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ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY (ACPS–CP)

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Advisory and Consultant Staff Conference Room
Room 1066
5630 Fishers Lane
Rockville, MD 20857

PAPER MILL REPORTING
(301) 495–5831

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P R O C E E D I N G S

Call to Order

DR. VENITZ: Welcome to the second day of the Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology. I am Jürgen Venitz and I am the Acting Chair of the Committee.

As always, we would like to start the Committee proceedings by going around the table and have everybody introduce themselves for the record. Maybe we will go ahead and get started with Dr. Mueller. Please introduce yourself and your affiliation.

DR. MUELLER: I am Bruce Mueller from the University of Michigan.

DR. RELLING: Mary Relling, St. Jude Children's Research Hospital.

MR. GOOZNER: Merrill Goozner, Center for Science and the Public Interest.

DR. LERTORA: Juan Lertora from the NIH Clinical Center in Bethesda.

DR. GIACOMINI: Kathy Giacomini, U.C., San Francisco.

DR. FLOCKHART: David Flockhart from the Indiana

University School of Medicine.

DR. CALDWELL: Michael Caldwell from the Marshfield Clinic.

DR. VENITZ: Jürgen Venitz, Virginia Commonwealth University.

DR. PHAN: Mimi Phan, Designated Federal Official, FDA.

DR. MORRIS: Marilyn Morris, University at Buffalo.

DR. SICA: Dominic Sica, Virginia Commonwealth University.

DR. BARRETT: Jeff Barrett, the Children's Hospital, Philadelphia and University of Pennsylvania.

DR. CAPPARELLI: Edmund Capparelli, University of California, San Diego.

DR. TOPP: Elizabeth Topp, University of Kansas.

DR. LESKO: Larry Lesko, Office of Clinical Pharmacology at FDA.

DR. HUANG: Shiew-Mei Huang, Deputy Director, Office of Clinical Pharmacology, CDER, FDA.

DR. ZHANG: Derek Zhang, Office of Clinical Pharmacology, FDA.

DR. XIAO: Shen Xiao from the Division of Cardiovascular Renal Products, Office of New Drugs, FDA.

DR. STRONG: John Strong, Laboratory of Clinical Pharmacology, FDA.

DR. AGRAWAL: Mukul Agrawal from Roxane Laboratories.

DR. MAYER: Phil Mayer from Wyeth.

DR. KEARNS: Greg Kearns from Children's Mercy Hospital in Kansas City.

DR. MAGER: Don Mager, Department of Pharmaceutical Sciences, University at Buffalo.

DR. VENITZ: Thank you everyone for coming.

Our first official order of business is the reading of the Conflict of Interest Statement into the record. Dr. Phan is going to do that.

Conflict of Interest Statement

DR. PHAN: Thank you. Welcome to March 19 Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. Today's agenda topic is The Renal Impairment Concept Paper. Key issues that will be discussed are the effects of renal impairment on Cytochrome P and transporter, methods of evaluation of renal function and the effects of

hemodialysis on drug clearance.

The Food and Drug Administration is convening today's meeting of the Advisory Committee for Pharmaceutical Scientific and Clinical Pharmacology of the Center for Drug Evaluation and Research under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representatives, all members and consultants of the Commission are special government employees or regular federal employees from other agencies and are subject to federal conflicts-of-interest laws and regulations.

The following for on the status of this Commission's compliance with federal ethics and conflict-of-interest laws covered by, but not limited to, those found at 18 U.S.S. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of the Committee are in compliance with federal ethics and Conflict of Interest laws. Under 18 U.S.S. Section 208, Congress has authorized the FDA to grant waivers to special government employees who have potential financial conflicts

when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential conflicts when necessary to afford the commission essential expertise.

Related to the discussions of today's meeting, members and consultants of this Committee who are SGEs have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Committee will discuss an discuss and make recommendations regarding the Renal Impairment Concept Paper. This is a particular-matters meeting during which general issues will be discussed.

Based on the agenda and all financial interests reported by the Committee members and consultants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest.

Dr. Mukul Agrawal and Dr. Philip Mayer are serving as acting industry representatives, acting on behalf of all regulated industry. Dr. Agrawal is employed by Boehringer Engelheim and Dr. Mayer is employed by Wyeth.

With respect to FDA's invited guest speakers, we would like to disclose the following:

Dr. Lisa Shipley is employed by Eli-Lilly. Dr. Shipley owns stocks and has stock option in this firm.

Dr. John Wagner is employed by Merck. He owns stock and has stock option in this firm. Dr. Wagner also serves as Chair of the Pharmaceutical Research and Manufacturers of America's Clinical Pharmacology Technical Group.

We would like to remind members and consultants that, if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants

need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that they have with any firms at issue.

Thank you.

DR. VENITZ: Thank you, Mimi.

Our topic for today's discussion is a renal concept paper that was provided to all the Committee members as backgrounder and Dr. Shiew-Mei Huang, Deputy Director of OCP, she is going to set the topic up for us.

Topic 3: Renal Impairment Concept Paper

When to Conduct a Rental Impairment Study

DR. HUANG: Good morning.

[Slide.]

Yesterday, we had a lot of discussion of one of the key questions in the clinical pharmacology review; that is, how to dose specific populations appropriately such as pediatric populations, individuals with specific genetic makeup and also the approaches to reach the goal of individualized dosing in these populations.

Today, we are going to discuss one other very

important group, the patients with renal impairment.

[Slide.]

Based on the National Kidney Foundation, the chronic kidney disease prevalence is more than 40 million people being affected worldwide and about a million of them are receiving kidney-replacement therapy.

[Slide.]

Ten years ago, in 1998, we published a guidance to discuss how to evaluate for the dose that needs to be changed in renal-impaired patients and we have discussed data-analysis study design and the impact on dosing and labeling.

In that guidance, which you also have a copy of, we mentioned that renal-impairment studies are considered necessary when renal impairment is likely to significantly alter the PK and PD of the drug and its active metabolites, a dosing adjustment is likely to be required for safe and effective use and is likely to be used in this particular population.

In particular, we mentioned that a study with renal impairment is recommended when a drug has a narrow therapeutic index, or narrow therapeutic range, and the

elimination is primarily by renal mechanism, excretion or metabolism in the kidneys.

After the guidance has been published, we have received a lot of public comments continuously before and after the guidance was finalized plus there are comments from the sponsors during drug development and also literature data, new information on how renal impairment may affect metabolism/transport.

So we decided that it is time to revise the guidance. We have formed a renal working group last year. Initially, we looked at how the renal-impairment studies were conducted and whether they have been conducted.

[Slide.]

So we did a survey looking at the renal-impairment studies in the last five years--it is actually up to July, 2007--and then to look at all the new molecular entities after oral administration. That is our initial focus.

You can see that 71 percent of these applications have renal-impairment studies. This is compared to the previous survey which is a slightly different baseline where we look at all the NDAs from all routes of administration and a little bit more than half of them are renal-impairment

studies.

When a study is conducted, 67 percent, in the past five years, used the full study; that is, they look at the renal-impairment effect in a range of patients with different GFRs--I will discuss this more--whereas, less than half of the previous, back in '96 and '97, the studies used the full study design.

We see that 44 percent of the new applications have hemodialysis of patient data as compared to 15 percent about ten years ago. What is consistent in both of these hemodialysis studies, many of them only look at how the hemodialysis has an effect on the drug clearance and only occasionally they would use the hemodialysis patient as a comparison group how renal impairment would affect the drug's clearance.

[Slide.]

So let's look at the data from the current survey more. As I mentioned earlier, the new--we have data from old '94 new molecular entities through all different routes of administration. However, my discussion will focus only on the drugs, the 51 drugs, that are meant for oral administration.

Out of these 51 drugs, we looked at their elimination pathways, whether they are renal predominant or non-renal. In our definition for this survey, we say if it is more than 30 percent, it is done by renal pathway, then we consider renal. I will explain more.

One parameter is to look at percent of dose excreted and changed in urine, and that is very obvious when you have a large percentage excreted and changed in urine that is likely to be renally impaired--renally eliminated.

So, using that criteria, we see the 14 of the 51 drugs would be considered renally eliminated and 37 are non-renal. Out of these 51, 36 had renal-impairment studies. So, essentially, all of the renal-dominated drugs, they have renal-impairment studies. One of them that I didn't show here is post-market commitment. So they all have renal-impairment studies.

Out of the 37 considered non-renal, 23 have the renal-impairment study. So, how do we determine whether it is renal or non-renal. I mentioned earlier, one very easy parameter is to look at percent of dose excreted and changed in urine.

The 13 drugs, or the 14 drugs, that we considered

renal predominant, the renal pathway, or the percent excreted and changed in urine ranges from 30 to 100 percent with a median level of 70 percent.

However, there is one drug where the percent excreted and change is less than 10 percent. But we look at the other parameters such as percent absolute bioavailability, elimination pathway after IV administration, and also renal label studies looking at their distribution of parent compound versus the metabolites and we have determined that renal pathway is actually major.

For the 37 drugs that we considered non-renal, the percent excreted and changed in urine ranged from almost negligible, 0.01 percent, to less than 15 percent and the median level is about 3 percent. So there is significant--non-renal elimination was further substantiated by looking at in vitro and in vivo metabolite and transport data and also the drug interaction data to show the significant contribution of their metabolism.

[Slide.]

So let's look at, again, the 36 studies, 36 drugs, with renal study. Again, 13 of them are renally excreted and 23 are non-renal. So, when the studies were conducted,

we found out 13 out of 13 that are renally eliminated have their PK altered.

However, 13 out of 23 non-renally eliminated drugs also have their PK altered in renal impairment. All of the drugs with renal impairment, with the PK altered, have an impact on dose administration. There is something said about one or all of the groups of renal impairment.

About half of the non-renally impaired--non-renally eliminated--drugs, they ended up with either caution, contraindication or dose adjustment in Dosage Administration Section of the label.

So, from this data, we can see that renal impairment had an effect on pharmacokinetics for drugs that are renally eliminated, 13 out of 13 drugs, but they also affect drugs that are metabolized or transported, that is 13 out of 23 drugs.

So let's look at why renal impairment would affect the metabolized drugs or transported drugs. That is the 13 out of the 23 drugs.

[Slide.]

How would renal impairment affect the metabolism/transport. One obvious consideration it could be a

decreased renal metabolism, a decreased renal elimination of metabolites.

However, more recent data have suggested deceased non-renal elimination, and I think Dr. Vince Pichette will give us some data from both pre-clinical in vitro/ex vivo data to show that some of the uremic plasma or components in the uremic plasma can inhibit enzyme transporter activity and decrease enzyme transporter expression.

So what are the enzymes that are responsible for metabolism of the majority of drugs?

[Slide.]

Here is just a breakdown of Cytochrome P450 enzymes. If you look at, for the small intestine, the major enzymes are 3A, 2C9, while, in the liver, besides 3A and 2C9, there are many other enzymes such as CYP1A2 that are responsible for the metabolism of drugs.

What about transporters? There are many transporters that are being studies and evaluated and many of the new drugs are shown--or marketed drugs are shown--to be substrates for these transporters.

For example, one of the efflux transporters, MGL1, the Peachtree transporter, has been shown to affect many of

the drugs on the market, or some of the uptake transporters, such as OAT1B1, OAT, have also been shown to affect many of the drugs that are on market and many of them have been included in our drug label.

As we know more information, I believe these will be include in the label and we will understand more how these transporter and the change in the transporter activity would affect the pharmacokinetics in patients with renal failure.

[Slide.]

So let's just show five of the 13 drugs that are metabolized or transported and renal impairment had an effect.

Here I listed five drugs; duloxetine, tadalafil, rosuvastatin, telithromycin and solifenacin. If you look at the percent excreted and changed in the urine, it ranged from 0.3 to less than 15 percent and the bioavailability ranged from 20 to 90 percent when there now.

The elimination pathway included almost all the key subenzymes in the intestine and in the liver. Additionally, there is literature data to show the rosuvastatin, even its metabolite of 2C9, the other

transporters may be more important in its disposition.

So if you look at this, these are the results of AUC and Cmax change in renal impairment. I only listed here for the full change in the severe group. In our '98 guidance, we talk about mild, moderate, severe in patients undergoing dialysis. Most of these data are based on the

except the study in patients undergoing hemodialysis.

You can see the change from about 2- to 4-fold with Cmax a smaller magnitude. So you might say, well, all of these major CYP enzymes are involved. But let's look at the drugs that are metabolized but yet renal impairment has no effect.

So if I list the profile of the elimination pathway of the drugs that pharmacokinetically have been altered, these are the 13 drugs where they are being metabolized by almost all of the CYP enzymes and there are some of the transporter and non-CYP enzymes involved.

You look at the ten drugs that pharmacokinetics is not being altered. Here, you cannot see an apparent trend of certain CYP enzymes may be responsible for the change in pharmacokinetics and renal impairment. Although this is a

very limited study, we have 13 drugs here and 10 drugs here.

Also, for each drug, there may be several pathways responsible for their metabolism. In addition, many of the transporters have not been extensively studied. So they may be altered where we don't have an apparent trend from this type of evaluation.

[Slide.]

So the conclusion from our survey is that the '98 guidance had an impact on the determination of the need to conduct a renal-impairment study because renal studies have been conducted in 71 percent of the orally administered new drug, new molecular entities.

They have been studied in 13 out of 14 new molecular entities that are predominantly renally eliminated. There is one drug which is an oncology product, the renal study is a postmarket commitment.

[Slide.]

We believe more studies are needed for hemodialysis patients. Right now, even, we have 44 percent studies in dialysis patients. Some of them were studied to evaluate the renal-impairment effect on the drug clearance. The majority of them are to study the effect of dialysis on

the drug clearance.

There appear to be pharmacokinetic changes in renal impairment of new molecular entities that are predominantly metabolized or transported. The effect of renal impairment on drug metabolism and transport needs to be understood better.

[Slide.]

So, in our proposed recommendation, which I will point out those that are different than what we have in the '98 guidance, is, when a study is needed, we believe that renal studies need to be conducted for drugs that are metabolized, transported, in addition to drugs that are renally eliminated.

So we proposed a decision tree to determine when a renal-impairment study is recommended. This is a simplified scheme where we have more detail in the background.

So we said if the new molecular entity, or investigational drug, which would include the metabolite, and we have not addressed the biologics, so this could come out at a roundtable discussion. So we believe that the drug is for single-dose use. It is volatile inhalation. It is not likely to be used in renal-impaired patients.

Then no study is required unless there is a safety concern with a particular product.

If the investigational drug is for chronically administered use, oral, I.V., sub-Q, and is likely to be used in the target population--here I meant the renal impairment--then we look at the route of administration, route of elimination.

If it is mostly renal, and we can define what is mostly renal, the sponsor will have two choices. They could conduct a full PK study, which means a study in patients with different degrees of renal impairment or they could conduct a reduced PK study that is comparing the normal to either in end-stage renal-disease patients or in the severe group of patients who are ready to move to ESRD. We can discuss this more at our discussion.

However, for drugs that are non-renal, that are mostly metabolized or transported, then we will recommend to do a reduced PK study. If the study is negative, then we can label as such. However, if this study result is positive--by positive, our definition is based on the magnitude of change and impairment, the exposure response relationship and also the target patient population--we may

request the sponsor to conduct a full study.

This could be a combination of the reduced study with a population PK study or a full-range study in different groups. Depending on the outcome, certain impairment groups, maybe there is no dose adjustment needed and we will label as such. For certain impairment group, maybe there will be dose adjustment and we will label as such.

What we would like to discuss more is what would constitute a worst-case scenario. Is it the end-stage renal-disease patient that they are ready to get dialysis but not on dialysis yet or the patient that is already on dialysis and we do it in between dialysis. So we would like to get comments from the Committee.

And we also want to emphasize that it is important to study the effect of dialysis on the drug's clearance so we know whether we need to change the dose when the subject is on dialysis unless, of course, if the drug is a large volume distribution and, based on the calculation, we know that the dialysis may not be able to remove a significant amount of the drug or metabolites based on the scheduled dialysis.

[Slide.]

Another recommendation is the patient stratification. This is our current recommendation and it is consistent with the National Kidney Foundation's recommendation. Dr. Shen Xiao will talk about this more. This is compared to the '98 Guidance where we had a slightly different grouping, where we used the 80th cutoff and the 50th cutoff.

Here we just said less than 30 is the severe group and patients that needed dialysis as a separate group. Based on the comments that we have received, the sponsor has suggested that we use the new guideline. In addition, we also provide the provision in the Concept Paper that there is no evidence, or it is not apparent, that individuals with

change, disease, with other markers, whether the kinetics, or they would be subject to the adverse events.

So we are suggesting that the grouping can be such that you only have subjects more than 60, in between 15 and 60, and in kidney failure for drugs that are not considered to be a narrow therapeutic-range drug.

[Slide.]

Our third proposal is that renal function can be evaluated by MDRD based on the study Modified Diet in Renal Disease. That is the preferred method. Again, Dr. Xiao will elaborate on this further.

However, the Cockcroft-Gault equation that estimates creatinine clearance based on serum creatinine level has been used as a basis so we believe that it can be used as a reference.

[Slide.]

Finally, our proposal is we need to evaluate more in end-stage renal disease for patients under hemodialysis. They need to be studied for most investigational drugs, either pre-dialysis to evaluate the effect of renal impairment on drug clearance--and, again, we would like the Committee's comments on what constitutes the worst-case scenario; it is the patient that has GFR less than 15, they are ready to be on hemodialysis but not yet on hemodialysis or they are on hemodialysis but it is in between the scheduled dialysis.

We also need to study the patient on dialysis during dialysis to evaluate the effect of dialysis on the drug removal but, again, unless the drug has a large volume

distribution. Again, the pre-dialysis and the consideration of the worst-case scenario needs to be discussed.

[Slide.]

So the questions for the Committee are; does the Committee agree that renal impairment can affect metabolism or transport of drugs that are substrates of metabolizing enzymes and transporters?

[Slide.]

Does the Committee agree with the recommended methods, the MDRD vs Cockcroft-Gault as the reference, to determine renal function and the proposed stratification, which is a slight modification from the '98 Guidance?

[Slide.]

And what comments or recommendations does the Committee have on applying the decision tree to the determination of when a renal-impairment study is needed for an investigational drug?

[Slide.]

This is the chart that I have shown you earlier.

[Slide.]

Finally, what studies in hemodialysis patients does this Committee recommend for drugs intended for chronic

administration? This could be when we discuss what constitutes the worst-case scenario along with our discussion of the decision tree and perhaps more detail of what type of studies need to be conducted.

[Slide.]

I would like to mention the Renal Working Group constitutes individuals from our office, the Office of Clinical Pharmacology. Besides myself and Dr. Lesko, I have Dr. Derek Xhang to be at the table to help address any question you have on the survey.

We have, from the Office of New Drugs, Dr. Xiao who will talk about the methods of staging the renal function and the grouping. From the Office of Pharmaceutical Science, Dr. John Strong, who is also at the table. And we have a lot of comments, input, from individuals who were at the FDA for at least a month for scientific sabbatical and they have given invaluable input to us. I just want to mention Dr. Burckart now is with us at the FDA.

DR. VENITZ: Thank you, Shiew-Mei. We have time for a few quick questions. We defer the discussion of our--Dr. Topp.

DR. TOPP: I just want to add a little comment. First of all, I think it is very interesting where you are headed with this and to try and include the drugs that are metabolized when there are, in my opinion, obviously effects on PK for not only renally cleared drugs but also these metabolized drugs.

I wonder, and I just put this question out there, whether the effects are only due to changes in transporters or effects on transporters, as you suggest, because the uremic environment is quite damaging to plasma proteins. So I wonder if plasma-protein-binding effects are also at play here and that doesn't come out in your presentation.

DR. HUANG: We also have data--I don't think we have all of it on protein binding. There are some changes in protein binding but it does not affect the change in the overall PK when you look at the free or the total concentration, if that is to address your question.

I think after Dr. Pichette's presentation we will know more about how it affects the metabolism.

DR. TOPP: I'm sorry; I want to make sure I understand that. You are saying that there are changes in plasma-protein binding--

DR. HUANG: In certain studies.

DR. TOPP: But there doesn't seem to be an effect on overall--so, if I change the free fraction, it doesn't seem to change the overall half-life of the drug, for example?

DR. HUANG: I wouldn't say that. Derek, do you want to comment on that?

DR. ZHANG: From the slides Shiew-Mei just mentioned, the five drugs, two of those drugs I can mention, duloxetine and solifenacin, they did the protein-binding study in normal and hemodialysis patients and they found no changes.

The other, like, indirect evidence like telithromycin, they mentioned in the young and elderly population protein binding, also no change.

So, assuming the elderly patients that we know function would decrease a little bit. But, overall, from the survey, we don't see significant protein changes during the renal impairment.

DR. TOPP: I would like to interject one more thing, too, and just a comment on the presentation, and that is that, in focusing on patients with renal impairment, I

wonder whether the duration of their renal-impaired state is also an important factor.

So you are considering the extent of renal impairment but not the length of time that they have been impaired. So, for example, I have a young friend who is 17 who had to have his kidneys removed. So then he, at the time of his kidney removal and before he had a transplant, he was renally impaired but for a fairly short period of time.

That is quite a different scenario than what you would see in an older person who had been in steadily declining renal function for years. So I wonder if there is a time factor, also.

DR. HUANG: Right. Most of our studies are chronically--we do not address acute renal failure. Most of these are people who are at that stage for a period of time.

But I just want to go back on the protein-binding issue. There are some drugs that are not extensively protein bound and yet renal impairment has an effect just in general.

DR. VENITZ: I have one more question from Dr. Flockhart and then we have to move on. Dr. Flockhart, I

think you have the last question.

DR. FLOCKHART: That's okay.

DR. VENITZ: Then Dr. Barrett, you are next.

DR. BARRETT: Shiew-Mei, just a quick question about your decision tree. Have you taken a look at what the expected throughput would be if this is applied based on your survey results? In other words, this is more inclusive in terms of the number of drugs that this would likely affect. So, based on the number of studies and the number of drugs that fell under those categories, if you applied this decision tree, how would that affect the number of likely drug studies based on this classification?

And then I am trying to get a sense for--based on the number of studies that pharma companies would submit, what would be the likely additional kind of burden on this community. I mean, even though 50 million sounds like a lot of available patients, they are not infinite. So this would seem to have a greater impact in terms of studying this population.

I just wonder what the numbers would be. Have you thought about that?

DR. HUANG: Well, right now, more than two-thirds,

13 out of 23--let me go back. 13 out of 23 of the drugs that are metabolized, the sponsors have done interaction studies. So I would say 50 percent of the drugs that are metabolized, you will see an increase in the study. But it is a reduced study.

Drugs that are metabolized right now constitute about two-thirds of what we see. So, if you do the math, it is more than 60 percent increase. But it is one normal group comparing to one renal-impairment group, not a full study.

A full study, you have five groups plus one study. So it is two studies versus six.

DR. BARRETT: No, no. I am just looking at the number of agents. I guess the other thing is, based on your--you made and assessment that hemodialysis studies are needed more. I am just curious, though, with the information that you get from the standard, the full design, do you have data on whether or not you felt that that was predictive of the setting in hemodialysis?

In other words, have you looked back at all the historical data? Do you see that as a gap in terms of what we see in hemodialysis different from what would be

predicted in that setting from the standard design?

DR. HUANG: Do you mean the dialysis effect on the drug?

DR. BARRETT: Yes.

DR. HUANG: We did have one study, I think it was the second drug, that dialysis showed no effect. I think if you do a volume distribution calculation, it would predict it to have no response, no change.

DR. BARRETT: Okay. But there hasn't been the kind of--I mean, you haven't looked at all of the--you must have a lot of--

DR. HUANG: Yes, because we have very sparse. Would just don't have data.

DR. BARRETT: Okay. Gotcha.

DR. HUANG: I guess maybe I have forgotten to mention, if we want to use patients on hemodialysis as the worst-case scenario, I think the fifth drug that is on my list--where was that drug? Anyway, when you do the study--yes; right here--during hemodialysis, it didn't show a change.

However, if you study, in the severe group, then you see a change. So there is a risk of missing the effect

of renal impairment on pharmacokinetics if you don't do it, that patients are not on dialysis, because obviously dialysis has some effect. So you didn't see an effect here.

These are the patients--

DR. BARRETT: No, no. I am sure you have examined--I just wonder, is that risk 1 out of 5? Is it 20 percent?

DR. VENITZ: Can we defer this because we are already behind.

DR. BARRETT: Yes.

DR. VENITZ: Let's just defer that question until we have a general discussion.

Thank you, Shiew-Mei. Let me invite our next speaker, Dr. Vincent Pichette. He is Associate Professor of Pharmacology and Medicine at the University of Montreal in Quebec.

Effect of Renal Impairment on CYP/Transporter

DR. PICHETTE: Good morning.

[Slide.]

Thank you very much for inviting me. It is a pleasure for me to be here, especially the weather. It is a little warmer than in Montreal.

[Slide.]

So I will try to give you some information about the impact of renal failure on drug metabolism and transport. Just a brief--Dr. Huang already described it, but these are the last numbers of the prevalence of CKD in the U.S. population.

Just to summarize, in a ten-year period, there was an increase of over 30 percent in the prevalence of chronic renal disease in the U.S. population.

[Slide.]

More importantly, for our clinical pharmacologist or clinicians, the increase in the prevalence of CKD is increasing mostly in the older population where the administration of drugs are the most important.

[Slide.]

So, as Dr. Huang summarized, there is an accumulation of drugs in the kidney or in renal failure that could only be explained by a decrease in the non-renal clearance. Just as an example, and I won't go through all the slides due to the time.

[Slide.]

But just remember, for example, this study was

done to evaluate the effect of end-stage renal disease on the metabolism of warfarin. As you can see, there is an increase in the s over r ratio suggesting there is a decrease in the activity of 2C9.

[Slide.]

The same thing here. This is the erythromycin breath test for CYP3A, We can argue on the specificity business, in any case, here you have the test in end-stage renal disease compared to controls so there is a decrease of around 50 percent in the erythromycin breath test in the end-stage renal-disease patient.

[Slide.]

So I won't go through this, but to answer one of the questions previously, these are--it is an article we just published in CPT. It is a review article so we review all the literature that was available at that time.

Just to tell you, it is difficult in humans to evaluate what are the real impacts of renal failure on the kinetics of drugs because, firstly, it is done either in dialysis patients, in pre-dialysis patients, after, before, during dialysis. But just remember that, for a lot of substrates, there is either a decrease in non-renal

clearance in normal compared to CKD or either an increase in the AUC or in the half-life.

The pathways in humans are--there are many metabolic pathways, either transport or Cytochrome P450.

[Slide.]

So, in the past years, we have been interested in studying this phenomenon but in rats. So just for those who are not familiar with ratology, we have a model of renal failure in the rat which is called the 5-6 nephrectomy which is well accepted in the literature.

What we do is we isolated the left kidney. On the one, we do a two-thirds nephrectomy of the left kidney. So you have left the remaining one-third of the left kidney is left. Thereafter, you do a total right nephrectomy, a week after. After 42 days, you sacrifice the animals.

[Slide.]

So you have a chronic renal failure, a severe one, which is accepted in the literature which is mimicking, let's say, Stage 4 kidney disease, just to understand the result that will follow. Sorry; these are international units but there is a three-fold increase in creatinine in our model so there is a decrease of around 70 percent in the

creatinine clearance. So this is Stage 4.

[Slide.]

So, with model, we have been able to demonstrate over the time first that there was an important alteration in the metabolic enzyme in the rats. So, just to summarize, you have a decrease in several P450 isoforms, CYP2C11, 3A1, 3A2. So, in humans, it is 3A4 but, in rats, it is the main isoform.

So there is a sharp decrease in the protein expression which is secondary to a decrease in gene expression and it follows that you have a sharp decrease in the activity of these enzymes in the chronic renal failure rat liver. So the same thing for Phase II enzymes or for the Nat enzymes.

[Slide.]

So, in the intestine, we have shown the same result. You have a decrease in the protein expression of several P450 and the most important one is the CYP3A2 which is, again, secondary to reduce this gene expression and you have also a concomitant reduction in the activity.

So what about the drug transporter. So, in the liver, there are conflicting results we have found over the

years. But, to summarize briefly, we have an increase in the P-gp expression but you have an important decrease in Oatp2. So efflux transporter seems to be preserved or upregulated. However, the uptake transporters are importantly decreased.

On the other hand, in the intestine, you have a decrease of all the efflux transporter, mainly P-gp and MRP2 which could explain an increase in bioavailability of drugs in renal failure.

So, for Phase II UDP-glycuronyltransferase, there is no modification in the liver. Here you have UGT2B, UGT21A and these are chronic renal insufficiency compared to the control pre-fed rats. This was done two years ago and published in DMD. You have no modification of this Phase II enzyme.

[Slide.]

So thereafter the big question is what is the mechanism leading to a downregulation of enzyme and drug transporter in renal failure. We have hypothesized that it could be a circulating factor.

[Slide.]

So, briefly, what we did is we incubated

hepatocytes, rat hepatocytes, with serum of rats, uremic rats. Here you have, in white, normal rat serum. In black, you have the chronic renal failure serum. When you incubate it with hepatocytes, you can see that the urine makes causes or induces a sharp decrease in the isoform, the same isoform as I showed you before in vivo.

So this experiment suggests that there is a circulating factor that is implicated in the downregulation of the P450 isoform.

[Slide.]

So we did a lot of study, but this is a human study. So we took the serum of the control patient here, human uremic patient, and I will tell you a little bit later, these were on our pre-dialysis clinic so Stage 4, just before beginning dialysis. You can see that there is a sharp decrease also of several isoforms of the P450 when you incubated human uremic plasma with hepatocytes.

[Slide.]

So the same for all the isoforms. We found in vivo when you took serum, either control or uremic serum, and you incubate it with hepatocytes, you have a decrease in Nat2 protein expression, RNA expression, and the same in the

drug transporter.

[Slide.]

I should point out here that I said before that there is a little induction of P-pg in the liver but, as I said before, there is an important decrease in the way TP2 and this is secondary also to a circulating factor.

[Slide.]

When you take primary rat enterocyte culture, you have exactly the same result. So, again, uremic serum is inducing a decrease in the transporter.

[Slide.]

So the next question is what is the uremic serum. Unfortunately, I won't tell you the exact insert today. Unfortunately, I don't find the exact factors. But we have some idea.

As you know, there is a lot of uremic toxic accumulating in renal failure. I will talk later on that. There is, also, as you know, chronic renal failure as a state of chronic inflammation. Cytokines are elevated and they are known to downregulate several P450 isoforms.

But we were interested more in the role of thyroid hormone. As you know, in renal failure, there is a

secondary hyperthyroidism so you have eye-levels of PTH. A couple of years ago, several researchers have found that PTH could inhibit the protein synthesis of several proteins in the liver.

[Slide.]

So we tested this hypothesis for the Cytochrome P450 and it is--I will summarize this experiment to you. Here we incubated hepatocytes, again, with control serum or with serum from uremic rats. Again, you can see in white this is protein expression, RNA expression and activity of CYP3A2. You can see that, again, you have a sharp decrease.

But when you to a total parathyroidectomy to your uremic rats, so one week before inducing renal failure, you completely block the elevation of PTH and you block the inhibitory effect of the serum. When you put back PTH in the serum, exogenous PTH, at the same concentration as you found in chronic renal failure, you have the same effect as chronic renal failure.

So this experiment we are giving the idea of the role of PTH--sorry; there is a mistake here--on the downregulation of P450.

[Slide.]

Dr. Les Bennett in UCSF has been interested in other uremic toxins. Like I said before, there is a lot of toxin accumulating in chronic renal failure.

[Slide.]

So what he did recently, he incubated hepatocytes also with several toxins that could be found in chronic renal failure. As you can see, one of the ones is CMPF. It is decreasing the uptake of erythromycin. Others could decrease the metabolic activity like indoxyl sulfate.

[Slide.]

So there is toxin, uremic toxin, that could affect both transporter and enzyme. What about the effect of hemodialysis, just a rapid word on that. Like I said before, we were fortunate to have serum from our pre-dialysis clinics. These are patients with very low GFR just before the beginning of their chronic hemodialysis treatment.

[Slide.]

What we did, we incubated the serum with hepatocytes and we evaluated the expression of P450. Just beginning the treatment of dialysis, you can see that there is an important decrease in CYP3A2. After a month or six

months of dialysis, there is no recuperation. But I should mention that we were always taking the serum before the session and not after.

[Slide.]

What about transplantation? We were also fortunate to follow patients. So we have their serum before dialysis and after a successful transplantation. When I am talking successful transplantation, you have near normalization of their GFR.

[Slide.]

So what we did is we have control serum here. We have their serum before initiating dialysis and two months after a successful kidney transplantation. As you can see, you have a normalization of the CYP3A2.

[Slide.]

The last slide, and it is important for the recommendation here for the panel; there is conflicting results on the effect of dialysis.

Here is a recently published study by Dr. Nolin in Maine Medical Center. What he did, he did breath test, erythromycin breath test, just before dialysis and just after the session of dialysis. As you can see before--so,

pre-hemodialysis--when you repeat the breath test two hours after the session, you have an increase in the metabolic activity.

The main lack of this study is we don't have a control group so I cannot tell you if the control group is here or here. But, anyway, it has been published and these are the results.

[Slide.]

So just recently, we have been interested in this question, what was the effect of a four-hour high-flux session of dialysis on the uremic inhibition by the serum. Here you have the CYP3A2 again activity, messenger RNA--excuse me; protein--gene expression and activity. When you incubate hepatocyte with pre-hemodialysis serum, again, you have the same result as I showed you before.

When you took the serum just after dialysis, you have an increase as it has been shown for breath test.

[Slide.]

So, to summarize what we found in the rats, if we infer our results to humans, it is clear that kidney failure is obviously decreasing renal expression of drugs, either by decreased GFR or tubular suppression. But there is an

accumulation of several uremic toxins that could decrease the P450 in the intestine and also downregulate the efflux transporter. The main effect would be an increased drug bioavailability.

In the liver, on the other hand, it is clear that you have a decrease in drug metabolism, at least in animals, secondary to a downregulation of CYP3A, CYP2C11, also, not more recently. And the effects on the transporter are more conflicting. You have a decrease in the uptake transporter and upregulation of efflux transporter.

[Slide.]

So, it is clear that there is elimination, that GFR impedes the elimination of many drugs that are normally cleared by the kidney but also there is both humans and animals that are suggesting that there is a decrease in drug metabolism.

[Slide.]

So this is my lab, and thank you for the Institute of Health of Canada for financing my research.

So thank you very much.

DR. VENITZ: Thank you, Dr. Pichette. We have got time for two quick questions. Dr. Lertora.

DR. LERTORA: Thank you for a very, very interesting presentation. Now, I just want to make sure, when you tested the uremic human serum, did you apply that to culture rat hepatocytes or human hepatocytes?

DR. PICHETTE: Yes. This is a good question. We used rat hepatocytes because, unfortunately, we tried to have human, so from liver-transplant donors, and we had one time. This is rat hepatocytes.

DR. VENITZ: Dr. Morris.

DR. MORRIS: In your latter slides, you had some data with pre-dialysis serum and post-dialysis serum. With the pre-dialysis serum, where these from patients on dialysis, then, so they had been treated before? They were in a dialysis program?

DR. PICHETTE: Yes.

DR. MORRIS: Because I was wondering if there might be differences, if you were looking at patients that, you know, were in end-stage renal disease not being treated by dialysis and whether you would see some sort of graded effect.

DR. PICHETTE: This is a good question. When we were interested initially--so we always took patients before

the initiation of chronic dialysis, so let's say at Stage 5, you put it on chronic hemodialysis. Thereafter, to see what was the effect of a session, the patient must be at least a month on chronic hemodialysis to be included in this study.

I didn't present all data but, when you correlate, at least with rat hepatocytes--but when you correlate the effect of uremic serum, so when you correlate the GFR of the patient and the downregulation of CYP3A, you have a good correlation.

So the worst is the renal function at initiation of dialysis, the worst is the inhibitory effect. You should just remember, these were severely impaired patients, between 6 and 12 of remaining GFR.

DR. MORRIS: I just think that is of significance in considering the patients used for with the end-stage renal-impairment studies, whether they are in a dialysis program or haven't been treated by dialysis.

DR. VENITZ: Okay. Dr. Flockhart.

DR. FLOCKHART: Thank you again for a very interesting and important presentation that gets to many issues. Could you summarize your current view on the value of rodents relative to human studies in this context? And I

am thinking particularly about the relevance to the cytochromes because, if one is looking at drug specificity of cytochromes, rodents are close to useless compared with humans because they are so different.

But the regulation may be very similar and they may be a very good model in this context. So maybe the way to pose the question is, have you got reservations and how strongly do you believe, and in which context, it might be most valuable as a model for human renal disease.

DR. PICHETTE: Well, firstly, it is easier to study rats because, in humans, you cannot have a liver biopsy and everything.

DR. FLOCKHART: Right; yes. It is easier to study cells.

DR. PICHETTE: But the next step--because I was discussing with Dr. Strong the next step--is I think to use our model but with human hepatocytes which are regulated but not immortalized cells because we try with the EP7 and everything. All the regulations are changed. They lost the PTH receptors. So you must study--if you want to go, really, on humans, I think it is repeat some of these studies on humans, to see exactly what isoform of P450.

But I will agree with you that the regulation of P450 are mainly the same in rodents compared to humans.

I didn't talk about we now have some knockout models which is far away from human, but for studying precise factors like cytochrome, like PTH, so this could give us more details. But I agree with you that now the next step is to use human hepatocytes to confirm and to be--

DR. FLOCKHART: But just to be very practical, I mean, we are moving towards applying models like this. We are the FDA. We are in human pharmacology. What you seem to be saying is do more research, which is normal. You are an academic; right? We are always wanting more research.

But I am asking you to bite the bullet a bit. I am asking you to--really, are there situations, drugs with particular clearance pathways, where you would think that the rat data is valuable and others where it is not.

DR. PICHETTE: Well, to evaluate specific pathways, I don't think this study could tell you exactly it could be inferred to humans. So we saw CYP2C elevated, 3F4. But, to tell you that there is a reduction in either transporter--what--I think the CYP3A is certainly decreased and you have human data. But I cannot infer exactly what

are the--if it is the same mechanism in humans.

DR. VENITZ: Okay. Thank you, Dr. Pichette. We appreciate your presentation.

DR. PICHETTE: Thank you.

DR. VENITZ: Our next presentation is about methods of evaluation of renal failure. Dr. Shen Xiao, who is a medical reviewer at the Division of Cardiorenal Products.

Methods of Evaluation of Renal Function

DR. XIAO: Good morning.

[Slide.]

I am going to discuss how to evaluate renal failure in patients with chronic renal disease.

[Slide.]

Shiew-Mei showed you there are 50 million worldwide patients in 1994. So, currently, if you see Dr. Pichette's presentation in his first slide, there are about 26 million people in the U.S. It is an estimation about 2005.

So these patients need and have to get good care in the early stage to avoid these very poor outcomes. So regarding the diagnosis of CKD and the evaluation of renal

function, GFR, glumerulofiltration rate, has been already accepted as the best overall measure for the diagnosis.

[Slide.]

So all my talk will be focused on GFR. I will not talk about other renal functions. I will only focus on GFR. So the definition of the stage of CKD that initial impaired function are all based on the change of GFR.

I will also just briefly talk about how to measure the GFR and I will spend most of my time to talk about the estimated GFR by using some equations which we propose in our guidance. Finally, I will just propose my personal recommendation for what kind of equation we are going to use in our PK guidance.

[Slide.]

This is just a typical picture for the normal renal function which changes with age in men and in women. So, from this picture, you can see the normal value in males is about 130 ml/min, for females, about 120 ml/min. However, as you become older, the GFR gradually decreases, about 1 ml/min every year or 5 to 10 ml/min every ten years. So you can kind of formulate how much GFR is.

So, generally, when you reach about 80 or 90 years

old, your GFR will be gradually reduced to 60 ml/min.

[Slide.]

So 60 ml/min will be considered the threshold by the National Kidney Foundation and the two groups. The K/DOQI Group is the nephrologists and represents the United States. The KDIGO Group is representing 25 countries from all over the world including Asia, Europe and North America.

So they all agree, 60 ml/min has been considered the threshold for diagnosis of chronic renal disease.

[Slide.]

Shiew-Mei already showed you this picture so I will not repeat anymore. I just mention this is just for chronic kidney disease damage and not for acute setting.

[Slide.]

One thing we have to note is that the GFR in the range of 60 to 90 may be abnormal in a young adult, but it could be normal in an infant at the age of 8 weeks to 1 year old and the older individual. So, when we decide which number we should use, we should consider this situation.

[Slide.]

I will just briefly review how to calculate the GFR. If the drug is eliminated from the kidney, not

metabolized from the kidney, just eliminated from the kidney, we can measure the urine level of this substance times the urine volume and get the total clearance.

So the total clearance will equal the substance filtered by the glomerulus minus the reabsorption from the renal tubules then plus the secretion from the renal tubules. So GFR equals this equation.

For the ideal filtration marker, we use for major renal function, there should be no reabsorption, no secretion. So then the GFR should equal the total urine clearance divided by the plasma level of this substance.

[Slide.]

Other than that, for the ideal marker, the other should be freely filterable at the glomerulus, steady-state concentrations in the blood, no extrarenal route of excretion and easily and accurately measured.

So, in the next few slides, I will very briefly discuss the current available markers that have been used to measure the GFR.

[Slide.]

Inulin is the gold standard to measure GFR. However, because of these limitations, it is only limited to

investigational research, especially only for animal research.

[Slide.]

For other exogenous markers like unlabeled or labeled tracers, they are considered the golden marker for clinical research but this is still difficult to do in routine clinical practice and it is only recommended when some drugs may interfere with endogenous creatinine so you can't recommend to use these markers to measure GFR.

[Slide.]

Cystatin C is a small protein containing 122 amino acids, just recently a few years. So some studies have reported this substance may be more sensitive, more stable, than the serum level creatinine. However, this substance is not just filtered from the kidney, it is also metabolized by the renal tubules. So you cannot get a total clearance just based on uremic level.

So it is maybe used for the equation to calculate the GFR but, right now, it is still in the clinical research, not to apply the clinical practice.

[Slide.]

So, so far, creatinine is still the most commonly

used marker to measure the GFR or to calculate the GFR.

There are two ways to measure, to get the GFR from creatinine when we issue--make the 24-hour clearance of the GFR. So, in this way, you have to collect a 24-hour urine collection and there are also many ways you can cause error. So, right now, it is not really commonly used in clinical practice anymore.

[Slide.]

So another way is just based on serum creatinine level to get some equations to estimate the GFR. The equations just use the regression techniques to observe the relation between the serum creatinine level and the measured GFR. The measured GFR generally uses the labeled/unlabeled asolomine I-hexol or, as I mentioned before, to get the GFR. Then you compare the serum creatinine level. Then you add these somewhat variables like age, gender, to overcome the limitation of serum creatinine so you get the equation to calculate the GFR.

After you get these equations, you validate it in different populations and then you finalize which equation should be used in clinical practice.

[Slide.]

So far, two most common equations have been used in clinical practice in adults and in children. I will not talk about children. I will only focus on adults because we are going to decide which equation we are going to be using in our guidance.

So to pick out which one is better, I will focus most of the time to compare these two equations.

[Slide.]

First of all, how these equations come to be developed. Cockcroft-Gault, C-G, equation is derived from 249 men with the creatinine clearance as the standard in 1973. The patients included both normal people and kidney-disease patients. The MDRD is derived from 1600 patients with chronic kidney disease only in 1999. They used the I-hexol as the standard to get the GFR. Cockcroft only used the creatinine clearance as the creatinine clearance is less accurate than the I-hexol getting the GFR.

[Slide.]

Now, how do we get this equation? We all tested in different males and females, different races, patients with different disease, normal people, kidney transplant recipients and potential kidney donors. They all tested

these different populations.

[Slide.]

Variables. There are three variables in the C-G equation including age, gender and body mass. For MDRD originally, they have six variables. Other than these three, they also have race and albumen and urea. And, after the collaboration and the data analysis, they found four variables are adequate and no difference compared to the six variables. So they only have four variables right now.

For this equation, after this equation was proposed in 1999, they are expressed in 2005. The National Kidney Disease Educational Program thinks that creatinine have some variance from lab to lab. We know right now, the measure for measuring the creatinine level have 500 percent difference.

So the National Kidney Disease Educational Program initiated, in 2005, a program to make the creatinine the measurement standard, just like in 1980s to make the lipid the measurement standard.

So far, they have not gotten the constant agreement. They hope they can finish this at the end of this year. So they think, once the creatinine measurement

gets to be the standard, the GFR should be used 175, not 186, only 5 percent reduced.

But, right now, they are recommending using 186 instead of 175. I don't know what it is going to be next year.

[Slide.]

This is just an example to compare the accuracy between these two equations. We can see here the Cockcroft, this is the 35th percent coverage compared to measurements of GFR. This is the 30th percent coverage. So we can think the C-G equation is lower than the MDRD equation. So MDRD has a higher accuracy than the C-G equation.

[Slide.]

This is also another example. This example tested about 500 patients and this is about 1600 patients. So this both tests just showed you--try to mimic the measure of GFR. So the MDRD, you get this measure of GFR. So we, as the GFR ranges 6 ml/min, less than 6 ml/min, you can have a very good overlap.

Once you have more than 6 ml/min, MDRD also has less accuracy compared to the real measure of GFR. And the C-G has more division compared to MDRD. These are the

regression and the 30 percent difference.

[Slide.]

So just a brief summary of accuracy between the two equations. Overall, MDRD is more accurate than the C-G equation in some studies. But others also report they are similar. The study also reports MDRD is reasonably accurate in non-hospitalized patients with CKD. C-G--they already started to report to confirm the C-G equation is less accurate than MDRD in older and obese people. And we have found that, when the GFR is more than 6 ml/min, both equations have less accuracy.

[Slide.]

So, as we talk, all these equations are based on serum level creatinine. So any effect of the creatinine level will cause some error. Also, this equation cannot follow up quickly when the kidney function changes so quickly, and it is also not accurate with GFR more than 60 ml/min.

In addition, if some drugs interfere with the creatinine secretion, creatinine production is also cause some error.

[Slide.]

So, right now, the National Kidney Foundation propose the MDRD equation may perform better than the C-G equation but that both equations are acceptable in clinical practice.

Just before I sent my slides to Shiew-Mei, two days ago, I got an e-mail from the National Kidney Disease Educational Program with their attached newsletter. In the newsletter, all these societies work together, they proposed to use MDRD to replace the serum level creatinine in the evaluation of a patient with chronic kidney disease.

[Slide.]

As we said, there are some deficiencies in these equations. KDIGO Group from all over the world, 25 countries, this group is managed by the U.S. National Kidney Foundation although they come from different countries. So they propose, in these kinds of situations, which measure of GFR, use the I-Hexol or asolomine, to not use the equation. But this is all extreme conditions. Generally, it is not applied in the clinical trial, I think.

[Slide.]

So, in summary, we think PK studies should be conducted in patients with GFR less than 60 ml/min. The

MDRD should be recommended for PK study in patients with impaired renal function.

[Slide.]

However, this was proposed in 1973. So, in the last 20 years, all the pharmacists and clinicians are using this equation to propose or adjust the drug dose. So we suggest, at least in the recent few years, sponsors should be encouraged to provide data as the reference because, right now, all the data we have in clinical practice uses the C-G equation before 1999.

As I mentioned, in some extreme conditions, you cannot use equation but use this exogenous marker to get the GFR.

Finally, as we talked about, because once GFR reaches more than 60 ml/min, we suggest use--we hope we can get some new molecular marker or new equation to overcome these limitations.

[Slide.]

I thank my colleagues in this working group, my Division Director and the team leaders. They provided very helpful information for this presentation.

That's all.

DR. VENITZ: Thank you, Dr. Xiao. We have got time for two quick questions. Dr. Kearns.

DR. KEARNS: Thank you. That was very nice. Just a comment. You said very clearly you weren't going to discuss children. And I respect your decision not to do that. However, I wish to discuss them at this moment.

We heard yesterday about the need to do pediatric studies. Assessing renal impairment in children with regard to its impact on drug therapy is just as important as doing it well in adults. So I think a guidance document that addresses this issue has to consider children.

I will tell you that the Schwartz equation, while it is there, is only a shade better than horrible at estimating GFR in kids. It is used because there is, honestly, nothing better. A case in point; if you look at some children who are walking around the street at two years of age and you give them a fever, they can have a GFR of 200

2

But, because it is so high, it will impact the clearance of a renally excreted drug. So there are some issues there and I would even say in the decision tree, as you think about cutoffs, that is to be considered.

The other end of the spectrum is the first year of life when renal function is developing. And the need to do drug studies in renal impairment, that oftentimes is accomplished in the course of a pediatric program where physiologic renal impairment exists because of development.

So, oftentimes, we can get data in children. A good example of this was when famotidine was studied because it was studied down in babies to two weeks of age, and we produced some wonderful data looking at the clearance of famotidine as a function of creatinine clearance.

That, think, actually satisfied the Review Division that we did not, then, have to go do the studies in kids with renal impairment.

DR. VENITZ: Dr. Giacomini.

DR. GIACOMINI: That was a very nice overview presentation.

DR. XIAO: Thanks.

DR. GIACOMINI: A couple of questions. One is the MDRD formula, it has a correction for African-American race. Does it also--like in California we are dosing a lot of Asians and people of other ethnicities. Does it have other ethnic corrections?

DR. XIAO: It has a correction, I think, of 0.782 if you are African-American.

DR. GIACOMINI: Yes. But what about Asians? Is there a correction there or is it--

DR. XIAO: They did not specifically use Asian group. They don't have that many people, I think, at that time.

DR. GIACOMINI: So they have not really tested it in Asians. Then, also, in obesity, I suppose it would not be--

DR. XIAO: The tests were basically in diabetic obesity patients.

DR. GIACOMINI: And there it works okay or there were--

DR. XIAO: It works better than Cockcroft-Gault.

DR. GIACOMINI: Cockcroft and Gault.

DR. XIAO: Yes. But still some variations. But much better than G-C, especially for obese people.

DR. GIACOMINI: Okay. Finally, when people do renal-clearance studies, they are often measuring their own creatinine clearance. They have creatinine in the serum. I know we do it. We have got creatinine in the urine and so

we are measuring creatinine clearance at the same time we can calculate an MDRD and we can calculate a Cockcroft and Gault.

I mean, is the plan going to be to recommend determined creatinine clearances or calculated creatinine clearances, or to use the formula in categorizing people into the different groups when you actually have a measured creatinine clearance?

DR. XIAO: The National Kidney Foundation Guidelines said after several studies, the measurement of the creatinine clearance is not better than the formula. Also, there is a really large burden for the clinician, for the clinical trial, you have 5,000, 7,000 patients, you have to do. So it is not necessary to do the creatinine clearance anymore, not just in 2000.

Before that time, we, in clinical practice, still like to use creatinine clearance. We think this is more accurate than the formula. But after 1999, this paper was published. And they already compare the MDRD and the creatinine clearance and they found creatinine clearance does not do a better job.

DR. GIACOMINI: I mean that might be true in a

large--when you are doing lots of patients. But I think, when you do a small targeted study, my own feeling is that, when we calculate an MDRD versus our comparison of creatinine clearances, the creatinine clearance appears to be much better in terms of predicting the clearance of the drug, the renal clearance, of the drug, et cetera, the creatinine clearance that we have actually used urine and plasma and actually did that in our small targeted study.

So I, personally, wouldn't throw away a calculation of creatinine clearance, actual creatinine, determination of actual creatinine clearances, in favor of the MDRD.

DR. VENITZ: One more. Dr. Capparelli. And then we have to move on.

DR. CAPPARELLI: Well, I think there is a difference between categorization and I totally agree with collecting that information within the scope of the trial to actually look at excretion issues as well.

You did show, though, that there was a different bias between the Cockcroft and Gault and the MDR1 equations, and also the MDRD equation. The MDRD equation also sort of truncates at 60, at least that is what it was developed at.

So, with the new structured guidelines, or at least proposed guidelines, and different cut points, how is that going to affect the categorization of patients that would be studied in the trials based on these guidelines maybe with the MDRD equation versus sort of the Cockcroft and Gault with the old criteria of 50 versus 60.

Have we looked at what--are we going to be actually looking at different patients?

DR. XIAO: So, right now, I think, when we propose the guidance, we would like to follow the scientific community, the nephrology community, because, when the patients gets treated, gives the drug to the patients, they are going to check which stage they are in so they can adjust the dose if they need to.

So I think the guidance, right now, the new guidance right now, proposes 60. But I don't think there should be a big difference between 60 and 50 right now for the drug-dose adjustment in order for classification for the kidney disease.

DR. VENITZ: Dr. Sica.

DR. SICA: Kathy, actually they have not been standardized by ethnicity from Asian-Americans. So that has

not been done with the MDRD.

The 24-hour creatinine clearances, as you probably know, add a layer of complexity, have to be done carefully and the coefficient of variation for replicate measure day to day can be substantial. So you almost have to do an averaging phenomenon rather than just an isolated variable and then determine from that.

When you do that, it gets real tough to beat the MDRD both for convenience and the capacity to give you a more predictable number. Even under GCRC conditions, it is hard to get reproducible creatinine clearances within 20 percent, one of the other day-to-day, particularly when you get below 60 ml where there may be dramatic differences based on differing tubular secretion of creatinine--day-to-day differences in tubular secretion of creatinine.

So just some thoughts.

DR. XIAO: My personal experience is when the patient is in the hospital, you may get a good result. When the patient is at home, you want them to collect 24-hour urine and at certain times it could be very difficult.

DR. GIACOMINI: No; I am talking about controlled trials in which you bring them into the GCRC and you are

actually monitoring all of that.

DR. VENITZ: Thank you, Dr. Xiao.

DR. XIAO: Okay.

DR. VENITZ: Our next presenter is Dr. William Smoyer. He is Vice President of Clinical and Translational Research at the Research Institute at Nationwide Children's Hospital in Columbus, Ohio. He is going to talk about hemodialysis and drug clearance.

Effect of Hemodialysis of Drug Clearance

DR. SMOYER: Good morning.

[Slide.]

I would like to thank the Committee for giving me the opportunity to speak to you all this morning. I would like to spend the next 15 minutes or so speaking about the impact of renal-replacement therapy on drug clearance.

[Slide.]

As most of you know, there has been a dramatic increase over the last ten or 15 years in the use of renal-replacement therapy. This includes intermittent therapies such as we have been talking about with hemodialysis but also a significant amount of increased usage of continuous therapy such as continuous renal-replacement therapy.

Importantly, there also has been a marked increase in the variety of renal-replacement therapies that have been used and I would like to run through just a few of these here. These include continuous veno-venous hemofiltration where solute clearance is primarily convective, continuous veno-venous hemodialysis where solute clearance is primarily diffusive, and continuous veno-venous hemodiafiltration which is a combination of these two forms of solute clearance. The last two are slow, low-efficiency dialysis and extended daily dialysis.

[Slide.]

So, importantly, each of these new forms of therapy requires new drug-dosing knowledge in order to optimize the pharmacotherapy associated with them. At this point, there are precious few data that are available on effective drug dosing with many of these newer forms or renal-replacement therapy.

So this has created a growing challenge for those of us that actually prescribe these medications with respect to pharmacotherapy and created dilemmas with regard to trying to maximize drug efficacy but also trying to minimize drug toxicity.

[Slide.]

So what I would like to do is just run through a few of what I see as some prominent trends in renal-replacement therapy in the U.S. with you all.

The first is that there has been a huge growth in the continuous forms of renal-replacement therapy and, although these data are now almost ten years old, as early as 1999, almost three-quarters of U.S. nephrologists were using continuous renal-replacement therapy in critically ill patients.

Some of the other key features of this is that these membranes are much more permeable than the hemodialysis membranes that we have used and tested in the past which result in altered drug-removal characteristics. So I think it is very important to point out that, when we look at drug removal with these newer forms of continuous renal-replacement therapy, they are, for sure, very different than drug removal with standard hemodialysis.

At this point, there really is no FDA guidance for drug manufacturers to evaluate drug removal during these continuous therapies. Similarly, there is not guidance that is currently in place for the device manufacturers to even

evaluate any drug-removal characteristics.

[Slide.]

Another trend is that there has been a clear move towards the use of higher volumes or higher doses of continuous renal-replacement therapy so, in my experience at the University of Michigan, in pediatrics for CRRT, our

of dialysate flow which correlates with a creatinine clearance of about 33.

When I first arrived at Michigan, the adult side was using 1 liter an hour standard for all size adult patients. They subsequently converted to 2 liters an hour which is much closer to what we had been using in pediatrics.

What is most important though is that there are now published data that have clarified that higher volumes of dialysate flow rates in continuous renal-replacement therapy, specifically 35 ml/k/hour has been associated with decreased mortality in critically ill patients.

There are currently some sepsis proposals for continuous renal-replacement therapies also that are recommending as much as 6 liters an hour of dialysate flow.

So this is 96 ml/min of creatinine clearance equivalent. In most of these presentations, there has been little to no discussion about drug removal in association with their efforts to try and manage the patient's sepsis.

Some other trends that I think are noteworthy are the increased use of high-permeability membranes. This is especially true in hemodialysis where there has been a change. These larger-pored membranes now are removing drugs that didn't used to be removed.

A good example of this is vancomycin. Vancomycin used to not be very significantly removed with old hemodialysis membranes. It is clearly removed with current hemodialysis membranes.

There also are a variety of non-renal indications for renal-replacement therapy that are increasingly being employed. It is being used for things such as inborn errors of metabolism, refractory fluid overload, congestive heart failure. An increasing number of intoxications are being managed with continuous renal-replacement therapy and even prophylactic removal of contrast dyes. These are all indications for people who don't have kidney failure that we are now dialyzing.

Another particularly relevant trend in renal-replacement therapy is that, in pediatrics, we are seeing a significant increase in the usage of all forms of renal-replacement therapy. This is in large part due to the fact that newer equipment has made it more feasible to do these forms of therapy in children that otherwise would have never had the opportunity to have those therapies. Also, there are improved techniques that have been developed for using them in even the smallest of children.

So I think it is essential to point out to the Committee that pediatric and neonatal renal-replacement therapy is dramatically different than adult renal-replacement therapy.

Perhaps a good example of this is that, if you were to compare the amount of blood involved in a dialysis circuit that is outside of the body compared to the amount of blood that is inside the body in a 3 kg child, you can see that it is a huge ratio. In fact, the volume for most adult circuits that we have to use is a third of the size of the patient's blood volume. So there is no way that that can't affect pharmacokinetics.

In contrast, in adults, it is considered trivial.

It is 100 cc's outside of their body. They have got a much larger intravascular blood volume.

Another relevant feature is that, for many of the smaller children, in order to initiate these therapies--in fact, every time we initiate these therapies, we have to prime the extracorporeal circuit, either with 5 percent albumin or blood.

Obviously, if you had drug concentrations that were present in the serum before you did that, they instantly get diluted.

[Slide.]

Yet another trend is the increased use of hybrid forms of renal-replacement therapy. To date, this has really been limited primarily to use in adults. I have already mentioned these slow, low-efficiency dialysis and extended daily dialysis.

So this basically involves using standard equipment and standard hemodialysis machines and running them more slowly for, let's say, 12 hours rather than running them at the more typical rates for three or four hours during the day. Obviously, this results in drug removal that is much different than what we are currently

aware of with regard to intermittent hemodialysis.

[Slide.]

So these trends together, in my opinion, have created a dilemma for us. It is clear, at this point, the that renal-replacement therapy technology has now surpassed the current guidance for drug dosing. With the increasingly common use of these newer forms of renal-replacement therapy, we now have huge knowledge deficits about how to use these drugs appropriately with these newer therapies.

An example of this is that we have estimated that CRRT drug-dosing studies have been conducted for something less than 20 percent of the drugs that we use in patients who require those therapies and are currently receiving them.

For slow low efficiency and extended daily dialysis, it is estimated that we have drug dosing and kinetic knowledge for less than 1 percent of that. So we also now appreciate pretty clearly that CRRT has markedly different effects on drug clearance compared to intermittent hemodialysis or even peritoneal dialysis.

So, as a practicing pediatric nephrologist, how am I to make informed decisions about how to answer the

questions of my colleagues in the critical-care unit who say that they want to put this patient on a therapy, what dose should I use.

I usually don't know. We make it up.

[Slide.]

The current guidance for pharmacokinetics in patients with impaired renal function recommends that, for drugs that are likely to be given in end-stage renal-disease patients who are treated with dialysis, a PK study is performed to look at the extent to which dialysis contributes to the elimination of the drug and the active metabolites with the primary questions being, should the dose be adjusted due to hemo and, if so, to what extent.

What I would like to do is spend the remainder of my time focusing on these two highlighted areas in the guidance here, end-stage renal disease and treated with dialysis.

[Slide.]

The first issue relates to end-stage renal disease. It is clear now that there are many and an increasing number of patients who are receiving renal-replacement therapy who don't have end-stage renal disease.

They actually have acute kidney injury. I think this came up in one of the earlier comments. Their kidney failure may be days or weeks old, not months or years old.

We recognize now that the drug pharmacokinetics are inherently different in this setting than in the setting of end-stage renal disease.

Dr. Pichette very nicely shared with us data showing that there are also significant differences in non-renal clearances between the normal state and chronic kidney disease or end-stage renal disease. But we also recognize that there are large differences in non-renal clearance in the setting of acute kidney injury compared to end-stage renal disease.

Probably the best examples of this are with vancomycin and Imipenem. So, together, these leave us with some key unanswered questions. They are, is studying clearance now only in the setting of end-stage renal disease really enough with the increasing usage of these therapies in other settings?

And, since these therapies are now widely used in acute kidney injury, should this also be a setting in which we should be collecting information.

[Slide.]

Ten to 15 years ago, the nature of dialysis delivery was very different than it is today. In the early 1990s, people were using primarily what we called low-flux membranes. Now, we are using high-flux or larger-pore membranes. Dialysis dose was oftentimes not quantitated in that setting whereas now it is quite clear among most treating nephrologists that we should be targeting a Kt/V of at least 1.2.

Comparatively, people were using membranes with smaller surface areas compared to what we use now and membranes that were not always biocompatible. Now we use membranes that are routinely considered quite biocompatible.

In addition to that, patients oftentimes that needed peritoneal dialysis would get continuous ambulatory peritoneal dialysis whereas both in adults and children now, peritoneal dialysis is almost exclusively done as continuous cycling peritoneal dialysis overnight.

So I think the important point here is that all of these changes in dialysis over the last ten or 15 years have resulted in things that cause increased clearance of drugs. Given that, even for drugs where we had previously

established guidelines, one has to question whether those previously recommended guidelines are still applicable.

[Slide.]

I would like to talk about a couple of issues also related to the verbiage of treated with dialysis. So what are the current trends in renal-replacement therapy?

Ten or 15 years ago, if an adult patient developed end-stage renal disease, he would be most likely to have gotten hemodialysis three times weekly in a dialysis unit. Now, that same patient may be likely to get assigned to nocturnal nightly hemodialysis at home, or nocturnal every other night hemodialysis at home.

Indeed, even the standard intermittent hemodialysis that we are now prescribing uses very different dialysate flows and very different dialyzers than we did ten or 15 years ago.

So the result of these changes is that drug-clearance rates now, for what we are currently doing, are not known and, therefore, we don't have guidelines for how to use doses currently with the therapies that are currently being employed.

[Slide.]

Another issue has to do with the treatment of acute kidney injury. So ten or 15 years ago, if a patient developed acute kidney injury and required hemodialysis in a critical-care unit, they would have received acute hemodialysis three times a week.

Today, we recognize that same patient would far more likely be treated with either continuous renal-replacement therapy or daily hemodialysis. Indeed, Shiffl, et al., has published a very nice paper demonstrating that daily hemodialysis decreases mortality compared to every-other-day hemodialysis.

Clark, et al., have published a series of calculations suggesting that, in order to maintain adequate clearance and metabolic control, that many patients would require daily rather than alternate-day dialysis. So, as is probably obviously, dosing of drugs, when people are receiving daily hemodialysis compared to every-other-day hemodialysis, is inherently going to be different.

As I have alluded to, we do not currently have guidance recommending collection of information in the setting of acute kidney injury.

[Slide.]

So another issue relates to recognition of the concept that now more than half of in-patient renal-replacement therapy is no longer hemodialysis. Instead, it is things like continuous renal-replacement therapy, the slow, low-efficiency dialysis or the extended daily dialysis.

Obviously, drug dosing for each of these therapies needs to be very different. We also recognize that CRRT is now clearly the most common form of renal-replacement therapy both in adult and also in pediatric intensive-care units around the country. We have very little data on how to dose drugs in CRRT and, as I have already alluded to, we currently have no recommendations in the guidance for collecting information to help us improve our ability to dose drugs in CRRT.

[Slide.]

So this knowledge gap that has been created by the advance of these technologies over the last ten or 15 years has led to some important patient safety concerns related to renal-replacement therapy as well.

I included this slide just to show you an example. This is a 3-kilogram, one-week-old, neonate who developed

acute kidney injury in the ICU in the first week of life and we got called to initiate continuous renal-replacement therapy on this child. You can see the dialysis lines here.

Clearly, this is a vulnerable patient population. But I would submit to you all that it is not just infants and neonates in this setting that are vulnerable. It is also older children and adults who are receiving continuous renal-replacement therapy because, although, as I have pointed out, we are using continuous forms of therapy more and more often, we don't have drug-dosing studies that are required.

Indeed, there is not an incentive for pharmaceutical manufacturers to actually perform the PK studies that could help educate us.

[Slide.]

So I have tried to point out what I see as the trends in renal-replacement therapy and some of the issues that are at hand. What I would like to do in my final minutes is request that the Committee consider making a few suggested changes to the guidance documents as we are considering updating the document.

With regard to hemodialysis, I would like to

recommend that all studies be done using a standardized dose of hemodialysis and the most accepted dose now is a Kt/V of urea of 1.2.

I would also like to recommend that dialyzers of a prescribed surface area and ultrafiltrate coefficient be used in all of the pharmacokinetics studies. Lastly, I also think that it is important that pediatric pharmacokinetic studies also be performed so that we can develop better pediatric drug-dosing information.

[Slide.]

With regard to continuous renal-replacement therapy, I would like to recommend that dosing guidance be developed for drugs that are likely to be used in the ICU setting, not necessarily all new drugs but drugs where we think that there is a reasonable likelihood that the patients, like the one that I showed you, would be needing those drugs.

For those patients, I would like to recommend that the dose of delivered CRRT for those studies should be set at what has now been proven to be an effective dose of 35 ml/kg/hour which is roughly equivalent to what we already

I would also like to recommend that these studies be performed using the most common hemodiafilters. The reason that I have worded it that way is because what was common when the guidance came out last is not what is common now. What the prescribing physicians need is information about what is currently being used on their patients.

Lastly, similar to hemodialysis, I would like to recommend that pediatric PK studies also be performed to better inform pediatric drug dosing.

[Slide.]

So, in summary, there has been a dramatic increase over the last ten or 15 years, not only in the use but also in the types of renal-replacement therapy that are being employed. This has resulted in huge knowledge deficits in the appropriate use of many drugs.

The FDA guidance, at this point, now, lags behind both the technology that we have available and also the current medical practice that is taking place. This has created for us concerns not only with regard to drug efficacy but also with regard to drug safety.

So, with that, I will close and I will be happy to answer any questions.

DR. VENITZ: Thank you, Dr. Smoyer.

Any quick questions? Dr. Lesko.

DR. LESKO: Thank you for the presentation. I like, towards the end, you try to give us some recommendations to sort of standardize these types of studies but my question relates to, in the hemo, the number of dialyzers that are out there that would have to be studied and, in the CRRT, the number of hemodiafilters. I don't know if these are tens or hundreds. How would we standardize that.

Then, secondly, I don't have a sense of the variability and the data you would get out of studies. As a result, what would be the number of patients that would have to be studied, given their variability and all the other things going on in the patients that would give data you would feel would be reliable.

DR. SMOYER: So this is where the rubber meets the road. This is the hard part. So I fully expect that the number of options for dialyzers--I mean, it already is greater than it was. It is likely to become greater. So, as I have thought it through, the best I think that we can do is try and identify the characteristics of those

membranes because the brand and the size may change, but the characteristics would be what is the membrane made of, what are its ultrafiltration coefficients, what dose would be used.

I think that, when you look at how you would develop data that then could be used by other people to make inferences about how that membrane might compare to the membrane that they have on their patient, I think that that, at least, would be a starting point for information for them to extrapolate.

I don't feel like it is feasible to try and cover a broad swath of all of the available dialyzers. But there are emerging data that are suggesting doses of dialysis and targets for clearance that I think are reasonable and could be extrapolatable to doing studies useful to people.

As far as the number of patients that would need to be studied, I can't answer that directly. But I would think that, if we knew the information about the characteristic of the membranes and the dose of therapy that would being applied, we could pick some reasonably small representative population of that because, again, for the continuous renal-replacement therapy, we are not talking

about improving the data. We don't have data.

DR. VENITZ: Let me just ask a follow-up question. How many of those studies would have to be PK studies in human subjects as opposed to in vitro studies where you can assess the dialyzer clearance, the removal.

DR. SMOYER: Another excellent question. So being able to do initial in vitro studies, I think, would be a much faster and cost-effective way to get a ballpark idea of what the renal clearance would be of a drug, if you will.

What it wouldn't and couldn't address is any of the things that Dr. Pichette mentioned which is all of the non-renal clearance. What I do think would be a very powerful practical advantage of using in vitro testing, however, would be that I think that it would make it far easier to convince institutional review boards, whose job it is to protect human subjects, that at least you have gotten some data that gives you an idea of the renal clearance of the drug.

You don't know for sure whether it would correlate completely with the total clearance in vivo, but I think it would be very reassuring to them that at least you had the right number of zeros in your estimate.

DR. SICA: You still have to convince them to get the blood from the blood bank which now requires IRB approval as well for that.

DR. SMOYER: Yes. Just for the record, we have to get blood from the blood bank every time we put a 3-kilo child on CRRT which happens every 72 hours. So they get exposed to--over a two-week treatment, they would get exposed to probably four or five blood transfusions just to allow us to do our therapy.

DR. SICA: Just one point; I think the CRRT, the issues--actually, you did a great job in discussing that. The blood-pressure issues become paramount in this in trying to interpret even the data because a significant number of people remain on pressers.

That is why CRRT is being done as opposed to conventional dialysis. So there are a lot of other determinants that fold over into this that create a horrible assortment of complexities, an inability to understand what to do with dosing. I would echo what you have said highly for the agency to think about us standardizing this with CRRT because we have no data right now.

DR. SMOYER: Let me just embellish that a little

bit. When I showed you the picture of that neonate, so I have taken care of dozens of neonates like that some of whom have passed away with no urine output on CRRT.

I really don't know whether an issue related to under- or over-dosing of some of the critical medications that were being used to support them might have been a contributing factor to why they did not survive. I literally don't know. We just don't talk about it usually.

DR. LESKO: Just one follow-up question. As we talk about the needed studies, we are thinking of premarketing studies predominantly, I guess, in our conversation. But are there any collaborative organizations that would be interested in doing these studies on drugs that are widely used in these patients such as National Kidney that could, perhaps, partner with FDA under, say, our Critical Path Initiative and form some sort of public/private partnership so that we are not strictly looking at companies.

Because a lot of old drugs are being utilized.

DR. SMOYER: Oh, yes.

DR. LESKO: It is going to be hard to go back and do these studies.

DR. SMOYER: Yes, yes.

DR. LESKO: But can we focus on these marketed drugs and somehow get some of these key studies done.

DR. SMOYER: I can assure you that all of the major nephrology organizations are supportive of this idea of gaining new knowledge about how to do it because, a few years ago, we spoke with the presidents of all of those organizations and addressed this issue with them.

They actually provided us with some letters of support of trying to pursue this initiative to gain more knowledge.

Now, that does not create an easy way to go to patients and begin to study them. There are interested parties. There are some clinical research centers around the country that have dialysis stations in the clinical research centers and large dialysis populations. But those will be doing them one at a time.

We have a consortium of pediatric nephrology programs that are very interested in things like this, but we would have to go back to each of the individual centers, get separate IRB approval to try and collect the information.

So the more you consider the logistics of collecting this information, the more appealing getting some initial in vitro data to at least have a ballpark idea becomes.

DR. VENITZ: Thank you.

Shiew-Mei?

DR. HUANG: For a premarket approval, would you prioritize to see maybe certain areas of therapeutics that you may want to as for CRRT study because you know we don't even have hemodialysis patients. So, if you go ahead and ask for CRRT, it is probably very difficult. But if there are priority areas, like in our decision tree, if this is the certain therapy area they use in the critical setting, you may want to consider this.

DR. SMOYER: Yes, sure. And there is a consortium of at least pediatric CRRT centers. There are about 13 centers that could get very interested in this. But we have collected a list of every drug that was prescribed in a Level 3 pediatric ICU over 12 months recently as part of putting together a drug-dosing book.

So I have a reasonable sense of the breadth of drugs that would be prescribed, at least in a pediatric ICU

setting. I am sure similar data would be obtainable from an ICU setting to kind of know which ones you would most like to target.

DR. VENITZ: Dr. Xiao.

DR. XIAO: Two questions. One question is regarding the hemodialysis part. You mentioned it should be conducted in pediatric patients. Okay, so--

DR. SMOYER: I am a little partial.

DR. XIAO: The reason is because, in the peritoneal dialysis patients are very rare in the elder but they are very common in children, especially younger children, peritoneal dialysis. So I am wondering if we should only focus on hemodialysis is not to ignore some populations. That is one question.

DR. SMOYER: No doubt that if you focused only on hemodialysis, you would miss out on the entire other population of CRRT and peritoneal dialysis. Even in pediatrics, though, there is a trend away from peritoneal dialysis toward hemodialysis dialysis as we see more problems with membrane failure and also noncompliance and things along those lines.

So the hemodialysis population, if you chose not

to focus on that, they would get excluded. But they are a shrinking portion of the entire population--not to be ignored, but just to be clear about that.

DR. XIAO: My second question is there are at least modalities mortalities in the CRRT, like CVVH, CVVHD, CVVHDF, this concept. Each modality has different drug clearance.

DR. SMOYER: Absolutely.

DR. XIAO: Or even one modality. Patients may have different conditions like different blood flow, different dialysis protein from infusion flow. But this can also affect drug clearance.

DR. SMOYER: Absolutely.

DR. XIAO: So which modality would we use?

DR. SMOYER: This relates back to Dr. Lesko's question as well. I think that, at this point, even if you chose dialysate flow and one form of those four variations of continuous renal replacement therapy, that would be infinitely better than the data that we have now.

I mean, we had previously thought that probably using 2 liters an hour of dialysate flow and using continuous veno-venous hemodialysis, which is one of the

more widely used ones, would be reasonable.

But, clearly, it is just not going to be feasible to study every variation. But I do think that it is important that we recognize what is happening in the clinical practice, how complicated it is to try and address some of these issues.

DR. XIAO: But for a dialyzer, you can use the coefficient of different materials and people can get this data to extrapolate, explore to other conditions. But, for the CVVH, CVVHD, it is a totally different treatment modality. So the drug is totally different. You cannot use the CVVHDF to get CVVHD results, or get CVVH results.

So my question is which modality are we recommending?

DR. SMOYER: Again, if forced to choose one of the four or five, I would probably recommend CVVHD so that there is continuous veno-venous hemodialysis. There are a fair number of programs that do CVVH, the convective clearance alone, though.

So there is not one--you are not going to study one population and make it widely extrapolatable. But, again, what I am hoping for is that we at least choose one

and collect some data so that people have something from which to extrapolate.

DR. VENITZ: Dr. Mueller.

DR. MUELLER: It would seem--it is true that convective and diffusive clearance is different. But, if you looked at a program that had, say, 2 liters of dialysate flow and then convective clearance appropriate to maintain fluid balance, you would essentially be doing a CVVHDF. Clearance values out of CVVHDF with contemporary membranes, at those flow rates and at contemporary blood-flow rates are close enough to CVVH, pure CVVH, or CVVHD for most drugs that I think that would be sufficient, personally.

Probably even using just one kind of membrane would probably be sufficient as well for the vast majority of drugs. But it would seem to me, to answer Dr. Lesko's question, if you have got a drug in a premarketing situation that is expected to be used in an ICU setting, so something that is for sepsis or something for ventilator-associated pneumonia or something along these lines, why wouldn't you do a study in CRRT when that is, in the United States, the vast--at least half, and probably more than half, of the renal-replacement therapy that is given.

To me, that is where I would start with premarket-type drugs. For postmarket-type drugs, it is easy enough to look in the ICU, what are the commonly used drugs, and make an educated guess as to what might be removed and make a list.

Some of these drugs have already been studied because they have been on the market so long. And I think we could make a pretty short list pretty fast as to what needed to be studied.

DR. VENITZ: Okay. Thank you, Dr. Smoyer.

Let's break. We are way behind. Let's break until 10:45.

[Break.]

Open Public Hearing

DR. VENITZ: As we are reconvening the meeting, the first and the last question, do we have anybody in the audience that wants to present as part of the Open Hearing?

Going once, going twice. Okay. So we have nobody to present which helps us to catch up with our timing.

Then our next order of business is a presentation from Dr. John Wagner on behalf of PhRMA. He is Executive Director of Clinical Pharmacology at Merck. He is going to

tell us about evaluating pharmaceutics in patients with impaired renal function.

PhRMA Perspective

DR. WAGNER: Thanks, and thanks to the Committee.

[Slide.]

First I want to give a disclaimer that this is not the PhRMA perspective. There was not the requisite amount of time, which takes a long time, to get a consensus PhRMA view. I think many of you recognize that. So this is an individual PhRMA company, Merck, perspective and, hopefully, still useful to folks.

[Slide.]

What I decided to do was, hopefully for the usefulness of the Committee, to talk about a general approach to renal insufficiency clinical studies in drug development and to specifically use sitagliptin to illustrate our approach.

I also wanted to touch on the severe renal insufficiency and end-state renal disease on hemodialysis with a couple of comparisons and a not-exhaustive survey of Merck data and then talk a little bit about renal insufficiency and metabolism and end with some of the

limitations that we have.

[Slide.]

So, in terms of the approach, it is not surprisingly guided by the 1998 Guidance. And we try to distinguish whether we are going to need to do a full study or a limited study. And, as we heard, a full study done on drugs that are renally excreted, a limited study--at Merck, we tend to study most of our drugs, even if they are 100 percent metabolized, with a limited study.

In our limited study, we typically use severe versus concurrent healthy controls. We would like to use end-stage renal disease on hemodialysis as a probe as to whether there is an effect of renal insufficiency on a metabolized drug. Our full studies are just per the guidance.

What we have been doing more recently is moving to an adaptive design where we test severe renal-insufficiency patients versus healthy controls. If there is a clinically important effect, then we would move that into a full study in a Part 2. We found that to be more efficient in addressing these questions in a timely way.

[Slide.]

So some of the other considerations are dose, whether to use the clinical dose or to down-dose and how far to down-dose. We try to make all of these studies hypothesis-driven so that the effect of renal insufficiency, we would ask the question where that is contained in a clinically important interval.

In the sitagliptin case that I will tell you about, we had a very wide therapeutic index and so we accepted a two-fold change in drug concentrations as being clinically unimportant for that particular drug.

We do contemplate whether to do single or multiple-dose studies but, typically, we would start with a single-dose study even if we ultimately wanted to go to multiple doses.

We have also struggled with concurrent versus historical controls. We are moving towards just using both in our final analyses.

Timing is very important. Timing for these studies depends on what the question is and when that data is needed, if we want to include renal-insufficient patients in Phase III and we suspect that there may be some need for dose adjustment, the study needs to be done relatively

early.

Mind you, in the U.S., the lead time for these studies is pretty long. For the CROs and other clinical sites that we typically use, the lead time can be about a year when, putting in, essentially, a reservation for a renal-insufficiency patient.

That is actually driven by an increase in paucity of severely renally-insufficient patients willing to do clinical trials. That also reflects on a growing openness to other geographical locations in emerging markets where medical practice is a little bit different. In the U.S., as we heard, there are more patients on dialysis and less patients who are in several renal insufficiency and not on dialysis. So there are other geographic locations where medical practice is a little bit different and we have gone to some of those for these types of studies.

We also consider whether pharmacodynamics is going to be an important part of one of these clinical studies. We will include that if it is well justified.

[Slide.]

So I just wanted to walk you through a typical study. This was actually a very nice study and came out

very well. This is for sitagliptin. We know that sitagliptin is largely not metabolized and 70 to 80 percent of its clearance is renal.

So we elected to do, of course, a full study with these 24-hour creatinine-clearance values from the 1998 Guidance. I would point out that the variability here is an important consideration in our clinical studies and, in fact, we will do two 24-hour creatinine clearances and then a third tie-breaker if there is a question.

2

then 31, we would do a third creatinine clearance and, if the average and both of the other two of the three measurements were below 30, we would consider that a severely renally-insufficient patient.

We down-dosed slightly from the clinical dose of 100 mg for sitagliptin. We measured just sitagliptin. There are no important circulating metabolites. And we measured both urine and plasma.

For the end-stage renal disease on hemodialysis, we were interested in understanding the effects of dialysis a little bit better.

[Slide.]

So we did two periods in these patients on dialysis, one where we dosed sitagliptin 48 hours prior to their normally scheduled hemodialysis session and then the same patients were also dosed 4 hours prior to their normally scheduled hemodialysis session so that we could collect the sitagliptin levels in both of those circumstances.

[Slide.]

This is just a plot of the pharmacokinetic profiles in this experiment. These are healthy volunteers with normal creatinine clearance. You can see that mean plasma creatinine clearance increases with increasing degrees of renal insufficiency and that half-life also increases.

[Slide.]

Here we plot creatinine clearance versus the dose-adjusted AUC of sitagliptin and also include additional healthy subject historical data. You could see a very nice predictable relationship between creatinine clearance and the AUC.

The dotted lines here are what we considered the clinically important bounds so that, if you scrutinize this,

you could see that patients with mild renal insufficiency are largely included in that two-found bound leading, as I will suggest later, to a lack of dose adjustment for sitagliptin in the label.

However, patients with moderate or severe renal insufficiency would require a dose adjustment and then that was recommended.

[Slide.]

As you would expect, sitagliptin renal clearance is proportional to creatinine clearance, just a confirmatory plot.

[Slide.]

Then this is the pharmacokinetic profiles resulting from the dialysis experiments. You can see that hemodialysis removes sitagliptin really only to a modest extent comparing the 48-hour versus the 4-hour, and timing of hemodialysis in end-stage renal-disease patients has just a modest effect on the plasma-concentration profile. So, therefore, sitagliptin can be administered without respect to the timing of hemodialysis.

[Slide.]

A couple of other observations. The dialysis

here, dialysis clearance, was about 241 ml/min. The fraction of dose that was excreted unchanged during dialysis was about 13 percent for 4 hours and 3.5 percent for 48 hours. We also measured in vitro plasma protein binding that was not significantly changed in any of the groups. Interior varied from about 33 percent bound to 37 percent bound.

[Slide.]

So we concluded from this experiment that patients with mild renal insufficiency would not require a dose adjustment. Patients with moderate renal insufficiency would require half the usual clinical dose--in this case, 50 mg--and patients with severe renal insufficiency or end-stage renal disease would require a quarter of the dose, or 25 mg.

I would also point out that this study drove the design of a Phase III study in diabetic patients with renal insufficiency where sparse sampling was obtained and confirmed these pharmacokinetic findings but, more importantly, confirmed the safety and tolerability in those patients.

I would also comment that we, as a company,

struggled with the labeling here for physicians. As we think about other calculations of renal function, like MDRD, we would just caution that we really do have to think about the label which I am sure the Committee is doing.

For sitagliptin, we ended up having both serum-creatinine value cutoffs which are admittedly imperfect but then also referred the physician to the Clin-Pharm Section where the Cockcroft-Gault equation was quoted if physicians wanted to use that as a calculation.

I could envision that that MDRD might be a little bit more complicated for many physicians to do in their office and that is just something for your consideration.

[Slide.]

I wanted to turn to sort of our experience between severely affected renally-insufficient patients and patients with end-stage renal disease on hemodialysis.

[Slide.]

This is the same data from the sitagliptin experiment that I showed you where severe renal insufficiency and end-stage renal disease on dialysis, at least at 48 hours, are very similar.

[Slide.]

I also wanted to show you another very different drug. Sitagliptin has a large volume of distribution of about 200 liters and is not so protein-bound. This is Drug A, unpublished data, was highly protein-bound with a smaller volume of distribution and was largely metabolized.

The experiment that we did was just severe renal-insufficiency patients, patients in dialysis, and then compared to historical controls.

[Slide.]

That experiment is shown here. All of the pharmacokinetic profiles are largely overlapping and you can see that it is really similar between patients with severe renal insufficiency and patients undergoing dialysis as well as healthy controls. Drug A is really not dialyzed to any significant degree and also there was some increase in Drug A concentrations during dialysis suggesting possibly a hemo-concentration effect.

I also to just briefly mention our very limited experience with renal insufficiency and metabolism. For Drug B, which is in development at Merck, again, this drug is largely metabolized. It is almost exclusively metabolized by 3A4. Its renal secretion is very small.

Here we did matched controls versus severely affected renally-insufficient patients and measured Drug B concentrations for up to 360 hours.

You can see here these are the individual AUC and Cmax values for the severely affected patients versus the concurrent controls. You can see that this would look like a relatively substantial effect of severe renal insufficiency on this particular drug. However, we were perplexed by this data given our complete lack of effect in hepatic insufficiency. And looking at some of the historical controls, when you overlay that, it was not so different, leaving us still perplexed about this group of matched controls.

Because of the ambiguity here, we have gone back to do a full renal-insufficiency study on this particular drug. And I don't have the answer here. This is really just cautionary, that it can be somewhat more complex than we would like it to be.

[Slide.]

I would like to just end with some of the limitations that we observe in these studies. There are limited numbers in these studies and sometimes that does

cause an issue with the interpretation.

The timing of these studies has to be carefully considered. There is a long lead time. It is very important to do appropriate planning and understand exactly why and when this data is needed. If these studies are rushed, it can take quite a long time because you end up being last in the queue of a particular research center and they will recruit patients as they can. But it can take quite a long time.

Recruitment is an issue in the U.S., particularly of severe renal-insufficiency patients. Recruitment of patients with end-stage renal disease on dialysis is not a particular issue in terms of recruitment.

We clearly recognize that assessment of safety and tolerability in these single-dose studies is limited. So, in the cases where we are going to go on to, like with sitagliptin, to where renal insufficiency is a real issue in the diabetic population. We are going to have to do later-stage clinical studies in order to adequately assess both efficacy and safety and tolerability.

The single dose versus multiple dose is a related issue and we still would propose that single dose is

appropriate. In addition, special populations are also an issue here. We do have drugs in our pipeline that we really can only dose to diabetic patients because of hypoglycemia. That would restrict our renal-insufficiency study to diabetic patients. Of course, there are quite a few diabetic patients who develop renal insufficiency so that is not an undue problem.

A larger problem is cancer drugs, cytotoxic drugs, that we would not want to dose in non-cancer patients. This can be a real issue in assessing renal or hepatic insufficiency although we do get help from NCI-sponsored groups in those sorts of situations.

So that is all I had for you today.

DR. VENITZ: Thank you, Dr. Wagner. Any questions? Dr. Lertora.

DR. LERTORA: Thank you very much for that very interesting presentation. I have a question regarding hemodialysis and the recovery of drug in hemodialysis fluid that I am sure you have thought about. Perhaps the previous presenters may help answer this question, but if you have a drug with a very large volume of distribution, a priori, you might anticipate that hemodialysis would not be a

significant factor in terms of removal.

But, even if you have drugs with a smaller volume of distribution, and you consider hemodialysis-induced hemodynamic changes that may impact on intercompartmental clearance, you may actually be sequestering drug in a peripheral tissue compartment during the hemodialysis procedure and then not recover all the drug that you could have recovered if that change in intercompartmental clearance hadn't taken place.

So this has been reported in terms of experimental studies in hemodialysis years ago. I just wonder how that would factor in our discussions today regarding the impact of hemodialysis on recovery of drug and hemodialysis clearance of drugs.

DR. VENITZ: Do you want to take a shot at that, John?

DR. WAGNER: I will take the first shot there. So, clearly, that is an issue in the design of these clinical studies. For the sitagliptin example I showed you, we carefully considered that and collected pre- and post-dialyzer concentrations.

As we would have expected for a high-volume

distribution drug like sitagliptin, there was not much effect. In other situations, we would need to study empirically.

DR. VENITZ: We have Dr. Lesko next.

DR. LESKO: John, I was interested in Drug B and maybe you don't have data on that yet from a full renal-impaired study, but may you have some prior experiment to address my question.

On Drug A, you had a typical, I would say, curvelinear relationship between creatinine clearance and area under the curve, or drug clearance. And that could either be estimated creatinine clearance or measured. Is the shape of that curve similar or different when you study drugs that have non-renal clearance pathways?

DR. WAGNER: In this case, the shapes of the curve were very similar between the patients with normal creatinine clearance and those with impaired creatinine clearance. That was another reason why we were sort of scratching our heads about this, this particular case.

This was the only example of a case where we were even suspecting that there is an effect of renal insufficiency on a metabolized drug in my experience. I

can't say that I did a completely exhaustive examination of all the data, but within the last ten years or so at Merck, I did take a pretty good look.

DR. VENITZ: Dr. Huang.

DR. HUANG: My question related to your study design when you compare the sitagliptin, although it actually confirmed what you said, the drug was a large-volume distribution so whether the study was done on or off dialysis makes no difference.

But you did the study, it was 48 hours. So, practically--is that practically doable if patients are on intermittent hemodialysis Monday, Wednesday, Friday. So you will have to study Saturday and Sunday. Or, if you have to study another day, would that offset the patient's schedule and is that ethical? Would it pass the IRB?

DR. WAGNER: So there is quite a bit of clinical research that goes on on Saturday and Sunday. In fact, that is exactly what we did was the drug was dosed on a Saturday and then the dialysis was on a Monday.

DR. HUANG: If you have a much longer half-life drug?

DR. WAGNER: In cases of longer half-life drugs,

this experiment is still worth doing. But you are going to have to accept that there may be--if you are going to see a change in dialysis, with dialysis, that you are going to see that when the dialysis is instituted.

It does lead to one of the issues in interpretation that I was referring to.

DR. SICA: Juan, just a comment for you. It is less the blood-pressure change because, if you do the study correctly, then you don't have the blood-pressure drop. But it is actually the ultrafiltration amount that occurs. So, typically, you don't want to pull more than 3 to 4 kilo during a run. That may have more of an effect on compartmentalization than blood pressure. Blood pressure we can typically control there.

So precautions to the patient coming into the study are not to overdo it lest that will complicate interpretation.

DR. VENITZ: I have a couple of questions for you. You mentioned that for all metabolized, or highly metabolized, drugs, at Merck you are doing a reduced PK study; is that right?

DR. WAGNER: I didn't say all.

DR. VENITZ: Okay. For most.

DR. WAGNER: But for most.

DR. VENITZ: The rationale is that you are worried about the metabolite or the rationale is that you think the metabolism might be affected by renal disease?

DR. WAGNER: Actually, it is a very practical rationale for most of the drugs that we are working on in diabetes or atherosclerosis or what have you. There are a significant number of patients who are renally impaired and this study will find its way into the label and is very reassuring to physicians, even if there is not a theoretic possibility that there would be an alteration.

DR. VENITZ: So the likelihood of being used in that population is what drives that.

DR. WAGNER: Yes.

DR. VENITZ: Have you ever done a limited study and then followed up with a full study and found contradictory results?

DR. WAGNER: So, we are only in that situation right now.

DR. VENITZ: With Drug B.

DR. WAGNER: Yes; with Drug B. So I will have to

report back to you at some point.

DR. VENITZ: Then I have questions about the sitagliptin, the kinetics that you reported. You stratified on ml/min per body surface area; right?

DR. WAGNER: Yes.

DR. VENITZ: But, on your slide, you are presenting creatinine clearance as ml/min. Is that coincidence?

DR. WAGNER: No; that is an error.

DR. VENITZ: So this should be per 1.73.

DR. WAGNER: Yes.

DR. VENITZ: The Drug A, you mentioned, is highly plasma-protein bound, when you did the limited study. And you didn't find any difference in exposures. What about unbound drug? Did you look at unbound drug or plasma-protein binding?

DR. WAGNER: In that case, we didn't look at unbound drug. That drug was very--it had greater than 99.9 percent protein binding. And the experiment is technically challenging to do the protein binding, and we did not do it in those samples.

DR. VENITZ: So you could have changes in the

unbound exposures that you wouldn't be able to see.

DR. WAGNER: It is possible.

DR. VENITZ: Okay. Any other specific questions for--Dr. Xiao?

DR. XIAO: In our concept paper, we proposed to use the high-flux dialysis modality. So I am just wondering what kind of dialysis do you in your drug testing? Is it high-flux or routine dialysis, because the high-flux compared to traditional dialysis causes different membrane, different clearance. It is difficult to extrapolate it from the routine dialysis to the high-flux dialysis.

Right now, in the U.S., maybe 50--more than 70, I think--hospitals use the high-flux dialysis. So I am just wondering what is your opinion on what kind of dialysis you use.

DR. WAGNER: I would be personally a fan of making this a uniform requirement. This is not something that we have addressed in our protocols. We don't mandate that a unit uses high-flux dialysis. And, in short, I don't know the answer to that question, especially some of these studies are a little bit older, in the early 2000s.

In short, I don't know the answer to that

question, especially, you know, some of these studies are a little bit older, in the early 2000s.

DR. VENITZ: Dr. Barrett.

DR. BARRETT: John, just to put you on the spot a little bit, in light of Dr. Smoyer's presentation when he talked about in particular the increase in the renal-replacement therapy.

Your comments about doing these studies are reflective somewhat of the therapeutic area that your portfolio tends to be in. Can you see any obstacle for moving in that direction with renal-replacement therapy from the standpoint of Merck or perhaps is this something that you would bring to the PhRMA Committee as well?

DR. WAGNER: Again, I am speaking, you know, essentially for myself and for Merck. The way we have been looking at it is that the population of patients on renal-replacement therapy, at least in the U.S., is large and growing. The population that is accessible for doing severe renal-insufficiency studies is small and diminishing.

I would favor studying the patients with end-stage renal disease on dialysis for that reason alone. It is really likely going to become more representative of the

patient population that we really want to give the instructions to, in the limited study design.

DR. SICA: John, why do you normalize creatinine clearance to body-surface area? Isn't the creatinine clearance an absolute term measured in the patient? It is a number and then we normalize it. But, for that patient, their GFR, the surrogate, is that number not normalized body-surface area. I have always found that curious on why we always take that approach.

DR. WAGNER: I have to confess I never thought about that. I had always thought it about it as just a simple standardarization.

DR. SICA: But, for the individual patient, this is no standardization needed.

DR. WAGNER: Yes; that's true. That's a good point.

DR. SICA: Across the population. So it is very easy to fudge the numbers by body-surface area. You get someone to fit an entrance criteria, because you would normalize the number, but that is not their GFR. It is something much different. So that is a systematic error in all the data that is really done when we are trying to

create this GFR or creatinine clearance versus AUC or whatever measure of drug elimination we are using--or drug buildup.

DR. VENITZ: That is why I asked you about the units because I am fully agreeing with Dom. What is really important for a given patient is not body-surface area. It is the total creatinine clearance. That is presumably what drives renal elimination. Or maybe even non-renal elimination.

DR. WAGNER: Yes.

DR. SICA: In fact, if you do the numbers correctly, probably up to 30 percent of the variance in the values we see for AUC and similar PK parameters probably relates to the normalization number. When you look at the spread for the entrance criteria into the studies based on BMIs, and a BMI range of 18 to 35 is often permissible, you have got a doubling of your BMI right there.

So that is at least a halving with the reciprocal on what is going to occur with creatinine clearance so that is a major imputed or brought-in parameter change that we don't need. I would advise the agency to think differently about standardization for the individual patients.

For groups--

DR. WAGNER: That is an excellent point. The only thing I would add, in addition to that, although I don't remember what the individual inclusion criteria were for BMI in these particular studies, but even when they are wide enough to something like 35, typically, these patients have lower BMIs.

DR. SICA: I don't know anymore. I mean, most of our population is diabetic, as you know.

DR. WAGNER: That's true.

DR. SICA: 50 percent of all new ACRD is diabetic. Their corpulent BMIs are clearly about 30 so they meet obesity Category 1 in most cases. We don't see many lean people who develop ESRD. I think those around the table who deal with them would probably agree.

DR. VENITZ: Dr. Kearns.

DR. KEARNS: I think the issue of normalizing or not is a good argument that you could make for adults. But, in pediatrics, to be able to normalize it, whether it is 1.73--it is the only way we can compare normal to abnormal renal function in a child who maybe has a serum creatinine of 0.2 instead of 1.0. So there is some utility to doing

that.

DR. SICA: But what I said, Greg, was a measured clearance. A measured clearance is a fixed number. That is the GFR for the child if you were able to measure the clearance and trusted the measured value.

But if it is a calculated value from a serum creatinine, then that changes. But it even becomes more complex when you normalize and MDRD-derived GFR value by body-surface area because you have two different variables now at play defining a potentially imported error into the calculation.

DR. KEARNS: I don't think we would ever use it. The MDRD method is not for kids.

DR. SICA: Your circumstances are very much more select to what goes on for interpreting the numbers. So I would say I probably was not inferring that it related to everything you do or what you think about everyday in that regard.

DR. KEARNS: I just want to be clear. I found myself at a moment and I just needed to get out of it.

DR. VENITZ: Just to follow up, if you report the MDRD estimated creatinine clearance--right now, it is

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clearance for that patient. You have to multiply that by the BSA to get the particular clearance that drives whatever kinetic changes there may or may not be.

Even though the stratification and everything that I have seen, at least in the documents here, always look at body-surface area corrected. That, to me, is not relevant for a given patient. That is why I am in full agreement with Dom. And we even work at the same institution; right?

DR. SICA: Do I know you? I have seen you before.

DR. VENITZ: Okay. Any further questions for John before we start a general discussion?

Then thank you, John.

Advisory Committee Discussion And Recommendations

DR. VENITZ: So now we are asked to review the questions that Shiew-Mei posed. So maybe we can put them back up again. We have two, and this is one of them, questions that we have to vote on, Question 1 and Question 3. So let's first have a discussion, or any further discussion.

So here is the question that we are asked to respond to. Does the Committee agree that renal impairment

can affect metabolism or transport of drugs that are substrates of metabolizing enzymes and transporters?

Is there any discussion? Is everybody ready for the vote? Then I would ask everyone that is in favor, meaning answering yes, please raise your hand and keep them up until you mention your name to Mimi and she can collect that information.

[Show of hands.]

DR. VENITZ: Starting with Bruce.

DR. MUELLER: Yes. Bruce Mueller.

DR. KEARNS: Greg Kearns. Yes.

MR. GOOZNER: Merrill Goozner. Yes.

DR. MAGER: Don Mager. Yes.

DR. LERTORA: Juan Lertora. Yes.

DR. GIACOMINI: Kathy Giacomini. Yes.

DR. FLOCKHART: Dave Flockhart. Yes.

DR. CALDWELL: Michael Caldwell. Yes.

DR. VENITZ: Jürgen Venitz. Yes.

DR. MORRIS: Marilyn Morris. Yes.

DR. SICA: Dominic Sica. Yes.

DR. BARRETT: Jeff Barrett. Yes.

DR. CAPPARELLI: Edmund Capparelli. Yes.

DR. TOPP: Elizabeth Topp. Yes.

DR. PHAN: We have 14 yes, 0 no, 0 abstain.

DR. VENITZ: That is a quick one.

Question No. 2. This is not a voting question. Does the Committee agree with the recommended methods of determining renal function in the proposed stratification of patients based on renal function? Can we maybe put the proposed stratification back on? It is one of Shiew-Mei's slides. It is Slide No. 16.

So this is the new stratification, right, that you want us to discuss. So what you see here is the current guidance based on estimated creatinine clearance, Cockcroft-Gault and the new based on the MDRD.

Dr. Giacomini.

DR. GIACOMINI: Shiew-Mei, I thought that you said you wanted to define three renal-function areas. You were going to greater than 60 and something to 60 or this?

DR. HUANG: Yes. Dr. Xiao can comment further. We said there is a provision. If you know that the drug is not a narrow therapeutic-range drug--that is, you already have the information by that time--then you could do a three-group study.

DR. GIACOMINI: Okay.

DR. VENITZ: Any further discussion?

DR. SICA: Just one caveat for you. The 15 to 30, which is now designated Stage 4 CKD through NKF criteria, nobody really cares about the 30. Everyone cares about the 15. If you go to Stage 5, everyone cares about 15 or below. So I would just say, when we utilize boundaries, we arbitrarily determine that there is some change that occurs in the functionality of drug elimination or clearance that is benchmarked by this and it isn't.

So, if you really try to emphasize in the document, you want to emphasize that 15 or below as much as possible. But, in most of the groups, if you went through all the PK papers in the literature, you would find that very few are 15 or below. But, if the criteria is 30 or below, then everybody clusters in 15 to 30, because those are the easy ones to recruit.

So, therefore, the true data you need is often absent. I think the recommendations should take into account every effort to bring those patients in to have an appropriate regression line and not a regression line that stops at 20, which it often does in these studies.

DR. VENITZ: I would also make the observation that this stratification, as far as I see it, is primarily to enroll patients and to provide for equal distribution in those different categories. So, when you ultimately proceed to the analysis, you do regression.

I would also say that, in my interactions with some of my colleagues, lots of times this is perceived as a way of analyzing the data. In other words, we have to demonstrate differences or similarities between those different groups using some sort of an ANOVA.

It may be helpful in the guidance to point out that this is just to allow equal distribution among those ranges so you can do a better job doing your regression in your ultimate creatinine clearance, drug clearance, area, whatever relationship.

Dr. Lertora.

DR. LESKO: Could you please remind us the 1998 Guidance, was that also normalized to body-surface area?

DR. VENITZ: No; it was not. It is ml/min

DR. SICA: I thought it was normalized.

DR. VENITZ: It is ml/min. The old guidance?

DR. XIAO: In CG equation, originally, they don't

body-surface area correction, when it is in the CG equation.

DR. VENITZ: The current guidance uses Cockcroft-Gault and does not normalize based on the BSA.

DR. XIAO: It does.

DR. VENITZ: It does?

DR. SICA: Yes; it does.

DR. GIACOMINI: Not in the guidance.

DR. SICA: Because every study done by industry now normalized as per guidelines.

DR. VENITZ: But, if I read the guidance, I didn't see that in the guidance. Maybe they do it, but it is not in the guidance.

DR. LESKO: It is in the text. It is not in the table in the guidance. I don't know if it is in the text or in the footnote.

DR. VENITZ: Any other questions or comments about the second question that deals with the stratification? Yes.

DR. MAYER: This is a continuous variable, is there an intent in having a certain number of patients in each of these categories or is it, like--because some of these may be hard to find within a certain range. I would

hate to have to hold off in analyzing your data until you get that sixth person in a group, for example.

DR. HUANG: Before the '98 Guidance, we don't always have more than two or four. But, after the '98 Guidance, even if we didn't specifically say how many, we, most of the time, get six patients per group.

DR. VENITZ: Any other comments? Okay. Moving right along, let's look at Question No. 3. That is another vote of a question.

DR. HUANG: So I guess no more discussion on MDRD; right? Okay.

DR. VENITZ: Dr. Giacomini?

DR. GIACOMINI: Can you go back through? So when you say methods, as part of Question 2--

DR. HUANG: Methods is the MDRD.

DR. GIACOMINI: That is the MDRD method.

DR. HUANG: Yes.

DR. GIACOMINI: Which you are now going to switch to, with that recommendation that Cockcroft and Gault be used as some kind of a--

DR. HUANG: A reference.

DR. GIACOMINI: A reference.

DR. HUANG: Just to connect to the other vast database.

DR. GIACOMINI: Again, I would like to encourage measurement of creatinine clearance in those patients.

DR. SICA: I don't think we go to the label with both because the spread could be substantial, particularly when you look at your crossover group stratifications. 15 to 30, between MDRD and Cockcroft-Gault, you may have a cohort of six with an MDRD and a cohort of six, same patients, with Cockcroft-Gault that fall outside the boundaries on your average value of what you have.

So I think we are going to have to really think about how we word that and not just presume you want to do it with both, because our cut criteria in the label is either exposure, an AUC of 2, 2-and-a-half, or 3 with the drug with a narrow therapeutic index.

So I think we have got to be really careful about this lest we get to the point where the label is uninterpretable because we don't know which one to use.

DR. HUANG: Our recommendation is to use the MDRD but also include the information on creatinine clearance for us to look at. When you label, we only use the MDRD. That

is the current concept.

DR. SICA: Okay.

DR. VENITZ: Dr. Kearns.

DR. KEARNS: Promise me that you will put something in here about the right way to do this for children. Okay?

DR. HUANG: We did put in something there.

DR. KEARNS: Not the MDRD--even the horrible Schwartz equation. But just something so that people don't go about it--seriously, we see protocols not infrequently that come from a sponsor for children that have Cockcroft and Gault in it and we have to change it and educate people. So not everybody knows it.

DR. HUANG: Okay. So please let us know which that you would recommend.

DR. KEARNS: I will.

DR. VENITZ: Dr. Lesko.

DR. LESKO: I have a pragmatic question, maybe a dumb question. But when people use MDRD in practice, the equation isn't exactly straightforward. It has exponents and what have you and probably most people would calculate it wrong. How do people actually do that in clinical

practice and, if it had to use that in the label, how would practitioners do it in bedside?

DR. VENITZ: If you have Internet access, there is a calculation on the Internet. That is what I do.

DR. KEARNS: Calculator on the Internet. But if I don't have access to a computer and what have you, I can do Cockcroft-Gault on a napkin. But the other one, I am not so sure.

DR. CAPPARELLI: It is more complicated than calculating BSA. The discussion we had yesterday about the sacrifice for ease of use, to me, it is problematic outside of on-the-fly estimation that needs to be done. So I do agree it is an issue that needs to be addressed.

DR. SICA: Larry, it is less an issue than you think. Right now, a National Kidney Disease Education Program has the professed goal to have all GFRs below 60 with an MDRD calculated and put out in all the labs. So, in Richmond, you can't get a GFR below 60--you will know, automatically. It is done for you by the lab.

So the plan is to import that for everything below 60 so you get a reported EGFR to come out in the laboratory work. So, if you have the creatinine, you are going to get

that. That is going to be standardized nationally.

DR. CAPPARELLI: Do you actually have all the demographic information?

DR. SICA: Well, they have got the information. It is necessary in all the reference labs. We have been doing it for two years in Richmond.

DR. CAPPARELLI: I am just thinking across the board, in dealing in other settings, it may not be as easy to--

DR. SICA: I mean, the plan was to originally get a standardized serum-creatinine measurement so the MDRD was valid along those lines. Once we got the standardized serum creatinine in most of all the labs in the country right now, then the next step was to do this where you had the calculated formula built in to what occurs.

So, if it ain't where you are at the moment, it is coming. So it is going to play out nationally. That is part of the initiative for CKD. That is why we have the National Kidney Disease Education Program is to highlight the frequency with which we have it. Unless you report it, you don't know that it is there most of the time, particularly for the 40 to 60 GFRs.

So there is a light at the end of the tunnel.

DR. VENITZ: Any further discussion of Question No. 2? Okay, then let's move to Question No. 3. Question No. 2 is not a voting question, is it? Oh; I'm sorry. I misunderstood. All right. So they want us to vote on this question.

Does the Committee agree with the recommended methods of determining renal function and the proposed stratification based on renal function. Any further discussion before I call for the vote?

Everybody that is in agreement, meaning would answer yes to that question, please raise your hand.

[Show of hands.]

DR. VENITZ: We play the same game. We start with Dr. Mueller.

DR. MUELLER: Bruce Mueller. Yes.

DR. KEARNS: Greg Kearns. Yes, with the provisions for small people.

MR. GOOZNER: Merrill Goozner. Yes.

DR. MAGER: Don Mager. Yes.

DR. LESKO: Juan Lertora. Yes.

DR. GIACOMINI: Kathy Giacomini. Yes.

DR. FLOCKHART: Dave Flockhart. Yes.

DR. CALDWELL: Michael Caldwell. Yes.

DR. VENITZ: Jürgen Venitz. Yes.

DR. MORRIS: Marilyn Morris. Yes.

DR. SICA: Dominic Sica. Yes.

DR. BARRETT: Jeff Barrett. Yes.

DR. CAPPARELLI: Edmund Capparelli. Yes.

DR. TOPP: Elizabeth Topp. Yes.

DR. PHAN: We have 14 yes, 0 no, 0 abstain.

DR. VENITZ: And now Question No. 3 which is not a voting question; right? So this is where Shiew-Mei wants us to look over the decision tree and provide her with any comments, any feedback.

Dr. Mueller.

DR. MUELLER: I have a couple of comments. One of them echoes what Dr. Smoyer presented and that is that there needs to be information about the hemodialysis session that is given. In this case, when I look at hemodialysis data from manufacturers, I can't tell very much about the dialysis session and the guidance didn't recommend anything.

But I think the best accepted hemodialysis practice is to have a Kt/V of at least 1.2 during the

session, and that is Kt/V urea. It would seem to me that that is what a patient is getting.

It doesn't do very much good for us to a pharmacokinetic study in a patient with Blood Flow X and Dialysate Flow Y and have the same flow rates in a 200-kg subject and in a 50-kg subject because clearances and drug removal for that patient are quite different.

So, by normalizing the Kt/V, although not perfect, will better reflect what is the clinical practice today. So my recommendation would be to do that.

In terms of dialyzers, which was a question that came up before, I would probably recommend to use a high-flux hemodialyzer. And I want to make it clear that that is different than high-flux hemodialysis. But, using a high-permeability membrane, I think, is done in the majority of places already and I think that is going to grow.

It would seem to me that using a high-permeability dialyzer and the Kt/V of at least 1.2 would be the way to go and probably would be the best way to standardize drug clearance.

The second comment I would make relates to the CRRT. I have to kind of echo what I said before and that is

it would seem to me that, if we have a drug that is likely to be used in the Intensive Care Unit, then it would seem to me that that ought to be in the decision tree.

A company knows if that is the population they are looking for and it could be part of the situation. In fact, many drugs would never be used in ESRD patients with chronic hemodialysis because they are critically ill because that is the kind of drug that it is. It would seem to me that that sort of situation, that sort of known-in-advance clinical scenario could be in this decision tree and it would help answer a lot of questions.

In terms of whether this would be a full PK study, which I think would be very difficult to do versus using in vitro, I think, in the guidance, there is some information about how to do an vitro CRT study and I wouldn't do it the way it is written here. I think there are a lot of problems with doing it that way and I would be happy to work with the group to come up with a better way to do that.

DR. VENITZ: Dr. Mager.

DR. MAGER: I had a question concerning the negative and positive boxes on the bottom left-hand part of the figure. So, in the determinants of a positive, you have

the magnitude of PK which rings true. But you have exposed the response relationships there as well.

I just throw out the idea of exposure-response relationships supported by pharmacometrics as a determinant of the negative. So you have the case where a statistically significant change in PK would be a flag for positive. But if you had a clinically meaningful biomarker and safety intolerability data supported by pharmacometrics modeling and simulation, and you could show that, given high inter-subject variability and pharmacodynamics coupled with a wide therapeutic window, that the further studies would not be necessary.

DR. VENITZ: Dr. Xiao.

DR. XIAO: I have comments about Dr. Mueller's comments. In the clinical practice, if you go to the National Kidney Foundation Guidelines, for dialysis patients, you have to reach a Kt/V of at least 1.2. That is the regular. If you do not reach this, that means the patient did not get adequate treatment.

So that is the regular in clinical practice so that is why we did not add it in the paper. Because, if it is less than 1.2, that means the patient did not get enough

treatment. That we consider malpractice. So that is why we did not add the 1.2.

Sometimes, you need to 1.4 based on the patient's condition. But 1.2 is the minimal point.

DR. MUELLER: And your statement is correct except that 1.2 wasn't known the last time we did that guidance. That is sort of a new-found thing. And so, to state it overtly, because the current guidelines don't say. The dialysis flow-rate could be whatever. The blood-flow rate could be whatever using whatever filter. There is no guidance to industry of what it should be.

I agree with you. It should be what the clinical practice is which is not less than 1.2 and it would be very easy to state. And, in fact, it is measured in clinical practice anyway because you have to demonstrate that you are doing this if you are going to be reimbursed anyway, so why not put it in the guidance and state it overtly.

DR. VENITZ: Dr. Giacomini.

DR. GIACOMINI: Just a comment on the full PK study. Are you requiring plasma-protein binding in that, because I think getting the real exposure of the unbound concentration might be important in this group?

DR. VENITZ: Dr. Sica.

DR. SICA: Shiew-Mei, how do you plan to deal with metabolites as to the PK study, full or otherwise, active or inactive? Is there a plan yet? Or does that have to be thought about a little bit further? You know, an inactive metabolite that has an AUC of 3 at a CDK level of 5, you don't know the concentration side-effect relationship going into this. Is that going to necessitate a full profiling to determine the GFR change in the inactive metabolite? Or food for thought.

DR. LESKO: Yes; it is food for thought. But it would seem you are focused primarily on the active species, whether it be parent or metabolite. My guess is, just thinking about these studies, that is all measured routinely in the PK study so that you can at least look at that data and make some judgment calls on it.

DR. SICA: All right. But if you have got a PK--if you do a limited study and the inactive metabolite is up, not a small number of people feel compelled, sometimes almost prodded, into doing--this is a single-dose study, for example--that you may have to look more carefully at that metabolite characteristics because of the unknown that is

there.

DR. LESKO: So the risk is that it would have some activity that we don't know about?

DR. SICA: Well, I said a concentration side effect relationship, so activity in that capacity. But, somehow, that we need to be certain we have offered a comment on that because, with many of the drugs we use, as you know, it is the metabolite. But I am thinking broadly on the metabolite basis.

DR. VENITZ: Dr. Huang.

DR. HUANG: This is a general issue that is covered in several guidances, in pharmacokinetic basic guidance and drug interactions and we do encourage the measurement. We did, in one of the guidances--we actually talk about the product of percent contribution and percent activity, although we also mention the drug may not be pharmacologically active but contributed to toxicity.

So we are getting variable results. Some studies, you do measure metabolites. And duloxetine, that is one of the drugs and you actually have the information to see a much higher degree of elevation in renal impairment and we put that into the labeling. It is also associated with our

warning, especially in severe renal groups, when the data are available. At times, we don't have the metabolite data to make a similar statement.

So, right now, it is variable but the recommendation to measure metabolites is generally stated. I wonder if you are recommending that we specifically say it in this guidance more than the others.

DR. SICA: If you do a limited study just with CKD5 and you have a metabolite perturbation that is--let's say the AUC is three-fold increased. The question arises, what does the person do with that. Economics say, leave it be because it is inactive pharmacologically although, if you have got either a narrow therapeutic window, even with a small contribution, or the possibility of unknown side effects in CKD which happen all the time, and they are peculiar side effects oftentimes, then you are trying to figure out what guidance to give people to go forward in exploring that.

I am going to suggest that you look more carefully at the full study if there is even the slightest hint that a metabolite may have some role in side-effect generation in the people.

Remember, what we also don't do in this population, we never have, we never quantify the side effects in the individual patient leading up to the study. If you do a careful profiling, many of the side effects we unfairly attribute to the medicines are just background side effects that are just there because, at the Stage 5 CKD, they are feeling like a dog.

There are just a lot of symptoms and it is just not carefully done, although I would submit part of this is just doing this carefully because it is not just PK, now. It is also the pharmacodynamics and it is also the side-effect profile, and we don't have enough information, even with sparse sampling with PK data, we don't have enough information about side effects with these people.

So I think the better you could get a side-effect profile, the better served we are for safety for that. So, even n equals 6 in CKD5 is worthy of a careful side-effect profile both pre and post.

DR. VENITZ: Do you want to respond to this?

DR. HUANG: No; I just never responded to Dr. Mager's comment. When we mentioned the negative-positive, again in several of our guidances about whether the results

are negative-positive really depends on exposure response.

Just like drug interaction, we are assuming the systemic exposure response remains constant, remains the same, in renally impaired patients. So there is no change in PD based on change in exposure.

So we give that allowance to the sponsor. You have seen an example from Merck. They actually set up an exposure response in, say, 50 to 200 percent. That is the no-effect boundary. Therefore, you can use that to guide whether it is important for the parent compound. Obviously, when you have to consider metabolites, well, whether you need to do a full PK. That is our proposal.

DR. VENITZ: I have a couple of comments, then. The first one is on, on one of your slides, Shiew-Mei, you said, renal studies need to be conducted for drugs that are metabolized, transported, in addition to drugs that are renally eliminated. So, what that means is that they have to be conducted for all drugs.

I want us to realize that, with the one exception that you mentioned--the gasses; right? So we are now saying that we think all drugs, regardless of their elimination route, should be studied in one form or another, in renally

impaired patients.

Having said that, I would like for the FDA to then use their discretion to use the last statement here and decide about how likely those drugs are being used in a renal population and not just make this an academic exercise but actually use triaging. Because, otherwise, we are really saying everything but a gas has to be studied in renal-dysfunction patients.

Number two, about the specific decision tree, as you know, I am opposed to the reduced PK study design for various reasons. A practical reason is I don't think you can ever rule out that there may not be a drug interaction, even if you match, because you are not going to be able to have a matched control that are taking the same concurrent medications as for the Stage 4, Stage 5, renally impaired patient.

On the kinetic side, I am always worried, and that is one of the reasons why I asked Dr. Wagner about it, about changes in total exposure that might hide a true change in the kinetics in the unbound fraction because what you might have in that population is a change in the free fraction, so they have more free drug. They also have a reduced

clearance, but the two effects offset each other and, as a net result, you are not seeing any difference in the total exposures.

You can never rule that out. If you had done a full study, which, to me, is the gold standard and should be the gold standard--the only gold standard, that is--you would see that because you would see something like an inverted U shape.

And there is some data in the literature that that has been shown for drugs that are highly plasma-protein bound and metabolized. So, to me, the reduced design can give you both a false positive and the false negative and we just don't know.

Can I just make one more comment and then I will let you respond. What I haven't seen--I think it is a little bit discussed in the guidance but I haven't seen that on the decision tree is the role of pop-PK screening. For some drugs, at least, there is enough of a bend with an inclusion-exclusion criteria in Phase II and Phase II studies that you actually do have patients all the way down to 30 ml/min creatinine clearance.

And you can use that at least in lieu of a reduced

PK study to see whether there are any gross changes and then decide whether you need to do a full study or not.

DR. HUANG: Actually, that was my proposal to modify this decision tree. If you look at our drug-interaction decision tree, there is always something after the negative. We would say, further exploration in population kinetics. So, if it is negative, I would consider to look at population pharmacokinetics.

We do say something in the concept paper but not exactly as described. But I would say anytime that we say negative that we say consider--

DR. VENITZ: But I am basically proposing to replace what reads right now, reduce PK study in ESRD patients by population PK screen if appropriate. Lots of times, it is not appropriate because the inclusion criteria are too narrow so we don't have the moderate and severely impaired. But it may well be the case, and that should be taken advantage of short of requiring to do what I think is a nonsensical study, the reduced-design study.

Dr. Barrett.

DR. BARRETT: I would like to follow up on that point as well. This is an earlier comment I was basically

asking along these lines, too, and you had brought up, Shiew-Mei, about the concept of the boundary conditions here. This is where the pop-PK kind of screen can facilitate as well because you leak into some of these renally impaired populations.

It is also why we are asking about the historical data. Have you seen instances, are there generalizations you can make from the historical data on types of agents where you feel comfortable maybe reducing the designs.

So, even though I think it is good to have this proposal, kind of state these new criteria to align with new guidelines, I think it is still reasonable to take a look at some of the data and see how that would play out if you rebend the data into these new categories.

A couple of other comments. When you go down to the label piece, here, I think it would be helpful to actually work through the kind of information you want to appear and then label this kind of a decision tree.

In the past, there has been this kind of confidence-interval approach and I am wondering, now that you have increased the number of strata, is that still reasonable or is there something more informative that we

can do in terms of reporting guidance, particularly dosing guidance, in these populations.

Another more practical issue, in terms of applying the MDRD formula, how do you apply mixed races to this equation when you have black as a category? So I think there are some practical issues of how to apply that.

DR. VENITZ: Dr. Lesko.

DR. LESKO: I just want to get back to your interpretation of the decision tree. It sort of splits out as chronically administrated on the left and volatile inhalation on the right. But it also includes drugs that are intended for single-time use. So it isn't necessarily renal studies required for all drugs.

You would have to ask the question, if it is single dose, what would be a single-dose drug, maybe something used intermittently for some particular symptom. You may not want to necessarily do a renal study in that case.

DR. VENITZ: But even for chronically used drugs, I mean, you said, unlikely to be used in renal-impaired patients. And, again, I can't give you specific examples where I can tell you it is unlikely to be used. All I am

saying, use that on your end, at your discretion, because, otherwise, we have now expanded the pool of drugs to be studied by two-fold at least.

DR. LESKO: I just want to clarify the other recommendation or comment that you had on the part that is circled in red. So, you are suggesting, rather than do a reduced PK study as an alternative, do a sparse-sampling strategy that would get the same answer.

DR. VENITZ: If you loosen up your inclusion-exclusion criteria and allow for that range of renal function which may or may not be possible. If not, I would suggest to do a full study as opposed to a reduced study. I, personally, don't see any use in doing a reduced study.

DR. LESKO: Even if you have no effect.

DR. VENITZ: Correct; because, as I said, there are examples where you have no effect if you look at the extreme ends, the healthy volunteers and the severely renally impaired. But, in between, you have a change because plasma-protein binding effects and clearance effects offset each other and what we call right now the worst-case scenario. It may not be the worst-case scenario.

DR. MAYER: I think the survey you had had very

few companies performing that reduced survey and we wouldn't run that reduced PK study. We would just run the full study to begin with.

DR. VENITZ: Dr. Morris.

DR. MORRIS: I just had a comment with regard to dialyzer clearance. I would think that in silico predictions of clearance might be useful, certainly based on the membrane properties, flow, physical, chemical characteristics of the drug, you should be able to predict, to some extent at least, clearance of drugs by various dialyzers in order to get some sort of initial estimate.

I don't know if you considered in silico approaches in order to get initial estimates of clearance.

DR. HUANG: The only thing we have in the current concept paper is exclusion. When you have a very large volume distribution, you don't think it is going to work and that is the end of it. Similar to our drug interaction, you have certain criteria--you don't think there is an interaction. Stop. But, if there is an interaction, we need some confirmation. So, right now, we are using a similar approach.

If you think it will be clear, then we want to

know how much. It is difficult for me to conceive that you can actually say 40 percent, 50 percent, or 60 percent to that precise--

DR. MORRIS: And it might be useful as an initial approach to try to determine the extent of clearance or amount cleared.

The second question I had was with regards to No. 2 in yellow. It says, during dialysis, unless large volume distribution. You give an example in the concept paper of a compound but you don't really define large volume distribution. Maybe that would be useful.

DR. HUANG: Well, we did give an example if, for example, the dialyzer clearance. The one we put in the concept paper is 1.2 L/hr. But then we heard there is 2, 4, or I don't know if the highest is 6 L/hr. So I guess, depending on the dialyzer, the efficiency, then it really depends on how big a serum volume distribution can do a calculation based on what we have put into the concept paper and to estimate.

So it depends on the dialyzer. A large volume distribution for 120 ml/min that we put in the guidance, may not be applicable to a faster one. But that is just the

beginning. But I am sure that we will get feedback on how exactly to discuss for different dialyzers.

DR. MORRIS: It is just, it says to include, unless volume distribution.

DR. HUANG: So we will refer back to the text.

DR. VENITZ: Dr. Lertora.

DR. LESKO: Again, with regard to renal-replacement therapy, and I think Dr. Morris' suggestion is a very interesting one, our nephrology colleagues earlier had recommended that we get in vitro data with a variety of hemodialyzers, membranes and so forth.

Maybe that could be coupled with a modeling exercise that could be helpful in terms of having some tool for predicting behavior of certain methods, if you will.

DR. HUANG: Do you feel that we need to give more detailed recommendation than what we already have. We say the in vitro data--this is about CRRT--in or clearance rate calculating from the drug concentration of both arterial site and venous site between the filter, plus the available data from intermittent hemodialysis, should attempt to provide some appropriate dosing recommendation in these patients.

That is what we have right now in the concept paper. So we did mention in vitro.

DR. LESKO: Right. But, again, this would be an additional exploratory test, if you will, that may lead to useful data if you have that in vitro data being generated and you were to approach it as Dr. Morris suggested. That is just a thought.

DR. VENITZ: Dr. Mueller.

DR. MUELLER: Just to follow up on that. I don't want to mix up CRRT with intermittent hemodialysis because I think we might be doing that right now. I actually didn't have a problem. I don't know--Dom, maybe I would like to hear what you say--but I thought the writing in the proposed document of suggesting, in the hemodialysis situation, what should be studied and what shouldn't be, was relatively clear.

I think, if the volume distribution is 360 liters, as an example you gave, it is not likely to be important. It is not going to be removed by dialysis.

Walking over to CRRT, where I think the in vitro data probably need to be used because it is going to be very hard to get in vivo data at all, I wouldn't, as I said

earlier, do this pre- and post-filter.

Just to give you an example, if you were running CVVH, a convective therapy, it is possible that the post-filter drug concentration is higher than the pre-filter concentration because you are removing all the liquid but not the drug. So that is not the way--as I said before, this is not the way to do it. And I would be happy to work with you on that because I think it would be very confusing.

But, in terms of hemodialysis, I don't even think we need in vitro data. In silico is a neat idea, but I think you kind of did in silico, but you did it in your head, that these are probably reasonable parameters to determine whether something is ruled by intermittent hemodialysis to an important degree or not.

DR. VENITZ: Any other comments or any more questions from our FDA colleagues about the decision tree, or have we belabored the point?

Okay, then. I think we have already answered most of Question No. 4. This is specific, now, to the dialysis; what studies does the Committee recommend for drugs intended for chronic administration. Any additional comments other than what has already been talked about.

Dom?

DR. SICA: I think you have got it covered. You have got an acute study. You have got the dialysis-interval study which will get you typically about--at max, about 56 hours is the most you can do if you did a Monday, Wednesday, Friday run, you wouldn't dose them until Saturday morning. Then you could run them on the last shift on Monday so that gets you about 60 hours tops with that.

I would echo that, in the background, you should have some consideration for peritoneal dialysis that should have something which usually can be done as a small study. The data tends to be much more consistent with PD than with hemo because the conditions are more easily controlled there.

But I think, with those two groupings--and then the only thing that comes up is what do you do with drugs that are therapeutic in this population because the pharmacodynamics have not been looked at by anybody, anywhere, anyplace, anytime.

I think trying to understand the target population for therapy could end up being quite useful. Diabetic agents, for example, you should be able to do that and,

therefore, the chronicity of therapy can be evaluated in a manner speaking with a patient because you are long term on a therapy.

So I would suggest that we just contemplate, maybe not act on, the issue of actual therapy choice that you would use in a patient as to how to go a little bit longer with what you are doing in surveillance with the patient. That is more safety than anything, I would imagine, because I don't think the PK is going to change very much.

We don't see much deviation in PK whether you do a dialysis session or whether you do between-dialysis sessions. Those are fairly consistent when you do replicate kind of surveys with PK sampling.

DR. VENITZ: Any other comments? It looks like we are, then, ready for the wrap-up, Dr. Lesko.

Summary of Recommendations

DR. LESKO: Thank you, Dr. Venitz. I sometimes feel like these meetings is a little bit like running a marathon. But I think the meeting over the last two days was enjoyable and highly intellectual. We had some significant insights into the topic of our clinical pharmacogenetics proposed guidance, our pediatric area which

is on the path to a guidance for pediatric clinical pharmacology studies and, today, on the renal impairment guidance. So each of those discussions were highly important to us as we continue to refine our thinking into what exactly we want to say.

All I can say is I kind of look forward to those draft guidances if they come out before our next meeting and hopefully will capture a lot of the insights that you provided us during the discussion.

I think our discussion of the non-small-cell lung cancer has caused us to pause a bit on this particular project. I think we realize that the model that we discussed needs a lot more work. It was limited by the data that we had, so I think we need to go back and incorporate a lot more information into the model to make it a little more selective and a little more applicable.

So we are going to be looking at the possibilities of incorporating, to the extent we can get it, dose information, exposure information. There are a lot of other covariates that we haven't thought a lot about, the genetic characteristics in non-small-cell. There are gender issues. There are racial, ethnic issues.

I think we really need to go back and look at the cofactors and try to improve on that model and see what our next steps are really going to be.

So we have a debrief meeting tomorrow on the advisory Committee at 3 o'clock. We will be discussing a lot of the input that you provided us.

So, in closing, if I get through this with my sore throat, I am going to say thank you to all the Committee members and the guests that participated the last two days, the FDA, non-FDA, presenters and people sitting here at the table. It was really worthwhile for us and I hope you enjoyed it as well from a scientific, clinical, intellectual standpoint.

Again, I want to extend thanks to the people that have been major in putting the advisory Committee together, Mini Phan at my left here, thank you, and Peter Lee, who was to my right over here, carried a really big workload because, as you know, the rules and what have you around these committees has changed over the last couple of months, and our group isn't the most cooperative in meeting deadlines so we make more work for people than they probably need.

So thank you very much. And I will just wish you all a safe journey home and look forward to seeing you at another meeting.

DR. VENITZ: Thank you, Larry. Without any further ado, the meeting is adjourned and have a safe trip home.

[Whereupon, at 12:05 p.m, the meeting was adjourned.]