think of the relationship between viral replication and drug concentration or inhibition of drug concentration as a continuum. And I guess the word that I wouldn't use that Charles used is "threshold." I don't think there's a threshold, per se. I think there is a continuous relationship between concentration and inhibition of replication.

Now, some of those concentration response curves, both *in vitro* and *in vivo*, are likely to be quite steep, so that relatively modest changes in concentration can take you from a high degree of inhibition down to a very low degree of inhibition of viral replication. But I think it's much cleaner and more straight-forward, in terms of thinking about the problem, to think of this as a continuous relationship between concentration and viral replication.

And as Jonathan said, I think the key is to maintain those concentrations as high as possible. I mean, one is thinking of should you approve another regimen. I think the question would be, is if that new regimen maintains the lowest concentration, $C_{min}$ at or above what it was with the other regimen, I would

be quite happy that that regimen is likely to be quite successful and probably equally successful to the original regimen, even if $C_{max}$ was a little less, if what we thought we were buying, by doing that, was a better dosing regimen, a more acceptable dosing regimen, and maybe even less toxicity.

But I do think that keeping the drug concentration at a very high level, even at the minimum time during a dosing interval, is really quite critical to maintaining suppression of viral replication and, as Dr. Pomerantz was saying, then potentially decreasing the probability of a resistant mutation.

CHAIRMAN GULICK: Yes, Dr. Mathews.

DR. MATHEWS: I wonder if there isn't something that could be learned from the whole discussion that took place years ago over how to evaluate surrogate markers biostatistically. And what I mean is, if you think about it, clinical trials have been designed and evaluated by giving a dose and observing a response, whether it's a clinical endpoint or a virologic response in the plasma. But the

discussion today is interposing a PK variable between the dosing event and the outcome, and you can view that as an intervening variable.

And the analytic approaches that were developed to validate the surrogacy of viral load or CD4 response, I think, could easily be adapted to look at what proportion of the treatment effect is explained by changes in particular PK parameters measured at specified times.

And I think what's been sort of missing -- as Dr. Hoetelmans discussed the few studies that have been done in this area up till now -- is that what's been talked about is correlations. But they're not really -- we don't have any sense of the impact of those correlations on the biologic responses. And I think if there was a standardized -- or work towards developing some standardized methodology where you could look at dose-ranging studies or formulation-varying studies where there is expected to be a difference in the virologic response, you could get more quantitative estimate of what the actual explanatory value of particular PK parameters are.

CHAIRMAN GULICK: Dr. Gerber?

DR. GERBER: Yes, I worry about dose-ranging studies, especially what we know now, because you don't want to be at a low dose, you don't want to be at a low concentration because of the resistance issues, especially for drugs that require one mutation for resistance or one or two mutations.

And, I mean, I agree with actually what Terry said. I think Terry made a very, very good point that my other question is: What can we save by PKs when you have a new formulation? Can that be -- can we use PKs to say that the new formulation or the new way to use that drug is equivalent to the way it was used? And I think it's not unreasonable to think that the -- achieving the $C_{min}$ in the two situations would probably give you equivalent response. And I think nobody -- none of the pharmacologists, hopefully, would disagree.

And I want to reiterate what Charlie Flexner says, that there is a concentration response relationship here. I mean, that is a basic pharmacological principle. And that's -- there are

all kinds of variables, and I think we've heard all the variables, protein binding. Should we look at free concentrations of all the drugs? I don't know the answer to that. That would be extremely expensive and difficult to do. But for some drugs we do that. For Fenetone we frequently look at free concentrations, because that's what you need to see a response. And maybe for some drugs we need to do that, for some antiretroviral drugs we should do that as well. But I think it becomes too complicated.

But the basic principle is that there is a concentration response relationship, and when you have a new -- a way to administer the drug, if you have very similar $C_{min}$, AUC, or whatever you want to look at, and it gives you this, then do you really have to do a gigantic efficacy study? And my guess -- and I can't tell you 100 percent I'm sure -- probably not if you believe that principle.

DR. MATHEWS: Yes, but my point is that these kinds of dose-ranging studies are done all the time in drug development, and PK measurements are done as part of the drug development process. And a lot of

these analyses could probably be done retrospectively or as part of ongoing clinical trials so that one gets a sense of what metric measured at what particular time is most predictive of virologic response.

DR. GERBER: But I worry about the percent of people who are going to fail therapy, develop resistance by doing that. And so I do have a problem in this dose escalation studies looking at virological responses. And I think we have to get away from this. In most situations, when you treat hypertension you do dose escalation, and you do dose response and concentration response relation. That's fine, because you don't lose the efficacy because of resistance issues. I think that this is much more complex, and I worry about that.

CHAIRMAN GULICK: Dr. Yogev?

DR. YOGEV: You see, you're doing dose escalation first for tolerability and safety. And I think you should use this opportunity to define your $C_{min}$ absolute that you need. You can find out that from a certain level, although it's in the range, will kill your $C_{min}$ much higher, but on the lower range, the

one which you're talking about, you're absolutely correct, you should not allow that.

So then when you go now to bioequivalence, to say I want the range that the lowest level would be "X" instead of take a median or mean. Because you take a median or mean, if you are too low, it's too wide. So while you're doing the escalation for tolerance, safety, to find out what the patient can take, use that opportunity to define the $C_{min}$ minimal that you need in the range, and then say every bioequivalent cannot go there.

That's a concentration curve that you're talking about, and I agree with you 100 percent. But because we give it the bell shape and we don't cut the low edge, we need to start cutting the lower edge, the one which cause resistance, to get less of a bell shape, which would put us in a safer level that we now say yes, I want the $C_{min}$ average "X," but the $C_{min}$ min will not go below "Y" because more breakthrough and we have to define what.

DR. GERBER: I mean, I think it's true for when we're talking about new drugs. But we're talking

about drugs that already we have experience with, and how -- if there's a new way of administering it, how can -- would PK be adequate, or do we need to do a whole bunch of new studies. I think that's her question. That's the way I interpret the question. And I agree with Terry, probably, that if you get above the $C_{min}$ with -- then that might be adequate.

DR. YOGEV: Well, you see, the drug we have today -- again, unfortunately, my experience pediatric -- are not effective. So we got the drug that they approve and the company refuse to go with a higher level in a dose, which we found out completely inaccurate, because the $C_{min}$ probably was the problem. When we increase it by more than almost 30 percent, we start getting a little bit better data. And if you look at whatever in the field, it's 50 percent failure. So not sure that what we have now is appropriate, because we use certain parameters which we need to redefine.

But you can say accept what is now, check on that, check what the $C_{min}$ or dose in a certain population, and it can be a very small number of

patient relatively, and that's what the minimal you ask for the new bioequivalent, if you accept it.

DR. GERBER: But the issue is -- I mean, 50 -- I don't know much about pediatrics. I'm an adult physician.

DR. YOGEV: That's why I take advantage of you.

DR. GERBER: I see. But my general feeling is that the majority of patients who fail therapy right now, hard therapy, fail because of non-adherence, I think. I mean, that's my feeling. And I was struck by the data that Margaret Fichel presented at the last retroviral meeting with directly observed therapy. Nobody failed. Everybody was below 400 with directly observed therapy, which should immediately tell us that maybe the problem is not necessarily that the drugs are not potent enough, but that it's the drug-taking behavior that could be the problem, just to throw it out.

CHAIRMAN GULICK: Dr. Jolson?

DR. JOLSON: I wonder if I could just probe a little bit further with Dr. Gerber. I wasn't

clear, and maybe you can clarify in terms of your level of comfort for a $C_{min}$ that's at least what the prior regimen demonstrated.

And I think we would agree that if the exposures were fairly similar or a little bit better than the current regimen, that that wouldn't be a problem. But what point would you start being uncomfortable that the PK profile is different enough that you would need to have some clinical data where -- and just to remind you of some of the examples this morning that Dr. Reynolds gave, where the $C_{max}$ is substantially reduced or the time profile is significantly altered. Do you have any feel for what would trigger the need for more data?

DR. GERBER: Maybe I spoke too much. But, I mean, I think if the -- the way I view it, I mean, the $C_{max}$ determines toxicity. If the $C_{max}$ is obviously much higher, then your concern should be toxicity. If the $C_{min}$ is lower than in the previous regimen, then I think you should be concerned with efficacy. But it also depends on what drug we're talking about and how far above the inhibitory concentration, whatever, you

are with that drug.

I mean, the problem was with the protease inhibitors that you're so close to the breaking point, in terms of efficacy, that there small changes could make large differences. I think a drug like Nevirapine, where you're very, very much higher, I think there the problem is the resistance issue, the 1A mutation which is in the background with everybody. So those are -- so the resistance, as well as the kinetic issue, kind of balance each other.

It's much more difficult to develop resistance to PIs than to NNRTIs. So you got to balance those two. But I think what I said before, if the $C_{max}$ is higher, I would be concerned about toxicity; if the $C_{min}$ is lower I would be concerned with efficacy, especially in terms of PIs. But I'll be happy to see what other people would say.

DR. FLEXNER: As a follow-up to that, I'd be curious, if we polled all of the pharmacologists here, how many of them think $C_{max}$ is an important determinant of antiretroviral efficacy. Does anybody think it's an important determinant of antiretroviral

efficacy? If you have two regimens that have an identical $C_{min}$, but one has a lower $C_{max}$, do you think that regimen's more likely to fail?

DR. POMERANTZ: I'm not a pharmacologist, but that was my -- part of my question. I mean, clearly I see what you're saying, Charlie, that that came up. If you're thinking about a drug that has the same -- or the same drug given different ways, both have the same, say, $C_{min}$, but you have a pretty flat curve with a low $C_{max}$, you could come up with a scenario where --

An example, protease inhibitors seem to work, at least *in vitro*, relatively poorly compared to T-cells and macrophages. If you have a lower $C_{max}$, you may see nothing for the time where most of what you're doing is active viral replication, 99 percent inactively replicating T-cells. But if you let this go on for a while, using now the macrophage as a way to make virus, which, by its definition, will eventually become resistant in sub-inhibitory therapy, you could come up with, hypothetically, a way where a low $C_{max}$, the same $C_{min}$, would lead eventually to

resistance. Whether that's happened or not, I think you got to keep trying it to see whether you're going to prove the point.

DR. ACOSTA: Just real quick, I think another issue that we need to -- to the effect of what Terry and John were discussing were two different regimens, if one $C_{min}$ is similar to the one regimen as the other regimen, is that equivalent? And I would just like to add that it may be, but we need to insure that the $C_{min}$ in the first regimen is the right $C_{min}$. If we know that, then fine. But if we don't, or if we have questions on that, then no, I would disagree with both John and Terry on that issue.

CHAIRMAN GULICK: Dr. Masur?

DR. MASUR: I guess I would like to get back to what the FDA is asking us. Because over the last ten years on the panel we have tried to focus on how rigorous the evidence is that a given drug is safe and effective. We're now getting into speculation as to whether we think that various parameters are useful.

I guess the question is: Do you want our

opinion on what we think is logical, or do you want our opinion as to whether the evidence suggests that we can provide you with operational definitions for what is equivalent and what isn't? So, I mean, I'm interested that we get an opinion, but the question is: Is it based on data or is it based on logic?

CHAIRMAN GULICK: And I guess the first comment made today was that although people have feelings about it, the data's incomplete. It's not there to support it. So you've kind of brought us around full-circle, which is a good place to be.

Dr. Blaschke, you want to have the last word, and we need to move.

DR. BLASCHKE: Well, I don't know if it's the last word, but I do think Henry's raised a very important question, in that we do have to separate the issue of what is the right $C_{min}$ from what is therapeutic equivalence, as far as the FDA is concerned.

Having sat on the Generic Drugs Advisory Committee for four years, the question here is therapeutic equivalence. And if we say that we can

achieve the same -- even if it's bad -- but the same therapeutic equivalence with a different regimen, a different dosing regimen, then that's really what we're -- what the FDA is asked to approve. Not to ask -- not asked to say: Well, is this a better regimen? Company wants to come in and show it's a better regimen, that's fine. But I think it is therapeutic equivalence. And while an important question is what is the best $C_{min}$, or what $C_{min}$ should be the target, that's a different question than I think the FDA is addressing in its regulations.

CHAIRMAN GULICK: Dr. Jolson?

DR. JOLSON: Just to get back to Dr. Masur's point, and also Dr. Blaschke's, I know I heard the word "reasonable" come up. And it probably is worthwhile, since you brought it out, to separate what we think is reasonable, and perhaps reasonable in clinical practice to do, versus what the regulatory standard for drug approval should be.

And that's what Dr. Reynolds was bringing out a little bit in her talk today; about, although the logic is similar, the level of evidence has to be

different because that's what the law requires. It requires substantial evidence, and we may interpret substantial evidence differently, depending on what end of the spectrum of drug development you are. But we really have to think that there's compelling evidence.

And to answer your question, it's based on judgement, but it really needs to be based on data. Otherwise opinions will change with time, and that that really doesn't form the basis for regulatory approval.

So in terms of what we're asking the Committee to grapple with, is really what should the standard of evidence be, versus a little different than what's reasonable to do in clinical practice and what seems intuitively reasonable.

CHAIRMAN GULICK: So can we pose the question again. Is there enough data available today to say that if we have two regimens, one in which we know the PK -- or the virologic efficacy, and the other which we know the two sets of PK parameters, can we say that the regimens are similar based on the PK

parameters alone? Do we know enough to make that jump?

DR. GERBER: Well, I think the problem is -- and I hate to bring this up, but I'm going to -- adherence. And if one regimen is simpler than the other, then sometimes it may look -- even if the PK is not quite as good, it may look better. Because there's more to prescribing than PK. There is also a step in-between of taking the drugs. And I think that's a component that I think we've underestimated or we have not paid as much attention to as we should.

So if you have two regimens that give you the same $C_{min}$, but one is impossible to take, the other one is very easy to take, you may turn out to have a totally different result when you look at efficacy. So you got to take -- there is something in-between.

CHAIRMAN GULICK: Dr. Fletcher?

DR. FLETCHER: To answer the question, I think across the board the answer would be no, we don't. I think to try to -- how would you get at it, though? I think it would come back to what is the -- the strength of, you know, the pharmacodynamic

relationship.

And if you have a drug that -- let's say you have a very good, strong quantity of understanding of the relationship between either dose and effect, or concentration and effect, then I think there you can feel better about making the decision on an alternative dosing regimen on the strength of PK only. But as those relationships become poor and as they become more qualitative, there I think you have to feel less confident about making the decision based upon only PKs, and you have to bring in, then, the clinical -- you know, the clinical trials. But right now you can't make a -- make any decision across the board for -- you know, for all these drugs.

CHAIRMAN GULICK: Okay. Boy, we solved that one, didn't we.

(Laughter)

So, just to try to summarize what people said a little bit, there was a groundswell of support for the traditional PK parameters, and I guess people lean very heavily towards $C_{min}$ as being associated with virologic efficacy, although people left room for AUC

and even the possibility of $C_{max}$ as having some impact there.

Also, just basic principles that this is a concentration response relationship that we're talking here, and that it's also highly complicated. There are a number of other variables that may come into play.

DR. FLEXNER: Dr. Gulick?

CHAIRMAN GULICK: Yes, Charlie.

DR. FLEXNER: I guess the one place where it's obvious you should be able to use PK data alone is in bioequivalence study, and I think that's still legitimate. The guidelines that the FDA has established I agree with, although it's evident from the presentations this morning that the agency's willing to look at studies individually and think creatively, based on the data presented, even if the PK parameters fall outside of the established bioequivalence guidelines; to believe that it's reasonable to approve formulation based on scientific grounds. And I would completely support that and hope everybody around the table would, also. So I think

that bioequivalence -- but think creatively -- is a good guideline.

CHAIRMAN GULICK: Dr. Yogev?

DR. YOGEV: Just one small point. I have a problem that the bioequivalence allow a lower level. And I think at least the lower should be as low as the previous one and not allow more lower, because already know it's not effective. We allow even more, just a population question, I can show you statistically in another 40 patient you'll get the same, only sacrifice a number of patient because it went lower. So I think bioequivalence, we need no lower than what was approved the previous one, and then the upper range, whatever it is, and decide.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: Some of this actually has been -- this has come up for other drugs, like Warfarin and Levothyroxine and things like that, to say the 125 percent range being too wide. And actually in -- in the private sector this has been solved by companies marketing, for example, generic Warfarin and getting hammered by the Coumadin people,

so therefore they tightened up their own range on their own. That was outside of FDA standards. So that's another potential way. Once these agents start becoming generic, for example, that this may be solved by industry.

CHAIRMAN GULICK: Dr. Piscitelli?

DR. PISCITELLI: I don't think our problem really is with these scenarios where the $C_{min}$ is similar. I think what we're faced with is you have a drug with a trough of 150, and now it's 2000 because we've added Ritonavir to it, or we have a prodrug that comes along that raises the concentrations fivefold. So I don't think we need -- clearly, if the $C_{min}$s are very similar or close, then clinical data may be needed.

But I think we're more faced with the issues of what happens when the trough level is fivefold or tenfold greater, then I think it's a safety issue. I think many people at this table would think the efficacy hopefully would be there.

DR. YOGEV: I was just relating to the more common currently is TID, BID, QD. And I don't

know if you noticed one of the slides which was shown twice, on QD at 12 hours the $C_{min}$ was the same. Therefore, the next one follows the QD you have no drug. And I don't think that should be acceptable. And that's what I'm trying to draw attention. But you're also correct, the safety of the other one. But if you change and you don't have -- at least have the minimum that you had before, that's what I'm talking about, possibility of keeping the efficacy.

CHAIRMAN GULICK: Can we flip to the next slide and consider the four parts to this question. We've already raised some of them. But just -- yes, that was the introduction.

So what data are needed to rule out -- we talked a lot about ruling things in or how they were important. But what data are needed to rule out the relevance of any specific exposure measure to efficacy? That's a tough question.

DR. FLEXNER: (Inaudible)

CHAIRMAN GULICK: Okay. Thank you.

DR. FLEXNER: I mean, that comment was a little bit flippant, for those of you in the audience.

I said randomize prospective control of clinical trial.

But I guess I don't think we can give you a definitive answer to this question. But I would exert a cautionary note here in using retrospective cross-sectional observational data to address any of these questions, because I think those studies are so subject to confounding that they're not going to answer these questions definitively. They can provide insight and they can provide hypotheses that can then be tested. But if we're talking about weighted evidence, the kind of studies that Dr. Hoetelmans reviewed this morning -- most of which were retrospective observational cross-sectional studies -- I don't think answer any of these questions.

DR. ACOSTA: I agree with that, for the most part, also. A prospective trial really is what's needed, with the incorporation -- solid incorporation of pharmacologic PK evaluation at some point during the trial, whether it's population PK or intensive PKs. And I'm not a statistician, but I would guess something along the line of a large, multi variate

analysis at the end of the study to see which parameters might fall off the -- into efficacy variable.

CHAIRMAN GULICK: Dr. Schapiro?

DR. SCHAPIRO: The truth of the matter, I think even that -- it's more complex than that, because our output and efficacy is not always reduction in viral load. For just taking the example, we sort of bashed $C_{max}$ a little bit. But I think body compartments are an important issue. And to do a study, we may find in pediatrics, at some CNS, improvement is related to $C_{max}$. And unless we study where that's an outcome, we'll miss it.

We may consider, for some of those, transmission to be important, and therefore we want a clear $C_{min}$. That may depend on $C_{max}$. We don't know that. And even if we were to have a study that looked at viral load, that's not our all-outcome. Therefore, I think until we can do 1A, it's really far off. And I think that to say you can rule those out, I don't think we'll be able to do it.

I think honestly we really are going on

very little evidence. There are a lot of outcomes of HIV which are important, which are not in our studies, and they also depend on which patient population it is. You may find body compartments which really are dependent on $C_{max}$. I would say that we can't rule them out, but I think we can say that for some parameters we know what's important, and we have to accept that we might be missing some others. And I don't think we'll be able to improve on that within the next couple of years, even if we do a big study.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: Dr. Gulick, I just would like to ask you if it would be all right for Dr. Pomerantz just to review, for those of us around the table that aren't really up with this, kind of the relationship with HIV in terms of the different exposures in AUC, $C_{max}$, $C_{min}$, and if there's a relationship with those. That might help us -- help me.

CHAIRMAN GULICK: Do you want to give that a shot?

DR. POMERANTZ: I'll do it.

CHAIRMAN GULICK: Okay.

DR. POMERANTZ: *In vitro*, as some of you -- I mean, if you read the papers from the different laboratories, it is much harder to get the numbers that you're used to doing *in vivo* to an *in vitro* analysis because, as you remember, this is not bacteria. You are dealing with an integrating latent or lowly productive virus. And because of that, it depends on what you measure per each drug to determine whether the virus -- and particular let's take a wild-type virus -- is quote-unquote, "sensitive to it" and what relates to its area under the curve, the amount of time that you treat in cultured $C_{max}$ or $C_{min}$, if you will, if you can even say that *in vitro*.

If you take a virus that is already integrated, you take chronically infected cells -- which is what most people have, remember, they're chronically infected cells and you're treating them -- you're not treating them at the same time that you give virus. People don't usually get it before they get -- before they seroconvert. And because of that, you will have a very different parameters based on the

type of drug you use.

If you use something that inhibits a pre-integration step, by definition an anti-RT drug, you will, in those cases, have the same level of production. You won't knock down the amount of virus, because they will still have these chronically infected cells churning out virus. So if you use an RT drug, you'll see it just sort of stay the same. And there the amount will vary, the effect will vary basically on your $C_{max}$.

If you're dealing with a post-integration drug, in this case in the ones that we have available, which are the protease inhibitors, protease inhibitors are even more complicated. Because again, in an *in vitro* study where you have chronically producing cells, it depends on how you measure the viral output to determine whether you're having an effect based on $C_{min}$; if you will, $C_{max}$. If you look at P24 antigen, remember that protease inhibitors stop the protease, so you don't get P24. That'll go way down. But if you look at, let's say, viral RNA, there's very little change.

So it depends on whether you're dealing with an *in vitro* study that already has infected -- chronically infected cells, whether you're looking at a pre-integration or a post-integration inhibitor. And therefore it's very different from what you're trying to figure out *in vivo*. That's why I sort of, at the very beginning of this whole thing, at least from a basic virology perspective, would take $IC_{50}$s and things that are doing *in vitro* somewhat -- I look at them a little carefully before you make them important *in vivo*. They're good ballparks to tell you that an antiviral is going to have possibly some effect.

But there's so much difference, depending on the cell type you use, whether it's chronically infected, whether it's actually being killed by the virus as opposed to just replicating as a chronically infected macrophage will, and whether you're dealing with a pre- or post-integration inhibitor, then using $IC_{50}$, or conversely, trying to do AUC or $C_{max}$, $C_{min}$ in an *in vitro* system is somewhat problematic. I hope that was quick enough.

CHAIRMAN GULICK: Thanks. Let's move on.

What is the role of intracellular concentrations -- this came up a little bit earlier -- in the evaluation of new formulations and alternative dosing regimens for approved nucleosides. Dr. Fletcher?

DR. FLETCHER: From a regulatory point of view, I don't -- I'm not sure there is one yet. The assays for these drugs are technically very difficult. They are feasible, but they're not yet, I believe, ready to form a basis for a regulatory approval. That may well come in time, but not right now.

CHAIRMAN GULICK: Has there been any study that's correlated intracellular concentrations with virologic parameters for nucleosides, intracellular?

DR. FLETCHER: Yes.

CHAIRMAN GULICK: Okay. Thank you.

(Laughter)

DR. FLETCHER: I was trying to be quick. Yes, I mean, there are data, both published and in an abstract form and emerging, that are showing relationships between the triphosphate concentrations.

It's been shown for AZT and been shown for 3TC, and I think coming for D4T and some measure of response. But the numbers are very small.

CHAIRMAN GULICK: Dr. Flexner?

DR. FLEXNER: Just to add to that a comment I made earlier, that it may not be necessary for most nucleoside analogs. That is, plasma concentrations may correlate linearly with intracellular concentrations over most of the human concentration range, such that you don't need to measure intracellular triphosphate, you can estimate from plasma concentrations what kind of changes you'd expect to see in intracellular triphosphate for every drug except AZT.

CHAIRMAN GULICK: So there's reasonable --

DR. FLETCHER: And I agree with Charles. I think to get to that point we have to measure the triphosphates and then count back, so that we can understand that relationship. But I think that may well be the case, that in a sense we could be able to use plasma nucleoside concentrations as a surrogate, if you will, for the intracellular triphosphate.

CHAIRMAN GULICK: And there's enough data to say that today, that there's a very good correlation between those two?

DR. FLEXNER: I can't comment about investigational nucleosides, but I think for D4T, for 3TC, for -- let me think about it -- DDI probably. Well, the problem with DDI is you can only measure intracellular triphosphates *in vitro* with radio-labeled drug because there's no good assay for DDATP. But I think for at least two of the approved nucleosides that's true, there is both *in vitro* and *in vivo* data that support the relationship between concentrations of parent drug outside the cell and concentrations of triphosphate inside the cell. And based on *in vitro* data, I think that's true of the other nucleoside analogs that are out there.

CHAIRMAN GULICK: Dr. Yogev, you're shaking your head.

DR. YOGEV: Yes, well, for a non-pharmacology, I'll pretend to be one. The data are very limited. But what's fascinating, they are much better correlated with what happened to the viral load

and AZT. And when you have three drug tested and two of them correlate and one doesn't, I think it would be dangerous to suggest that every new one would be the same. Prove it to me and then I agree with you.

So we need some preliminary data, because what is always fascinating, and Dr. Somatozi made a career out of is how beautifully they did correlate. And that's why many of us thought that the intracellular is much more important and accepted the DDI without good data yet. And just recently some data to suggest we are not correct.

So I think we need to have them, and because we don't have them, we shouldn't enforce them. But when they are available, that should be the standard.

DR. FLEXNER: I tried to apply the standard of reasonableness. I mean, if you wanted to get crazy, you could require measuring free drug concentrations and correlating those with outcome, or measuring intracellular concentrations of protease inhibitors, as Dr. Hoetelmans suggested. But I think what I'm talking about is looking at available

*in vitro* data and available *in vivo* data, and saying what's reasonable.

CHAIRMAN GULICK: It's interesting, to get back to Dr. Jolson's point about the word "reasonable," what's reasonable to make the jump, and then what's reasonable from a regulatory point of view may be different hurdles to jump. Dr. Fletcher?

DR. FLETCHER: Just another quick comment again. I think Charles is right, that if we're looking at alternative dosing regimens, that at least the part of that that I've not seen yet, Charles, is where you could change -- let's say for D4T, that you could change the dose of D4T, therefore change the plasma concentrations, and in some manner also change the intracellular. So, in thinking about it from a basis to change dose measurements, that's the part that I'm not certain of yet, and I'd like someone to show that that system does work.

CHAIRMAN GULICK: Dr. Schapiro?

DR. SCHAPIRO: Just a quick comment on the protease inhibitors. I agree that reasonable is an issue, but I think there's still a lot to be

determined about what happens with the protease inhibitors from outside to inside the cell. As Dr. Hoetelmans mentioned, there's some very conflicting data to what degree protease inhibitors accumulate. Do they accumulate differently; and is or is this not affected by drugs such as Ritonavir.

I think the data is weak, but I think we consider a drug level to be sort of, again, the end of the journey. But if a lot happens between that drug level and when the bug sees the drug inside the cell, that could become important. I think right now it'd probably be a lot of work to do that, but I wouldn't be surprised if ultimately, when we start combining drugs which possibly work on these transports of the cell, we see that we lose some of the correlation between the drug level and the intracellular drug level. I think it's something to at least keep in mind. And it might explain why it might be more challenging to get these correlations when we start doing combined PI or combining drugs that work on these.

In addition, we might find in the future

that there are other agents which increase drug levels which also may work on the cell transport systems, and that might have implications. Again, to what degree does the drug level correlate with efficacy?

DR. FLEXNER: I'm beginning to think that for some of these scenarios it might be quicker and cheaper just to do a 500 patient safety and efficacy trial than to do a 30 patient intensive intracellular, nucleoside, triphosphate, PI, et cetera, protein binding, blah, blah, blah study.

CHAIRMAN GULICK: So Dr. Flexner has very strategically moved us on to the next question.

(Laughter)

What circumstances would clinical efficacy data be necessary? So you made the suggestion that we do a large clinical efficacy trial.

(Laughter)

DR. FLETCHER: I may be an exception here, but I feel confident enough about just simply measuring plasma concentrations of protease inhibitors and correlating that with outcome, that if someone gave me data from two different protease inhibitor

formulations, and the trough concentrations were identical or the trough concentrations of one regimen were higher than the other, I would feel confident that they were very likely to be equivalent in terms of efficacy. But if the $C_{max}$ was higher, maybe there'd be a greater chance of toxicity, and if the $C_{min}$ were higher, maybe there'd be a greater chance of toxicity.

So then the clinical data I'd want to see was toxicity, the safety data, not so much antiviral data. But having said that, sample size calculation is such that I think, for most of these drugs, if you do a safety and tolerability study, you'll wind up with more viral efficacy data than you will safety and toxicity data, given the incidence of major toxicities for most of these agents, in that you can collect antiretroviral efficacy data in everybody, but you need a fairly sizable population to show that the incidence of nephrolithiasis is different or the incidence of lipodystrophy is different.

So it may be a moot point to say we're only going to do -- it may be irrelevant to say we

only want you to collect safety and tolerability data, because inevitably, if you do such a study, you're also going to collect anti-HIV data, and so you'll have that as well.

CHAIRMAN GULICK: So, in a sense, you're implying that any new formulation of a protease inhibitor would take into account the $C_{min}$ right from the beginning, that it wouldn't be acceptable for someone to come in with a lower $C_{min}$ with a new formulation?

DR. FLEXNER: Unless they also had clinical data to back that up with saying that even though we dropped the $C_{min}$, yes, we did not affect anti virologic outcome at 24 weeks or 48 weeks.

CHAIRMAN GULICK: So that would be an example of something you'd like to see the clinical efficacy data to support?

DR. FLEXNER: If you lowered the $C_{min}$. Yes.

CHAIRMAN GULICK: But in other cases you feel comfortable?

DR. FLEXNER: I do.

CHAIRMAN GULICK: Dr. Mathews?

DR. MATHEWS: Part of the problem is that changing a formulation obviously changes more than just the pharmacokinetics. And so if you consider the major factors other people have already mentioned, adherence and dropouts from participation in a trial are going to be affected by formulation which is designed to improve, say, tolerability or improve $C_{min}$.

And so it's hard for me to think of a situation right now, given the data that's been presented, where you wouldn't want to have clinical data on long-term outcomes. Let's just say you've had a scenario where somebody presented data that said, "All right, the $C_{min}$'s less, but there's 20 percent fewer dropouts, and the average virologic response, because adherence is better, is equivalent or superior in the arm that had the lower $C_{min}$, you know."

And if you think back on the issue that -- for example, with the tovaquonin receptor evaluation of pneumocystis treatment where you had a drug that appeared equivalent on balance, but actually was probably inferior on an efficacy basis. So I'm not

sure right now in my own mind that I would be persuaded that pharmacokinetic data, in the absence of clinical efficacy, would be fully acceptable for regulatory purposes.

CHAIRMAN GULICK: Dr. Wong?

DR. WONG: I agree with that. I haven't heard anything today that would convince me, I think, if it came to a vote to prove something in the absence of any clinical efficacy data.

DR. FLEXNER: What if you had two formulations of DDI that had identical pharmacokinetic parameters --

DR. WONG: Right. I believe that if it's identical --

DR. FLEXNER: -- for different formulations?

DR. WONG: Right. If it's identical, it's identical. But as soon as we get off of that --

So if it's equivalent, if we're talking about the same thing as a generic substitution, right. So absolute bioequivalence, I would say fine. But I haven't heard anything today that would convince me

that we should proceed with a change of formulation, change of dosage in any situation that I can think of in which I'd just say, "Don't do the clinical study; we don't care." I just can't imagine it.

CHAIRMAN GULICK: Dr. Pomerantz?

DR. POMERANTZ: I'm not disagreeing. But I would ask you, then: What clinical study would you require of this hypothetic little new drug from this hypothetical company? Would you say, "I need 24 weeks that shows similar efficacy"? Do you want 48 weeks to show similar -- what do you want, then? Because if you -- I'm not disagreeing.

DR. WONG: I guess that I can't answer in the hypothetical case. We'd really have to -- it'd depend on the individual drug. But clearly, if it's a drug -- I mean, we ordinarily expect a sponsor to demonstrate that the drug is efficacious. So if the drug is already known to be efficacious, the standard of evidence is less than it would have been the first time through.

But I don't think the standard of evidence is zero. That's all I'm saying. And deducing from

first principles that it has to be other than zero would not be good.

DR. POMERANTZ: Just to finish that, I mean, you've heard me talk. I don't disagree with you. I have probably as much evidence as anyone, because we've all spoken in the hypothetical.

But, I mean, with all due respect, if you've shown $C_{min}$ as being the *sine qua non* -- that if everything else is different that we would just say let it pass -- I probably, going with Dr. Wong on this Committee on a vote, would not vote in that way without being shown something else. I am somewhat troubled with what I would ask for otherwise, though. And would I be willing, in certain cases, to say 24 is enough because it's sort of close, or would I make them go 48? I don't know.

But I also, a non-pharmacologist, have not been convinced that in the cases, with except an identical curve in the formulation, that I would vote that you don't need any clinical data.

DR. ACOSTA: Yes. And I don't completely disagree with both of you, either. However, Indinavir

BID and Indinavir Q8 were similar at 16 weeks, but were not similar at 24 weeks.

DR. POMERANTZ: Well, that's why I said that.

DR. ACOSTA: And so the point here is, to get back to your comment, it's a matter of time.

CHAIRMAN GULICK: Dr. Yogev?

DR. YOGEV: I think I try to jump into some. What I would like to suggest is you don't need that many number of patient or do you need the lengths of time. Because, interesting enough, we saw in those drug we saw side effect on an equivalent pharmacological dose, area under the curve where the $C_{max}$ was different, $C_{min}$ was different in Ritonavir, that they had more toxicity after 24 weeks, to our surprise.

So you need to take the period of time both for toxicity and efficacy, but they probably can cut down the number of patients. I don't think we need 500. We can take just one number, if we get a trend is there, but for longer period of time, and check for the safety and tolerability.

CHAIRMAN GULICK: Dr. Fletcher?

DR. FLEXNER: Flexner.

CHAIRMAN GULICK: Flexner. Sorry.

DR. FLEXNER: That's okay.

(Laughter)

I'm flattered to be confused with Courtney.

(Laughter)

I guess personally I have not been holding out $C_{min}$ as a standard for which there is the weight of evidence. I'm simply presenting what a big group of pharmacologists, I think, take to be logical. And, as Dr. Jolson pointed out earlier, those two things have different implications for a regulatory agency.

I do, however, want to point out that if this Committee does choose to apply a standard that anything other than absolute bioequivalence warrants a new clinical efficacy study, that has major implications for how rapidly new formulations -- not to mention new drugs -- will be developed for this disease. And maybe that's not all that bad, with 14 drugs already on the market. But that is a real

consequence of making that recommendation.

CHAIRMAN GULICK: Dr. Jolson?

DR. JOLSON: And just for clarification, so it's sort of clear what scenarios we're talking about, I don't think we're putting that out on the table. Because I think I just wanted you all to remember, in Dr. Reynolds' example, that we do recognize the need for flexibility when new formulations may not be bioequivalent according to the definition, but there's other extraneous data that we can use to more flexibly look at it and say that we can make a reasonable judgement that the drugs are going to be similar or not. And she used the example of the newer formulation of Ritonavir.

We're really talking about we need your advice for the scenarios where that's not the case, where we can't use external data to make the link, and we're faced with those pharmacokinetic profiles that, at least on a figure, look like different. And the question is: How do we know that those differences are clinically significant?

So we're not putting that out for sort of

a change in the way the agency would handle that, because that's really a different issue.

CHAIRMAN GULICK: So I guess there's a groundswell of opinion that a lot of times you can't tell that there's no clinical significance when the curve's quite different or the parameters are quite different.

Let's move to 1-D, which is an issue that we've only touched on briefly. Are these relationships applicable to achieve in experienced patients, given that most of the studies have been done in naive patients? Dr. Schapiro?

DR. SCHAPIRO: I think this is a very important issue, and I think here, although we have many drugs, we don't have many drugs for these patients. So I think in this patient population there's a dire need to find new drugs or to find new applications for the drugs we have.

And I think that, especially when combining protease inhibitors, we have found that for these patient population we can do better when we use the same drugs. And there's some preliminary

evidence, even in the book we received from Zolopa's study from Stanford and some others, that there actually -- it does matter how you give these drugs. So I think this is a calculation which has not been addressed enough, and definitely there's a need.

I think, looking at the issue of resistance -- which is often very important in these patients -- resistance, again, is relative. And as the pharmacologists here have been discussing -- and Terry mentioned you always have, in a continuation of the curve -- we still have resistance. Resistance is not a "yes or no" phenomenon. It never is. As you accumulate mutations, you get more resistance, and this continues basically to infinity. So, theoretically, if you could increase drug exposure enough, there would be no resistance, you would just overcome whatever resistance there is by giving more drug.

So I think for these populations the game is totally different. I think the outcomes are different. I think, in a very experienced patient population, we don't always treat the patient

clinically, the outcome is not the same as what it'll look in naive patients. I think if we take very experienced patients and our outcome is "look at how many are below fifty 48 weeks later," the study will show nothing because the number will be very small. But if you look possibly at those that a year later have had a stable CD4 count and not had any clinical progression, that might be very relevant in some very experienced patients.

So I think everything we've been doing has been very biased towards naive patients; and this patient population, who don't have 14 drugs, needs to be looked at different. I think the outcomes have to be reconsidered. I think Steve Deeks of San Francisco, and others, have been doing a lot of work looking at this patient population as different. I think resistance here has to be considered as relative.

And another issue here, I think: Are we willing to pay a different price? I think the issues of adherence and toxicity are different in this group. I would definitely agree with John, in the naive

patients it's adherence, adherence, adherence, adherence. I think in some of these patients, who really are having clinical symptoms, I think we can sometimes see patient improvement with their adherence. But the issues here really are: Can we get enough drug into the patient? And we may be willing to accept greater toxicity in this patient population than we would in a naive patient.

So I think it's really an informed issue. I think you have to treat this patient population differently, and even design the studies differently when considering them.

And the last point would be, there's a luxury in going to 48-week data. Like all tests, it's a sensitivity-specificity tradeoff. The longer you go, the greater your chances that you'll catch late toxicity. But again, here, to demand 48-week follow-up, these are patients who need the drugs more urgently. As a regulatory agency, there may be also some consideration accepting a little bit of a more risk since these patients have a very great risk right now for their life.

CHAIRMAN GULICK: Dr. Fletcher?

DR. FLETCHER: I agree with Jonathan. I think the underlying response the nature of the response is going to be the same. Concentrations are going to matter. It's just they're going to be different. So some $EC_{50}$ that you find in a naive is not going to be that in an experienced patient.

And so I think, from a regulatory point of view, if a study for an alternative regimen was done in naives, and let's say the drug had not exactly the same PK profile -- $C_{max}$ was a little bigger, $C_{min}$ was a little lower -- but after 48 weeks in a naive patient population, no difference in proportion undetectable. But to have confidence to extrapolate that to a treatment experienced patient I think would be very low.

CHAIRMAN GULICK: Dr. Struble?

DR. STRUBLE: So, Courtney, are you saying that we should require data both in naive and experienced patients when we're going from like a TID to BID regimen, and it's not applicable to everyone?

DR. FLETCHER: Actually, yes.

DR. STRUBLE: I guess I'd like to hear comments from other members how they feel about that, as well.

DR. MASUR: Are most of the drugs approved for both treatment in naive and treatment in experienced patients? If there's no initial approval for treatment experienced patients, it doesn't seem any reason to -- it doesn't require the new formulation.

DR. STRUBLE: The approval is for the treatment of HIV infection. The majority of these studies have been done in a naive population or a new experienced population.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: Dr. Struble, I take what Courtney said a little further than that. I think the agency needs to look at longitudinal data in both naive and treatment experienced patients in terms of PK. They need to look at patients at different time periods in terms of viral load, or whatever marker you want to use, for severity of disease to see if PK changes, so that we can use these drugs more

effectively, more efficiently, and smarter, so maybe we would avoid some of the other problems that we see. So I think we need a lot more data in both those populations in terms of PK data.

And also, specifically I would suggest genotyping people, phenotyping people using accepted markers, and then trying to correlate that with some of the kinetics that we see.

CHAIRMAN GULICK: Dr. Pomerantz?

DR. POMERANTZ: I just want to remind everyone when you use -- and I know you all know this. But when you use the term "naive patient," that is a running target that's changing.

When I had to write an editorial on this last year, you saw Doug Richmond and David Ho's group show that in the United States that primary resistance was about two to three percent. It's now close to ten percent in some places; in Europe it's in double-digits routinely. And that's going to -- if we look at what you can prognosticate, is going to change. And unfortunately there may be less difference between the treatment naive and the experienced as this goes

along, unfortunately. So I think you got to be careful even when you put the naives.

CHAIRMAN GULICK: Dr. Yogev, and then Dr. Blaschke.

DR. YOGEV: I think you should not forget the patient. To me it's a completely different population. An experienced patient over the more advanced disease, kidney involved, liver involved, some thing you don't even aware of, only to see if the PK is even the same on the same dose, let alone everything else we mention.

And we know from our own experience that we have much more toxicity on the same level on patient with AIDS, which we always confuse: Is it AIDS or is it the drug? And in more than half of them, when we stop the drug, they improve. So to me it's completely different population that you have really. And what was said over here by the person from New York is, this is exactly the point. They have to have a separate consideration.

CHAIRMAN GULICK: Dr. Blaschke?

DR. BLASCHKE: Well, I think Henry made a

key point here, and that is, most of the drugs that are approved, when a company comes in and asking for an alternative regimen, if they're asking just for an alternative regimen, with no change in the label, then I don't know that you could ask them to do a study, for example, in a population that they didn't originally study, and then demand or ask for therapeutic equivalence.

I agree with everything that Jonathan has said about the experienced patient. Those issues, though, it seems to me, are issues for the research community and for people involved in investigating the best treatments for HIV, and we certainly should be doing lots of trials looking at combinations and alternative regimens and so forth in experienced patients. But I think unless that is something that the company wants to come in and ask for, a change in the label of their drug, that it doesn't make sense, from, again, a therapeutic equivalence point of view, to ask them to do studies, for example, in experienced patients, if the original approval was not based on experienced patients.

CHAIRMAN GULICK: So the consensus seems that the issues are quite different in treatment naive and treatment experienced patients; and, reading between the lines, that there is much less data available for treatment experienced patients; and that your thresholds for safety and efficacy are quite different.

The second part of this question is asking about: Are there cases where additional data are necessary for different patient populations? We're going to consider pediatrics separately. Other populations that have been brought up over the day have been pregnant women, breast-feeding women, people with hepatitis C.

Comments? Dr. Flexner?

DR. FLEXNER: I just think we have enough information about the pharmacokinetics of NNRTIs and protease inhibitors and the relationship between antiretroviral efficacy and drug concentrations, and probably some inkling about relationship between drug concentrations and toxicity, to begin to look more systematically at patient populations where we know

there's going to be altered pharmacokinetics. And the one place where that is most obvious is the patient population that Jules brings up, and that is people with hepatic insufficiency in general, not just hepatitis C infection.

And so there is substantial data on pharmacokinetics and hepatic insufficiency in some, but not all, of the package inserts for the antiretrovirals. And I would just encourage the agency to encourage the industry to provide us with more of that, because we are going to be taking care of more patients with concurrent hepatic disease and HIV disease, and it sure would be nice to have at least rough guidelines about how to adjust doses in those patients. And Dr. Gallicano's done several nice studies on pharmacokinetics in patients with hepatic insufficiency. There is some work out there, but we need more of it.

CHAIRMAN GULICK: Okay. Let's turn to safety issues, which we've already touched on several times. I guess we haven't addressed this specific question: Does the scientific data at present

correlate any particular exposure measure with toxicity? We've heard a lot about $C_{max}$ today provided as an example. Dr. Gerber?

DR. GERBER: Well, I mean, I think you're asking a difficult question. I think overall exposure, if you increase the AUC overall exposure and you increase the $C_{min}$ 20-fold, you may have more toxicity, irrespective of what the $C_{max}$ is. I mean, versus just seeing more drug over a period of time. So there you would definitely need toxicity data as part of the trial.

CHAIRMAN GULICK: Dr. Schapiro?

DR. SCHAPIRO: Well, I think, to answer that question specifically, I think we don't have one parameter because toxicity is not one event. I think the mechanisms of different toxicities are different, and therefore we really -- if we had trouble with efficacy, this is much harder, since some of these are hypersensitivity reactions, other accumulations. I think here it's pretty safe to say that whatever we said for efficacy, worse.

CHAIRMAN GULICK: We got that.

(Laughter)

Next: What amount and duration of safety data are needed to support new formulations or new dosing regimens with increased exposure measures? So I guess we're looking for duration of time.

DR. FLEXNER: I mean, it depends on what you mean by "increase." If drug concentrations of an AUC or a $C_{min}$ is increased by 25 percent, that has very different implications than if the $C_{min}$ or AUC is increased by five- or tenfold, as Dr. Piscitelli points out. And I think the agency surely can take that into consideration when they decide how to approach a new formulation or a new regimen. And I think higher standards of safety would be necessary, the higher you push the drug concentrations with your new regimens.

CHAIRMAN GULICK: So there are regimens that we're using every day in clinic right now which are many-fold greater than what's been tested, with no safety information at all, or very little. What would you require? Dr. Fletcher?

DR. FLETCHER: Well, to me it seems, in

general, in terms of at least the duration, you'd at least want to mirror the period of time that whatever, that adverse event profile looked like with the drug, without the enhancement.

Nephrolithiasis is the only thing that comes to my mind. But if that occurred -- let's say, typically in 16 weeks -- and then we boost the drug, I would at least want to see a safety database that covered 16 weeks, so you've covered that same period of time that the adverse reactions were known to occur before you increased the exposure. Now, there's probably good reasons to go beyond that, but at least I'd cover the same period of time.

CHAIRMAN GULICK: Dr. Masur?

DR. MASUR: I mean, I would think that we'd want at least the same 24- and 48-week data we wanted before, because I guess there are two concerns. One is to see what the frequency of the data that we know to expect is. But the other issue I'm sure we're all concerned about are the unusual events that either occur at such low frequency we didn't pick them up at all, or we didn't know if they're related to a higher

concentration. We may find that at 16 or 20 or 40 weeks they may suddenly become a substantial problem. So I think I couldn't see any rationale in decreasing the interval.

CHAIRMAN GULICK: I guess one of the other challenges is for more infrequent side effects, such as a hypersensitivity reaction. You'd need to study large numbers of patients to pick that up with a change of regimen, which is also a challenge.

Dr. Yogev?

DR. YOGEV: Just educate me why you think the hypersensitivity would be higher with a higher dose? The hypersensitivity, the beauty of it, it doesn't matter on the dose. So, or we're missing something, or we mean new, which I saw Dr. Masur was afraid, something new. That, for example, a drug was never toxic in a low level, become toxic in Week 26. But hypersensitivity, for me, doesn't matter what the dose is.

CHAIRMAN GULICK: I guess not everything we call "hypersensitivity" is true hypersensitivity.

DR. YOGEV: So we're talking about the

same, a new thing, new --

CHAIRMAN GULICK: I guess we're either talking about new or uncommon toxicities, occur in two percent or two percent of patients.

DR. YOGEV: But those should come at the Stage 4. Clofenacol took three years to find out it's one in 48,000 in California. So I don't think it'd be fair to impose it up front. And in this type of disease, the world -- high toxicity, the more acceptable it is, just because of the severity of the disease. So I think it's important to follow, but I would not impose increase of time.

CHAIRMAN GULICK: Well, I guess you're making a good case for post-marketing surveillance, which is how some of these unusual toxicities happen. Dr. Gerber?

DR. GERBER: I'd just like to say something about hypersensitivity not concentration-dependent. It is concentration-dependent; it just may require a very small amount to cause a response. So everything is really pharmacology concentration-dependent. It just may require one molecule or two

molecules.

(Laughter)

I have to make that response.

CHAIRMAN GULICK: Thank you, Dr. Gerber.

Dr. Struble?

DR. STRUBLE: I guess I'd like to hear some more comments on what amount of safety data is needed. As with the Fortovase example, there were 500 patients followed for 16 to 24 weeks. As you know, 500 patients is typically what we require for a new molecular entity. So you're saying that we should require that same standard, or is there something in the middle? I'd like to hear some comments on that.

CHAIRMAN GULICK: Dr. Schapiro?

DR. SCHAPIRO: Well, going back to the introductory talk which focused on the fact that regimens will then be used for a long time that aren't being addressed by the agency, and what Trip said, that in clinic we're using, all the time, combinations which are not approved and there's nothing in the insert. I definitely agree with what was said, that you have to really, by the book, wait at least as long

as you waited for the lower dose. But we will then have a situation where for a very long period of time there'll be no guidance from the FDA for the physician, and that's what's happening today.

I would bet that most of the drugs are not being given the way they're labeled by the FDA today. The protease inhibitors, at least, are not. And what happens, there's a lot of confusion on these doses. It was shown very nice in an introductory slide. And I think a lot of the time what we're doing is, when we're asked, "What dose should I give my patient?" you know, it's a tough decision.

And there may be a need here for something creative, and post-marketing or some way of doing surveillance where it is allowed, especially if we again go back to the issue of the very experienced patients. Again, we may find that there's a dosage which appears to give good efficacy, but we're not sure about the toxicity. To wait 48 weeks until we're really, really sure, I'm not sure that's the best option. It's the safest option.

But if there's some sort of creative

solution where you can allow it, but demand the study that follows up, it's something to consider in this unique situation.

CHAIRMAN GULICK: Dr. Mathews?

DR. MATHEWS: Everybody's raising a real serious point that's only getting worse, that we're increasingly forced to practice in an environment where we really don't know what we're doing. And because many of us are believed to be experts, that somehow adds some credibility to it.

It's my understanding that a sponsor cannot promote a new regimen or a new combination unless it's in the label; that's correct? And yet it's going on all the time. Sub rosa people are giving you slides that you can't say our company supports this, but this is the data that doctor so-and-so presented based on five or ten patients or whatever.

So my bias would be that this somehow needs to be tightened up. Otherwise there's going to be no way to really control the outcome with these kinds of therapeutic adventures.

CHAIRMAN GULICK: Dr. Jolson?

DR. JOLSON: Well, just to address Dr. Mathews' point, and I think we understand it. Actually this is an issue that the courts are debating in terms of what pharmaceutical companies can disburse by way of medical literature. And currently the court has ruled that if something's published in the literature, FDA can't prevent companies from distributing it, because presumably anybody could go get it out of the library or go search it on the Web. So it's a controversial issue, and right now there's no clear resolution of where that's going to end up.

CHAIRMAN GULICK: Dr. Kweder?

DR. KWEDER: Yes, and I would simply add to that, that because the discussion often turns in this direction, that there is no -- the definition of "appearing in the literature" has, to date, been considered very, very broad; some would say "loose." So it might be literature that appears in your mailbox, unsolicited in a pharmaceutical company-sponsored journal, but has some imprimatur of peer review that would be acceptable, which would have the

same standard as an otherwise -- what most would consider a rigorous scientific journal.

DR. ACOSTA: So that includes abstracts as well?

DR. KWEDER: Yes.

DR. ACOSTA: Abstracts and peer review?

CHAIRMAN GULICK: Dr. Kumar?

DR. KUMAR: I want to add clinician's perspective to what was just raised, and I want to give you a very specific example. Last Thursday we have a clinic in which number of different physicians see patients. And as part of HCFA regulations, not directly seeing patients they write lengthy notes. And there were a combination -- four different physicians wrote combinations for Efavirenz, Amprenavir, and Ritonavir. And they're all esteemed physicians. And the dosing was different, also.

And I actually called them up the next day, on Friday, and said, "Can you give me a rationale for this dosing?" And it all depended on, oh, that conference or that speaker or that one put that in my box.

So to me as a clinician, it has huge implication, because there's no room for error. This pharmacokinetic, all my colleagues spoke so eloquently on what is $C_{max}$, $C_{min}$. But to a clinician, how many angels do you want dancing on the head of a pin?

There's no room for error to a clinician. And this is huge implications to us, that we are asked to practice, and given a lot of -- little bit of data, and we make mistakes that cannot then be modified. And so I think we need to come to some kind of understanding on what will be labeled and what information is going to be given out.

CHAIRMAN GULICK: Dr. Jolson?

DR. JOLSON: That's an interesting point, and I think we appreciate that sentiment. And I think you're starting to see the dilemma that we're in. On the one hand, we can be perceived as holding up science or holding up drug development, allowing the labels to get increasingly farther away from clinical practice by our regulatory requirements and what are perceived maybe as unnecessary bureaucratic requirements.

On the other hand, if we don't have some sort of standard of evidence, we're basically allowing pharmaceutical companies -- with all due respect -- to be promoting potentially misleading or dangerous information without having done very much work to support the regimens, and not providing the information that you all need as clinicians.

And that's why we bring it to you today, to see what is reasonable. And I know it's saying, you know, we don't have, like, a reasonableness standard, but we actually do. But that's based on some sort of requirement for some reasonable amount of evidence. And we're trying to reach that happy medium of what's a reasonable amount of data that's not overly burdensome, but that doesn't let you all down and leave you all without a prescribing information.

DR. KUMAR: I think part of the issue is not so much of misleading information; it's really not what really translates into clinical efficacy. Even within this room there is differences of opinion on people who are leaders in their field.

But, again, when it comes to translation

to clinical medicine, that is huge implication, because there really is no room for error in these very advanced patients.

CHAIRMAN GULICK: Just an observation that there is a tension right now between -- most of the information we have on PK is on older regimens which are challenging to adherence. And many of these drugs we simply don't use that way anymore.

Yet, as was said, we're using regimens in clinic which there may be little or no safety information on, and we're taking this chance. What are the repercussions? I guess we'd all like to see more data. That's the unifying theme here. Dr. Pomerantz?

DR. POMERANTZ: I enjoyed what Dr. Kumar said, because I can relate, I can empathize with that.

But just a point, though. The problem with pharmaceutical companies giving out data and slides, or published literature is different than the abstracts, that's where I've seen it become most difficult, in that there are lots of meetings, there are lots of abstracts, and certainly different

companies will copy a poster and will put it in somebody's mailbox, or a number of them in a book.

And for me, I mean, sounding somewhat elitist, I don't mind if they give it to me, because I think I can sort of sort out most of it. But where it comes into a problem and where I hear it -- and I think Dr. Kumar is nodding her head -- is that I get this question from the local doctors or from someone who doesn't see or study the field, and they get these posters, these abstracts. And if they'll come to someone who does think about the field, and so they can have someone to bounce it off, it can actually be a good educational experience. But if they don't, and they just say, "Oh, well, I can use Ritonavir at 40 grams a day," that's where you get into trouble.

So there is a plus-minus to that, because drug companies can be informative, because there are so many meetings and there's so many abstracts, and every once in a while something even gets by me or Charlie, even. But you get into trouble; yes.

(Laughter)

You get into trouble, as Dr. Kumar was

alluding to, with people who are told these ways, that are given the abstracts, that cannot critically review them, and just take them as gospel and, "Oh, yes, we can do this."

CHAIRMAN GULICK: Dr. Acosta?

DR. ACOSTA: And abstracts are preliminary data. And I agree with you completely.

DR. POMERANTZ: But they're published, so it's hard to tell a court that it -- but it's in the public domain, which is how I think they get away with it.

DR. ACOSTA: Yes. But they're not peer-reviewed.

CHAIRMAN GULICK: Okay, Dr. Hansen.

DR. HANSEN: Maybe it's who you think your peers are.

(Laughter)

But getting back to the Question No. 3, we talked about duration of safety data, but we didn't answer actually her question about numbers of patients. And in an experienced population it seems to me that duration might be more important than

numbers, and smaller numbers than the 500 that we traditionally use might make more sense. I don't know how anyone else around the table feels, but just to try and answer the entire question.

CHAIRMAN GULICK: Thank you.

Response? Dr. Yogev?

DR. YOGEV: It's sort of responding. I was listening to my colleagues, and obviously they went through the same experience, and find out that there's no education from the FDA to our colleagues about the danger of these type of things. So there's nothing to counterbalance what the pharmaceutical company and the like are doing.

I think it's important to put maybe some sort of educational caution that if you see such a thing, just be aware what you're doing with that data. We need to educate our own colleagues and ourself.

And I had an experience with a couple of those situation like were mentioned, and we were able to convince the pharmaceutical company to do levels for us, just because we believe in pharmacokinetic on patient which we go with. And sometimes we cannot.

But there's nothing to back us up. They don't listen to everything.

And today it's even worse, because our journals not anymore Nature and Science. They are The New York Times and The Washington Tribune and Chicago Tribune. That's what the problem is. So we need maybe to consider from the agency some newsletter from time to time that does combination around recent data, blah, blah, blah, and give some data of disasters which happen or that you're aware of, that will help to educate ourself.

CHAIRMAN GULICK: Dr. Kweder?

DR. KWEDER: Okay. I'd like to address that point, and then another one made by Dr. Schapiro earlier.

As an agency as a center for drugs, we recognize all too well and all too painfully that for the most part our voice about drugs is only heard through drug companies. And most of the time the focus tends to be on the label.

However, we tend to have a lot more information available or that comes from meetings like

this, or from hearing your opinions, and have more to say about things in general. We recognize that; not only in this field, but much more widely.

And as a center, we're looking into ways to begin to address that. And I can't promise a quick fix, but I can give you an example that is, I think, quite embarrassing; that a clinician can't go to the FDA Web site and get information about a drug. I think that's shameful. So we're beginning to try and address that, but it's not a quick fix. It's very, very complicated.

I also wanted to address Dr. Schapiro's point about thinking creatively. And we have done that, particularly in areas of risk and trying to make risk assessments once a new regimen or even a new drug is approved. I can give you an example of an antibiotic that was approved last year that seems to have a propensity to prolong the QT interval. And one of the things that the company committed to, as a Phase 4 requirement -- that term's been put out on the table today -- was not to simply rely on post-marketing surveillance, as most of us know it, "if

someone remembers to call the hospital pharmacy, it might get reported," sort of thing. But rather, to institute an active surveillance study to assess what that risk might be, broadly and in selected subgroups of patients with concerns. So we've certainly done some of that, and that might be the kind of thing you're referring to.

DR. SCHAPIRO: Absolutely. That type of solution would be very appropriate.

CHAIRMAN GULICK: Dr. Jolson? Dr. Wong?

DR. WONG: I guess just on this question I would say that if the dosage is going to be higher than the dosage that was registered, I would want a full safety profile based on the same number of patients at the same duration that was required the first time through. And I think that prescribing physicians ought to have that kind of information.

I would say that it would not necessarily interfere with an approval, but the data set should be available. I mean, you probably remember that for example, I said that had Gilead come in with Adepavir at 60 milligrams per day, I would have voted for

approval. And I think if people know, they can deal with it.

And the criteria would be different for people who are failing multiple drugs as compared to people who are getting their initial treatment for the first time. But I can't really imagine very many situations in which a substantially larger dose of the same compound should not have the same rigorous safety set, data set as it did the first time around.

CHAIRMAN GULICK: So, just to draw some consensus on this, we heard that safety data is sorely lacking right now on new formulations. That we would all like to see more of it. There was a bit of a disagreement about how much and how long, and how to get the word out to people. But we all felt pretty strongly that we need it.

With that happy thought, why don't we take a 12-1/2 minute break. We'll reconvene at 3:30.

(Whereupon, the foregoing matter went off the record at 3:21 p.m., and went back on the record at 3:35 p.m.)

CHAIRMAN GULICK: Okay, we're on the home

stretch. Question No. 4 is drug interaction issues. And we've begin to touch on this already.

If one or more exposure measures are decreased, should additional clinical data be required? And if so, how much? I guess the consensus before, when we addressed this, was yes.

DR. STRUBLE: There's actually a question before that.

CHAIRMAN GULICK: There is? Oh, you're right. There we go. Thank you, Dr. Struble.

Which exposure measures should be considered when providing labeling information on concomitant administration of antiretrovirals? And your attention here is these PK enhancers rather than -- both? Okay. Mr. Cheng?

MR. CHENG: I have a question on this issue, but not directly on this question. I guess when you look at the package insert, a lot of the drug interaction data is in people who are HIV negative. And I'm wondering how appropriate that is compared to people who are HIV positive and with perhaps some of the kidney or liver dysfunction that we've also talked

about, and how that should be addressed.

CHAIRMAN GULICK: Dr. Reynolds?

DR. REYNOLDS: We recognize there are differences, and most of the time it is just easier to conduct the studies on healthy patients, because we don't have to worry about other drugs. And we are talking about a difference of maybe, in this population, a 20 percent increase. The other population it's a forty percent increase. We feel you can make a determination there.

And then sometimes for clinical trials we also have safety data for the combinations. But it's really just cleaner to do in the healthy patient. But if there's a way to do it in regular patients, that's fine, also.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: I think this drug interaction issue is another area where pharmacogenetics becomes very big again. If you have patients -- because these antiretrovirals tend to be adequately metabolized -- that by genotype are poor metabolizers, or by phenotype, because of their

disease, are poor metabolizers, and you do a drug interaction study in these people with an inhibitor, you may in fact not find a big effect, because they don't have a lot of enzyme to inhibit. That kind of gets to Mr. Cheng's point about normals and HIV-infected patients.

So I think we need to broaden kind of how we look at drug interactions in these people. It makes me kind of nervous when you see data with, once again, a wide variability, and let's say the effect of Rifabutin on Indinavir or something like that, that in fact some people are going to have a big effect, some people are going to have a small effect. And the same may be true with Ritonavir in terms of an inhibitor.

So, I mean, I think we need to factor in genotype, phenotype, and diseases, and get away from the normal volunteer studies of these drug interactions.

CHAIRMAN GULICK: Dr. Piscitelli?

DR. PISCITELLI: I'm glad we're into the questions now that have answers to them.

(Laughter)

I think one major problem that I've found is that we have these two-way drug interactions to these, and that helps no one in the clinical world, when the phone calls I get are the patient taking six and seven antiretrovirals and someone says, "What do I do with the protease?"

Now there are data emerging looking at mostly three drug interactions, but in some cases four; and I think it's imperative that that sort of information gets into these labels. Now, it may not be a company-sponsored study. It may be a study from an individual, university, what-have-you. But it'd be nice if some of that information might still be used, if there could be collaboration between those groups. So that would be one issue.

Certainly the variability is critically important. Presenting an AUC, for example, there's several interactions where there's a 30 percent drop, so we raise the drug 30 percent. I mean, I think this panel's well aware of the inherent dangers in that. So variability is absolutely crucial to these labels.

In some cases I'm amazed. I don't want to

pick on any drugs, but there's some of these interactions where there's an NF5 and it's in the label, and there's a large decrease to a large increase. Well, that's absolutely useless to the clinician. And I think we need to be worried about that.

And also I found this accidentally, that not all these studies are crossovers. Sometimes the drug interaction information is across patients from across studies. But you wouldn't know that by looking at the label; you just see a 50 percent change and you assume that was a crossover study.

So I think there are several issues that could be addressed in the label. Those are a few of them.

CHAIRMAN GULICK: Dr. Flexner?

DR. FLEXNER: I agree in theory with Dr. Bertino's comments about pharmacogenetics and pharmacogenomics and intercurrent diseases. But I think as a practical matter, the data that HIV infection, per se, affects pharmacokinetics of any drug is lacking.

And the biggest change, comparing healthy volunteer data to HIV-positive patient data, is variability, with the patient data being more variable, which is predictable, given differences in body surface area and intercurrent diseases and intercurrent drugs, each of which, taken individually, can explain why an individual patient's pharmacokinetics look further away from the mean than you would expect them to be.

I also think, in terms of genetics, that genetics will turn out to be an important issue for some drug metabolizing enzymes. So far it does not appear to be an important issue; at least a common issue for 3A4, which is the enzyme largely responsible for metabolizing the drugs we're talking about today. And so I think we're a long way from being able to use genomics to predict who's going to be a rapid or a slow metabolizer.

And unfortunately the phenotypic tests we have for predicting 3A4 metabolism are not very clinically useful, in that the rate at which you metabolize one prodrug -- for example, erythromycin --

does not very precisely predict the rate at which you're going to metabolize another drug, like Saquinavir.

CHAIRMAN GULICK: Dr. Gallicano?

DR. GALLICANO: Just to follow up on Steve's comments. Regardless what exposure parameter you choose for a drug interaction, whether it's AUC, $C_{max}$, or $C_{min}$, the ultimate success still depends on study design. There are a number of choices out there, some which are better than others, and certainly it depends on the specific study that one is trying to design.

There's very little long-term drug exposure data for drug interactions, particularly with combination PIs and PIs plus drugs used for opportunistic infections. What I would like to see in a label, too, is for drugs that have time-dependent pharmacokinetics; that is, the total plasma exposure changes with time once the PI is started. There should be information on drug interactions during an acute dosing of the PI, as well as chronic dosing of the PI.

I think a very good example that just appeared in the literature has been Ritonavir and Alprazolam. Ritonavir increases Alprazolam during acute dosing of Ritonavir, yet it decreases Alprazolam during -- sorry, Ritonavir increases Alprazolam during acute dosing of Ritonavir, but decreases Alprazolam during chronic dosing of Ritonavir. And there have been requests for those types of labeling information.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: I guess I probably take a more optimistic view of probes, Charlie, than you do. And I think there is some data with 3A in terms of prostate cancer and certain types of leukemias that suggest that polymorphism may be important. There's one paper out there that looked at using probes.

But one of the questions is: If you induce people, are they going to look different? Probes like erythromycin really are PG3 substrates as well as 3A. They really aren't pure 3A probes, so I would think that there wouldn't be a real good relationship between Ritonavir and erythromycin elimination.

CHAIRMAN GULICK: Question for our pharmacologists. Do we have any idea how much drug failure is related to polypharmacy in our patients with competing drug levels?

No. Okay, thanks.

(Laughter)

Dr. Yogev?

DR. YOGEV: Maybe I'm misreading the question, but is that for the agency what exposure to look for before labeling, or what exposure properties should be in the labeling?

DR. JOLSON: In other words, what would you recommend basing your dosing recommendation on? Are you looking at -- assuming that everything is going to change a little bit, what's most important to you all to look at, on which to then base a dose recommendation? Are they for regular drug interaction, or for the situation of PK enhancers?

DR. YOGEV: See, because what was surprising to me in the presentation was that colleague from The Netherlands suggested that dose action which we're doing now to increase level of one

drug with the help of another one, they didn't find any correlate with any one of those exposure parameters. And one of the possibilities is that it did so well, that they have so few patients failing, that's why they couldn't find it.

For me, in the labeling, what important is what to read on the other side; is not the expert, is the physician that is going to see one or two patient, and looking to an information. For me, important what exposure parameter cause more side effect.

And more important maybe even is, to my surprise, some of our colleagues don't realize that Ritonavir, for example, is enhancer, is not active. And that should be part of the warning, that although you're using a PI, you should be aware that it's not a PI, and decide what exposure level you are. So that's why I was asking the question.

Because for me we're probably going to see an increase in efficiency. We're not yet sure what the toxicity of the $C_{min}$, because supposedly it's connected more to $C_{max}$. But we find out not to be that true in the pediatric, for example, before Indinavir

with Ritonavir, at least, preliminary data suggested maybe the $C_{min}$ is also contributing.

So I don't think we still know which exposure is what, and that's why we need to look at all of them and interpret, for the reader, what those mean or what he or she should look for, and what is not there, the enhancing portion.

CHAIRMAN GULICK: A lot of heads shaking "yes," people would agree with those points. Okay. You can go. Everyone else has to stay.

We've sort of gone on and tackled the next one. If one or more exposure measures are decreased, should additional clinical data be required? And I think the consensus was yes, particularly if it's $C_{min}$.

If so, how much? I would venture to guess people would say the same length of time required for the initial formulation, so 48 weeks; 24 to 48 weeks.

In what circumstances are clinical data necessary? We've covered that, also.

DR. YOGEV: Obviously we need our pharmacologists to help us, because I got the impression the pharmacologists say that $C_{max}$ is not as

important in certain situations, so maybe we don't need those type, maybe define better the dose which are going to be identified as connected to efficacy linked to $C_{min}$. If there is a reduction, we need a full study; if it's another parameter which are not yet connected, maybe we need less.

CHAIRMAN GULICK: Dr. Flexner?

DR. FLEXNER: I mean, I think the discussion we had earlier, in which the pharmacologists all kind of felt that $C_{min}$ was the important determinant of virologic outcome, and that if you had identical $C_{min}$ but decreased your $C_{max}$, probably you would not be at increased risk for treatment failure. I don't think that argument convinced either the regulatory agency or the panel, in that I think our thinking was based on logic and interpretation of data, rather than hard data that specifically addressed that question.

However, there have been clinical studies in which regimens have been compared, in which the $C_{min}$ was the same and the $C_{max}$ was decreased, in which clinical outcome was equivalent. For example, the

Nelfinavir BID to TID regimen. And then there have been regimens where the $C_{min}$ was decreased, but the $C_{max}$ was increased, where the virologic response was not as good; for example, comparing 1250 BID of Indinavir to 800 TID of Indinavir. Those were regimens where the TID regimen had the higher $C_{min}$ but the lower $C_{max}$, but performed better in terms of virologic outcome.

So, I think even though those studies were not specifically designed to address those questions, I think the weight of the evidence that I'm aware of suggests that that's a reasonable -- it's certainly a reasonable thing for a pharmacologist to conclude.

CHAIRMAN GULICK: Dr. Blaschke?

DR. BLASCHKE: Well, Charles gave me a hard time about using clearance and volume and distribution. But basically, what's being changed in these drug interactions is clearance and/or volume and distribution, or bioavailability. And that's what determines the $C_{max}$ or the $C_{min}$.

And so a drug interaction isn't a drug interaction that affects $C_{max}$ or $C_{min}$, it affects volume, distribution, and/or clearance. And that's

what determines, then, what's going to be the $C_{max}$ and the $C_{min}$.

So I think the issue, as I see it, the question that was being asked on this and the earlier side is, again -- as Charles, I think, has just addressed -- what is the exposure parameter that we want the clinician to focus on. And I think, as best we can guess at the moment, it's going to be $C_{min}$.

And most interactions are going to increase. Well, shouldn't say that. They can work both ways. But if we're looking, for example, at Ritonavir where we're decreasing the clearance, for the most part, and maybe increasing bioavailability, then the change that's going to occur is if we don't change the $C_{min}$; if we adjust the dose not to change the $C_{min}$, we're going to reduce the $C_{max}$. That's the way it will be based on the pharmacokinetics.

CHAIRMAN GULICK: Dr. Piscitelli?

DR. PISCITELLI: Just a clarification. For example, did I hear you right that if exposure measure is changed, we need 24 to 48 weeks of data?

There's many instances -- Efavirenz and

Indinavir, and Nevirapine-Indinavir -- which a drug interaction was noted and a dosing recommendation was made, but a clinical trial wasn't then put into place to verify that. Just wanted to make sure that we're on the right track, that we're not now saying if we notice interaction and suggest a dosage change, we now have to go back and verify that clinically.

CHAIRMAN GULICK: Dr. Jolson, can you clarify that point?

DR. JOLSON: I'm glad you ask the question, so we can clarify it. Even though I think the term "drug interaction" is very, very broad, and so Dr. Reynolds this morning pointed to examples of more typical or conventional drug interaction, such as Indinavir-Efavirenz, Indinavir-Rifabutin versus -- and those we would not require a clinical trial to verify the recommendation. We would use our best judgement in terms of which parameters were most important to base a dosing recommendation.

On the other hand, the other example would be the PK enhancer issue, where a second agent is added to intentionally alter the PK profile of the

primary PI, with the hope that the primary PI will be more bioavailable, and that will translate into increased effectiveness.

And then the question there is: In that circumstance, for labeling purposes, how much clinical data is reasonable to ask for? And how much do you all, as clinicians -- having heard the frustration that right now there's not clinical data to base that decision on, there's certainly the strength of logic and evidence from other sources, but not direct clinical data about the safety and efficacy of that regimen -- what do you all think is reasonable that we, as an agency, require? Here more so for the issue of PK enhancement, which is the harder situation.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: Could we go back to that Indinavir 1200 BID, 800 TID study. Do we know why, as patients got further out, why more patients failed on the 1200 BID regimen? Was it a change in kinetics, was it a -- what was it? Do we know why? Because that data could be explainable and adjustable.

DR. JOLSON: We haven't reviewed the data

as an agency.

CHAIRMAN GULICK: Dr. Blaschke?

DR. BLASCHKE: Just a comment about the PK enhancer. Jonathan made a very important point a little while ago which probably deserves emphasis again, and that is: We don't know, for example, with Ritonavir, what it does in terms of intracellular accumulation.

As Jonathan said, there are some data suggesting that -- well, we have data from our own laboratory suggesting that's a pretty potent inhibitor of P glycoprotein, which would suggest, in fact, that it might also increase the intracellular concentrations of a drug like Saquinavir. But I think we don't know for sure. And that's one of the things that we really do need to think about in terms of drug interactions, is that particularly with the 3A4 inhibitors, we're talking about other potential interactions outside of the cytochrome P450 system, and that really then, I think, does call, in some cases, for some more clinical information, if at all possible.

CHAIRMAN GULICK: Dr. Pomerantz?

DR. POMERANTZ: Yes, sir, just to go back to Dr. Jolson. With the inducers, I think there are two things you try to do with them. One is to make it more effective, intensifying the effect, to use the term, or to make it more bioavailable to be used so that you could spread out the dosing interval of them.

I think that it depends on what you're asking that inducer to do. Are you asking it to intensify an antiviral effect, or are you just changing the pharmacokinetics so you can dose it differently? Wouldn't that matter, depending on whether --

I think that what I'm trying to say is that the question you're going to ask or what you're going to ask of adding a second agent, like Ritonavir, would be whether you're doing it to change the potency of the primary drug, or whether you're asking it just to change the pharmacokinetics of that drug. And I think that you might think about what you would ask to approve it or to put in a package label, depending on what the company is asking of it. Don't you agree?

CHAIRMAN GULICK: Dr. Murray?

DR. MURRAY: Well, let me just kind of put out a proposal on the table, something that we thought might be middle ground, and using a PK enhancer situation in where your $C_{min}$ -- well, think of the Amprenavir-Ritonavir situation where you have a higher $C_{min}$, maybe a higher AUC or about the same, but your $C_{max}$ is lower for certain regimens. Do we feel comfortable enough about what we know is $C_{min}$ in response, even though it's more based on logic, to maybe cut down the clinical safety database from a study that's powered with a ten percent delta, so that we know with 90 percent, 95 percent confidence that we're no more than ten percent worse? I mean, do we feel confident that if the $C_{min}$ is in the right direction, that we can primarily look at what the treatment effect is between two different arms in a smaller number of patients? I mean, can we have that middle ground? Do we feel confident enough for that? That might help to reduce the burden a bit.

DR. POMERANTZ: So what you're saying, though, is that if you're adding a double protease

inhibitor combination and you're doing it to intensify the antiviral effect, you would be proposing that we need less patients to show that this actually did that?

DR. MURRAY: Well, I don't know if we know ahead of time we're intensifying the effect. I guess in this case we would be at least trying to maintain the same effect as with a standard dose. If it intensifies, great; that would be a good outcome. But we're trying to reduce pill count, lower dosing frequency, and maintain at least the same effect.

DR. POMERANTZ: Right. But that's not how it's being used in the field now. It's being used in two different ways. It's being used to either give it less often, or you're using it to people who can't get below 400, to try to intensify the effect.

DR. MURRAY: Oh, I see what you're saying. I guess --

DR. POMERANTZ: And that's being quote-unquote, "studied."

DR. MURRAY: Yes, I guess, yes, that's a different claim. And maybe you want to discuss that.

But I guess the first claim we were thinking about is --

DR. POMERANTZ: All right. That's what I wanted to --

DR. MURRAY: -- is not the intensification for somebody who's above 400 and you want to try to do better, or you think somebody has a less susceptible strain and so you're trying to get them down further. I think the first one is just the different dosing regimen, the convenience of the dosing regimen.

DR. POMERANTZ: I understand that. I wanted to clarify that.

DR. MURRAY: Yes.

DR. POMERANTZ: And I'm sure you guys know that that's how it's being used, though, at times.

DR. MURRAY: Right. No, I know it's being used in both situations. I appreciate that. I mean, what we're interested in now is a proposal: Is there middle ground? Because we kind of came to this meeting thinking that the slides were that well, 48 weeks is burdensome. And actually I don't think we have any feedback that would suggest that we could

decrease that burden.

In fact, I've heard more that we should follow patients longer and do it more populations and do it in naive and experienced. Is there any situation where you have some good PK data and you feel -- and let's say it's a drug that's been on the market for a while, like Indinavir, and you're combining it with an enhancer, and you have some pretty good PK data. Or maybe Amprenavir. And that maybe you'll be willing to accept less than a strictly powered, what we call equivalence trial.

And when we talk about a clinical equivalence trial, it's really just a trial where we're looking for comparability, but it's powered enough so that your confidence intervals are going to set so that you'll rule out a pretty narrow difference between treatment arms.

CHAIRMAN GULICK: Dr. Wong?

DR. WONG: I guess, Jeff, the way I'd answer that is, I mean, I'd separate out the questions. And if the question is, "Does the enhanced regimen achieve the desired pharmacokinetic

parameters?" that could be in the label; it does that; and you wouldn't need a huge number of patients followed for a long period of time to show that.

But if the question is, "Does the enhanced regimen achieve an equivalent virologic effect?" you can't answer that without measuring the virologic effect. So I think that you could pose it as two different questions.

DR. MURRAY: Well, you can't answer it -- oh, I'm sorry. You can't answer it, but it's your certainty in that. And I'm saying can we sacrifice some of the certainty that the sample size requires for you to -- powering your study for a certain delta, can you sacrifice some of that certainty by using some other data, which is PK data, to say, well I guess we're less certain about the treatment effect, but maybe the point estimate was similar? But the confidence intervals are a little bit wider than usual, but we feel, even though those confidence intervals give us less certainty we have PK data that looks really good, so it's all falling in place. See what I mean?

It depends on what your definition of "clinical equivalence" is, and right now for a new molecular entity it's pretty strict. I mean a ten percent delta means a 500 to 700 patient sample size. But here I think we're trying to move to a different area in the standard of evidence.

And knowing that the drug's already approved, and you have some PK data that, according to logic, would seem to indicate you'd have a good response, can we loosen up the uncertainty around -- as affecting the power of the study, as far as the confidence intervals?

DR. WONG: And my answer would be you accurately describe what's known. So if the PK data is good, put it in the label and let people decide based on the PK data. But if the virologic data is less than what would ordinarily be expected, I would not permit a claim based on virologic data.

CHAIRMAN GULICK: Dr. Piscitelli?

DR. PISCITELLI: I would agree with that. I think in that case where the $C_{min}$ is very large and there's a very modest change in the $C_{max}$, I think

that's very reasonable, and I'm comfortable with putting that in and not having such a strict trial.

Because if you're going to make companies -- or if there's a new formulation with a similar profile, if you're going to make companies do a 48-week study of a new formulation versus the old one, or Amprenavir-Ritonavir versus Amprenavir alone, they're never going to fill those trials. Patients aren't going to want to go on those studies, so it'd be very difficult to get that data.

DR. FLEXNER: I can second that, having just explored whether or not we could do an antiretroviral prodrug trial at Johns Hopkins. Patients don't want to participate in those trials, especially if they're already taking the parent drug. Why should they go through all the rigamarole of enrolling in a study to take essentially the same drug they're already taking, with all these requirements and all this blood-drawing and all these clinic visits, when they can just go on low-dose Ritonavir and the same drug, and achieve what they think is the same outcome? I mean, patients do not want to