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

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

DR. HUANG: Exactly.

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

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drugs that prolong QT, we put it in the contraindication because we're sensitized with a lot of experience from the withdrawn drugs.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

interaction, then you can stop right there.

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

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

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

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

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

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

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

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

DR. HUANG: Are you talking about in vitro?

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

DR. HUANG: Okay.

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

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

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

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

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

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

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

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

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

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

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

DR. HUANG: Thank you.

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

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

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

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

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

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

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

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

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

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

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

DR. RELLING: Right, but that's your criteria

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. HUANG: A lot more population

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

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

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

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

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

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

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

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

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

to come up with a constant number for that.

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

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

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

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

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

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

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

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

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

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

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

That gets us to our concluding remarks. Larry?

DR. LESKO: Thanks, Jurgen.

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

achieving that goal of advancement.

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

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

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

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

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

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

DR. FLOCKHART: Yes.

DR. LESKO: So there you go.

(Laughter.)

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

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

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

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

DR. DERENDORF: 7th and 8th.

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

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

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

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

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

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

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

MS. REEDY: Thank you.

DR. VENITZ: Thank you, Kathleen.

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

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