling, I think the patients and health care providers
3 hopefully will get the message that with grapefruit juice,
4 you could expect anything that could happen.

5 DR. VENITZ: Any further questions or comments
6 by the committee members?

7 DR. SADEE: I just have a general comment on
8 this. I look at drug-drug interaction as sort of a
9 phenocopy of the genotype situation, so the two are
10 intricately linked, and the phenomena you observe can be
11 interpreted with knowledge that they're really that closely
12 related. So I think that helps to look at it that way.

13 DR. VENITZ: Thank you again, Shiew-Mei.

14 That gets us to our concluding remarks. Larry?

15 DR. LESKO: Thanks, Jurgen.

16 My concluding remarks are going to be very
17 brief and represent an expression of appreciation and
18 gratitude to the committee. I think we all feel from the
19 agency that the last two days have demonstrated the
20 commitment and engagement of the committee members in the
21 discussion of clinical pharmacology issues. I think we're
22 all looking to a common goal and that is to advance
23 clinical pharmacology not only into regulatory decision
24 making and policy but also into the drug development
25 process. I feel that this committee has succeeded in

1 achieving that goal of advancement.

2 So I can't really express my appreciation
3 enough for the work of the committee over the last day and
4 a half. Besides, it was just a lot of fun. There was a
5 lot of intellectual discussion and I enjoyed it immensely.

6 As you can see us writing very vigorously here,
7 all of us on this side of the table, we've carefully
8 recorded the opinions, recommendations, and advice that
9 this committee has provided us. I often felt that the
10 comments and advice were like putting a microscope and
11 looking at a slide of the issues and they slowly came into
12 clear focus. As we go forward with this committee, we'd
13 like to maybe spend time at our next committee meeting
14 reflecting on the advice given at this committee meeting
15 and talk about a little bit how we've utilized the
16 information that came out of the committee to try to keep
17 some continuum to our discussions.

18 So with that, I think I just want to say again,
19 thanks to the committee and thanks to Dr. Venitz for his
20 great job as chair. I hope we all made it easy for him.

21 We look forward to the next meeting. I know we
22 have talked about some tentative dates that Dr. Venitz may
23 discuss.

24 I also understand from a break that coincident
25 with this discussion of the committee meeting on

1 | pharmacogenetics, there was also a broadcast on National
2 | Public Radio, which I wasn't aware of. So I hope I can get
3 | a transcript. One of our own advisory committee members
4 | was involved in that, as I understand it, Dr. Flockhart.
5 | Is that correct, David?

6 | DR. FLOCKHART: Yes.

7 | DR. LESKO: So there you go.

8 | (Laughter.)

9 | DR. LESKO: So our next step is a public
10 | broadcast production of pharmacogenetics and drug
11 | development. I'm just kidding about that.

12 | Anyway, let me close with saying thanks very
13 | much and all of you have a safe trip from Rockville back to
14 | your home, wherever you're going.

15 | DR. VENITZ: Before we adjourn, just one thing
16 | for the record that I forgot to mention. We didn't have
17 | anybody sign up for the open public hearing. That's why we
18 | didn't have any problems in running over as far as time is
19 | concerned.

20 | As Larry indicated, we are looking right now
21 | tentatively at October 8th and 9th, which is a Tuesday and
22 | a Wednesday, as the follow-up meeting for this committee.

23 | DR. DERENDORF: 7th and 8th.

24 | DR. VENITZ: I'm sorry. 7th and 8th, right.
25 | Tuesday, Wednesday, the first week of October I guess.

1 We'll get in touch with you to confirm that and put an
2 agenda together.

3 Then lastly, I agree with Larry about not only
4 having a lot of fun over the past day and a half, but also
5 this being a very productive meeting, and I hope we can
6 continue next time we meet.

7 DR. FLOCKHART: And thanks to the chair,
8 excellent chairing.

9 DR. VENITZ: I just found out that our
10 Executive Secretary who's responsible for the logistics and
11 for the smooth running of this operation, Kathleen, is
12 going to retire.

13 MS. REEDY: No. I'm going to another division.

14 DR. VENITZ: She is going to transfer out of
15 the Advisors and Consultants Staff, and I really want to
16 officially appreciate what she's done.

17 MS. REEDY: Thank you.

18 DR. VENITZ: Thank you, Kathleen.

19 (Whereupon, at 11:52 a.m., the subcommittee was
20 adjourned.)

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04/23/03

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