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then you can greatly reduce the enteric or increase the enteric efflux transport and greatly reduce the bioavailability.

But the other issue is, you know, I'm uncomfortable with the bottom half of the slide, because we don't know what KI means. Again, it's going to be different for enteric versus blood-brain barrier. We don't know what I is. We don't know if it's total or unbound, and we don't know about 0.1, whether that's too conservative or too liberal.

So, you know, we want to give guidance, but we don't want to over guide based on the validity of the existing data.

DR. HUANG: Can I ask you a question? Some of the issues that you just mentioned also are applicable to CYP?

DR. GREENBLATT: Yes.

DR. HUANG: So you're essentially commenting based on the experience from CYP basic direction?

DR. GREENBLATT: Well, but the -- or commenting on, you know, that for transporters, we're not there yet. We need more information on, you know, let's gather information on ICT50, on I, on KI, and look at, you know, .1, point .05,

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.2 and gather some information before launching into guidance, because we just don't know yet.

And the same would go for labeling; okay? If obviously a label wants to warn appropriately when there is a hazard, because when you do that and you avoid a hazardous combination, that's good for public health. But if you over warn against hazards that don't really exist, that's also bad for public health, because it deters drug use or encourages insufficient dosage. So you need to be very careful that you balance appropriate warning versus excessive warning.

CHAIRMAN VENITZ: Thank you. Howard?

DR. MCLEOD: While you still have the microphone, is your worry that you don't know what this will do or is your worry that you -- I guess what I'm trying to get at is it -- is your worry that there will be too much harm done or is there's just not enough knowledge? Because if there's not enough knowledge, you have to start some place.

DR. GREENBLATT: Okay. I think guidance is one thing, and labeling is another.

DR. MCLEOD: Right. Okay.

DR. GREENBLATT: With regard to labeling, I want to

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make sure there's appropriate warning, but not over warning based on insufficient knowledge, and with regard to guidance, you know the numbers that you put up here that's going to launch many sponsors into expenditure of resources that may or may not be needed, based on the validity of the information.

So before launching into guidance, I think we need more information on the validity of those paradigms.

DR. HUANG: Although if we have this guidance, we probably can reduce the number of studies that we're seeing

--
DR. GREENBLATT: Ultimately.
DR. HUANG: -- right now.
DR. GREENBLATT: Ultimately. Ultimately. Ultimately.

DR. HUANG: Well, right now, we would recommend quite a few Digoxin studies not to be conducted, but we're seeing them.
DR. GREENBLATT: That's because I think sponsor remain worried that maybe these guidances are not, you know, don't have enough substantive data to validate them.
CHAIRMAN VENITZ: Kathleen?

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DR. GIACOMINI: Well, I mean if you're seeing extra studies, you know, that people -- because there's always in the last and the .1 and having some guidance at your .1. If you include, but that's ridiculous that there has been some studies who have been less than .1 have been considered.
DR. HUANG: Well, it's partly because we don't have a standardized criteria or threshold.
DR. GIACOMINI: And that's -- they have no way. All they know and we have no way of knowing?
DR. HUANG: Right.
I mean based on this?
DR. GIACOMINI: That says --
DR. HUANG: It's an inhibitor, so we're trying to -- similarly with the CYP criteria to determine for -- or maybe for our reviewers not to ask for a study as well.
DR. GIACOMINI: So my feeling might be you have to start somewhere. You start somewhere, but you get the data.

DR. HUANG: The information.
DR. GIACOMINI: You get -- collect the data so that you actually have this based on the substrate in some form, but you start somewhere to give them some guidance.

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CHAIRMAN VENITZ: Let me just follow up on Dr. Greenblatt, because I think I'm coming down to him, and his friend in New Hampshire. I think the answer is not yet.
So I don't think you're ready yet for a decision tree like this I just don't think we have the knowledge. My concern primarily focuses around this -- and what the I means. And we've talked about bound, unbound. I personally believe it's the KI concentration as well. Think about how the KI is determined. You know, the concentration of the inhibitor is on the abscissa. And we're now comparing that to the systemic concentration, the circulating concentration, about on-would not make a difference.
Okay. So I don't believe that those numbers right now on this empiric evidence comes out. It can mechanistically justified.
DR. HUANG: So can I ask you that maybe you also do not agree with our decision we made for CYP3A?
CHAIRMAN VENITZ: No, but CYP3, you can make a coherent argument that it's at circulating levels.
DR. HUANG: Because it's the same thing: a lot of intense 3A --

CHAIRMAN VENITZ: I understand.

DR. HUANG: -- and this concentration will be much higher.

CHAIRMAN VENITZ: I understand. I understand. I believe that's it, but we have more experience with it. So in addition to the mechanistic uncertainty that here to me is large, we have some empiric evidence to support that it seems to work. At least we haven't found any big discrepancies.

For P-gp, I just don't think the experience is there yet, and I don't know whatever implement this, whether you have fewer studies or more studies. And even if you have fewer studies, does it mean you have more pause for negatives, but then it turns out whether the study should have been done.

I don't think we're there yet.

DR. HUANG: Okay. I just want to clarify: this is like the CYP system. All we want to do is to make sure we do not have negatives. But like with the CYP system, as Dr. Greenblatt has pointed out, there are a middle range where based on the I over KI, you really don't know the extent of interactions clinically, and that is okay, because all we want is to set a threshold where below that there's no possibility of interaction and you don't need to do a study.

Above this, you will have to find out what is the extent of interaction based on clinical interaction, as you have published many studies to show there is -- this is important between in vitro and in vivo that's based on the projection of in vitro data to in vivo.

However, if you look at the cut off, anything below that value, most of the time we find concordance. When we don't see concordance that's because there's an additional transporter-based interaction. So this is based on what we learned from the CYP.

So we're trying to set a threshold. We don't -- we're not that step yet to say based on in vitro data, we can project percent increase or percent decrease in the clinical. We only want to set a threshold, and we are trying to propose something similar to P-gp.

We're not going to say this system will help us project the extent of interaction, but just anything below this level, you do not have to do a study.

CHAIRMAN VENITZ: Can we give the Committee members a chance to hear their opinions, because right now we have obviously again a diverse number of opinions, and I think we would like to have a more representative feedback for our friends at FDA.

How do the rest of your feel? Is this something that you framework or inclined to just say we're not ended?

DR. MCLEOD: I care, but I don't know why. I think that we don't have the amount of data that -- to really know whether this will achieve the goal. I love the concept of being able to help folks avoid doing expensive studies that

will be informative.
There needs to be more meat behind the cut point, and, you know, if that can be done by trolling through the various literature studies and showing graphically the -- that .1 would have avoided the few positive controls that are out there, then it might be easier -- it should be more convincing.
But right now, I just don't -- part of it is I just don't -- I'm not deep enough into this field. I don't know what's behind this data, whether it's going to be a fantastic situation or one where there will be too many old.

DR. WATKINS: Well, just to second Howard's, but first

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to say, you know, I think the whole story of the cytochromes P40 of being discovered 20 years ago and going on the guidance as it relates is fantastic. You know the story of applying science and Shiew-Mei and everybody at the FDA should be applauded for that, and I think going on to transporters and calling the question is great. And, you know, even putting out a recommendation like this forces people to think about what the cut off is and forces people and industry who may have unpublished data or academics or something to come and, you know, meet the challenge of finding out what that, you know, the right KI and, you know, I to IC50 is.
So I'm with Howard. It would be great to see a slide that sort of summarized applying these principles you know where there would not have been a problem, but would have been a problem, but I guess I kind of favor myself going with it, and being prepared to modify the guidance as it goes forward unless people come up with, you know, with solid examples of where these cut offs are -- should be modified.
I mean we have to start somewhere. And P-gp we certainly know a lot about. I mean a hundred and ninety

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studies have of P-gp clinical interactions in people. I mean that's a lot of clinical studies, and it would seem like it should be possible in fairly short order to do the in vitro studies and sort of, you know, come up with the right data. Anyway, that's my point.
DR. BARRETT: I think the problem it is it just -- I agree with Dr. Greenblatt. It looks fine at the top, but then you get to the coin flip era, and it's just hard to see the bottom part of this in application without understanding the distribution of I over KI. I mean and even in the CYP era, you know, you know regions of performance because you've got all that historical data, so you know where your comfort zone is.
So looking at it as a decision tree, it doesn't have the same kind of teeth as other decision trees would, so I think that's kind of the discomfort level with it. You know I agree for getting things started if it's with the intention of reducing experiments that are not meaningful and, you know, overall that reduces the cost of drug development. It's all good. But I think the application

would be the uncertainty of the bottom tier of this is where I just have a hard time with it.

DR. JUSKO: I'm sort of in favor of this from the viewpoint that I think this train has already left the station. People are doing these kinds of in vitro assessments. They're making these kinds of measurements and trying to use those measurement to decide on how to proceed, whether to do an in vivo interaction study. I would caution that use of that 0.1 number because it's probably not a firm number at this point to go by, and these are guidances. I'm sure it is not going to be treated like a bioequivalence study, where specific numbers have to be met.

Where I see some concerns, where there's more complications for transporters compared to CYP enzymes is the decision at what to do for in vivo study.

When one is concerned about interactions that pertain to drug absorption or drug elimination, pharmacokinetics is very clear in giving what information on the importance of the drug interaction. But for transporters, since there's so many internal tissues that are involved -- the brain has been mentioned, tumors, placenta, many other tissues -- it's not going to be possible to judge from pharmacokinetics as to the importance of the -- the clinical importance of the potential interaction, and I see the future that there's

going to be more need for pharmacodynamic assessments to determine as the basis for the in vivo interaction study.

CHAIRMAN VENITZ: Any other comments? So I think it's fair to say that there's split opinion among the Committee?

DR. THANG: Yeah. I want to add some comment. Yes, I know at some point we want to determine the potency, and, as Dr. Greenblatt said, some potent ones that we are worried and also we want to correlate the potency with the in vivo exposure, so -- originally we put like IC50 is less than 10, but we want to put into context, so that's how we get I over KI ratio.

But we also heard a counter-proposal from Dr. Joe Cody [ph.] from GSK. What his counter-proposal is based on just the what's in the literature, they like all the co-array of the drugs shows -- with the drugs, and most of them they have IC50s of less than 15 micro molar from the in vitro system, and also they show drug doses more than 100 milligrams.

So maybe we can somehow instead of saying exposure, say dose. If it's high dose, this drug somehow -- you need to give a high dose for the inhibitor, and it's also shown in vitro is less than either 10 or 15 micro molars, and we

can discuss what that cut off should be; then maybe we should consider an in vivo inhibition study with a P-gp substrate. I'm not sure how everybody views about that comment.

CHAIRMAN VENITZ: Any comments by the Committee? Paul?

DR. WATKINS: Just for clarification is the dose then just designed to account for the fact that the intestine

will see a -- is that it? So it's just the intestine that the dose is formalzing for?

DR. THANG: Initially, that's what I thought, but based on my conversation with him, it's not necessary. It's just based on historically those drugs show that you happen to have a dose higher than 100.

But you can calculate the use of 250 and maybe stomach. You can calculate a contribution.

DR. GIACOMINI: Yeah, I guess I'm following up on Paul. I mean if it were in the intestine concentration, I could get why the dose -- that method would make some sense. But I don't see it in the systemic. I just don't see the reason for that.

DR. MCLEOD: Shiew-Mei, when you talked with some of

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the companies -- this is going to affect them more than us -- was your .1 number the lowest of the bunch? Is this -- was there a range there that was put forward? I mean how much due diligence has been done in this area?

DR. HUANG: We -- initially, when we published a paper in Molecular Pharmaceutics, we got a lot of comments from individual companies, and in that paper, we put on 10 micro molar as the cut off for IC50 or KI. And the comments we got is it has to be compared to a systemic concentration. And the example the sponsored used is actually a .1 ratio, although they did say that it's a -- if I have a concentration of one micro molar, I would be worried that even if the KI is a little bit more than 10 -- so, in a sense, even they did say you must use I over KI. The example they gave us is .1, even to micro molar was considered about right or not too conservative or not too liberal. But they want us to compare. This is from one major pharmaceutical company, based on our publication.

So we have received different comments, and some are jus the opposite of the others. So there are some recommendations that say maybe we should look at IC50 by itself.

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So I think if we can modify our proposal. If we look at IC50 or relative to the concentration, if we would use the most conservative one. So either approach that -- because the comment we got is really if the concentration is really high, even if your IC50 is larger than 10, you need to be worried. That's the comment we got.

So 10 is not too often, but yet in case you have a drug that has a very high systemic exposure, you need to be worried.

So based on that comment, we modified the 2.1 for further consideration, and we thought the -- somehow the exposure needs to be here to the dose of the systemic inhibition numbers.

DR. LESKO: Yeah, as you get down to the last part of the decision tree, on the right-hand side, you're worried about false negatives; that is, I do an in vitro study that says I don't have an in vivo, and then I do the study, and I have one.

But from the submissions we've received, my impression

is we haven't received any false positives. We've seen Digoxin studies. They've been negative, as you would have predicted them to be. So it would seem that the criteria of

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less than .1 seems to hold up well on the submissions.

Now, why people do those studies may have nothing to do with this. People can do drug interaction studies to have a competitive label or to make an advertising claim that my drug doesn't interact with Digoxin, and here's the evidence to show it.

On the other hand, on the left-hand side, it seems more of a weaker point in terms of the .1 because you're worried about false positives, and if .1 is too low, would something like 0.5 be better to eliminate the risk of false positives and when Dr. Greenblatt presented, he said it was -- I think you said, David, if it was 0.5 or greater, it's probable or likely that there's going to be an in vivo interaction.

That does leave a gray area in between, but at least it moves you to the point of not having this discrete, you know, less than .1, greater than .1, but is kind of the bookends again, which is a nice place to start, and then we continue to deal with uncertainty in the middle as we get more data.

DR. HUANG: I believe so. As was mentioned earlier, we know less than .1, probably it's not likely. And those

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were way above .1. We know there's a direction, but we don't have enough data to be concerned. There's a lot of drugs we have in vitro data, but we don't have in vivo data in the middle range in order to -- for us to make a firmer recommendation.

So I think this site is probably relevant, but this one we don't know. We may be too conservative on the right.

DR. WATKINS: Larry answered my question exactly.

CHAIRMAN VENITZ: Any other comments about question number one?

Okay. Then let's move along to the next question, Shiew-Mei?

DR. HUANG: So this is a very similar question, except here we're evaluating the new drug as a substrate.

CHAIRMAN VENITZ: I have a question. When you see those studies, is it actually done as a secondary screen or do companies or sponsors traditionally just look at efflux with and without inhibitor. In other words, they're trying to answer two questions with one experiment?

DR. HUANG: Yeah. But most of the submissions -- and John or Lei can comment -- most of the submissions they have

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both data.

CHAIRMAN VENITZ: Right. So to me, I'm not sure whether the first decision that you have with the efflux is above two or less than two. In my experience, usually inhibition studies are done early on, and then the question would be do you have an inhibitor effect or not regardless of what the efflux is, because the efflux is -- if there is

no efflux, you won't have an inhibitor effect.
You see what I'm saying? That gets you away from this magic number of two or one and half, whatever that ratio will be as an issue.
DR. HUANG: So we collapse it?
CHAIRMAN VENITZ: Yeah. The first question would be is there an effect or in vitro effect of inhibitors by one or more P-gp inhibitors as opposed to having another decision point on top of that whether there is efflux or not and what constitutes a significant efflux?
DR. HUANG: Okay. But we saw -- by doing this, we put also cut off some studies. So instead of doing another inhibitor study, you can just go ahead and stop.
CHAIRMAN VENITZ: Right. But my experience at least is that they're not separate studies. They're one study,

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where they look at efflux or no efflux with and without inhibitor. But maybe my experience is not representative.
DR. HUANG: Mitch, would you like to comment?
CHAIRMAN VENITZ: Yeah, Dr. Taub.
DR. TAUB: I think it could be specific to the indication that you're looking for. So for example, if you definitely want to avoid having a P-gp substrate, then you might consider doing the flux ratio study first to determine whether or not you have a P-gp substrate.
The other consideration might be the cell line that you use and so, for example, if you're using KPRO-2 [ph.] it's going to express multiple transporters and if you don't see any flux ratio there, you can be reasonably sure that you don't have a substrate for it and making sure three different flux transporters as opposed to getting into a slightly more complicated experiment. Admittedly, not that much more complicated when you add a series of inhibitors to see, to ascertain whether or not you have a P-gp substrate.
CHAIRMAN VENITZ: So you think this additional decision point is going to screen out some compounds?
DR. TAUB: I think that the flux ratio study is a very common study. It's a certain something that we would do.

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Perhaps, you know, I guess you could argue whether you would do it first or second, as per your recommendation.
But you could almost do them in parallel they're so close.
CHAIRMAN VENITZ: Yes.
DR. GIACOMINI: Are you specifying that this is transfected KACO-2 or MDCK cells or -- because obviously you get a different flux ratio in different cell lines. So are you specifying the cell lines?
DR. HUANG: Yeah, we said all can be done, and we in specific said we must have positive control and they have to be within certain values so people can assume this is a value in a controlled experiment.
CHAIRMAN VENITZ: What indeed were inhibitors do you usually see when you're using a non-specific target?
DR. HUANG: In vitro?
CHAIRMAN VENITZ: No, in vivo.
DR. HUANG: Oh, that's the -- so are we past that?

CHAIRMAN VENITZ: Well, I mean it's my question. Other members can ask other questions. Go ahead.

DR. GREENBLATT: I think you also need to -- I don't know about the number of two again. I think that may be --

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may or not be too aggressive, and again I don't think that you have enough data to support that, but I think you need to consider the absolute value of the flux from apical to basal, because that will allow you to put the flux ratio in context -- in the context of passive diffusion.

And I think it's enormously useful supportive data is the brain plasma uptake ratio in P-gp knockout mice compared to controls, and that in vivo data, experimental data, together with this kind of in vitro data, considering the uncorrected apical to basal flux, the absolute flux, I think will put you in a better position to make a decision.

CHAIRMAN VENITZ: Okay. Any other comments?

I guess my question still remains. Going down the left-hand column, what in vivo inhibitors do you see?

DR. HUANG: Oh, when what we have seen?

CHAIRMAN VENITZ: Yeah, right.

DR. HUANG: We have seen, as I mentioned earlier, because of the experience with statins, there are -- the companies are using Cyclosporine, although we know it's not specific inhibitors, and we know that it's a great inhibitor for OATP1B1. But that one has the least.

You know what I'm saying? In both the -- well, a

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Verapamil study has been done for other drugs that are a substrate of the 3A. I'm not sure if they're a substrate for P-gp, but it didn't specify that because of the in vitro results, and it was used.

We have seen Ritonavir. We have seen -- not specifically Quinidine.

CHAIRMAN VENITZ: That's my concern in looking at this. If you bind with the in vitro screen, which I do just to some extent, then what are you going to do? What specific P-gp inhibitor do you have?

DR. HUANG: That's our next question.

CHAIRMAN VENITZ: I understand, but that is related to your diagram and your approach here; right? I don't believe that there is no specific P-gp inhibitor. I might go along with your decision making, but then I don't know what study to do, because I'm going to use another interaction that has other effects and not P-gp, which is the baseline for the study in the first place.

DR. HUANG: Yeah.

CHAIRMAN VENITZ: In other words, it becomes a non-mechanistic study.

DR. HUANG: Right now, our guidance recommends this

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use -- the extension of Cyclosporine and Verapamil and Atonavir. We just gave the examples, but in our table it's more extensive. I'm just trying to see the analogy.

CHAIRMAN VENITZ: Looking on your table, I was looking --

DR. HUANG: We have Erythromycin, Ketoconazole, and

Triconazole, Quinidine, and then we also put in three available caplets. The LY335979, the PSE853, the GS1209.

CHAIRMAN VENITZ: I was looking for P-gp inhibitors that wouldn't inhibit anything else. And that's why I asked you about Verapamil. I don't know what that was. Well, but that's -- so even if you do the screen, you arrive now on the left-hand column, you're then still in the position where you're going to have to use a clinical -- you're going to have to do a clinical study with an inhibitor that you know in all likelihood if it's other, it may not be relevant. That's something that is not considered here.

DR. HUANG: Right, and, yeah; this was a decision tree based on P-gp. However, we know there are a lot of transporters being evaluated right now, and if you use one of these non-specific transporter inhibitors, you might also have uncovered or found out unexpected interactions. So

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that's why we --

CHAIRMAN VENITZ: For the wrong reason; right?

DR. HUANG: Yeah.

CHAIRMAN VENITZ: You're looking at what the interaction that applies to --

DR. HUANG: Because we don't have any other specific inhibitors, although it will help our understanding of possible interactions. So there's some advantage of using general inhibitors. If it's negative I think we feel very good of where we will label it, and that's what we have been doing with the statins.

DR. LESKO: Getting to the question on the table, when you looked at Cyclosporine as an inhibitor for in vivo studies, admittedly it's not the pure inhibitor that people are asking about, but doesn't the magnitude of the effect when the substrate is a P-gp -- when the drug is a substrate for P-gp, isn't the magnitude of effect much greater than you would expect by inhibition of an enzyme alone?

Like you showed data with the statins, for example, and you had close to a 10-fold increase in the area under the curve with Cyclosporine, with Prevastat, not Cyclosporine.

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DR. HUANG: Yeah. Right now, a lot of statins they're also substrates of OATP1B1.

DR. LESKO: Well, let me get to this point, though. If you were just inhibiting an enzyme, would you see the magnitude of increase with those statins and is that any signal that you have a substrate for P-gp?

DR. HUANG: Most of the statins that we have studied right now -- well --

DR. LESKO: So would Ketoconazole. I mean what kind of magnitude do you see? You might want to give us statin with the three and four substrate.

DR. HUANG: Yeah, well, most of the statins I believe we have --

DR. LESKO: No. There's --

DR. THANG: Yeah, I know for those solo statins, there's no substrate on a 3A substrate or a very minimum, so you won't see an interaction. But it is in Japan.

DR. LESKO: Well, that's my point. If it's a dirty inhibitor, if there is no enzyme in the drug's normal metabolism to worry about, then it doesn't matter that that's a dirty inhibitor. It's doing the job you want it to do, namely, prohibit the in vivo exposure change, so you

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have to sort of build a little bit of thinking into this. What are the normal pathways based on the drug, and while Cyclosporine may not be perfect, you could, by elimination of pathways decide that it would be a pretty good inhibitor of P-gp.

DR. HUANG: Oh, I agree. I think if it's a CYP-related interaction usually you can sort it out with other inhibitors such as Ritonavir, although it is also inhibiting P-gp. But --

CHAIRMAN VENITZ: But it was also inhibiting P-gp. That's why -- I mean I agree with you fundamentally, Larry, that you can sort it out. We really can sort it out. I'm not sure whether you can do it, but the important thing is more likely more convenient. But it may be very difficult.

DR. HUANG: Right. But the -- okay. But if you take Quinidine as an example, the drug is not a 2DC substrate, then you come to the sort of question is do you have -- is Quinidine an inhibitor.

CHAIRMAN VENITZ: I think what you're hearing is it might depend on individual cases. This kind -- this flow chart obviously is so general that I think there is some

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discretion involved here in implementing a new individual case.

When you look at this flowchart overall, how do you think it's going to fit along with all the other flowcharts? The CYP flowchart. Maybe a UGP flowchart in a couple of years.

But what about overlap, because obviously you've got as much as the P-gp substrate portions. They are subject to all kinds of other things is the first question.

The second question, the way I understand what you're proposing here, that is primarily looking at P-gp is related to drug absorption. In other words, we're not primarily using this to look at brain transport, uptake into other tissues where systemic levels may be meeting this potential.

DR. HUANG: Well, but if you -- the second question first. Up to this point whether it's a substrate, then you might be able to understand whether it will have an effect for brain penetration. If it's not a substrate, you don't have to worry.

Well, then that's what -- the very basis of the evaluation. I mean we don't have a lot of data on P-gp

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inhibition effect on brain concentrations or effects that -- and, you know, the example that Dr. Greenblatt has shown. We really haven't seen a lot of that.

CHAIRMAN VENITZ: But the primary application is one you're solving?

DR. HUANG: For the other organs.
DR. THANG: Yes, because if you do find that your drug is a P-gp substrate and you find that compared to the whole clinical PK of your compound, and I mean P-gp is a determinant of function in your elimination, if you do like attach the study, I'm sure besides the systemic change, you may see some -- you may not measure the brain level, but if your just therapeutic will do -- it's not that wild. You might see some side effects in the CNS, just like.
CHAIRMAN VENITZ: I don't disagree with you. I'm just saying that once you go down that route, then you want to do a prospective study. What's your end point?
DR. THANG: Your end point will be from our perspective if she have this too for monitoring some, you know, safety profiles. You will see if it's very significant.
DR. HUANG: Right now, the primary import is PK.

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CHAIRMAN VENITZ: All right.
DR. HUANG: It's pharmaco PK parameters.
CHAIRMAN VENITZ: And then you didn't answer my first question. How would this flowchart and all the other flowcharts map to this?
DR. HUANG: When say mapping, you mean the time of the study? Tied together to explain the results? This would be just like right now we're looking at pair -- drug pair interactions so the implications for the labeling right now would be a single pair -- this drug's effect with one inhibitor. And hopefully, we'll develop or we understand more what is the outcome of multiple inhibitor effect, but where we can integrate them altogether.
But right now, for CYP, we will evaluate all major CYPs, so we'll understand the effect, whether they're substrate or inhibitors. I think the results really will help when we evaluate whether they're substrate or an inhibitor or inducers for that matter for this new drug. Then you can eliminate where you see an interaction, and where you can select your substrate or inhibitor appropriately based on what you know about CYP.
CHAIRMAN VENITZ: So the idea would be if you go down

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this chart for, let's say, B4 to B6 and AGB inhibitor interaction studies would be --
DR. HUANG: Yeah. Right now, for each major CYPs, we do follow that route.
CHAIRMAN VENITZ: Why?
DR. HUANG: Everyone. Yes.
CHAIRMAN VENITZ: Any other comments by the Committee? I'm not sure whether I can summarize the Committee's opinion.
DR. GIACOMINI: One more. I mean I like this decision tree except I agree with Jurgen that when we get to the point of what in vivo interactions that's going to be a question that there's, you know, which one do I choose from your menu.
So you may want to consider refining, you know, giving some advice on what might be appropriate to use as your

interacting substance, and it might have to do with whether your compound is metabolized, which enzyme it's metabolized by, so you could put a little bit more refinement there instead of just do an interaction study.

And also maybe even if your compound has CNS effects. I don't know if you should think about things like that --

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whether it has CNS effects and you're thinking about interactions in the blood brain barrier. Here is what you might also be looking for.

And then I think at a later date -- again, I'm for implementing both this one and the other one and gathering information which should go to refining that guidance would be important.

DR. BARRETT: Yeah, I think the difficulty with the question is really just to see the application of the decision tree, and you know as the discussion went on this afternoon, there's a certainty on one side of the decision tree and maybe not on the other side for both of them. And that's okay. I think I -- you know in terms of the spirit of what this is intended to do, I think we're probably all of the same mindset as far as that goes.

It's really that the decision tree has to be explained in the context of how you position it in the rest of the guidance and explain exactly what Jurgen and others have commented on in terms of the actual conduct of some of these steps; that the details associated with getting further down the pathway. So I think that's really where the rub lies as far as, you know, comfort in this is that you can't just

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look at this in the context of how to perform it relative to all of the other text that would go around it explaining how to really apply it.

So I'm in favor of collecting the information and getting, you know, getting started on that. I think it's a question of putting the right caveats on this decision tree so that we're aware I think of the application, and again it comes back to what I think Dr. Greenblatt left us with: it's really the labeling that's to be concerned. It has nothing to do with the guidance. It's really what this manifests in terms of labeling. That's the only issue in my book.

DR. WATKINS: Just one comment. If you get to the -- you know things obviously being transported, but a specific P-gp inhibitor doesn't change that, and it says further in vivo to determine what she wants transporters, and I guess it could be further in vitro, too; right? I mean there would be no reason necessarily to go right in vivo, and that might -- to figure out what transporter is involved.

DR. HUANG: Well, that's really two questions.

CHAIRMAN VENITZ: Okay. Any more comments? I think you have the support by the Committee for this flowchart

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with all the strings attached.

Okay. Let's move on to question three, which I think we already answered to some extent.

DR. HUANG: This is related to the left-hand side of

the previous chart; that if you -- what you see is P-gp substrate, and in our guidance we have -- we said that shouldn't evaluate it in vivo based on some of the inhibitors that we have listed here -- Retonavir, Cyclosporine, and Verapamil -- whether this stays.

CHAIRMAN VENITZ: Okay. Does the Committee need to add anything to what we've already said?

DR. HUANG: So the 3A is the same.

CHAIRMAN VENITZ: Right.

DR. HUANG: Okay. So number four is -- can be related to the right-hand side of the second decision tree, although we can modify that to the in vitro. So does the current knowledge base for the recommendation of drug interaction studies for other transporters such as OATP1B1, MRP-2. We didn't really discuss BCRP. In other words, we touched around it. OCT and OATs. You know we could expand on the decision two, on the right-hand side.

It's not a P-gp substrate, but there's an efflux

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difference. Although the decision tree only discussed as a substrate, but we do not discuss the drug as an inhibitor, and when we posed this question, we tend to ask whether to evaluate -- you're looking it as a substrate or an inhibitor of these transmitters.

If in vitro will -- can do -- can't give us enough information, for example, to give proper labeling as the most important end point.

DR. GREENBLATT: Are you suggesting that basically you do -- if you go down this route, are you suggesting that you initially do your in vitro homework so to speak to get some idea of what needs to be done in vivo?

DR. HUANG: Yes. Our guidance is recommending that, which is start with in vitro and then based on in vitro or come to determine whether to do in vivo. We've recommended that for that of the P-gp and we also recommend that for other transporters.

DR. WATKINS: So I think the question is at this point should you have the same decision trees as, you know, as you do for P-gp, and I think we heard no just in terms of having the cell systems and sort of the accepted knowledge base.

But on the other hand, the percent of OATP1B1

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interactions studies that have been positive as defines 20 percent increase was the same as P-gp. And I know just of examples in industry where a Cyclosporine interaction study was done to see whether the new molecular entity would interfere with Cyclosporine and then, in fact, found just the opposite: that Cyclosporine had -- and then led to a series of discoveries with OATP1B1.

So that's why I kind of like the idea of Cyclosporine being the P-gp inhibitor, because it's not specific. And if you see a large interaction, then it might lead you down the path, but it's a little bit of an aside.

But I think the answer is at least from what I've heard is the knowledge base and the technology is just not there yet. But it's the next transporter probably.

DR. HUANG: Are you commenting on OATP1B1

specifically?
DR. WATKINS: OATP1B1 specifically.
DR. HUANG: Oh, okay.
DR. WATKINS: Not the others.
DR. HUANG: Not the others; yeah.
DR. THANG: I just have one correction. In our original, in our guidance actually it says further in vitro

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studies in the decision tree to determine whether other inhibitions.
CHAIRMAN VENITZ: But we've got to question four?
DR. THANG: Question four, the first decision tree, because they didn't -- somebody asked Shiew-Mei whether that's --
DR. HUANG: My -- it's in error.
CHAIRMAN VENITZ: Any other comments?
DR. GIACOMINI: I think I'm on the record as saying that I think there are compelling data for the OCTs as in the kidney. The magnitude of those interactions are not enormous, but I've shown that there is compelling data for those interactions, and OATP1B1, as I said, it's the next. There is good data on the interactions and unlike Cyclosporine also.
DR. HUANG: So are there others besides Cyclosporine that you recommend as a general defense order? Because I think we're going beyond this question of general inhibitor.

DR. GIAMCOMINI: You mean like a Gemfibrizole of something like that. You know Gemfibrozole is pretty good, but again it's more specific for OATP1B1 than Cyclosporine

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and P-gp as well.
CHAIRMAN VENITZ: You could argue going outside the scope of this guidance, you know the guidance is driven by in vitro mechanistic findings that you try to confirm or disprove. Now, you're saying well, let's use a non-specific inhibitor that you shot gun and see what happens?
DR. HUANG: Well, the reason is because we don't have any specific inhibitors for P-gp, and that's why I wanted right now that we put in Cyclosporine.
CHAIRMAN VENITZ: Well, then, I think we had in the previous discussion we had said as long you consider what else is going on with the drug in terms of the importance of these things, the choice of the in vivo P-gp inhibitor, even if it's a dirty one, should be selected in a way that it's possible -- it's as selective as possible.
DR. HUANG: Okay.
CHAIRMAN VENITZ: I think that's.
In response to question four, I'm very much with Kathy on Probenecid, Cimetidine. I mean interaction studies have been going on for a long time, and we have experience on it. But obviously if we can use an in vitro to kind of screen whether you should do studies such as this; yeah,

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absolutely.
The other transporters, I don't think we're there yet in terms of recommending drug interaction studies.

DR. HUANG: So your opinion would be OCT and OAT?
CHAIRMAN VENITZ: And -- okay. If the drug is renally cleared or it's an important component, then a Cimetidine, Probenecid interaction study should be done, which is already taken place anyways.
DR. LESKO: Presumably, that's renal clearance and then involves a transporter?
CHAIRMAN VENITZ: Secretion.
DR. LESKO: Yes, secretion. You have to have secretion.
CHAIRMAN VENITZ: Yes, yes.
DR. HUANG: Yeah, the example that I've shown -- there's several compounds that have renal clearances like three-fold or four-fold, GS1 and --
CHAIRMAN VENITZ: Yes.
DR. HUANG: -- this comment actually -- the earlier study they just came up with very general Probenecid and Cimetidine interaction studies, but the reason for the specific transporters.

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CHAIRMAN VENITZ: And I would be in favor of that.
DR. HUANG: The latter?
CHAIRMAN VENITZ: Yeah. Any other comments, suggestions?
Okay. I think you successfully knocked us out. I turn the microphone over to Larry, who's going to put us to sleep; right? But us to bed, I should say.
DR. LESKO: Yeah. He didn't say get to the podium and show your next slide set. I think I'm beginning to feel like Dennis the Menace and my colleague, Bill Jusko. I think we've had a long day and a very productive day. I want to express my thanks on behalf of FDA to the Committee. It's been very helpful to us. And I think the questions have been really well addressed and other issues have been raised that we need to think about. So thank you and have a good evening.
CHAIRMAN VENITZ: Okay. Then thank you, everyone, and we adjourn and get together again tomorrow at 8:30 a.m. Thank you.
[Whereupon, at 5:15 p.m., the Committee stood in recess until 8:30 a.m. the following day.]