misleading.

DR. HOETELMANS: Well, if you look at the data that I just presented of studies that did show relationships, I don't really agree that in all cases the relationships are very poor. It is, of course -- we should realize that all attempts in which those relationships were not found, it's very likely that we don't find them in the literature. So it's also the selection of cases where these relationships did work out.

But in most of the studies that I just went over, the relationships I think were quite clear, but they were defined in well-defined populations, patients with same backbone of nucleoside analogs, which is something completely else when you look at the patients that are being treated with drugs at this moment outside of clinical trials.

DR. BERTINO: But given the large variability in antiretroviral pharmacokinetics, I still think it's misleading to say, well in this study we found a relationship between protease inhibitor exposure and reduction in viral load. Because, as you

said, this may only apply to that small population that was being studied.

And the only point I want to make is, I think you need to look at the combination of drugs and see what their contribution to viral load reduction is to really -- you need a bigger picture.

DR. HOETELMANS: Yes. That's generally not been done, because the other drugs -- the one I showed you, most of the studies concern single PI therapy with two nucleoside analogs, and most studies did not look into nucleoside analog concentrations, because it's known that it's very difficult to correlate the exposure to those drugs on any efficacy parameter. So they all focus on only one drug. That's true.

CHAIRMAN GULICK: Dr. Gallicano?

DR. GALLICANO: I'd like to second what Joseph was talking about, about trying to separate the contribution of the other antiretrovirals. Also, Richard, I think most of these studies do not take into account the within-subject variability. That is because they were all single location studies.

And are you aware of any work that is done, more longitudal work maybe on different days or different months and then -- to see if these relations still hold in, say, Month 1 versus Month 6?

DR. HOETELMANS: Well, not -- all studies that I showed you were single-point studies, as to say. Most of the studies indeed look at one time point, determine either a trough level or an AUC, and that's been used as a measure of exposure over the whole period of maybe six months.

But, for instance, the Adams study, the ENCAS study, they all looked into drug level determinations over the whole period of the study, and those studies still find the relationships. But it's a minority. Most studies indeed looked at only one time point.

DR. GALLICANO: And second, I would like to support your rationalization for using EC versus IC. There's always a lot of discussion on these two components. The main problem I see with EC determinations is that they're quite model-dependent. And, as you know, they need a wide range of

concentrations in order to develop a good model. And it's -- the data that I've seen in the literature, you rarely get concentrations at the low end of the curve to really adequately define a true EC_{50}, because you really need patients that are close to failing if you're going to get these very low values that are actually less than the EC_{50}.

DR. HOETELMANS: Yes, I agree. I don't think it's very difficult to cover the whole range of concentrations, because the intro variability and exposure is quite large for these drugs. But you do need a lot of patients before you are able to build a model that is good enough to be used.

CHAIRMAN GULICK: Dr. Flexner?

DR. FLEXNER: Richard, thanks for a very nice summary of what I agree with you is a somewhat disappointing field right now.

A couple of comments. First, to perhaps refocus the debate, we're spending a lot of time talking about whether or not a concentration response relationship exists. It always exists. What we're trying to do is discern it. And so when you can't

find a concentration response relationship in a clinical trial, it's an error of discernment, not an error of science, unless you don't have an active drug in the first place or a toxic drug in the first place. Because in the simplest of circumstances, if the concentration of drug is zero, there's no effect; if the concentration of drug is something, there is an effect.

And so that relationship is always there. The question is: Is it worthwhile measuring it, determining it; and what can you do with that information you get? And I think that's why we're here today.

Couple of comments related to your talk. The first is the issue of relationship between nucleoside, NRTI exposure, and outcome. There actually have been several studies looking at this relationship in patients. We published data with deoxyfluorothimidine in 1993, looking at the relationship between AUC and C_{min} and viral load changes, showing a quite clear and precise relationship, although that was in concentration

controlled clinical trials. George Drusanos published data with DDI also showing the concentration response relationship.

And so even though the active metabolite is the nucleoside triphosphate, for many of these drugs there is an apparently well-behaved relationship between plasma concentrations in parent drug and intracellular concentrations of the active metabolite. So I'm a little more optimistic about the possibility of using that plasma effect relationship in a beneficial way for nucleosides than perhaps was implied by your presentation.

And I think one of the things that has led us into thinking that plasma concentration effect relationships are not very good for nucleosides is the AZT story. AZT's probably an exception to the rule rather than the rule maker, in that the intracellular concentrations of AZT triphosphate are orally correlated with plasma concentrations, because the rate-limiting step in its conversion to triphosphate is the conversion from monophosphate to diphosphate, and so you get very high concentrations accumulating

of monophosphate, and very low concentrations of triphosphate. And that's probably why the AZT concentration effect relationship is not a good one. But I think for most other nucleosides we can probably be more optimistic that the relationship between plasma concentrations and intracellular concentrations will be better behaved.

The final point I want to make is that we've spent a lot of time so far this morning talking about dose -- or talking about concentration response relationships. We haven't said a lot about dose response relationships. But, in fact, dose is often quite a good surrogate for concentration, and there is substantially more information out there on dose response relationships for antiretrovirals. And I think we shouldn't neglect that very large body of data.

And as we start to talk about modeling, that may be one very nice area using dose and regimen response relationships, to convert that into a concentration response relationship. And I think that information might be quite useful in mapping out the

future.

DR. HOETELMANS: Yes, I agree.

CHAIRMAN GULICK: Dr. Yogev?

DR. YOGEV: I was intrigued by your comment that IC_{50} may be better than IC_{90} or IC_{95}, taking into account that we have so many quasi species in human being, and the more we treat them, the higher the quasi species.

And especially the NNRTI are telling us that one mutation is there already which we are just going to select and is a question of time. We see failure after Week 24. When Week 24 we do mathematics, it seems like anti-infective drugs combination thirty-six out of forty-eight failing. Isn't it more logical to check more to have the assimilation of quasi species which are in the human being?

DR. HOETELMANS: Well, the point I wanted to make is that we should not only focus on the fact that a trough level, for instance, should always be above an IC value, whether this is an IC_{50} or an IC_{90}. Because there may be many factors that make -- that

this ratio should be well over 100, for instance, for the non-nucleoside analogs, or may even be smaller than one.

But the fact that -- in the case of this being used, I think it's important to use the value for the IC a parameter that can be best determined, and this is the IC_{50} rather than the IC_{90}. So it might well be that for Drug A the IC_{50} -- sorry, the trough versus IC_{50} value should be over 100; whereas for Drug B it should always be over two in order to have a good clinical response in most patients.

CHAIRMAN GULICK: Dr. Pomerantz?

DR. POMERANTZ: Yes. I want to comment on this, because I understand what Dr. Yogev is saying about the need to inhibit quasi species or substrains in HIV *in vivo*. But there's some misunderstanding about what you usually do *in vitro* with IC_{50} and IC_{90}. The only reason that you use IC_{50} is because it's easier to determine on an accurate sense.

And remember that for the most part, when you do these studies *in vitro*, they're not done with quasi species; they're done with either molecular

clones, or even biological isolates which are not -- which don't have this resistance pattern that you're seeing. That problem is inherent, whether you use IC_{50} or IC_{90}, and that's important to realize, because you're not going to get --

Your issue's a good one. But IC_{50} or IC_{90}, as done by most studies, is going to have no interaction with what you may see *in vivo* when quasi species develop. So I see your point, but that's not how you're going to get at it.

DR. YOGEV: And I agree with you in principle. But I think we are just repeating what we stayed with in the past, which is so far removed from what we did in viruses, that we used the IC_{50} for a long time, to find out that the IC_{90} is much closer to what you really need to kill the virus.

For me, the IC -- the inhibitory concept is an issue that we relate *in vitro*, we accept it. I'm just tackling the issue. That's why the EC is better. I don't know how to define it. But the EC is telling you what -- the phenotype or what happened in real life versus the IC_{50}. If we accept it, we're

saying it's okay not to have the variation in nature or take the molecular clone or whatever and accept it, even in 50 percent of what we can test. And to me it just push a little bit closer with the IC_{90}.

And I agree with what you're saying. It might not interlock if they are very close in drug sensitivity. But we get a huge variation in certain drugs, especially in bacteria, that might be the same here. And that's why I wonder why not use it.

DR. POMERANTZ: That requires some comment as well. I agree -- I see what you're saying. But, once again, you can't make bacteria into viruses or vice-versa. The reason you use MIC_{90}s or when you're using MBCs, they're easy to measure compared to what you do with a viral inhibitory concentration. If you could do IC_{90}s and be accurate with them, you would use them.

It's just, as was said in this presentation, they have this variability, and so the data there may be actually making it harder for you because it is less accurate. I don't think you can make viruses into the same problem we've had for

bacteria because of the technical differences in studying them.

DR. YOGEV: You're right. I'm challenging just the issue of the IC_{50}, 90, 95. Should it be used as a parameter for when we're making decision because it's easy, or because it reflect what's in life? And if it doesn't reflect what's in life, we should challenge that specific issue. That's my point.

CHAIRMAN GULICK: Dr. Piscitelli?

DR. PISCITELLI: So it's clear there's a gaping hole in our knowledge in terms of the experienced patient and what to do in that population. And the reason that these studies aren't done or we're not finding relationships is we don't know what to shoot for in those patients.

It's easy, in naive patients, to give everyone the same dose or look at some certain relationships. In the experienced patient, we need some target to shoot for, so in defines of the C_{min} to IC_{50} ratio, it's probably buying us some information about where we need to be. I think that can be very useful, where we keep forgetting the virus end.

CHAIRMAN GULICK: Dr. Schapiro?

DR. SCHAPIRO: Just to follow up on that, I agree it gives some parameters, but I think if we look at the data, it -- and along with what Dr. Yogev said as well, it really underestimates to a great degree. And if we look at a lot of the studies, we have these incredible ratios which blow away all of the viruses in the body, and when we see the clinical results they're very disappointing. So it does give us possibly a ballpark figure, but I do think that the clinical EC-something is required, and I think a lot of that comes from what we saw with Richard, that we're really not at the final journey when we get to a drug level. You know, that's not where it's working.

But to extrapolate from that to what's actually happening in the cell, it's difficult. I don't know if we could do -- intercellular levels might be more effective, but without that, I think in a way we're lulling ourselves into very optimistic data, when we look at the IC_{50} to C_{min} ratios, and clinically they don't pan out.

DR. POMERANTZ: Well, I mean, I think there's clearly a lot of work to be done with intercellular concentrations. I'm sure one would agree with that. Likely, many of these failures, again, it gets back to adherence and tolerability issues and things of that sort.

CHAIRMAN GULICK: Dr. Mathews?

DR. MATHEWS: One of the problems that I see with the EC_{50} concept is that there's much more heterogeneity in each system, and so it's -- how would you begin to standardize from one trial to another what the EC_{50} actually means, because it's a function of the heterogeneity susceptibility of patients enrolled in that trial, as well as the range of viral loads that were observed in the trial, besides the drug potency.

DR. HOETELMANS: Yes, I think you're right. I think the -- if you would determine an EC_{50} value, for instance, in a certain study or in a cohort, it will always be linked to the features of those patients, so whether or not they were naive and treated with what other drugs. And it might

be possible that for Drug A you find an EC_{50} of 100 when you look at patients with high baseline viral loads treated also with two nucleoside analogs. But you find a totally different EC_{50} value when other drugs are being used, when the patients are pre-treated. And this makes the use of these EC values also quite difficult in the long term. So it will depend on many parameters.

CHAIRMAN GULICK: Did I understand you correctly when you said that in your review there is no current information linking dual protease inhibitor parameters to virologic efficacy?

DR. HOETELMANS: Yes. I was not able to find, at least by the published data or presented data at conference, that looked into this concept. Recently in our own group -- but these are unpublished data -- we did do an attempt to look at drug levels of Saquinavir and Ritonavir used 400/400 BID, over 100 patients, with a median follow-up of one-and-a-half years, and we were not able to find any relationship.

DR. POMERANTZ: There actually is one paper which is in the background materials, looking at

the combination of the Saquinavir/Ritonavir. It's showing a relationship with viral response. So that's the only one that I'm aware of.

CHAIRMAN GULICK: Dr. Masur?

DR. MASUR: There's one concept maybe you could expand on for me. I guess I'm a little confused as to how you can do an EC_{50} when you're always doing combination regimens. You could do an EC_{50} if you have a constant background of whatever your companion drugs are. But how are we going to devolve this in a way that is relevant to something other than the exact combination background that you're using?

I mean, if you're looking at Indinavir, if you always have the same concentrations of AZT and 3TC, perhaps you could define it. But how do we develop this system where we can't do monotherapy?

DR. HOETELMANS: Well, I think it's important, when defining EC_{50} values -- for instance, for a protease inhibitor in a certain population -- that we should try to do it with different backgrounds of nucleoside analogs, for instance, and see if there is any influence of the use of other nucleoside

analogs on the value of this EC_{50}.

We have to assume that the effect of the other drugs that are also applied to those patients are the same, regardless of their exposure, because there will be differences, of course, in the exposure to the other drugs in these patients. Or we should use very, very complex models that also take into account the exposure to the other drugs that are being used in the patients.

CHAIRMAN GULICK: Any other questions, comments? Thank you again.

Our final speaker this morning is Dr. Terry Blaschke from Stanford.

DR. BLASCHKE: I'd like to add my word of appreciation to the FDA staff for allowing me to come and present at this meeting, and also for the excellent background material that was provided to those of us attending this meeting.

I'm going to do a little graduate thing here. I'm going to say one word, and I hope that it will permeate through the rest of my presentation this morning. And the word is "integrate."

You're going to see, from some of the material that I present today, that we've talked a lot about a variety of different issues: pharmacokinetics, pharmacodynamics, drug-taking behavior, and so forth. And in order for us to come up with useful information with respect to the basic question that we're going to discuss today -- and that is changes in dosing regimens or alternative dosing regimens -- we really have to consider all of those factors, as well as, I think, both *in vitro* and *in vivo* data that will be generated in the course of drug development, as well as in the clinical trials that are done. Next one, please.

I'm going to focus on this issue for my discussion this morning. And I'll thank the earlier speakers for leaving me plenty of extra time here to go through the slides that I have. But what I want to focus on is: Can PK/PD modeling help to devise dosing regimens that will have better efficacy and/or safety, without adding time or cost to drug development?

I'm also going to start out with this premise which I haven't heard anybody else talk about

yet this morning, and that is: There is a need for alternative dose-finding methods, since all reasonable regimens cannot be studied using the standard that Dr. Jolson mentioned this morning. We have limited patient resources, as she mentioned. The time requirements would be excessive, and delay in patient access to alternative regimens is an important consideration. And of course, HIV therapeutics is a fast-moving field, and approved regimens may not be acceptable as controls to patients or investigators in studying alternative dosing regimens.

And again, this is a slide I've shown in a number of different venues to talk about the numbers problem with commentorials. This is a formula back from your high school algebra, talking about the number of combinations of "n things taken p at a time." And the important thing to point out here is that when we begin dealing with two or three drug combinations -- and most of these days we're dealing with three drug combinations -- if we consider that for a number of different drugs --

These numbers were picked up a few years

ago based on the number of antiretroviral drugs that were on the market. And if we are dealing with something on the order of 31 drugs taken three at a time, we have over 4,000 possible combinations, and that doesn't include differences in dosing regimens or dosing schedules. That's just the number of combinations of three drugs that we would have to consider.

So the reality is that we have to use other methods to help us design dosing regimens. And then the question that we're going to be addressing this morning is: What can we do with other PK/PD relationships to help us then provide that evidence that Dr. Jolson and Dr. Reynolds were talking about, without having to do large-scale clinical trials?

I think we need to be careful about our definitions of what we mean by PK/PD modeling. We've heard the term used a number of times this morning, and I'm going to spend just a minute or two talking about what we really mean by this expression. Next one, please.

And Kellie already put these definitions

on the slide for you earlier, that "pharmacokinetics" describes the time course of drug concentrations in plasma, and sometimes in other tissues and fluids, resulting from a particular dosing regimen. And "pharmacodynamics" expresses the relationship between drug concentrations in plasma, and sometimes in other fluids or tissues, and a resulting pharmacologic effect.

A PK/PD model consists of the following components: It's a model describing the drug concentrations versus time -- that is, the PK model -- along with the model describing a relationship of the effect versus concentration -- that is, PD.

And the third part and the most key part of the PK/PD model is a statistical model that describes the variation in intra- and inter-individual PK/PD models that's used to predict the time course and the variability of the effect as a function of time.

So we have PK/PD. These are not time-independent models. We have to put the dependency of time into these PK/PD models to really have an

understanding of the outcome. And then I've made a note here at the bottom which I'll come back to later on in the presentation. And that is that only mechanistic PK/PD models can be relied upon for extrapolation; that is, for prediction versus just descriptive models.

So I'm going to talk at some length about mechanistic models as opposed to statistical correlations, and talk about the value and the use of mechanistic models in PK/PD modeling, and then I'll finish in discussing some of the ways that we can generate those mechanistic PD models.

The process that we go through is to build a PK model, to build a PT model, to link the PK and the PT -- PD models, and then to simulate treatment regimens or trials to obtain some useful predictions. So this is what I mean by integration of the different components of the modeling process of the PK and PD model in order to come up with useful information.

And in the next two slides I'm going to show you an example of some PK/PD modeling that was done by colleagues at Abbott in conjunction with

colleagues of mine at Pharsight Corporation. And I'm going to use this mainly to illustrate how the PK/PD modeling can be used to help give us information and predictive capacity about outcomes. Next one, please.

This is the model that was used by Abbott in conjunction with Pharsight, which was a model to link adherence, pharmacokinetics, and viral pharmacodynamics to treatment outcome in a patient population. And we have on the left-hand side here the prescribed PI doses, we have adherence based -- and I'll come back to this later in terms of what our sources of information are. We have the actual dose that the patient took in. We then have a pharmacokinetic model, and as you see in a moment, that involves both a pharmacokinetic model for a single drug, as well as a drug interaction model that generates plasma concentrations as a function of time. And that's then input into a pharmacokinetic model that's based on *in vitro* data, as well as antiretroviral experience in disease severity, and the output from that model then is a measure of viral load.

The pharmacokinetic model as a component of this overall PK/PD model accounts for -- in this case with Ritonavir and a protease inhibitor -- dose-dependent bioavailability, competitive inhibition of the other PI by Ritonavir, and exposure-dependent enzyme induction on the part of Ritonavir.

So we have a very complicated pharmacokinetic model that both incorporates the pharmacokinetics of both drugs, as well as the effect of one drug on the pharmacokinetics of the other drug, as well as the effect of one drug on its own pharmacokinetics. So this is a standard approach to generating pharmacokinetic model. Next one.

Now, this is the pharmacokinetic model, and this is worth spending just a moment or two talking about, because this model is what I would call a mechanistic model. This model, which has been presented and published in abstract form, includes two viral strains, both a wild-type and a preexisting mutant strain. It incorporates both long-lived infected and actively infected cells. And it incorporates different sites of action between the

protease inhibitors and the nucleoside reverse transcriptase inhibitors.

Now, I won't go through this model in great detail because it would take too much time to go through the details of the model. But let me just give you a quick overview of this pharmacodynamic model.

Basically we see two different types of virus, a wild-type virus and a mutant virus infecting T-cells, and we see the reverse transcriptase as agents that prevent infection of uninfected T-cells. Those T-cells, when they become infected, can either be long-lived or short-lived T-cells which produce virus, and viruses released from those T-cells as the virus replicates, that can be blocked, of course, by the protease inhibitors.

And you see that there's two symmetric halves of this particular model: Again, the mutant virus and the wild-type virus, with the possibility of the wild-type virus mutating at a given mutation rate to a mutated virus and infecting other cells. We also have -- this occurs at a much lower rate -- but at

least the probability of a mutant virus mutating back to a wild-type virus.

So we take this entire model and we essentially fit our plasma concentration data to these entire pharmacodynamic model, and the model also then incorporates, for example, differences in the fitness of virus of a mutant virus versus differences in the replication rate or the fitness of the wild-type virus. Next one, please.

So the model that I showed you was used to assess the effect of pharmacokinetics and adherence variability. And the simulation that was done with this particular model incorporated 400 subjects simulated at 40 weeks of therapy in six different regimens. And there was a dose-time perturbation that was introduced into the model based on data that was available about patient adherences.

And adherence was also incorporated into the model with the distribution and the standard deviation, again based on the published literature data. And the regimens that were modeled in this particular experience were a BID and a QD regimen with

these different average levels of adherence and the variability thereof in adherence. Next one, please.

And as I said, Abbott used this approach to compare various combinations of PI dosing regimens which included low- and then moderate-dose Ritonavir. And by using this model, they were able to predict the range of the peak and trough concentration for each of the PIs in the regimen, and the ratio of the trough concentrations, the IC_{50} values for the virus. They were also able to look at the effect of varying degrees of non-adherence on the fraction of patients who are likely to experience virological failure.

And they took this model, and assimilations from this model, and compared it with actual data that they had generated in clinical trials, and found that there was a good correlation, a consistent relationship between what was observed in the full simulations using the full model, and what was observed in the clinical trials. And I'll come back to that in just a few minutes in talking about what do we need to do when we evaluate a pharmacokinetic/pharmacodynamic model. Next one,

please.

I'm going to spend a little bit of time -- because I was asked to do that and then I think it's important -- to talk about how we build and evaluate PK/PD models. Pharmacokinetic models are fairly straight-forward. And the way we do that is the classical way that we do that; that is, as part of conventional pharmacokinetic studies, we need to obtain information on inter- and intra-subject patient variability.

We heard someone mention earlier about this issue of intra-subject patient variability, and that is an important factor that needs to be incorporated into these models. And we can generate those data early on in the process of drug development.

Now, for drug combinations we need to study interactions and we need to evaluate those interactions at steady state with dosing regimens that include and bracket those likely to be used clinically. In other words, we know that we can't always extrapolate these kinds of interaction studies

beyond our actual data, so that in planning to do a pharmacokinetic model we have to study interactions, and it's best to study those interactions at steady state.

And we've heard a little bit of mention about protein binding. One needs to consider measuring binding protein, such as $alpha_1$, acid glycoprotein, and the unbound drug concentration during the pharmacokinetic studies, because there is some variability, particularly for those drugs that are bound to $alpha_1$, acid glycoprotein, and to know that relationship has some significance.

I'm going to go back again and just talk a little bit about the issues of where do we get the data that we need to generate these pharmacokinetic/pharmacodynamic model so that we can use it for helping us design dosing regimen. So, for example, if we talk about the adherence component of this model, in the Abbott study the adherence information was generated from adherence data that was in the public literature, had come from some of their own studies, and that was what was used to develop the adherence

model in the particular modeling situation that I just described to you.

As far as the pharmacokinetic model was concerned, those data came from multiple-dose Phase 1 studies, and one Phase 2 study, and then generated two one-compartment PK models as I showed you earlier, with enzyme induction and enzyme inhibition.

And then the pharmacodynamic model was generated from *in vitro* data, as well as information that was available from the clinical studies on antiretroviral or experience and disease severity. For example, we do know, and we know from a lot of experience, that the baseline RNA count, et cetera, is an important predictor of the efficacy of the compounds that are used. So we use that information and the information from the *in vitro* data to come up with the model -- the pharmacodynamic model that I showed you earlier on.

And again, then, this entire model -- that is, the adherence model, the pharmacokinetic model, the pharmacodynamic model, and the dosing regimens that one wants to understand -- are then put into the

entire model, the simulation is run to give us the information on the predicted viral load outcome from those particular input parameters; that is, the prescribed PI doses. Next one, please.

So, in building and evaluating that PD model we need a combination of *in vitro* and *in vivo* data that's incorporated into this mechanistic model of viral dynamics. And as I said, that model will incorporate baseline CD4, RNA copy number, and possibly prior treatment into that PD model. And we relate *in vitro* and *in vivo* sensitivity data hopefully using early monotherapy data from naive subjects with wild-type virus. And this, I think, goes back to Henry's question earlier on. Much of these data can and should be generated during the initial development of a drug before we get into issues about changes in dosing regimens and so forth, so that we can get that information about the relationship between the *in vitro* and the *in vivo* data, and we can do that in the early phases of drug development and get useful information at that point in time.

And then we expand that model to pre-

treated patients using additional *in vitro* data by using the various resistant mutants that are found *in vivo*. So we can then incorporate that into the overall pharmacodynamic model dealing with all the different quasi species that are found in the *in vivo* situation. Next one, please.

Again, the point to be made here is that essentially most of the data that we need to create these PK/PD models comes from data that's already preexisting about the drug itself. And the challenge here is to incorporate that preexisting data into our pharmacokinetic/pharmacodynamic model. Next one, please.

Now, I want to take a little parenthetical aside here for a moment to talk about one *in vitro* approach that's been used at Johns Hopkins, and that's the use of an *in vitro* pharmacokinetic/pharmacodynamic system, essentially a model that allows pharmacokinetic profiles to be generated *in vitro* that can be matched to any *in vivo* profile that might be generated. And again, I won't go into detail here. There was a publication in Antimicrobial Agents and

Chemotherapy a few years ago.

But basically the concept is that cells are grown in a dialysis type cartridge, and then that cartridge can be profused with drug concentrations with or without protein, if you choose to do that, and you can generate an individual profile essentially that can match any *in vivo* profile. And this could be potentially a very useful way of addressing some of these questions that we have, for example, about post-antiviral effect, C_{max}, C_{min}, in terms of its effect on viral replication. So this is just something to keep in mind. I'm sure others will have other suggestions for how we can generate better *in vitro* data. Next one, please.

Going back to the PK/PD model, we evaluate PK/PD models by comparing the outcome of trial simulations using the full model to actual data from trials in experienced patients. And the response variables that we look at in those clinical trials are treatment failure and/or the presence of genotypic and phenotypic resistance, because those are also important outcome variables from the clinical trial.

And we have to incorporate -- and those of you who know me will appreciate this. We have to incorporate realistic estimates of drug-taking behavior into the simulation. And for the clinical trial that's used for the comparison, we can either make actual measures of drug adherence, or we can use literature values for adherence and use those in our model. Next slide, please. Next one after that.

Now, I want to go through just one other short example to talk about a simple PK/PD relationship to help understand potential consequences of changes in dosing regimens or formulations. We've heard a lot about C_{max}, C_{min}, area under the curve, and so forth. Those aren't really pharmacokinetic parameters. The parameters that we usually think of are clearance and volume distribution. Those parameters describe the plasma concentrations of a drug after a particular dosing regimen. And what I want to do is talk a little bit about how that really factors into thinking about changes in dosing regimen. Next one, please.

I'm going to show you two hypothetical

relationships between inhibition of viral replication from a given species of virus that may be present in the plasma -- for example, a very sensitive virus with a low EC_{50} -- and different dosing regimens that might be used for this species as well as for another species that's a little less sensitive. Next one, please.

So, for example, here would be a dosing regimen in which the drug is being given every half-life. It's being given three times a day, and we start out with concentrations that are very much in the flat part of that concentration response curve. And then at the end of the dosing interval in the C_{min} area here -- next slide, please -- we essentially have essentially complete inhibition of viral replication at the trough concentration. So we don't see much of any viral replication. And the integrated -- the overall antiretroviral response is really the integrated response over time, over the entire dosing interval. Next one, please.

If we give essentially the same dosing regimen -- that is, the same total daily dose -- but

now split it into a BID dose instead of a TID dose, we essentially have the same average plasma concentration. But what do we have? We have a little higher peak concentration and a little lower trough concentration. Next one, please.

So in this case, with a sensitive virus, even though we have a lower trough concentration, we still have, at the end of the dosing interval, essentially a concentration that would produce a 98 percent inhibition of the virus replication at the trough concentration. So let's go to the next one.

And now we're dealing, again, sensitive virus; we're going to give the drug once a day; and again we have a slightly higher peak concentration and a slightly lower trough concentration. Next one.

What that means is that even with this long dosing interval, now three times the original dosing interval, we still have 96 percent inhibition of viral replication at the trough concentration. Next one, please.

Now, let's consider a drug that has a somewhat higher EC_{50}. Not a particularly resistant

virus, but one that's more resistant perhaps than the wild-type virus with about a fourfold increase in the EC_{50}, and this is an *in vitro* EC_{50}. Next one, please.

So again we start out with a TID dosing regimen. And, next one, we see that now, with the more resistant virus, even with the TID dosing regimen, we have only 90 percent inhibition of viral replication at the trough concentration. Next one.

With a BID regimen, again, same average plasma concentration, but now -- next one -- at the trough concentration with a BID regimen we only have 85 percent inhibition at the trough. And remember that what we're really seeing here again is an integrated response. We're going essentially from almost complete inhibition at the beginning of the dosing interval, down through this curve down here to the point where at the trough concentration we have only 85 percent inhibition. Next one, please.

Now let's go to the daily dose. Again, same average concentration, higher peak concentration, lower trough concentration. And here at the trough concentration, with the QD dosing regimen, again, same

average daily dose, same average plasma concentration, same area under the curve as far as the area under the curve is concerned. But, here again, the dosing regimen of a QD dosing regimen, we have only 72 percent inhibition at the trough.

Now, I won't go into -- there's some very interesting estimates that one can make of what happens with non-compliance in a QD dosing regimen versus non-compliance in a BID dosing regimen. I think those are important considerations, and those are the kinds of things that we can actually simulate quite well using these kinds of modeling to try to understand whether partial compliance on a BID regimen is better or worse than partial compliance, for example, on a QD dosing regimen.

But again, the point here is that when we're dealing with sensitive viruses -- for example, in naive patients -- we can give practically any dosing regimen and we're going to get good inhibition of viral replication. But when we're dealing with multiple different species in the plasma, then we can estimate that with a change in dosing regimen that

gives us a lower trough concentration, we're going to have less inhibition of viral replication. So we do have to consider the entire range of the concentration response relationship in trying to understand that relationship. Next one, please.

So I'll finish up and talk a little bit about where I think we stand as far as PK/PD modeling in HIV therapy. I think it's fair to say that we have some well-defined PK models for antivirals that have been defined during drug development. I think we are limited in some cases in terms of the PK models for drug-drug combinations. But basically, for single drug therapy, we have well-defined PK models.

And I would also state that we have several good models of viral dynamics that have been developed. The model that I presented to you; there's other models that are out in the literature from Perleson and Ho; other models from Roy Anderson; number of good models that are in the literature for viral dynamics. And I think what we are doing and what we want to do is to link those relationships. And I think that for the PIs and for the NNRTIs, we

have plausible mechanistic relationships between the drug concentrations in plasma and the inhibition of viral replication that we can use to develop this full integrated PK/PD model. Next one, please.

Now, simulations using that full mechanistic model are consistent with the observed data, but the robustness of these models in a variety of different settings and dosing regimens has not yet been demonstrated. I tried to indicate that the model that I described for you with the Ritonavir, the Abbott model, did provide good relationships or good comparisons with the observed data in the trials, but we don't have a lot of that so far. We don't have a lot of these kinds of models and simulations that we can compare to actual clinical data, and we need to do more of that.

And I think that it's too soon to conclude that we could use simply a PK/PD model to substitute for the confirmatory trials, and I don't think that's what we're asking for in any event. We're asking: Can they be supportive evidence of efficacy rather than a substitute, and how much can they substitute

for the need to do the full therapeutic comparison, the comparative clinical trial? Next one, please.

So I'll finish with just a couple of comments. Where do we go in terms of PK/PD modeling? We have to continue to improve and refine these mechanistic PK/PD models using both *in vitro* and *in vivo* data. And as I mentioned before, for individual drugs the *in vitro* data needs to be related to the *in vivo* data, and those data can be generated early in development when monotherapy are still -- monotherapy data are still being generated. And then we need to generate concentration response data early in development. And that can be done by careful measurements of concentration response relationships, again during the early phases of drug development. Next one, please.

And I would ask the question: Can we use -- we should use -- or make the statement that we should use PK/PD models to plan trials, and therefore limit the dosing regimens and drug combinations to those that are likely to demonstrate acceptable efficacy and toxicity, and be robust to non-adherence.

And then my own personal view is that we need to be measuring adherence more often during both the clinical trials, as well as in the observed data that we're using for comparative purposes. Next one, please.

And then finally I think we need to consider whether PK/PD modeling, based on the short-term comparisons -- for example, studies up to 24 weeks --can be used as a surrogate for evidence of long-term efficacy. And my own view, again supported by John, I think, is that the differences in outcome between 24 and 48 weeks are more likely due to non-adherence than to regimen failure. That is, use effectiveness versus method effectiveness.

So I think that we actually have come a long way in terms of the sophistication of our PK/PD models. I think that we can continue building these PK/PD models, and if the Abbott experience is representative, then these PK/PD models, at minimum, can be used to help design those dosing regimens which are likely to produce the kinds of long-term benefits that we all want to see. That is, simpler regimens

with improved adherence and better outcomes. Thanks.

CHAIRMAN GULICK: Thanks, Dr. Blaschke.

Dr. Masur?

DR. MASUR: Well, Terry, that was a very provocative presentation about modeling. But probably the most provocative thing was your last statement. I mean, is it reasonable to assume, from a virologic point of view, that 24-week data is predictive of everything except adherence in terms of durability of response? And from a virologic point of view, I would think there might be other explanations. And I think that's obviously a very important point, whether we're flogging a system unnecessarily, if we could really make predictions based on 12 or even shorter data.

DR. BLASCHKE: Henry, I think it depends frankly on the quality of that baseline PD model. And the baseline PD model has to incorporate the knowledge that we already have about the various quasi species that are going to be present in patients; for example, heavily pre-treated patients versus naive patients. Now, we won't always know this, obviously, for sure. We won't necessarily have measured it. But we

certainly have a lot of data already in the literature about that. And that needs to be incorporated into the pharmacodynamic model. If it's not incorporated in the pharmacodynamic model, then it's not going to be predictive.

If it is incorporated appropriately into the pharmacodynamic model, then I think the model is predictive, and I think we can use that early data, then, to essentially confirm the model, confirm the pharmacodynamic model in data up to, let's say, 12 to 24 weeks, to go beyond to that 48 week data.

That's an assertion, and I understand that. But I believe that that's really the key to the good pharmacodynamic model, is that the pharmacodynamic model has to take into account more than one species, quasi species of the virus, in order to be a good pharmacodynamic model.

CHAIRMAN GULICK: Dr. Pomerantz?

DR. POMERANTZ: Yes, I also thought that was a really helpful talk, but I do have some questions. First I'd like to follow up on that. I think that it's obvious, I don't know anyone who would

disagree that adherence is a major problem after 24 weeks, and probably the major problem. What I think Henry was saying, what I agree with and I think, if you look at the models that you're using, including the Ho-Perleson model, out past 24 weeks we really don't know a lot about the dynamics of viral replication.

And there are more and more studies that are showing that out past there, whether you're dealing with people who are inhibited to below 400, below 50, or if you look at Luc Perrins' study from Geneva, less than 20, there are differences. And saying that what you see during active viral replication in 99 percent of the cells is going to be the same as basically what are question marks in the Ho-Perleson model in long-lived cells and in the latently infected reservoir, I think is a jump.

I would say I would agree with you, adherence is going to be the biggest problem. But I don't think we have enough data by any means, looking even at what you've put up there, to say that after 24 weeks compared to 48, or time after that, that you're

going to be able to have -- state precisely what you're going to get with these 24-week models.

DR. BLASCHKE: Well, let me take a somewhat tangential answer to your question. What we're trying to do here, and what we're trying to do, is to understand the efficacy and the safety of different dosing regimens. We're trying to ask the question not in the grand scheme of things whether a drug that's given for 24 weeks, because it's going to have a different effect at 48 weeks, because it probably will. Even if adherence were perfect, there's going to be other long-lived cells, et cetera, et cetera, that are going to produce a different response.

What we're interested in, for the purposes of this meeting, I think, is to ask the question of whether a change from one regimen to another is going to produce a similar outcome in terms of efficacy or safety.

And I think one can do that from the modeling short-term. It would have to imply that there's some difference in the way the drug works

from 24 weeks to 48 weeks. If we can show that the drug works the same or similarly under a different regimen up to 24 weeks, then despite what might happen between 24 and 48 weeks, we wouldn't necessarily expect a difference due to the regimen itself.

DR. POMERANTZ: I have to continue on. Sorry. Because I thought this was a great talk. Then we agree on that.

The second thing is, you mentioned and you showed a nice example of 99 percent inhibition. I want to get on Dr. Yogev's good side here, because I think this brings up his good point before, only we're talking about ECs now and not IC_{50}s.

When you look at 99 percent inhibition and you show 98 percent inhibition and 96 percent inhibition, since that may be a significant difference in retro viruses as opposed to bacteria, where we've not shown a post-antibiotic effect or antiviral effect, and because of the quick generation of resistant quasi species, how do you see the models determining or how do you see the data fitting in with what we're going to say is enough? Is 99 percent as

good as 98 percent?

DR. BLASCHKE: No.

DR. POMERANTZ: You know, that's what I mean. "Close" only counts in hand grenades and horseshoes. And for this, 98 versus 99 may be a profound difference in some patients.

DR. BLASCHKE: Well, I mean, I agree with that. I think what this -- the reason I showed the second half, for simple simulation, is basically to say that if you extend the dosing interval and you change the ratio between the peak and the trough concentration, the integrated response is going to be lower automatically. That's follows -- the theory behind that is complete.

So the issue then becomes if we go from a TID to a BID regimen, is that so much better in terms of the ability of the patient to comply with the regimen that perhaps a slight loss of efficacy, theoretical loss of efficacy, is offset by better patient compliance, and therefore it's a good regimen, and therefore we want to approve it. That's the issue we're dealing with.

DR. POMERANTZ: Final question. You bring up another very important point that I think this Committee is going to deal with, as we did with phenotypic and genotypic resistance, and that's viral fitness. You said that in the model that you're showing, and in future models, fitness is factored into that.

One of the things that you didn't mention, which I think that's maybe as important, is viral virulence. Because a fitness usually is sort of defined as the same or similar replication rate. And yet they're showing now, in preliminary data from different groups, that a virus may be as fit, replicative, but not as virulent; i.e., killing T-cells. Are there any models or any thoughts about modeling in viral virulence changes?

DR. BLASCHKE: Yes. I think there should be and there are; and yes, that would be an important thing to incorporate into this mechanistic model. And again, we can do a lot of this -- a lot of this is really actually doable. I know we've heard a lot of criticism of *in vitro* studies, but I think we can get

a lot of information from *in vitro* studies that we can incorporate into an *in vivo* model.

CHAIRMAN GULICK: Dr. Wong?

DR. WONG: I also found this really helpful and useful, to kind of outline the issues. The question I have is: As these models become -- you know, as you become more sophisticated in developing these models and taking more -- you know, more factors into account, at what point do they require specific prospective experimental validation? I mean, how much can we conclude, if the question is if we go from three times a day to two times a day, one can predict that a certain result can be achieved.

But before we accept that that prediction is valid and the third or fourth or fifth time we do this, do we have to demonstrate directly that it worked the first and the second time we did this? And what are your thoughts on -- you know, on experimental validation of the general approach, especially as relates to antiretroviral therapy?

DR. BLASCHKE: Yes. I think we're at a stage where it has to be -- I don't like to use the

word "validation," because that implies certain statistical tests and so forth. But I think the models, as they become more sophisticated, have to be evaluated against actual data. We're not at a point now where I think we can say, well, we're so smart at developing these models and we can add all these extra features and covariants and so forth to these models, and don't have to actually test whether that model is a good descriptor of the actual clinical data.

So I think we're a long way away from being able to say we know enough about the modeling and the models and so forth, that we don't have to have clinical validation.

DR. WONG: And what sort of standard would you want to see? I mean, would you want --

DR. BLASCHKE: Well, I think we usually --

DR. WONG: -- you know, deliberate or specific experiment designed to answer that question?

DR. BLASCHKE: Well, the nice thing about modeling is that it can take a variety of different inputs. You don't -- the model is input-independent. In other words, it should work. If the model is

constructed properly it will work with a variety of inputs, and therefore it should work with a variety of clinical trials and clinical data. We don't have to do the exact experiment. What we should do is model the exact experiment that we're -- model the exact trial that we're comparing our data against.

And let me just add to one other point that you alluded to. We would be looking, for example, in evaluating the model, whether it predicted -- and that's why I listed that on a slide -- both viral load; that is, how many patients appear to fail. But also look for the presence of genotypic or phenotypic resistance and whether that was consistent with the model. But I think you do need to evaluate all of these models against clinical data.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: Thank you. This corner of the table's a little nervous since Dr. Pomerantz made his hand grenade comment, so, but --

DR. POMERANTZ: I also said horseshoes.

DR. BERTINO: Horseshoes. Okay. I've been hit by a horseshoe.

But in the models that you presented, I didn't -- you didn't present anything in terms of factoring in toxicity to the patient. And is that a -- presumably that should be another part of the model.

DR. BLASCHKE: It would be another part of the model. And again, it goes back to what Richard was talking about, and we need to know, because we don't necessarily have a good model, empirical model. Maybe we do for nephrotoxicity in some cases or -- or urologic toxicity. But that would have to be factored into the model.

We certainly need more data of the type that Richard said wasn't available, but we need to begin generating it, that is relating, for example, peak concentrations to -- or area under the curve to various safety issues and toxicity issues. Absolutely. And it certainly can be -- there's no real difficulty in incorporating another outcome measure, a toxicity outcome measure into the model.

CHAIRMAN GULICK: Last question, Dr. Gerber?

DR. GERBER: I think this is great, Terry. I mean, this is a really exciting model that's at least sophisticated. But any model is as good as its weakest link, and I really believe it's modeling human behavior, and that's what you're trying to do with it here. And it's going to be a very difficult task. And over a period of time, to be a consistent measure of human behavior or drug-taking behavior, that's going to be a difficult component. And I'm just wondering, how are you going to be able to put that into a formula?

Because most of -- when we look at adherence, we're only looking at a certain time frame, and I think it may change over time. As you mentioned, maybe adherence in the first 24 weeks is quite different than in the second 24 weeks or the third, et cetera. And how is that going to be able to be put in there, when I think modeling human behavior is going to be a challenge?

DR. BLASCHKE: Well, I agree, John. And I think I would certainly in the beginning probably try to use mostly clinical data that came from

clinical trials where we have, in many cases, better information about patient drug-taking behavior, rather than comparing it to observational data from clinical treatment regimens. Because I think there, you're right, we have pretty limited data.

But, again, once you've got the model, then you can play with the model and play with different information, different patterns of drug-taking behavior, and see how they affect the outcome. That's the big advantage.

CHAIRMAN GULICK: Okay. I'd like to thank Dr. Blaschke and all the morning speakers once again, and the panelists for a lively conversation so far.

We're going to break now for lunch. We'll reconvene promptly at 1:00.

(Whereupon, the foregoing matter went off the record at 11:52 a.m., and went back on the record at 1:06 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:06 p.m.)

CHAIRMAN GULICK: Okay, we're ready to begin the afternoon session. Welcome back from lunch.

DR. CHAMBERLIN: Okay, I have to read another conflict of interest statement. Before we begin this afternoon's session, we'd like to disclose that Dr. Charles Flexner, one of FDA's invited guests, has interests that we believe should be disclosed so that the participants can objectively evaluate his comments.

The following was inadvertently omitted from this morning's disclosure statement. Dr. Charles Flexner would like to disclose for the record that he has received consulting fees from Roche and Abbott, and that he has received speaker fees from Abbott, Agouron, DuPont, Glaxo Wellcome, Merck, and Bristol-Myers Squibb. In addition, he has received research funding from Abbott, Agouron, Glaxo Wellcome, DuPont, and Merck. Thank you.

CHAIRMAN GULICK: We're ready to begin the open public hearing part of this meeting, and two

people signed up in advance. The first person to sign up was David Pasquarelli from ACTUP, San Francisco. If he's here, could he come forward to the mic. Okay.

Second person to sign up was Jules Levin from National AIDS Treatment Advocacy Project in New York.

MR. LEVIN: Hi, everybody. I just have a few brief comments. I don't want to get off topic here, because I think this is a very important and interesting discussion, and focused. But, and it's -- I run an organization in New York, NATAP. And I have HIV. I've had HIV for 17 years, and hepatitis C for probably just as long. And I just have a few brief comments, some of which were sort of brought up, I think, this morning. They were touched on.

But I wanted to just mention some of the things that I think are important to the community, related to this subject. And a lot of people are concerned about potential drug level and PK differences related to gender and dosing. A lot of women are concerned about maybe they're taking too much drug, maybe they don't need as much drug because

maybe their body weight is smaller. And that could be the case for a man, too. Also, women are concerned that there may be gender PK differences. And it was mentioned this morning potential PK differences during pregnancy.

And things of this nature I think are important to keep in mind when discussing this issue. And I think what's important is not just that the FDA and some of the academic researchers are hearing this, but I think it's very important for the industry to take note of these concerns, because these are concerns that the community have and that industry ought to give due consideration to.

And I just want to bring up one important subject which relates to me personally, but also relates to a lot of other community people, and I think it deserves some attention. And I know that there are a couple of people on the panel that I've already spoken to, and they feel similarly to me about this and they may bring it up this afternoon. And that's the fact that there's so many people who have hepatitis C today who have HIV. And there's a lot of

concerns about how to take antiretrovirals in the context of having hepatitis C. Is the liver metabolizing the drugs the same? Are people getting too high levels of drugs? When you take treatment by interferon or Ribavirin, does it change how your liver metabolizes the antiretroviral drugs?

That's if it's -- I might as well mention that I went through all this personally, and I think there are a lot of people who have this on their mind. The question is: Should you test drug levels when you have hepatitis C, and should you check -- is your liver's ability to metabolize the drugs going to change after you take treatment for HCV? And so should you wait and check your blood levels then? And what's the potential damage to taking normal dosing to drugs on your liver if you have hepatitis? Can you reduce your doses and still have adequate antiviral activity? And what's the long-term implications for all this? And so I don't know the answers to any of this, and I'm not sure how many people do know any of the answers to this. But I think these are questions that need to be addressed and discussed.

And one of the concerns I have, and finally -- this is my last statement on this -- is not to look at these questions three years after drugs are marketed, but maybe the industry and the FDA can work together to try and figure out a way to figure this out before the drugs come to market. What dose should a person with hepatitis take for a medication before it comes on the market? After it comes on the market, I think it's too late. They're going to take the standard dosing. And we don't know the implication of that down the road. So, I think that's about all I have to say. Thanks.

CHAIRMAN GULICK: Jules, thanks for those thoughtful comments.

Is there anyone who didn't sign up who would like to make a statement at the open public part of this meeting?

Okay, we'll close the open part, then, and move to Dr. Kim Struble, who will give the charge to the Committee.

DR. STRUBLE: Thank you. I'm going to review the questions that we're going to pose before

the Committee this afternoon, and also give some examples in hopes to focus some of the discussion.

Our current recommendations allow us to support the approval of a new formulation or regimen on the basis of the following types of data:

First, bioequivalence data in which there are similar PK profiles. In the absence in which bioequivalence data cannot be met, PK data, in the setting of a well-defined exposure response relationship, can be used.

And finally, clinical efficacy and safety data are necessary when different PK profiles and exposure response relationships are unknown or unclear. Two recent approvals, where efficacy and safety data were required to support approval of a new dosing regimen, were DDI once a day and Nelfinavir twice a day regimens. These approvals have been based on 48-week trials, with 24-week interim analysis submitted to the agency. These trials included approximately 500 to 700 patients.

At the division, we acknowledge the need to streamline the amount of data required to support

the marketing of new regimens and formulations for approved antiretroviral drugs. One approach could be using PK/PD information, along with data from a clinical trial, to support the approval of a new regimen or formulation. With this approach, it may be possible to enroll fewer subjects; however, the duration of the trials is still unknown. Longer trials still may be necessary.

This consideration in part stems from two examples in which efficacy results between two regimens diverged at later time points. In the Indinavir BID versus TID regimens, these regimens appeared similar at Week 16. However, at Week 24 differences were apparent. With recently available data regarding DDI once a day, DDI once a day regimen and the comparative regimen appeared similar at Week 24. However, differences between these regimens were noted by 48 weeks.

There are also cases in which all exposure measures may be increased for a new regimen or formulation. These situations require additional safety data prior to approval. One consideration may

be to design a trial that would be powered for safety considerations rather than equivalence between two regimens or formulations with respect to HIV RNA. This approach may also require fewer subjects to be enrolled.

Discussions this afternoon are important to our division. Our goal is to take the advice heard this afternoon and draft a guidance document for industry on the use of PK/PD data to support approval of new regimens or formulations for approved antiretroviral drugs. Our document will hope to address trial size and duration. In addition, we hope to provide guidelines for placing drug interaction information labels, and note when additional safety or efficacy data is necessary to support this information. It will also address the implications for pediatrics with respect to new regimens or formulations.

Our questions to the Committee are divided into five topics for this afternoon: PK and efficacy; PK and safety; drug interaction; pediatric; and future research issues. Okay, first I'd like to start with

the PK efficacy issues.

On this slide we've provided a summary of the PK parameters that were noted to correlate with virologic response. Information on this slide was derived from Drs. Hoetelmans and Reynolds' presentation this morning. Also, data from the available literature, abstracts, and submissions we received from industry.

It appears that AUC and/or C_{min} correlated with virologic response for many of the antiretrovirals. Of note, there are many ways to define virologic response, some of which used mean change, proportion undetectable, and they are used various time points ranging from a week to over 24 weeks in duration.

So our first question is: What is the role of PK data in the evaluation of new formulations and alternative dosing regimens for approved antiviral drugs? We would like you to discuss the strengths and limitations of specific exposure measures, such as AUC, or C_{min}, or other measures, in predicting virologic response. Also, what data are needed to

rule out the relevance of any specific exposure measure to efficacy?

What is the role of intracellular concentrations in the evaluation of new formulations and alternative dosing regimens for approved RTIs?

And finally: In what circumstances will clinical efficacy data be necessary?

PK and virologic response relationships have mainly been evaluated in antiretroviral naive patients. And our prior approvals have focused on naive patients as well. Are these relationships applicable to treatment experienced patients? And are there cases where additional PK and/or efficacy data are necessary for different patient populations?

Our next topic will be PK and safety issues. This slide summarizes the different exposure measures that correlated with toxicity. AUC and/or C_{max} appear to correlate with toxicity for many of the PIs and Abacavir.

And our second question to the Committee is: Do the scientific data at present correlate any particular exposure measure with toxicity?

There are circumstances in which a change in formulation or dosing regimen or a drug interaction may increase all exposure measures. In this case, additional safety information is required to insure that the increased concentrations are not associated with additional risks or objectionable tolerability profile.

In the Saquinavir example, the sponsor sought approval of a new formulation, Fortovase, with increased bioavailability compared to the approved formulation, Invirase. In addition, the new formulation was to be dosed at a higher total daily dose. For the approval, the division required additional safety database, along with a clinical study, to support the higher Saquinavir concentrations. Approximately 500 patients were followed for 16 to 24 weeks. This is a safety database similar to that required for new molecular entities. However, there may be cases where the amount and duration of safety information required may vary, depending on the clinical significance of the increased concentrations for the new formulation or

regimen.

We'd also like to insure that increases in certain parameters are not associated with an objectionable tolerability profile. For example, Indinavir and Ritonavir are dosed at either 800/100, 800/200 milligrams twice a day, and these regimens are widely used in clinical practice. Based on reports in the literature and preliminary data presented by Dr. Hoetelmans this morning, increase in AUC or C_{max} may have impact on the overall safety profile.

This brings us to our third question. What amount and duration of safety data are needed to support new formulations or new dosing regimens of approved antiretroviral drugs with increased exposure measures?

Our third topic is drug interaction issues. Currently there's no information labels with respect to PK enhancers or uses of subtherapeutic doses of Ritonavir plus a protease inhibitor, although data on the use of therapeutic doses of Ritonavir with other antiretrovirals are found in several labels. Preliminary data on certain interactions show an

increase in AUC and C_{min}, with a decrease in C_{max}. We'd like you to discuss which exposure measures would be considered when providing labeling information on concomitant administration of antiretrovirals.

If one or more exposure measures are decreased, should additional clinical data be required? If so, how much? And other circumstances in which clinical data are necessary.

This slide illustrates the numerous dosing possibilities that are currently under study for Indinavir, Saquinavir, and Amprenavir. The number of dosing possibilities is complex, and the exposure response relationships may be difficult to determine in a setting of combination therapy. So how should several dosing possibilities be addressed in labels? And what criteria should be used for placing specific recoomendations in labels?

Our next topic will be pediatric issues. Dosing recoomendations in children are based on achieving similar exposure measures in adults -- in children as seen in adults. As the case with Nelfinavir, the original dosing recommendations in

children greater than two years of age were based on similar AUC, C_{max}, and C_{min} as seen in adults. However, for some antiretrovirals, all exposure measures may not be similar for adults and children. And this may in part be due to clearance being greater in younger children. Therefore, it may not be feasible to match all exposure measures.

So, once an alternative regimen has been identified in adults, should we require identical PK profiles in children; that is, all exposure measures equivalent, or only equivalent critical parameters such as AUC or C_{min}? And does this apply to all drugs and all pediatric sub-populations, or are there some situations in which more clinical or virologic data will be necessary?

And finally, our last topic is future research. What kinds of studies are needed to better define PK and PD relationships?

We recognize that the questions we pose for this afternoon is quite ambitious, but we look forward to the opportunity to begin to address these issues in an open public forum. We look forward to

the Committee's input into these many difficult issues regarding alternative dosing regimens. Thank you.

CHAIRMAN GULICK: Thanks, Dr. Struble.

Maybe we could use the slides to keep the questions up as we consider them. Thanks.

DR. FLEXNER: Okay, so let's go through these one by one. We'll just tic them off very rapidly. Take a while afterwards. Right. Yes, yes, no. Thank you.

(Laughter)

So what is the role of PK data in the evaluation of new formulations and alternative dosing regimens for approved antiretroviral drugs? And specifically discuss strengths and limitations of specific exposure measures. We turn to our pharmacologic experts. And let's get rid of the easy things first.

Terry Blaschke talked about the fact that we're used to dealing with concentration response relationships in terms of concentration as a parameter, meaning C_{min}, C_{max}, AUC. Whereas, the important pharmacologic parameters are really

clearance and volume and distribution. And that is true, except that I think the public and the non-pharmacologists have a very hard time dealing with clearance and volume and distribution as parameters to relate to clinical outcomes. And so I think we recognize that C_{min}, C_{max}, and AUC are all related in some way to those other more important pharmacologic terms.

But I would recommend that we not use those terms in trying to evaluate performance of the drugs. Not use the volume and distribution and the clearance. Instead, stick with what's spelled out in most of Dr. Struble's slides, the AUC, the C_{max}, and the C_{min}. So, stick with that which I think is most intuitive and most easy to grasp by the non-pharmacologically sophisticated community.

DR. PISCITELLI: Clearly we just don't have the study designs at this point to answer the question of use AUC or C_{max} or C_{min}. We saw everything seemed to be correlated. So at this point it's very difficult, based on the designs that we have, to answer that question. We have to give smaller doses

spread out over longer intervals so you'll have differences in AUCs and C_{min}s. But that's certainly a trial that I don't think anybody wants to do. And certainly patients aren't going to want to take a drug four or five times a day to answer that sort of question. So that'd be difficult.

In terms of the intracellular concentrations -- and maybe Courtney could address this, he's done some work -- but it appears that we're not in any position at this point, in terms of analytical advances, to make specific comments whether accumulation inside the cells are useful. I think Courtney could comment there.

DR. ACOSTA: Well, just real briefly. Analytically, if that's your point, I think we are slowly getting there, mass spec technology. We're able to pretty much quantitate most of the intracellular metabolites, the mono-, di-, and triphosphates simultaneously. So, analytically, I think we're slowly getting there. But if -- it's back to the same problem with where we were after protease inhibitors relating those to efficacy or changes in

viral load. I think we have very little data at this point on those drugs.

But just back to the first question, I think I'd have to agree with Charles that I'd still like to see clearance and volume in a package insert. But that's -- along with the variability of all those parameters, looking at standard deviation, looking at coefficient variation. But clearly the C_{min}, C_{max}, and the AUC are also extremely important parameters. But I think for the -- as Steve mentioned, we really don't know if an AUC or C_{min} is more important, and at this point all we can really do is express our opinions.

And my opinion is that the C_{min} is, at least in my head, no question the most important parameter that needs to be looked at. There's clearly a very strong correlation between the two parameters. What drugs that are essentially have linear absorption and disposition kinetics. And, but over the long term, in terms of preventing or developing a resistance, and again, it's just my opinion and a guess, but I would have to say the C_{min}'s the most important parameter.

CHAIRMAN GULICK: Dr. Gerber's next.

DR. GERBER: I just wonder why you would want clearance and volume and distribution. Let me just say volume and distribution at a steady state does not affect the concentration. If it's a steady state concentration, it basically is a term -- if the term is a half-life of a drug. And the clearance is very difficult to determine, systemic clearance, unless you're giving the drug intravenously, and most of these drugs can't be given. So what you get is oral clearance, which is kind of a term that means nothing to me, because that may be an absorption problem, or at first best, metabolism issue and all that.

So, and the AUC issue, from my perspective, it very much depends on drugs. Drugs have a very, very short half-life, and you give a lot of drug. For example, like Indinavir, the AUC is very top-heavy because it very much depends on the early dose. And the AUC may not really estimate the amount of drug that needs to be around for efficacy. So, I agree with you that I think C_{min} might be the better

thing to look at, although we don't have data to prove that. The drugs with long, long half-lives, the C_{min} and the AUC correlate extremely well.

CHAIRMAN GULICK: Dr. Flexner?

DR. FLEXNER: I'm sorry. I just want to again throw away another set of terms. I think that Dr. Rakowsky talked about time-dependent factors with regards to antimicrobials. That is, the time above some critical concentration as determining efficacy. I'm not aware of any clinical data suggesting that time above some threshold is a critical factor in determining antiretroviral efficacy, although it may be an important factor for toxicity. And so I think we don't need the time-dependent factors, at least when dealing with antiretroviral efficacy.

The toxicity issue we still don't understand very well, but the -- for toxicities that develop in the long run, like lipodystrophy and lipid changes. So that will have to go on the back burner. But for now I think we can stick with the concentration-dependent factors: C_{min}, C_{max}, AUC.

CHAIRMAN GULICK: Dr. Schapiro?

DR. SCHAPIRO: I think, looking at the biology of it, I don't think we have really any basis to determine which of those factors really correlates best with virologic response. I think, from the data we've seen and from the studies we've seen, we don't know enough of the science to know which of those impacts really the viral replication; we don't know which of those impacts accumulation of the drugs in the cells, if it's different for different ones. So I think that we really have to move away from trying to compare this to bacteriology.

And on the C_{min}, it's something we consider maybe from looking at bacteria. I think we have to consider this just based on the statistics and the evidence. I think it looks like, from most of the trials, the C_{max} seems to not pan out. I'm not sure if it has anything to do with the science, I think it tends to be very variable, the C_{max}. And some of these studies that show small numbers, there may be a trend which doesn't reach significance. I think the area under the curve and C_{min} seem the two parameters that most correlated statistically.

It would appear to me that it's easier to get a C_{min} than the area under the curve; and although both of them are beneficial, if we were to go with one marker based on what I've seen so far, my vote would probably be for C_{min}. But I would probably put in a real disclaimer caveat that we have a long way to go and will probably have to do a lot of other research to find out what we're missing regarding this.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: It seems like we're trying to put the cart before the horse here. We're trying to come up with rules to use, but we don't really have the tools to use. And I didn't make that up on purpose, rules and tools.

But if you go back and you look at bacteriology as kind of just a model -- and I wouldn't disagree with what Dr. Schapiro said about not correlating virology and bacteriology -- but the tools are *in vitro* models, so how whatever model to get some information on pharmacodynamic indices, which we don't really have for antiretrovirals, for different drugs.

And then, in bacteriology we use animal

models, and then we look at some human data. Most of it's in retrospective, a little bit of it is prospective, that kind of thing. You know, there is -- Dr. Drusano, I think, published a paper in AAC in the last year or so, looking at some *in vitro* data. And then there was some data from Dr. Leipman's group a number of years ago at Hopkins, trying to use some *in vitro* models to try to give us some idea about pharmacodynamic relationships.

So maybe we need to go back a little bit and see if we can develop these tools. And I think then, once we go into the animal or the human model, or the human model -- maybe there's not an appropriate animal model, but probably -- I don't know -- then I think what we need to do is to look at the contribution of all the antiretroviral agents. Because just to separate out one agent I think leads to a false sense of security because of the large variability in the PKs with these agents.

CHAIRMAN GULICK: Yes, Dr. Masur.

DR. MASUR: Maybe I can pose a question to the pharmacologists, because I've been looking to them

for some leadership here. You know, in the basic-size laboratory, often when you get a test, everybody's eager to view that test because it's something you can measure, and then you apply to other laboratories. And often you get very focused on the test rather than on the question you're asking.

I mean, in this situation you have PKs, it's something we can measure, and we have numbers, and we'd like to start using them. Yet nobody has come up with any correlation that we can, I think, find credible in any convincing way that it really correlates with the outcomes we want.

Right now we have a long track record with 24- and 48-week clinical trials. So we know that that is relatively predictive of virologic response, immunologic response, and safety; although not perfect. So the question is, there are lots of things that we can't measure. We can't measure the effects of -- or at least it's harder to measure all the other variables about whether adherence, gender, body weight, metabolism, hepatitis C affect this.

Here we have some numbers. But are we

really saying that, while we have these numbers, we really don't have any way of knowing how to apply them to know whether a new regimen is really comparable to the original regimen that was -- or do we say that perhaps in the year 2000 that's the best we can say? We can come up with something logical, but we don't have any data in which to say that really helps us know that this new regimen is comparable to the original regimen that was studied with virology and immunologic endpoints.

DR. FLEXNER: I can attack that, but let him go first.

DR. MASUR: It was meant to be attacked.

DR. FLEXNER: Let's flip a coin here. Dr. Fletcher hasn't run in yet, so we'll let him go first.

DR. FLETCHER: The challenge that you've extended here is a good one, in that: Has there been a prospective demonstration that concentrations have improved -- the use of concentrations have improved the -- have improved the outcome of patients. I think that's what you're challenging.

But let me take a step back and first say,

well, why would we even look at that in the first place? First of all, I think, going back to Dr. Blaschke's presentation where he talked about all of the factors that will ultimately contribute to patient response, think about what you can actually control. You can't change inherently the susceptibility of the virus; you can't inherently change someone who is pre-therapy, immunologic status; you can do something about PKs. You can probably do something about adherence.

So of those things we can begin to identify that may contribute to response, it's reasonable to focus on pharmacology because it's a variable we can control. We can alter the dosing regimen, we can give more drug, we can do things about it. So I start from that point in terms of why we ought to focus on this. But I think, going back to where I started, your challenge, in terms of the need to demonstrate that role of concentrations contributes to outcome in a prospective manner, that still needs -- I think it needs to be done. In fact, come back kind of --

DR. MASUR: All I'm saying -- I'm not saying I'd like to do away with all the pharmacotherapists. But the question is -- and the model, for instance, that Terry described sounds like it's very promising. But the question is, while we can say something logical, in the year 2000 do we have a parameter that, from a regulatory or a rigorous scientific point of view, we can say this really correlates with a given desirable outcome, virologic, immunologic, clinical? Or are we saying we're still in the process of guessing?

DR. FLETCHER: Well, we're still in the process of learning.

CHAIRMAN GULICK: Dr. Flexner?

DR. FLEXNER: Well, we don't have perfect information or perfect tests yet. But let me state for the record what I think is obvious to all the pharmacologists sitting around the table here. If you have higher drug concentrations you're going to do better at suppressing replication of the virus, given the same drug. I think everybody would accept that as a given. However, if you have higher drug

concentrations you're going to increase your risk for toxicity, regardless of the drug. So those are pharmacologic truisms.

How does that relate to HIV? Now I think we need a little input from the virologists around the table, from Dr. Pomerantz and his colleagues. But my understanding of how this virus replicates is that it persists in the body, as far as we know, forever, even in the presence of effective drug therapy. And once drug concentrations drop below some critical threshold which has not yet been defined, the virus starts replicating again, probably almost immediately, based on the amount of time it takes to have a complete viral rebound after you stop taking your antiretroviral drugs.

So that suggests to me that the critical pharmacologic parameter for suppressing replication of the virus is some perhaps single concentration, and that if you maintain your drug concentrations above that threshold the virus won't replicate, in a simplistic sense. And as soon as you fall below that threshold, the virus starts replicating again, and

there's no such thing as a post-antiviral effect. That is, with this -- these drugs are not like penicillin or vancomycin. They don't continue to keep the virus from replicating after they disappear from the cell or from the circulation.

So that says to me that the real value of clinical pharmacology of antiretroviral drugs is something that should be obvious to everybody here. That is, the real value comes in comparing one regimen of the same drug to another regimen of the same drug. And we have enough information at hand today, I believe, to make some intelligent comments about what could be expected when you change the concentrations of a known drug, either higher or lower.

If you make the concentrations lower, you'll increase the risk that the virus will replicate and become resistant. If you make the concentrations higher or equivalent, you will -- if they're equivalent, you should suppress viral replication to the same extent. And if they're higher, you should suppress virus replication even better. And, alternatively, if you lower viral concentrations you

may decrease your risk for toxicity; if you raise antiretroviral concentrations, you may increase your risk of toxicity.

So, that -- I think we're ready to offer that now as what we can do with clinical pharmacology today if you want to compare one regimen to another. Where we're going to have a problem is trying to extrapolate from information about one drug to information about a second drug.

Because I agree with Courtney and a lot of my colleagues, I don't think we have enough information about first principles of antiretroviral pharmacology to be able to say that a new antiretroviral with these PK properties will be expected to do the following to the virus over the long term. Because I think that's perhaps more complicated than we'll be able to do for a while. But certainly if you want to compare one regimen to another, I think we already have enough information to know what to predict, and perhaps how to make recommendations to the FDA about what studies are necessary to know whether this regimen is effective,

safe, approvable, et cetera.

DR. MASUR: Could I answer?

DR. FLEXNER: Sure.

DR. MASUR: I mean, just as a quick response. I mean, I agree conceptually. The question is, operationally, how do you use that? Because you can say if the concentration is ten percent, 20 percent, 30 percent, higher, it will be more effective. But A: Will it be equally safe? That is very hard to say. And B: If you don't get a perfect, symmetrical increase in concentration, the C_{max} goes up and the C_{min} goes down, then how, operationally, do you transform that concept into a policy that you can use even with a class of drug? I guess that's what I'm looking for guidance for. I don't deny that you could do it, I'm just looking for guidance.

CHAIRMAN GULICK: Dr. Pomerantz?

DR. POMERANTZ: Since Charlie threw the gauntlet down, I might as well pick it up. I think that what we're arguing about in the short term, which I would never try to go past what our pharmacology colleagues talked about, is the short term. And a lot

of that is what you might call teleological reasoning, which is: Things make sense, but there isn't prospective data that suggests that it really happens that way.

So we do a lot of that in medicine, and pharmacologists are no different than the rest of us. So, for the short term, I think that, listening to what the pharmacologists say and a little bit about the minimum inhibitory concentration, fine.

The points that I think that Charlie brings up that I was going to bring up anyway -- so, thank you -- is that this is a very complicated disease, both in the short term, but especially as you go farther out. And one thing I did want to sort of get to people about, and that is that there is no real latency when it comes to HIV. The virus is not off. If you look at our work, Steve Wolensky, David Ho's, now some more work, there is latent virus. But it seems to be in most patients always replicating. It's a matter of where you're drawing the line, how far down are you going to measure it, and what parameters are you using to measure it.

So the reason that people rebound is not because it's coming out of latency, but because you're taking your hand off of a not-completely-stopped process. And that makes sense with the kinetics of rebound. And so that makes it even more important that when we make changes in therapies that we know a little bit about, at least over a few years, that we're careful about -- not what you're going to find 24 weeks or 48, but even past that. Because if you have low-level replication, different in different compartments of the body, changing something that has the same area under the curve but doesn't go to the same maximum height in a particular compartment, may be very different; not in the short term, but in the longer term.

There -- we don't know yet -- if you have a drug that in one formulation gets 70 percent of people to below 50 copies, while if you change the formulation they have the same number below 400 but less below 50, is that a success? Well, I think it might depend on the drug and how you're going to use it. But it could also be a failure, since there's now

clear data that if you don't get below 50 and you stay between 50 and 400, that is more likely to lead to resistance and to later rebound. But you wouldn't find that if you power it to less than 400 copies only, or if you look at it within a short amount of time.

So what I'm trying to say is, for the short term I think I would also look to our pharmacologists for some guidance, because I'm clearly not going to tell Charlie and his group there what -- which is the best parameter. But I do think that if you look at the complexity of the pathogenesis, that the FDA will have to be very careful that, even if they accept the drug being equivalent within 24 to 48 weeks, consider asking the drug companies to make sure they follow these patients longer and keep your eye on what you're using as a definition. Are you using less than 50, less than 400; and where and what time period of the infection?

CHAIRMAN GULICK: Dr. Yogev?

DR. YOGEV: Let me try to start from the beginning. We're using terminology which is not clear

to me, and maybe our pharmacologists can correct me. When you say C_{min}, when you say area under the curve, what are you talking about? Arithmetic median, what?

In pediatric we have two logs, differences in C_{min} sometimes, and even more in C_{max}. And I that is our problem. It is that we're taking all variety, trying to squeeze it into certain number, like we just did in the virology. We felt very comfortable when we couldn't measure more than 1000, and said the 400 are great. Now you're talking about 50, and I'm laughing, because the European standard, now method, 2, 20, and 2, make sure the differences.

So I think we need to first to verify what we're talking about, because I think that's where the problem starts. If we even look to what we want to compare to, we're talking about virological efficacy. If you do the mathematical model, at least couple of papers suggest it 65 percent predictable of the disease. Is that what we want? Because if we're there, we have a less of a tough task to do. Do we accept 64, which are around 35, 40 percent? And I think pharmacologies are around that area to predict.

I wonder why not try to find a method on the individual to see if it's working. For example, do virological cidal level in that specific individual by checking the viral or checking the level of C_{min} or whatever in that specific person to see what ratio you need to get in a patient to show that it's working. And if you find out that you need one to eight, you know then that you need a certain level most of the time or part of the time.

The way we're doing it today, we take population, which I think are knocking us down up front, at least in pediatric. It's all over the board. And for me C_{min} is meaningless. Yes, there is a number, but at best it's an indication. And the best example is, we have anecdotally four patients that were mistakenly given four times the dose of Ritonavir and did superbly well. When we went down to the normal dose, although they have no toxicity, they came up. And we have a beautiful C_{min} in which both of them, interesting enough, fit to the range which was reported by the NCI group. One was in the higher range, the other one was below range.

So I would like to suggest, if we don't know what the C_{min} needed is there, more consistent we know the range that probably give us the problem.

DR. FLEXNER: I'm not actually suggesting -- I think we're talking about different things. I'm talking about using PK parameters to compare different regimens and make recommendations about how those regimens are used. I'm not talking about measuring PK parameters in an individual to predict what's going to happen to that individual. I think we're -- that's beyond the scope of today's discussion.

DR. YOGEV: But I think that's where the problem is, because of the overlapping view. Lot of difference in C_{min}. You can go from zero to 100 and still be okay if you compare. And the question is: Is a change in the median really will tell us that we need to see individual first to define what we need? I don't think we define what we need to have, and that's my problem. Because then if you don't define for Drug X and overlap too much, you're going to show -- and we just saw the difference if it's 99

versus 98, look at the differences.

CHAIRMAN GULICK: Dr. Fletcher?

DR. FLETCHER: I was just going to -- I think this -- we'll probably come back to this issue, Doctor, when we get to the pediatric -- till we get to the pediatric issues. Because I think there are some issues, because I phrased my other question of equivalence.

Where we're talking bioequivalence you heard about the 90 percent confidence interval. But when we're looking at design of a dosing regimen that would be equivalent between adults and children, I think this begins to get at some of the issues that you raised. Should we settle for the mean or the median or arithmetic mean or whatever that is to be the same between two groups? Because the pitfall is that doesn't take into account who's at the low end. So you could have an adult and a pediatric regimen that provide the same median concentration in some population of patients, but the low ends look very different. And I think that is part of the concern that -- you know, that you're raising.

DR. YOGEV: Just to continue, for example, protein binding. We have a percentage. But if you do patient by patient, you find out such a variation which was never come into effect that might be very important to what we're doing.

And again, I'm forging my results only for pediatric. But if you say average is 70 percent protein binding, or 90 percent -- in that specific case it was 97 to 82 -- that make a huge amount of drug in the system that reacted. We never look into those, we just accepting numbers. So all I'm challenging is, is median the right thing to do, or should we define the base and say you have to be at least that minimum in whatever it is to compare, to see bioequivalence.

CHAIRMAN GULICK: Dr. Schapiro?

DR. SCHAPIRO: I think one problem we have with answering this question is, it's very difficult, in clinical use of these drugs, to really separate efficacy and tolerability. Because I think, as Dr. Flexner said earlier, and I think also from Dr. Pomerantz, it's a losing battle basically. We want

more drug; more is better. I think, as opposed to some situations in medicine where we're really giving enough drug, I think basically, if there were no toxicity, we want to give more.

And to give one threshold is going to be a problem in HIV, since the patient populations are so different. Not only is it different within that population, as Dr. Yogev pointed out, but if you take patients are naive and have relatively low viral load, and you compare them to very experienced patients who may have a very high set point to start with and have developed quasi species mutations, the numbers are totally different. And unless this was really, really the same population studied, the numbers you get will have very little relevance. So really, we want more. We want more. Now, the question is what price are we willing to pay for that? And that goes to the flip side.

So all these numbers are always going to be we want more. And you really can't take these issues separately. We have to put them together. We have to put together what price are we willing to pay

to have better chance of success. And I would say less toxic drugs, we want to give more and more. And of course you worry about price of adherence; if it's a drug that has to take a lot of pills, we worry about that. But the ideal drug, which is one pill once a day, we would just say, "Give me a big old one if there's no toxicity."

So you can't put these aside. You can't say how much. I think you always have to look at the side of toxicity, and therefore we have to make sure we're talking about the same patient population. And I really suggest answering the first two questions together. Because otherwise the answer really just is more. And I think when we -- when we consider that we're going to go into toxicities, and here it gets more complicated. Because I think toxicities is not just one outcome. I think there are a lot of toxicities. There are short-term toxicities, there are long-term toxicities. They probably also have different parameters that are important to them.

And I think, you know, how much can we prove? As a clinician, what I sometimes do with

experienced patients is I give them the dose and I go up, until they get a manifest toxicity, and then I go a little bit down. And that's my way of using my rule-of-thumb PK without doing measurements, and I think we have to see what we have that's better than that.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: I think I just heard the definition of a concentration-dependent killing drug. More means more killing.

One of the things, when you talk about variability in C_{min}, and as some of the data that we saw this morning illustrates the large PK variability that you see with these antiretrovirals. And I'm not sure that we can ascribe failure to -- always to court compliance, because I think it may be change in PKs.

And one of the things, as we were talking over lunch, is there's very little data -- and, Keith, correct me if I'm wrong, because we had this discussion -- but there's very little longitudinal data on intra-subject variability in PKs. And we're talking about drugs that undergo hepatic metabolism to

the extent that the antiretrovirals do, and we're talking about concurrent therapies like interferon and hepatitis C as a good example, where initially a patient's drug metabolism may actually be suppressed.

And so, at the regular doses of antiretrovirals they're getting a big exposure. But then as viral load drops and cytokine production drops, drug metabolism increases, or the course of interferon is over with for hepatitis C after the prescribed time period it's stopped or whatever. And there is a little bit of data on this genotype/phenotype divergence that's coming out in the literature.

And I know when the antiretroviral people talk about genotype/phenotype, you're talking about for the virus. But I'm talking about for drug metabolism, how your genotype is -- what genetically you should predict for drug metabolism is different from your phenotype in real time; how you do metabolize drugs. And it looks like there's this fairly big divergence when viral load is high. And maybe it'll change. But we don't have a lot of

longitudinal data, and I think we need to know that, because that may help to explain some of the observations that you've made about big differences in C_{min}s in your patients because of PKs improving over time as viral load drops.

CHAIRMAN GULICK: Dr. Hansen?

DR. HANSEN: I was just going to say that earlier I heard a lot of conversation about NRTIs and our ability to very accurately measure them. And just to remind us all that we're talking about PK and efficacy for protease inhibitors and NRTIs, which are rarely used without the context of an NRTI backbone, which changes at the same time that you change.

So I wonder how much that confounds your ability, in the treatment experienced patient, or even as you're looking at equivalence in new treatments or new PIs or new formulations as they come on board, to say with any kind of sense of clarity or even confidence that the things that you propose to us really will be useful. We've already heard it's going to be difficult to do anything with intracellular measurements. These things are not delivered without

the context of NRTIs. Won't that always confound us? I'm just asking.

DR. FLEXNER: I think all the statements we're making with respect to a single drug imply that if you change that single drug, all other things remain equal. And that -- I can think of some situations where that won't be the case.

For example, if the single drug you're changing is Ritonavir, it might alter interactions with other metabolized drugs in the regimen. But I guess as a general principle, if a higher trough concentration is more likely to suppress the virus for a longer period of time, that's going to be true, I think, regardless of the other regimen you're taking.

CHAIRMAN GULICK: Dr. Blaschke?

DR. BLASCHKE: So we can still speak here on the back bench?

(Laughter)

I was initially going to say I agreed with a lot of what Charles had said about the concentration response, and also what Jonathan had mentioned. I do want to reemphasize something I said, and that is to