

1 number of weight metrics. Then whichever one fit best I
2 would use and then proceed to looking at what an age
3 effect, in the absence of a weight effect, would be to see
4 if I can describe one, and if so, what it is. That's my
5 intent here.

6 The reason why I did this in this way is to try
7 and not have the effect of age confounded by weight and the
8 only weight metric I had, which I couldn't pull out in any
9 other way, was kilograms.

10 The path, in addition to what I've just
11 indicated for the models that we would consider -- and this
12 is speculative. It will be driven by data, but this is
13 sort of how I see it going and thought it would be useful
14 to share.

15 First, we would consider adding exponentials if
16 the data supported it. You've seen a two-exponential fit,
17 and as Dr. Sheiner said, it's effectively both descriptions
18 of weight. But the idea is if we should discover that at
19 early ages there appears to be a unique phase of the curves
20 -- it doesn't occur at later ages -- and is not as simple
21 as a single exponential fit, then we would consider adding
22 additional exponentials, a structural model, if you would,
23 of more than one term.

24 One thing also I haven't shown here is an
25 offset for the age effect. That is, you might not expect

1 | that the age effect would be 0 at birth. Whatever
2 | processes are occurring, maturation may begin -- almost
3 | certainly did begin -- in utero. So you might want to add
4 | a term that would give an offset for the age effect.
5 | Again, this is speculative, but not based upon a real data
6 | set that I'm currently evaluating.

7 | Finally, we would begin to look at more
8 | physiologic covariates. Can you enter covariates such as
9 | the percent excreted unchanged, the Km for a given enzyme,
10 | the Km ratios across the enzymes for which metabolism of
11 | the drug is responsible?

12 | Finally, the approach I've shown is very
13 | empirical. Whether or not it will be successful is a
14 | question, and if it were unsuccessful, the next step would
15 | be to consider models which are more mechanistic.

16 | The first mechanistic model perhaps to be
17 | considered would be one that is less than a full-blown
18 | PD/PK model but which does incorporate what I'm calling
19 | process constants, such as GFR, such as Km and the percent
20 | non-renal eliminated.

21 | Finally, if even such mechanistic models were
22 | not successful, you might have to go into more of a full-
23 | blown physiologically based pharmacokinetic model. The
24 | difficulty with that is clear. Usually it's difficult to
25 | obtain data to support such a physiology-based model.

1 Would anyone like to tell me if they think this
2 is reasonable?

3 DR. VENITZ: Thank you, Gene.

4 DR. DERENDORF: I have a question for
5 clarification. Are these all lumped together, hepatically
6 cleared drugs, renally cleared drugs, high extraction, low
7 extraction, no difference?

8 DR. WILLIAMS: Yes. The initial cut would be
9 the raw data is age versus clearance independent of the
10 physiologic mechanism by which drug is excreted or
11 eliminated.

12 DR. DERENDORF: Well, then I would not agree
13 with the first question that it's logical because I would
14 expect there to be major differences depending on the
15 mechanism of clearance. Obviously, for a renally cleared
16 drug, the enzymes don't matter, and for high extraction
17 drugs, the intrinsic clearance would matter, and so on. So
18 I think to break it down into several subgroups would make
19 a lot of sense.

20 DR. WILLIAMS: You might expect that as the
21 physiology differs, so will the relationship between
22 clearance and age. But I guess it's dependent upon a few
23 elements. One is to what extent is each one of those
24 different elements not a function of allometry. In other
25 words, if the enzyme maturation and, say, GFR are both

1 | linear functions of weight, then you might expect that this
2 | approach would work.

3 | Now, the clear difficulty is at early ages,
4 | there's a whole literature, which many of the members of
5 | this committee have helped develop, that speaks to the fact
6 | that that is sometimes or perhaps oftentimes not the case.
7 | So the question is perhaps, how much data do I have that
8 | can address that? Specifically, do I have a lot of data at
9 | early ages or how much does it vary?

10 | Would you agree that --

11 | DR. DERENDORF: I'm not an expert, but if I
12 | recall correctly, glomerular filtration rate in a 2-year-
13 | old is almost like an adult. Right? There's no
14 | difference. Whereas, clearly the number shows that for a
15 | 2-year-old the clearance per body weight is almost twice as
16 | high. So there are differences depending on the route of
17 | elimination, clearly, because you wouldn't expect a
18 | difference for a renally cleared drug.

19 | DR. LEE: Can I add to that? What we're
20 | planning to do is look at different drug classes. For
21 | example, we will look at a drug class which is purely
22 | renally cleared and then try to see what's the relationship
23 | between clearance and age. Then we will look at a bunch of
24 | drugs, for example, 3A4, purely 3A4, and then see how it's
25 | going to change in our clearance versus age. So that will

1 probably address your question. And we know from the
2 literature that the maturation of different enzymes are
3 very different. I mean, 2D6 may be fast and 3A4 may be
4 slower. This is what we planned. We want to look at
5 different drug classes and build a model perhaps about one
6 drug class at a time, and then finally we have an
7 individual model. Then we will look at a drug that has a
8 combined pathway, maybe a drug with 20 percent 3A4, 40
9 percent 2D6, and see if the model can actually predict the
10 age effect.

11 DR. SADEE: Do you consider changes between
12 males and females and the various sexual developments and
13 so on? If you talk about maturation of enzymes, which
14 sounds a little fuzzy of a term, but males and females are
15 probably very different, but that may also depend on the
16 age. I don't know.

17 DR. KEARNS: Actually with respect to drug
18 metabolism, they're not very different at all. There are a
19 few examples of substrates for P450s that during
20 adolescence differ a bit and it probably has to do with the
21 things that make for differences in linear growth more than
22 sexual maturation. But for the most part, it's pretty
23 boring, boys and girls, before puberty.

24 DR. SHEINER: If you go back to that picture,
25 the one with the graph that we had the problem with, if I

1 | just connected the dots, I'd have a function defined by
 2 | line segments of that y axis value, the relative clearance,
 3 | versus age. And everybody would be completely clear that I
 4 | had totally explained all the data with my function, and
 5 | consequently there's no way to partition out the effect of
 6 | age from the effect of something else in your case that is
 7 | a function of age, which is weight. So the fact that you
 8 | could partition out, means you made some kind of very
 9 | powerful assumption that allowed you to take this function
 10 | of the x axis and see it as a separate contributor to this
 11 | curve which is practically connecting the dots. So that's
 12 | the point I'm making.

13 | It's nice that you started with this one
 14 | because here we all know there's only one variable age. We
 15 | don't know anything about weight, not the real weight. So
 16 | you've got perfect what's called multi-colinearity or
 17 | you've got a perfect problem that the one substitutes for
 18 | the other. The value from your table can be translated
 19 | back exactly into the ages and the other way around.

20 | So this is what's called, you know, an ill-
 21 | posed inverse problem or an unidentifiable model. It
 22 | depends on what field you're in. And the only way you can
 23 | get something out of those -- and I'm going to get to the
 24 | key question here in a minute.

25 | But the only way you can get something out of

1 | those, if you're trying to learn about these different
2 | effects, is you have to make some very powerful
3 | assumptions, some assumption that allows you to separate.
4 | Here, the assumption you made is the exponentiality.

5 | So I could say, if I didn't know anything about
6 | this, if you have a solid basis in physics for that
7 | exponential equation, something at the level of theory
8 | that's as powerful as physics, that says each of these has
9 | to influence and the only way it can influence the spread
10 | of these points is through a rising exponential, then I'll
11 | believe that what you sort out of the two effects is right
12 | because that's the key piece of information that you've
13 | added that you told me essentially everybody knows this is
14 | true. But if you say, well, I just -- the exponential
15 | because it kind of went up and then it went over, you know,
16 | then there's no reason to believe you've got it sorted out
17 | right now.

18 | I don't want to criticize this picture because
19 | you were clear this was an example, but you're going to
20 | have a similar problem with the real data. That is to say,
21 | there's going to be very high correlation between age and
22 | weight. So you got an almost ill-posed problem. You got
23 | an almost unidentifiable model.

24 | So if your goal is to sort out the independent
25 | effects of things we can measure like size -- even that's a

1 surrogate for something else -- and what we will all agree
2 is an unknown age-related something called maturation or
3 something like that that we don't measure when we measure
4 renal function, that we don't measure when we measure these
5 other things, if your idea is to sort that out and then
6 look at the shape of that thing, we're going to have a lot
7 of trouble believing it even when you're not as bad a
8 situation as this because of that high colinearity.

9 So I told you I'd get to the question. So my
10 question is, what's the question? What do you really want
11 to learn? If you want a predictive equation, you could do
12 anything. I'm not being facetious. If you want a
13 predictive equation and you're not going to interfere with
14 the system, you're not going to deliberately change
15 people's ages or weights or whatever, you can just let it
16 come as it falls, and you find some general predictive
17 equation for clearance of all drugs as a function of a few
18 easily measurable things, that would be completely valid as
19 long as you don't go in and mess up the system, even though
20 it doesn't give you an understanding necessarily of what
21 the causes are.

22 But on the other hand, if you say no, I want a
23 predictive equation for a whole new drug, then you're
24 interfering because you're not sampling from the same
25 world.

1 So I guess my question is, what's your
2 question?

3 DR. WILLIAMS: First of all, I would say if it
4 does turn out as you're saying and you do have this high
5 colinearity and this difficulty, it seems to me that would
6 be good news because it means that you have the ability to
7 describe the relationship between the ratio and the age as
8 only a function of weight. If the data is well described
9 by small or perhaps a single parameter, that would be
10 fantastic.

11 But to get to your later question, perhaps you
12 can educate me some more. It's not so clear to me if you
13 had the situation that you're defining where you did have
14 this high amount of colinearity and you then parsed out
15 your drugs as a function of all of the things that you can
16 look at, metabolic route, percent renally eliminated
17 unchanged, et cetera, and you found that you could not
18 identify covariates which interfered with that
19 relationship, then wouldn't it be legitimate to extend it
20 to the new drug?

21 DR. SHEINER: That would certainly be an
22 empirical basis on which you would guess that a new one
23 would look just like the other ones because you had a whole
24 bunch that all looked the same and you hadn't chosen them
25 for that purpose. I agree it wouldn't be a mechanistic

1 basis. That's why I said sort of a whole new drug class.
2 Somebody might say, sure, you know, you've been right 85
3 times out of 90 so far, but you've never looked at one like
4 this before. So that's the problem. That's what I'm
5 saying.

6 I agree with you, it's good news if they all
7 look the same because it gives you more faith that the new
8 one, even though we know it's a little bit different, will
9 also look the same. But that's just counting how many
10 times have I been right out of how many times I've tried.

11 So is that your goal?

12 DR. WILLIAMS: Yes, that would be the goal.

13 I'm new to this area, but from my read of the
14 literature, I think it's unlikely that we would see that at
15 young ages. Now, the question is the quality of my data.
16 Do I have a lot of data at young ages? Because I would
17 expect that that's where they will separate from a simple
18 function of weight.

19 DR. JUSKO: Don't you at each age have data
20 from many children where there's a distribution of weights
21 at each age?

22 DR. WILLIAMS: Yes.

23 DR. JUSKO: So if you do have that, then you
24 have the ability to discern the separate effects of age and
25 weight. So I don't understand Lew's --

1 DR. WILLIAMS: Yes. Our data set will be an
2 improvement of that. But if the colinearity is -- if
3 they're very highly correlated --

4 DR. JUSKO: Certainly they're highly
5 correlated, but there are factors in addition to age that
6 control weight that you would be able to discern through
7 this kind of analysis.

8 What do you select as the upper limit in age or
9 weight to reach the maximum? Because for many
10 physiological functions, the graph will look like this for
11 a certain age range, but reach a maximum at about 18, and
12 then as we all know, we steadily deteriorate until we reach
13 some lower level.

14 (Laughter.)

15 DR. JUSKO: So a more insightful empirical
16 function may be more of a U-shaped type of --

17 DR. WILLIAMS: I didn't grapple with that here
18 obviously. What I did is I just fixed it to 1. But yes,
19 it's a question. I guess what I would do is I would try
20 and look at as great a wealth of adult data as I can to see
21 if there is an age relationship, and if so, where's the
22 maximum I suppose. But you're right. That's something
23 that will have to be worked through.

24 DR. SHEINER: Bill, I think you're right except
25 I'm not sure what you get out -- so if I've got different

1 | ages and I've got a lot of weights at different ages, then
2 | it's quite true that if I want to say there is some sort of
3 | sum of these two effects that's operating, then if it were
4 | only weight, then I should be able to go across age and
5 | find it at the same weight. Everybody had the same
6 | clearance. And if I didn't, then I'd have to explain that
7 | by age. Is that sort of where you're -- yes.

8 | DR. JUSKO: Age is likely to be the strongest
9 | determinant, but then we have to bring in genetics and diet
10 | and the rest as additional determinants of weight.

11 | DR. SHEINER: Yes. I think Bill is completely
12 | right, that having independent variability in age and
13 | weight will help. It's just how much of that do you need
14 | to feel comfortable about what you get out. And strange
15 | things like Simpson's paradox can happen where, as you move
16 | from age to age, the regression within each age versus
17 | weight could be actually opposite the direction that it was
18 | when you do the whole thing. These sorts of things happen.
19 | So it's just a matter of what the data contain.

20 | I guess one of the things that bothers me is
21 | that with kids it's going to be a very, very strong
22 | relationship; whereas, with adults we expect a small age
23 | effect -- the deterioration that Bill is talking about --
24 | and a large weight effect.

25 | But again, for predictive purposes, it doesn't

1 | make any difference. If you're not going to do anything
2 | different the next time, then your data has got all the
3 | information. I suppose what you're saying is an
4 | interesting result here would be if there was a relatively
5 | simple equation that predicted most of what you see across
6 | lots of drugs.

7 | DR. WILLIAMS: Yes. I anticipated that I would
8 | get the reaction that I believe Hartmut is expressing,
9 | which is this is sort of naivete to expect that it would go
10 | that way and that it's probably very important to
11 | incorporate physiologic covariates. But one of the things
12 | that drove me to think about it in this way is it made
13 | sense to operate on parsimony and start simple and see what
14 | the data set would support.

15 | DR. DERENDORF: But you want to use anything
16 | that you already know. So if you know that you have
17 | gentamicin, you can use glomerular filtration rate as a
18 | pretty good estimate. So if you know what the
19 | physiological value is for that, you should use that and
20 | not ignore it.

21 | DR. KEARNS: Just two comments, one to speak in
22 | support of doing this in the context of getting you in the
23 | ball park because I think it clearly has the ability to do
24 | that. You're right in that for very young infants and
25 | perhaps even up to 6 or 8 months of age, it's not an issue

1 of weight for much of the maturation. Probably post-
2 conceptional age falls out as a way to best predict these
3 things because you do come to the field with a little bit
4 of activity depending upon when you come to the field.
5 That's clear.

6 But from a practical standpoint, I was sharing
7 at the break our experiences in doing a study with a drug
8 that was 100 percent renally cleared. This drug was
9 studied under that list of 72 who've been given
10 exclusivity, and they got their 6 months of extended
11 marketing exclusivity and had a big party and everyone was
12 happy.

13 But in going back in time and looking at those
14 studies, we were able to simulate the results of the trial
15 before we enrolled one patient, as you might believe you
16 could do. We made an argument that we thought was
17 reasonably passionate, but perhaps not sufficiently so,
18 that the trial that was done needed only to contain
19 children in the first 3 months of life, that everything
20 else could be predicted. We were sent away believing that,
21 indeed, some revelation would occur. We could use the
22 knowledge that we had to simplify and improve and
23 streamline the process only to find out that we were wrong,
24 that ultimately we were expected to fill in all the pieces
25 of the puzzle of the barnyard despite knowing that it

1 | indeed contained animals of identity that was known. At
2 | the end of it all, there was a lot of time, effort, and
3 | money spent for no good reason. No good reason.

4 | So for all the pimples on an approach like this
5 | mathematically, this has the ability to improve the design
6 | of pediatric studies if, within the halls of this wonderful
7 | agency, it would just be used to do so.

8 | DR. WILLIAMS: I guess, Larry, that helps
9 | justify my detail.

10 | (Laughter.)

11 | DR. LESKO: I was just going to comment on what
12 | is the question. Actually Greg's comments are discouraging
13 | to what I was going to say.

14 | (Laughter.)

15 | DR. LESKO: Nevertheless, when Lewis asked the
16 | question about what is the question, it would seem what we
17 | want to know is not necessarily the empirical relationship
18 | we're talking about, but rather the more mechanistic one
19 | where you can look at a drug and it would be a whole new
20 | drug, but look at it not as a whole new drug in a
21 | therapeutic class per se but a whole new drug with certain
22 | attributes of processes of elimination, cytochrome enzymes,
23 | what we know about Bmax and Km's of those enzymes, and
24 | based on that information and based upon the analysis of a
25 | pediatric database, know where there are breakpoints in the

1 | age groups and perhaps do a limited study that might
2 | bracket age groups, and then you can fill in the blanks in
3 | between based on some model to say I know this from these
4 | relationships between routes of elimination and age. I
5 | might do some limited studies, but then cover age groups I
6 | haven't actually studied in terms of extrapolating that
7 | information. It's kind of what you were saying in terms of
8 | knowing something in the first 3 months and then using that
9 | to predict the rest of the puzzle, but it just struck me
10 | that if there's a difficulty in doing that with a drug
11 | renally excreted, the difficulty becomes magnitudes more
12 | for a drug that is out the enzyme system.

13 | But nevertheless, that's our noble mission here
14 | to try to look at the database. Maybe we just need more
15 | examples of this using data we already have as opposed to
16 | something new. I don't know, but I think where we want to
17 | go eventually is to take attributes of a drug and be able
18 | to make better predictions and maybe even excuse pediatric
19 | studies from being conducted if we're confident enough that
20 | we can predict clearance in those age groups.

21 | DR. KEARNS: And the other thing -- and what
22 | I'm about to say is not mine. I really owe this to Steve
23 | Spielberg who began preaching this some time ago -- is that
24 | if you can define a breakpoint, if they really exist, then
25 | it's possible to design your trial in such a way to enrich

1 | it so that you can get the most information out of the
2 | least numbers of subjects studied. That's okay because in
3 | the process, we don't compromise the end game result, and
4 | we also don't put children in trials just for the sake of
5 | confirmatory purpose.

6 | Parents always want to know, especially for a
7 | nontherapeutic trial, they say, explain to me again why
8 | this is important. As an investigator, you really have to
9 | be able to tell them that. If they're convinced, you have
10 | a child on your study and you have good data. If they're
11 | not convinced, maybe you shouldn't be either.

12 | DR. KARLSSON: Maybe in addition to what you
13 | presented here, your analysis, if you looked at it, could
14 | also settle the debate that was before the break regarding
15 | what about variability in elimination capacity with age.
16 | Does it actually decrease? Does it increase? Is that
17 | dependent on the elimination pathway, et cetera?

18 | DR. WILLIAMS: Yes.

19 | DR. FLOCKHART: I guess I'm back to what's the
20 | question. It seems to me, Larry, that you gave a different
21 | answer to the question.

22 | Greg, I think if the playing field is so big
23 | and has very significant error within it, I've got to ask
24 | the question, what's the point of asking where it is on the
25 | playing field. I can't tell by looking at the playing

1 | field whether the ball is in the goal or is at the
2 | centerpoint. If it's a very vague thing from doing this
3 | kind of activity before, I'm not sure knowing it's on the
4 | playing field is a valuable exercise.

5 | On the other hand, I guess we're all biased as
6 | scientists towards believing that a more mechanistic,
7 | physiologically based approach would work better. But I
8 | have to say that that real hypothesis even in adults has
9 | not been really hard core tested. We don't really know
10 | that.

11 | So this becomes, therefore, a testable
12 | hypothesis. Each time you add a new drug, you're testing
13 | the idea, and if it turns out even between the ages of 1
14 | and 16 that things fit, that would be a tremendously
15 | valuable thing to know that we kind of got gratis, we got
16 | free as we went along.

17 | The error is the key, though, because it's very
18 | variable.

19 | DR. KARLSSON: Are these 72 studies intravenous
20 | studies, or are you going to mix IV with oral studies? If
21 | so, how do you handle bioavailability issues?

22 | DR. WILLIAMS: Until I look at the actual data,
23 | what drugs are available and pick them, I won't know that
24 | answer. In other words, how do I choose among the 72?
25 | Perhaps the easiest way to start would be to look at IV

1 | drugs, but on the other hand, perhaps you would have a
2 | willingness to accept drugs whose metabolic route is well
3 | defined and is thought to be largely one process. So the
4 | 72 will be a mix, but which ones I choose to look at first
5 | and how I develop it is something that we have to consider.

6 | DR. CAPPARELLI: I would just like to echo what
7 | Mats was referring to, that the oral component is going to
8 | be huge, especially in the younger age groups, and
9 | everything that's been said before about some of the
10 | formulation issues. So I think that it's going to take
11 | careful selection. I'm excited to see this direction, and
12 | I lean on the mechanistic fence of things, starting off
13 | with what we know and building on it. I think renally
14 | eliminated drugs make a lot of sense from the standpoint of
15 | what we know about renal function, how we can measure it or
16 | how we can, at least, estimate it in different pediatric
17 | populations and relate it.

18 | But you start getting into drugs where there
19 | are bioavailability issues in adults, it's going to go all
20 | over the map, and you're going to have the additional
21 | confounding issue if you've got active transport or gut
22 | metabolism. And those may not parallel what's going on in
23 | the liver.

24 | So, again, trying to simplify it and at least
25 | starting it at points that I think you'll have buy-in and

1 | belief in the model I think is very important.

2 | DR. SHEINER: How variable will be the way in
3 | which the clearance was determined in the individual
4 | children across these studies?

5 | DR. WILLIAMS: I guess fundamentally you can
6 | separate into sparse and dense, and we're likely to see
7 | both of those. But beyond that, how studies are conducted,
8 | sampling times, populations, numbers, probably a wide
9 | range.

10 | DR. DERENDORF: Just to clarify, because I was
11 | under the assumption from the beginning it was only IV
12 | data. Now you're saying that there was some oral data. So
13 | they were the ratios of the oral clearances between kids
14 | and adults that you showed in that very first table?

15 | DR. WILLIAMS: My recollection of -- oh, this
16 | is perhaps unfortuitous. This is slide 4, not data IV.

17 | (Laughter.)

18 | DR. WILLIAMS: So the answer to the question is
19 | yes. Certainly some of these or perhaps all of them are.
20 | I did not separate this out into oral versus IV.

21 | Now, when we actually perform this on the FDA
22 | database, of course, we will have the luxury of choosing
23 | the order in which we consider the drugs. Obviously,
24 | there's an advantage, especially given Dr. Capparelli's
25 | comments, of beginning with the simplest case which would

1 be IV drugs.

2 DR. DERENDORF: The probability of getting
3 anything useful out of it then is very low in my opinion.
4 I think you have too many things that are lumped together
5 here.

6 I'm amazed at the ratios, that they come out to
7 be so close to 1 in that figure there. If oral
8 bioavailability is included there, it's almost hard to
9 believe.

10 DR. LESKO: But in our own data set, we can
11 control for that. We can select drugs, as we said, taking
12 care of those differences. We would combine drugs in
13 different ways that take those similarities into account,
14 whether they're IV or oral, and not mix them. He's working
15 with a published data set, but I think your question and
16 issue would be resolved if we picked from the data set
17 appropriately that we have within the FDA. Isn't that
18 right? Am I misunderstanding?

19 DR. DERENDORF: If you stick to high
20 bioavailability drugs where there is not a big difference
21 and where we don't expect a big difference, but if you have
22 high extraction drugs in the group, you would really get
23 numbers all over the place.

24 DR. LESKO: But I think one of the plans would
25 be to look at different ways of categorizing the drugs that

1 we're looking at to see if that makes a difference or not.

2 DR. DERENDORF: Well, the question changes
3 completely. Initially it was a question of how do
4 metabolism and clearance develop, and now we have included
5 bioavailability. We have formulation issues. We have
6 transporter issues. We have intestinal metabolism, I mean,
7 a whole bunch of things that happen all lumped in one
8 number. And I think the chance of filtering out anything
9 that teaches us something is very, very slim. We'll get
10 some kind of an average curve and we can fit a line through
11 it, but what does it mean?

12 DR. KEARNS: But, Hartmut, if I told you that
13 the data set that they had had over 300 patients
14 intensively studied with midazolam, half of them on oral,
15 half on IV, from ages of 6 months to 16 years, all of a
16 sudden it becomes a little more interesting. And that's in
17 their data set. So there is some gold in there to be
18 mined. But your point is well taken in that it's not
19 something to be done in a reckless way not paying attention
20 to all the assumptions and limitations.

21 DR. DERENDORF: Again, I think where I'm coming
22 from is to utilize anything that we already know, and the
23 physiological information about blood flow, for example, is
24 something that doesn't vary that much. That should be
25 included in the data analysis. It should focus on

1 intrinsic clearance as the number to correlate with. I
2 think then it makes much more sense.

3 Then you have a chance that you can identify
4 maturation rates for the various enzymatic pathways that
5 you then can use to extrapolate for new compounds. Once
6 you know that for a new compound which is the breakdown of
7 different pathways, you already know how the rate of
8 maturation occurs and you can make good predictions without
9 any study.

10 DR. WILLIAMS: If you're right -- and I
11 initially tended to think that way too, but like I said,
12 this is new to me -- then we will get there because what
13 will happen is the simple models will fail.

14 DR. LESKO: Gene, do you know the size of these
15 studies, just speaking about the small to large of the
16 pediatric studies in the database? What's the typical n in
17 these studies in terms of getting an estimate of precision
18 of the pharmacokinetic measurements?

19 DR. WILLIAMS: I really don't.

20 DR. LESKO: Greg, what do you do? Or, Ed,
21 what's the typical size of a PK study in a pediatric
22 population in your experience in terms of a single age
23 group or all the groups?

24 DR. CAPPARELLI: When you say all the age
25 groups, that incorporates a little bit of gray as you get

1 further on down and looking at degree of maturation at
2 birth. Some of those studies get to be very large.

3 Typically most of the stuff that one sees may
4 not be optimal, but rarely do you see anything less than
5 50. Most of it is in the 100 to 200 range if it's
6 incorporated into the safety trial.

7 But the driving force isn't often the optimal
8 PK component. It's really the other aspects of the study.
9 So again, the precision issue really comes near the cut-
10 points which I think was brought up earlier. There is
11 often a lack of information where the action is,
12 unfortunately.

13 So having a large data set that has three
14 patients under the age of 2, and you get this spread that's
15 here, here, and here, and then trying to make some sense
16 that no, nothing is going on down there or there's
17 something very dramatic going on down there really is based
18 on the belief of who's looking at the graph rather than any
19 real aspect of the data.

20 DR. KEARNS: Larry, for the phase II things
21 done under most of the written requests that I've seen,
22 it's about 24 subjects to 36.

23 Some of it's -- I need to pick my words right
24 because we're on tape, but it's interesting some of the
25 ways the designs are done. For instance, if we had a drug

1 | whose metabolism we knew or believed changed greatly in the
2 | first 3 months of life, you might see a written request
3 | that asks the sponsor to include 24 infants from the age of
4 | birth to a year and that the infants should be equally
5 | distributed across the age spectrum, so there should be at
6 | least 3 infants or 4 infants in the first month of life.
7 | And oh, by the way, you can study babies all the way down
8 | to 800 grams. Now, the chance of coming out of that at the
9 | end of the day with a revelation of therapeutic utility is
10 | slim to none.

11 | But unless my experience is somewhat not
12 | representative, this is happening every day under the
13 | context of negotiating a written request for drugs studied
14 | under the Best Pharmaceuticals for Children's Act, which is
15 | why I believe that until we put some of this bit of science
16 | and ingenuity into the action plan, we're really not
17 | serving the intent of the people who put that act together
18 | or, even worse really, the children as we try to make a
19 | fact out of fancy many times.

20 | DR. VENITZ: Any other comments, questions, or
21 | further discussion?

22 | DR. WILLIAMS: Are there data sources anyone
23 | here can recommend?

24 | DR. VENITZ: Dr. Sheiner.

25 | DR. SHEINER: At the risk of stupefying Mary,

1 | are you going to go back to the original data, the
2 | measurements of concentrations versus time, or were you
3 | thinking to use those clearances?

4 | DR. WILLIAMS: The notion is that we would just
5 | go back to the clearances.

6 | DR. SHEINER: Okay. And those clearances will
7 | be some, you know, from 15 samples after a single dose and
8 | a nice area under the curve.

9 | DR. WILLIAMS: Right. Some of them would
10 | probably come from population post hoc and some would come
11 | from dense.

12 | DR. SHEINER: Well, you want to think about how
13 | you mix those because those posterior Bayes' estimates are
14 | funny creatures. They're centrally biased. So they do odd
15 | things to regressions when you use them either as the
16 | explanatory variable or as the variable to be explained.
17 | So you need to think about that.

18 | DR. WILLIAMS: Yes. It seems to me it gets
19 | pretty complicated if you don't do that, but would you like
20 | to propose an alternative?

21 | DR. SHEINER: Well, if you don't do that, it
22 | doesn't get complicated. That complication goes away. If
23 | you use the original data, the complication I was just
24 | talking about goes away because you're not summarizing the
25 | data with a strange estimate. But it does mean that you

1 | have lot longer run times and a lot more modeling to set up
2 | and all those nasty things.

3 | I don't know. I would almost be tempted to
4 | say, since you're going to use them in subsequent
5 | regression and you have lots of data, that you should use
6 | unbiased estimates of each individual's clearance which you
7 | would get essentially by taking the prior variant system
8 | infinity or fitting the trapezoidal rule with three points.
9 | I mean, that's bizarre to talk about. But I don't know. I
10 | have to think about it. It's not obvious.

11 | DR. WILLIAMS: Perhaps we can discuss this
12 | further and I can come to the committee as a whole or
13 | perhaps even yourself showing you the actual
14 | characteristics of the data set.

15 | DR. VENITZ: With that, I think we're ready to
16 | conclude.

17 | DR. WILLIAMS: Actually if I could make a --

18 | DR. VENITZ: You conclude.

19 | (Laughter.)

20 | DR. WILLIAMS: First, a number of the committee
21 | members are very active in this area. If you would like to
22 | share your data, we would certainly welcome it. As I said,
23 | some limitations of our data is we often don't see very
24 | young ages and we often don't see probe substrates. So if
25 | you'd like to contribute, we sure would welcome that.

1 Finally, should the very empirical models not
2 be successful, the form that you would use not as far as a
3 full physiologic-based model, but incorporating some of
4 these physiologic covariates into the description of age
5 versus clearance is not entirely clear to us. We've worked
6 on it a little bit, but we don't have any firm conclusions.
7 If anyone would like to contribute here or perhaps even off
8 line how they would see the form of those equations
9 running, we'd be grateful.

10 DR. SHEINER: Just a quick question about that.
11 Usually PBPK to me means the various compartments connected
12 in various ways and blood flow from the gut going to the
13 liver and things like that. Is there a large collection of
14 physiologic models of clearance?

15 DR. WILLIAMS: I'm not sure I understand.

16 DR. SHEINER: Well, I mean GFR and renal
17 clearance. They seem to be linked, and usually people do
18 it linearly. I haven't seen too many what I'd call
19 physiologic models of clearance. That would be a thing
20 where you'd have some model of the uptake mechanism and
21 then the transport and the metabolism. That might be
22 McHale-Smitton or something like that.

23 DR. WILLIAMS: Well, the ones I'm most familiar
24 with sort of group all those sorts of things into a global
25 parameter, intrinsic clearance.

1 DR. SHEINER: But you're asking for a model for
2 the intrinsic clearance. Right? Or for the Q times
3 clearance over Q plus clearance, or something like that.
4 Because you're not asking for a model of the drug level.

5 DR. WILLIAMS: Right.

6 DR. SHEINER: That's what we usually think of
7 when we say PBPK, models of how do concentrations relate to
8 physiologic processes. But you already decided that you
9 are looking at a physiologic process called clearance, and
10 I'm not aware of an awful lot of physiologic models, except
11 I guess everybody who thinks about it could come up with
12 things they think would be more, let's say, reciprocally
13 related and things that would be more directly related.
14 But other than that, I think -- most of those models are
15 empirical, and even in the middle of a population analysis,
16 there's some little equation that says that clearance is a
17 linear function with an intercept often, which doesn't make
18 any sense, of weight, age, and some measure of renal
19 function or of hepatic function.

20 DR. VENITZ: Sounds like a topic for another
21 meeting.

22 DR. WILLIAMS: Thanks, everyone.

23 DR. VENITZ: Thank you, Gene, and thank you all
24 for hanging in for today's agenda.

25 We are adjourning the meeting. We are

1 reconvening tomorrow at 8:30.

2 (Whereupon, at 4:10 p.m., the subcommittee was
3 recessed, to reconvene at 8:30 a.m., Wednesday, April 23,
4 2003.)

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