FOOD AND DRUG ADMINISTRATION

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ANTIVIRAL DRUGS ADVISORY COMMITTEE

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TUESDAY
JULY 25, 2000

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The Committee met at 8:30 a.m. at the Holiday Inn - Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Roy M. Gulick, Acting Chairman, presiding.

MEMBERS PRESENT:

HENRY MASUR, M.D., Chairman
ROY M. GULICK, M.D., M.P.H., Acting Chairman
EDWARD P. ACOSTA, Pharm.D., Guest
JOSEPH S. BERTINO, JR., Pharm.D., Voting Consultant
TERRENCE F. BLASCHKE, M.D., Non-Voting Consultant
BENJAMIN CHENG, Patient Representative
COURTNEY V. FLETCHER, Pharm.D., Member
CHARLES FLEXNER, M.D., Guest
KEITH GALLICANO, Ph.D., Guest
JOHN GERBER, M.D., Guest
I. CELINE HANSEN, M.D., Voting Consultant
RICHARD M. V. HOETELMANS, Pharm.D., Ph.D., Guest Speaker
PRINCY N. KUMAR, M.D., Member
WILLIAM C. MATHEWS, M.D., M.S.P.H., Member
STEVE PISCITELLI, M.D., Member
ROGER J. POMERANTZ, M.D., Member
JONATHAN M. SCHAPIRO, M.D., Guest
BRIAN WONG, M.D., Member
RAM YOGEV, M.D., Member
NANCY CHAMBERLIN, Pharm.D., Executive Secretary

FDA REPRESENTATIVES:

HEIDI M. JOLSON, M.D., M.P.H.
SANDRA L. KWEDER, M.D.
JEFFERY S. MURRAY, M.D.
ALEXANDER RAKOWSKY, M.D.
KELLIE SCHOOLAR REYNOLDS, Pharm.D.
KIMBERLY STRUBLE, Pharm.D.

PUBLIC SPEAKERS:

JULES LEVIN, National AIDS Treatment Advocacy Project

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:30 a.m.)

CHAIRMAN GULICK: Good morning, everyone. I'm Trip Gulick from Cornell in New York. It's my pleasure to welcome everyone today to this important meeting of the Antiviral Advisory Committee. It promises to be a very interesting day. We have some very important presentations to discuss.

I'd like to start by having the members sitting at the table introduce themselves and say where they're from. Why don't we start at one end.

DR. GALLICANO: Keith Gallicano from Axelson Biopharma Research in Vancouver, and formerly from Ottowa General Hospital in Ottowa.

DR. GERBER: John Gerber from the University of Colorado Health Sciences Center in Denver.

DR. ACOSTA: Ed Acosta, University of Alabama at Birmingham.

DR. PISCITELLI: Steve Piscitelli, Pharmacokinetics Lab, NIH.

DR. SCHAPIRO: Jonathan Schapiro from Tel

Aviv University and Stanford University.

DR. FLEXNER: Charles Flexner from Johns Hopkins University in Baltimore.

MR. CHENG: Ben Cheng from Project Inform in San Francisco.

DR. BERTINO: Joe Bertino from Bassett Healthcare in Cooperstown, New York.

DR. POMERANTZ: Roger Pomerantz, Thomas Jefferson, Philadelphia.

DR. WONG: Brian Wong, Yale University.

DR. MATHEWS: Chris Mathews, University of California, San Diego.

DR. YOGEV: Ram Yogev, Children's Memorial Hospital, Chicago.

DR. CHAMBERLIN: Nancy Chamberlin, Exec. Sec.

DR. KUMAR: Princy Kumar. Princy Kumar, Georgetown University Medical Center.

DR. MASUR: Henry Masur, Clinical Center, NIH.

DR. FLETCHER: Courtney Fletcher, University of Minnesota, Minneapolis.

DR. HANSEN: Celine Hansen, Baylor College of Medicine, Houston, Texas.

DR. REYNOLDS: Kellie Schoolar Reynolds, Office of Clinical Pharmacology and Biopharmaceutics, FDA.

DR. STRUBLE: Kim Struble, FDA.

DR. MURRAY: Jeff Murray, FDA.

DR. JOLSON: Heidi Jolson, FDA.

DR. KWEDER: And I'm Sandra Kweder from the FDA.

CHAIRMAN GULICK: Thank you very much. Nancy will now read the conflict of interest statements.

DR. CHAMBERLIN: Bear with me. It's three pages. The following announcement addresses the issue of conflict of interest with regard to this meeting, as made a part of the record, to preclude even the appearance of such at this meeting, since the Committee's discussions will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to all pharmaceutical firms that make antiretroviral products

for use in the treatment of HIV infection.

In accord with 18 USC 208, general matters waivers have been granted to all special government employees participating in this meeting. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to the FDA's invited guests, there are interests which we believe should be made public in order to allow the participants to objectively evaluate the guests' comments. Edward Acosta, Pharm.D., would like to disclose for the record that he has accepted consulting fees from Merck, DuPont, and Roxane, and has received speaker's fees from Merck and Roxane.

Ben Cheng would like to disclose that Project Inform has received educational grants from Glaxo Wellcome, DuPont, Hoffmann-La Roche, Roxane, Bristol-Myers Squibb, Merck, Pharmacia, and Agouron.

John Gerber, M.D., reports that he has received consulting fees, speaking fees, and grants

and contracts from Agouron and Merck. Dr. Gerber has also received speaker fees from Vertex, DuPont, and Bristol-Myers Squibb.

Dr. Richard Hoetelmans has received contracts and grants from Roche, Bristol-Myers Squibb, Glaxo Wellcome, Boehringer Ingelheim, Abbott, and Merck. He has also received speaker fees from Bristol-Myers Squibb, Roche, Abbott, and Boehringer Ingelheim.

Steve Piscitelli, Pharm.D., has received honorarium through unrestricted educational grants from Glaxo Wellcome, Agouron, and Bristol-Myers Squibb.

Jonathan Schapiro, M.D., would like to disclose that he has received support through unrestricted educational grants from Hoffmann-La Roche. In addition, Glaxo Wellcome, Hoffmann-La Roche, Merck, Agouron, and Bristol-Myers Squibb have provided research grants. Further, Dr. Schapiro has received consultant fees from Hoffmann-La Roche, Agouron, and has been a scientific advisor to both firms. Dr. Schapiro has also received speaker fees

from Glaxo Wellcome, Merck, Agouron, Hoffmann-La Roche, and Bristol-Myers Squibb.

Lastly, he is the chair of a National Educational Incentive, a CMU program through the University of Alabama at Birmingham. He has also received a substantial education -- substantial amount of honorarium from Hoffmann-La Roche through unrestricted educational grants.

In event that the discussions involve any other products or firms not already on the agenda for which any participant has financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusions will be noted in the record. With respect to all participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Okay, we have a pretty full agenda and we're going to try to stick to our schedules. And we've been asked to announce if there's any disturbances, that they will be escorted out. Thank

you.

CHAIRMAN GULICK: Thanks very much, Nancy.

I'd like to turn it over to Heidi Jolson for some introductory remarks.

DR. JOLSON: Thank you, Dr. Gulick, and good morning. I'd like to extend a welcome to our Committee who's joining us back today, and a special welcome to our invited guests and speakers.

We've enjoyed planning this meeting. We think it's really timely, and we're excited to have the opportunity to hear the presentations today and your discussion.

We'll be spending the bulk of today talking about the availability of data to evaluate alternative antiretroviral dosing regimens. And this is -- reflects a discussion that we've had internally with many sponsors over the years. This discussion's not unique to products for HIV, nor for products to antivirals, but we'll be focusing today on antiretroviral virals because of the tremendous amount of interest from industry in developing alternative dosing regimens. Next slide, please.

I'm sure everyone in this room knows that drug development does not stop at the time of product approval, indicated here by this bar. And the point of this figure is just to point out really the spectrum that the agency sees in terms of product development, starting with the innovator or original product that's approved, all the way to generics; and then the focus of today's discussion, which are new formulations which don't necessarily have the same pharmacokinetic profile as the innovator drug.

Prodrugs of the innovator drug, alternative dosing regimens, which are usually simplified regimens allowing for a lower dosing frequency per day, or something that's -- I think it's fairly unique to the antiretrovirals, which is coadministration with a PK enhancer such as low-dose Ritonavir in order to alter the pharmacokinetic profile in an advantageous way. Next slide, please.

And there are many reasons for all these post-approval changes. In general, these are looked at as positive changes. One reason might be that there's just some sort of a manufacturing improvement

to allow a better process for manufacturing product. But more likely the reasons are clinical, that the post-approval change results in better bioavailability which hopefully will translate into increased effectiveness; improved tolerability or palatability; or as I mentioned, simplified dosing which is believed to be related to better patient adherence. Next slide, please.

So the question that comes up then is: What's the evidence standard of the agency for these different spectrum of products? Because clearly it just wouldn't make sense if the same evidence standard were applied all along the spectrum. And so, as this Committee well knows, and it spends most of its time considering, it's the randomized controlled clinical trials that support approval of the innovator product. Next slide, please.

And that's what the Food, Drug, and Cosmetic Act defines as substantial evidence, which is evidence consisting of adequate and well-controlled investigations conducted by experts, which allow the conclusion that the drug will have the effect it

purports. And so those are the classic, randomized controlled trials that would support new drug approval. Next slide, please.

While that piece of information, that body of evidence is enough to support a new drug approval, at the other end of the spectrum is generic approval. And as again it wouldn't make sense to require the same amount of evidence to support a generic or a formulation that is essentially a generic, that is almost identical. And so the law recognizes a bioequivalent standard to approve generics. And Dr. Reynolds is going to discuss the type of study that would support bioequivalence. But it should be clear to everyone that that's a very different standard than required for the innovator. Next slide, please.

We're going to be spending our time, however, in this box down here which is around either new formulation --

(The overhead projector goes off.)

Well, that's all right. I can continue on without the slides, although they looked quite nice.

Before the lights went out, you saw the

question mark. And the question mark is really representative or symbolic of the questions that you all will be asked to discuss today, which are really: What's the level of evidence to support approval in those circumstances that were enclosed by the box, such as the new formulation, a prodrug, an alternative dosing regimen, and coadministration with a PK enhancer? How much data is really necessary?

And you might ask: Well, what is the agency's perspective on that level of evidence? And since I mentioned, this situation is not unique to antiretrovirals. There is a guidance document that's available that was published on the Web in May of 1998, a guidance for industry called "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." And that document represents many different things, but it includes our current thinking on the quantity of evidence that's necessary to support effectiveness. And it explicitly says that there are circumstances when effectiveness can be extrapolated from efficacy data for either another claim or another product, and then goes on to give

several examples. And if you had the slide, you could see the examples.

But the examples that the document references are pediatric uses. And that would be the case where the disease is thought to be the same in adults and children, and the treatment effect is reasonably similar. Bioequivalence, that I already mentioned.

And then what we're going to talk about today are modified release dosage forms and different dosage regimens or dosage forms. And the agency makes a distinction about the level of evidence that's necessary, depending on whether or not the exposure response is understood.

(The overhead projector comes on.)

Excellent. This is easier with slides.

So this was the box that I told you about. This is where -- these were the examples from the guidance document, and this is what we're really going to be focusing on today. Next slide, please.

So that the document, if you were to read it, says that even if blood levels are quite

different, if there's a well understood relationship between blood concentration and response, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of PK data, without an additional clinical efficacy trial. However, if the exposure response is not understood and the pharmacokinetics of the new dose, regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary. In that case, in general, a single additional efficacy study should ordinarily be sufficient. Next slide.

In our division -- DAVDP is the Division of Antiviral Drug Products -- we've been asked on numerous occasions by a variety of industrial sponsors how much evidence do they need to support their new formulation or new regimen, and this slide would summarize what our recommendation has been. In general we've required -- and consistent with the agency's guidance -- a single, adequately powered 48-week equivalence designed clinical trial, although there may be occasions where a superiority trial could also be acceptable. And we've routinely reviewed 24-

week interim results of that trial to include in the labeling with a Phase 4 commitment to submit the final 48-week results, and then that trial is then supported by PK and safety data. Next slide.

While there's some advantages and disadvantages of that approach, certainly having a clinical efficacy study with a new regimen or new formulation provides some level of confidence about both the safety and the effectiveness of the new regimen. However, we're well aware of several down sides, which are that a large sample size may be required, certainly if the design is an equivalence design.

The sample size is probably going to be many hundreds of patients, and there may be actually limited available patients in the given patient population. It provides for a longer delay in product availability in order to conduct the study. We certainly heard very loud and clear that it's resource intensive for the pharmaceutical sponsor, and that it results in a label which actually could lag substantially behind clinical practice.

And this brings us to today's meeting, to discuss in a scientific forum and group forum, and in the public, what really the current knowledge is of exposure response relationships for approved antiretrovirals, and to explore both their role and their limitations, and to provide advice to the division of how we should consider this data in support of new formulations and regimens.

We want to ask the Committee today to discuss the amount, duration, and circumstances when clinical data are necessary; to discuss the implications of available knowledge for special populations, which would include both pediatrics and also treatment experienced patients; and we hope, as a follow-up to today's meeting, to use the discussion to generate the basis for an industry guidance document on this topic.

In planning this meeting several months ago, the division issued a letter to pharmaceutical sponsors requesting any available data that they might have that would address exposure response relationships with either their product or another

product. And in terms of response, we were interested both in virologic response, as well as parameters of safety.

I'd like to acknowledge the contributions of these sponsors who very graciously provided very, very informative reviews of experiences with their products, and a summary of the data that they've been able to generate. And certainly we would not have been able to put together this meeting without the help from the companies listed here in providing us with data.

In today's meeting we're going to provide an overview of data that we've received in the public domain, and that will be presented in one of this morning's presentations. I'd like to just mention, as an editorial remark, that we can't discuss this issue without really seeing what we've learned, in order to figure out what we still need to learn.

And so, although we may mention specific products as examples or refer to their data, I just want to remind everyone that the purpose today is not to discuss any specific product or any specific

regimen or formulation. We're using the data to try and figure out really where the state of the art is for antiretrovirals. Next slide.

So in brief, today's agenda, we have the morning -- we have several invited presentations, both from FDA, an antiviral overview from the clinical pharmacology perspective from Dr. Reynolds. We've asked Dr. Rakowsky, our colleague in the Division of Anti-Infective Drug Products, to talk a little bit about what's learned from the antibiotic perspective and their experience. Dr. Hoetelmans will discuss PK/PD relationships for antiretroviral drugs. And Dr. Blaschke will conclude the morning with considerations for PK/PD research in this field.

Following lunch, we have an open public hearing scheduled to convene at 1:00, and then Kimberly Struble will give a charge to the Committee and introduce the questions for the Committee to discuss.

In closing, I would just like to reiterate that we look forward to the discussion, and I would like to acknowledge the folks inside of the division

who've worked very hard in putting together both the background -- or the meeting and the presentations for today. We've had a large working group who's been involved in this, and the scientific leadership has been Kellie Reynolds, Kim Struble, and Jeff Murray, who you'll hear from today.

Thank you, and I'll turn the meeting back to Dr. Gulick.

CHAIRMAN GULICK: Thanks very much, Heidi.

The next speaker will be Kellie Reynolds from the FDA.

DR. REYNOLDS: Pharmacokinetic data could potentially be used to increase the efficiency of the evaluations of new formulations and alternative dosing regimens. However, to use these data appropriately, we need to know the relationship between drug exposure, and safety and efficacy.

I'll first define some terms that will be used throughout all of the presentations today. Next, I will describe bioequivalence, which is the most frequent way that PK data are used for approval of new formulations, including generic drugs. I will then

describe several scenarios that we face with antiretroviral drugs. I'll describe how each scenario differs from the typical bioequivalent situation. I will also discuss important considerations when evaluating the available PK/PD data for antiretroviral drugs. Finally, I will discuss the standard of evidence that is necessary for approving these changes.

As Dr. Jolson just mentioned, throughout this presentation there will be several real examples of data, and these examples were chosen to illustrate our decision process, not really to comment on the drug or the sponsor.

"Pharmacokinetics" is the time course of drug concentrations in the plasma or sometimes other fluids or tissues, resulting from a particular dosing regimen. "Pharmacodynamics" is the relationship between drug concentrations and a resulting pharmacologic effect. And the resulting effect can be related to either efficacy or safety.

This graph illustrates the time course of plasma drug concentrations over 24 hours following

administration of a drug every eight hours. The "Y" axis is concentration and the "X" axis is time. The "AUC" is the area underneath the curve. The "C_{max}" is the highest concentration, and the "C_{min}" is the lowest concentration. And C_{min} is also referred to as trough concentration or predose concentration.

There's really not good agreement on the definitions of these terms, but I'm just going to give two examples that we use. "IC" is inhibitory concentration. So IC_{50} is a concentration of a drug required to inhibit viral replication by 50 percent.

"EC" is effective concentration. So EC_{50} is the concentration where patients demonstrate 50 percent maximal reduction of HIV RNA. And based on the scientific principle that it's essential to maintain plasma concentrations above a threshold necessary to inhibit viral replication such as IC_{50} or EC_{50}, many investigators consider C_{min} the most important exposure measure for predicting virologic success. Although this concept is highly plausible, clinical data have not yet confirmed this. And AUC or total exposure is also presumed to be related to

efficacy.

I will next discuss bioequivalence. You'll probably hear bioequivalence discussed most frequently in a context of generic drug approval. But we also evaluate it in other situations where a formulation change is made. When evaluating whether two drug products are bioequivalent, the bioavailability of a test product relative to a reference product is determined. And the test and referent products may be the proposed commercial formulation compared to what was used in pivotal clinical trials, it may be a generic drug versus a reference-listed drug or innovator drug, or it may be a drug product that is changed after drug approval, as compared to the drug product that was approved.

And this is the regulatory definition of "bioequivalence." And simply it states that bioequivalence is a lack of a difference in the rate and extent to which a drug becomes available at the site of action when administered at the same molar dose. In a typical bioequivalence study, healthy volunteers are studied, but it is acceptable to use

patients. Each subject receives a single dose of each formulation, with an appropriate washout period between treatments, and the formulation should be administered under fasting conditions.

The current design of bioequivalence studies is expected to be the most sensitive for detecting any differences between the two formulations. And exposure measures are determined for each formulation. The test versus reference ratio is determined for both AUC and C_{max}. And then we determine a 90 percent confidence interval around the ratios. Using log transform data, the 90 percent confidence interval for both AUC and C_{max} must fall entirely within 0.8 to 1.25 to determine bioequivalence.

And this graph just illustrates the concentration versus time profile for two products that would be considered bioequivalent. And you can see that the profiles are almost superimposed on each other.

When using bioequivalence to approve new products, we make the following assumptions. We

assume: That the plasma concentration data are a surrogate for drug concentrations at the active site. We assume that if rate and extent of absorption are similar, there'll be no significant difference in exposure to the drug over time. And we assume that we can extrapolate safety and efficacy data from the reference product to the test product.

With generic drugs there's really no flexibility in the bioequivalence criteria. However, with innovator drugs we do have some room for flexibility. We have safety and efficacy data or exposure response data that may make it possible to determine that differences in AUC or C_{max} are not meaningful.

And here is one example where we used that flexibility. These are the results of the bioequivalence study comparing the Ritonavir soft gelatine capsule to the approved liquid formulation. And the results of the bioequivalence study indicated that both AUC and C_{max} following the soft gelatine capsule was 35 percent higher when compared to the liquid formulation.

In our review of the data we noticed that there were several subjects, mainly following administrations of the liquid, who had very low, almost undetectable Ritonavir concentrations. Although it was not documented, we considered it was possible that these subjects vomited soon after the dose was administered. So we compared these data to previous studies using the liquid formulation, and it appeared that the 35 percent difference could be due to low bioavailability of the reference liquid, not due to increased concentrations following the soft gelatine capsule. We also evaluated the potential impact of higher Ritonavir concentrations in case the soft gelatin capsule did actually have higher bioavailability.

Supporting safety data from the original Ritonavir NDA indicated that the 700 milligram twice daily dose was not tolerated as well as a 600 milligram dose, but it didn't pose any new safety concerns, so we approved the soft gelatin capsule formulation.

I'm now going to discuss several scenarios

we faced with antiretroviral drugs that may benefit from pharmacokinetic comparisons similar to the determination of bioequivalence. There are several scenarios where sponsors may want to extrapolate from an approved dosing regimen or formulation to a different regimen or formulation. The sponsor may also want to make comparisons to approved regimens on their evaluation drug interaction data, and they may compare PK data from children to data from adults.

Although bioequivalence technically refers only to comparisons of two formulations administered at the same dose, the principles of bioequivalence can be used in other situations. And in these cases we attempt to demonstrate comparable pharmacokinetic profiles rather than bioequivalence. So I'll define each one of these scenarios, give some examples for the scenarios, and I'll indicate how they differ from the typical bioequivalent situation.

The first scenario is the development of new formulations. In this situation we can apply the typical bioequivalence criteria. However, in many cases we really don't expect the formulations to be

bioequivalent. And some examples include modified release formulations, prodrugs, and formulations with increased bioavailability.

This graph can either compare a modified release, delayed release product as the test product, to an immediate release product that was approved first; or it could compare a prodrug to administration of the active drug. And for both of these situations there may be a delay in the appearance of the drug in the plasma. This delay may lead to a plateau, rather than the sharp peak of the previously approved formulation.

And in many cases, when the exposure measures are compared in a bioequivalence study, the AUC is the same or similar between the two formulations. The C_{min} may be similar, but there may be a big decrease in the C_{max}, maybe around 50 percent.

The regulations do allow us to determine that products with such differences in C_{max} are bioequivalent, but there are some caveats to that. And particularly important to this discussion are the words "intentional," "not essential to the attainment

of effective body concentrations on chronic use," and "medically insignificant." So there really needs to be concrete evidence that the difference in C_{max} is not significant.

There are no approved antiretroviral drug products that are modified release products or prodrugs. But another situation in which bioequivalence criteria will not be met is new formulations with intentionally increased bioavailability. One example with increased bioavailability is the Fortovase formulation of Saquinavir. When the proposed 1200 milligrams three times daily dose of Fortovase was compared to the approved 600 milligram three times daily dose of Invirase, there was an approximately ninefold increase in Saquinavir AUC.

There was a safety question due to the increased concentrations, but there was also a need to demonstrate improved efficacy to provide a rationale for the dramatic increase in exposure. So we requested a safety database of approximately 500 patients who were followed for 16 to 24 weeks, and

efficacy data were submitted for a smaller number of patients.

The second scenario we encounter is a change in dosing regimen. Many sponsors are now attempting to simplify dosing regimens, three times daily to twice daily, or twice daily to once daily. And they attempt to demonstrate comparable plasma drug exposures to the approved regimen, but it's really not likely that all exposure measures will be similar between the regimens.

Nelfinavir is an example of a protease inhibitor where we have approved a less frequent dosing regimen. The originally approved regimen was 750 milligrams three times a day, and the new regimen is 1250 milligrams twice a day. The sponsor did conduct a clinical trial evaluating the new regimen. Pharmacokinetic data were submitted with the clinical trial data, and these data came from a subset of subjects in the clinical trial.

When we compared the exposure measures for the twice daily regimen to the three times daily regimen, AUC, C_{max}, and the morning C_{min} were increased.

And the afternoon C_{min} was decreased. And the afternoon C_{min} compares the end of the first eight-hour interval for the three times daily regimen to the end of the first 12-hour interval for the twice daily regimen.

So if we were reviewing these PK data with no supporting clinical trial, there would be a safety question due to the increased AUC and C_{max}, and an efficacy question due to the decreased C_{min} in the afternoon. And I want to point out that although Nelfinavir pharmacokinetic are complicated due to the presence of an active metabolite, the comparisons are really the same when we do just parent drug or parent plus active metabolite.

The clinical trial was conducted in protease inhibitor naive patients, and the results at 48 weeks indicated that similar proportions of patients in each arm had less than 400 copies of HIV RNA per mL, and the safety was similar for both regimens. The elimination half-life of Nelfinavir is approximately four hours.

For another example, we'll consider what

might happen with a protease inhibitor that has a much shorter half-life. In this case, if there is a change from three times daily to twice daily, we might expect similar or higher AUC every 24 hours, and this would depend on whether the pharmacokinetics were dose proportional, a higher C_{max} which would lead to a safety question, and a lower C_{min} which would lead to an efficacy question.

An example of efficacy data for this type of drug compares Indinavir 800 milligrams every eight hours with the 1200 milligrams every 12-hour regimen, in combination with two NRTIs in protease inhibitor patient -- in naive patients. At 24 weeks the efficacy, based on proportion of patients with undetectable virus, was superior for the Q eight-hour regimen as compared to the Q 12-hour regimen.

As both of those examples illustrate, it's really not likely that all exposure measures are going to be similar between the dosing regimens. But in some cases a sponsor may change a formulation and dosing regimen at the same time in an effort to match all exposure measures. The formulation change may

allow a change in regimen with little change in AUC, C_{max}, or C_{min}.

However, in addition to comparing these exposure measures, it's important to consider the shape of the concentration versus time profile, and that's illustrated with this example.

In this example, the two sharp profiles are for the original formulation administered twice a day, and that is in red; and the blue, broader profile is for the new formulation administered once per day. In this case, the C_{max} is similar for both regimens; the AUC over 24 hours is similar for both regimens; and the C_{min} is similar. However, the shape of the curve is different. For the new formulation administered once per day, there's only one peak, and there's a longer consecutive period of time with very low concentrations.

As indicated in the efficacy guidance to which Dr. Jolson referred, this type of change can be made using pharmacokinetic data, but there must be an understanding of the relationship between blood concentrations and response, including the time course

of the response.

The next scenario I will discuss is drug interactions. Drug interaction with antiretroviral drugs really occurs under two different circumstances. Under the first situation, coadministration of two or more drugs results in a change in exposure and the potential need for a dose adjustment. In the PK enhancer situation there's the intentional use of a subtherapeutic dose of one drug to increase concentrations of another drug.

The conventional dose modification situation occurs when antiretroviral drugs are administered in combination with any other drug. One example is the coadministration of Indinavir and Rifabutin. Because the sponsor already knew that Indinavir increases Rifabutin concentration, this interaction was studied using one-half the usual dose of Rifabutin.

When Indinavir exposure measures following administration of the 800 milligrams every eight hours with Rifabutin 150 once daily were compared to those following Indinavir 800 milligrams alone, the

Indinavir AUC, C_{max}, and C_{min} were decreased. And our recommendation, based on these data, was to increase the Indinavir dose to 1000 milligrams every eight hours when administered with Rifabutin.

The Rifabutin and metabolite exposure measures were also compared after the 150 milligram dose with Indinavir as compared to the usual 300 milligram dose of Rifabutin. The Rifabutin AUC and C_{max} were increased, and the metabolite AUC and C_{max} were also increased. Our recommendation here was to reduce the dose to one-half the standard dose of Rifabutin when administered with Indinavir. And this recommendation was made by evaluating previous Rifabutin and metabolite safety data, and considering the available dose strengths of Rifabutin.

We encounter a similar drug interaction situation when two antiretroviral drugs are coadministered. In this situation there was first a medical decision to coadminister two specific antiretroviral drugs. However, there may be an interaction between the drugs, and we need to know whether the dose of either drug should be altered.

For example, there may be a decision to coadminister Efavirenz and Indinavir. In the first study of this combination, following administration of Indinavir 800 milligrams with Efavirenz, there was no significant change in Efavirenz PK, but Indinavir AUC and C_{max} decreased. So based on those results, the combination was evaluated with an increased dose of Indinavir 1000 milligrams every eight hours. The AUC was similar to what's typically observed with the 800 milligram dose; the C_{max} was higher and the C_{min} was similar. This may lead to a safety concern because of the increased C_{max}. However, one of the clinical trials for Efavirenz included Indinavir 1000 milligrams every eight hours with Efavirenz, so we had safety data for this combination.

The pharmacokinetic enhancer situation is quite different from the examples I've just given. In this case the protease inhibitor is administered in combination with a potent metabolic inhibitor such as low-dose Ritonavir. The intent is to increase concentrations of the protease inhibitor, not to obtain antiretroviral efficacy from the second drug.

This usually also involves altering the dosing regimen for the protease inhibitor, decreasing the frequency. And the exposure measures may be quite different from what you see with the approved regimens.

In some cases, AUC, C_{max}, and C_{min} may be increased with the PK enhancer. And this is the case for the two dosing regimens that combine Indinavir with low-dose Ritonavir in BID regimens. When Indinavir 800 milligrams twice daily is administered with 100 milligrams of Ritonavir, Indinavir AUC, C_{max}, and C_{min} are increased. When the Indinavir is administered with 200 milligrams of Ritonavir, there's a slightly greater increase in AUC and C_{max}, and a much greater increase in C_{min}. So for both regimens the increased exposure measures raise safety questions. In other cases, the C_{min} may be higher with a regimen that includes the enhancer, but some other exposure measures may be lower.

The Amprenavir exposure measures for the Amprenavir-Ritonavir combinations are based on simulated data. These are not data from actual clinical trials. The simulated Amprenavir exposure

measures were compared to measures following the approved 1200 milligram twice daily Amprenavir regimen.

The first two regimens that include low-dose Ritonavir are twice daily regimens. In these cases there's no increase or a small increase in the AUC, and approximately 50 percent decrease in the C_{max}, and a large increase in the C_{min}.

The next two regimens are once daily regimens. And in this case there's again no change or a small increase in the Amprenavir AUC; no change or a less than 50 percent decrease in Amprenavir C_{max}; and again, a large increase in C_{min}. Of course, for all of these combinations, and for the Indinavir-Ritonavir combinations, there is a change in the overall shape of the plasma concentration versus time profile.

The final scenario, I will discuss pediatric dosing. As I have been discussing, there are many factors to consider when evaluating new formulations, alternative dosing regimens, and drug interaction results for antiretroviral drugs, and considering these factors in the context of dosing

pediatric patients as another layer of complexity.

The regulations do allow the inclusion of pediatric use information in the label without controlled clinical trials for the use in children. But for this to apply, the course of the disease should be similar in pediatric and adult populations, and the sponsor must provide other information to support the use in children. The additional information may include PK data for the drug in the pediatric population to allow dose selection. Evidence of comparable concentrations between children and adults or exposure response data can link the efficacy data from the adults to the children, and some additional safety data may be requested.

One example of the approval of pediatric dosing based on a comparison to adult PK data is Nelfinavir. The pediatric clinical study was ongoing at the time the NDA was submitted. Because early PK studies indicated that Nelfinavir clearance was more rapid in children, a dose two to three times the adult dose on a milligram per kilogram basis was selected for study.

The PK results submitted with the NDA indicated that after two weeks of treatment with 20 to 30 milligrams per kilogram three times daily, Nelfinavir plasma concentrations in children were similar to those in adult patients who received 750 milligrams three times daily. There was higher PK variability in the pediatric patients, however. We did request some safety data for the pediatric patients, and multiple dose data from 47 patients were submitted and reviewed. And there are no twice daily PK data available for pediatric patients, so we can't extrapolate the adult BID regimen to the children.

As a summary, I will indicate how each scenario I have discussed differs from the well-defined bioequivalent situation. With many new formulations, I have pointed out that they may not need the bioequivalence criteria, particularly for C_{max}. When there's a change in dosing regimen, the sponsor may target AUC or C_{min}, but other exposure measures will be different, and there's also a different shape of the concentration versus time profile.

When drug interactions occur, the change in dose and regimen may target AUC or C_{min}, but there's usually not enough flexibility to match all exposure measures to the approved regimens. When PK enhancers are used, there may be an increase in all exposure measures which would lead to a safety question; or there may be an increase in some exposure measures and a decrease in others, which would lead to safety and efficacy questions. With pediatric dosing, the sponsor may try to match AUC or C_{min}, but other exposure measures may be different from the adult regimen.

So overall, in most situations it's not going to be possible to match all exposure measures. In some cases there'll be lower concentrations where there'll be an efficacy question; and in other cases there'll be higher concentrations leading to a safety question.

Although we would like to determine PK/PD relationships for antiretroviral drugs that would allow us to use pharmacokinetic data to approve new non-bioequivalent formulations and alternative dosing

regimens, there are several important considerations that complicate matters. A goal, when evaluating a PK/PD relationship, is to identify specific exposure measures that are related as to pharmacodynamic endpoints.

One could then design exposure response studies that would allow the assessment of the clinical implications of changing formulations or dosing regimens. And it's important to remember that the PD endpoints include both efficacy and safety, and the efficacy endpoint of most interest is durable suppression of the virus.

During our preparation for this meeting, we consulted with the Pharmacometrics Group in the Office of Clinical Pharmacology and Biopharmaceutics, and this is a group that has a great deal of expertise in PK/PD evaluations and modeling. Drs. Peter Lee and Dan Wang from the Pharmacometrics Group evaluated the available data for antiretroviral drugs. Their ultimate goal was to provide suggestions for the design of exposure response studies that would allow the assessment of the clinical implications of

changing formulations or dosing regimens. And many of the considerations I'm presenting were either determined or confirmed during their review of these data. Due to these issues, it's not possible for us to recommend a specific exposure response study design for antiretroviral drugs at this time.

The pharmacokinetic considerations listed on this slide complicate the evaluation of PK/PD relationships. I'm going to discuss each consideration.

Many studies published in the literature correlate either AUC or C_{min} with the efficacy of specific antiretroviral drugs. However, the design of most studies does not allow us to rule out the contribution of other exposure measures such as C_{max}. In most cases, efficacy and safety data are available for only a few doses of a particular drug. And usually the same regimen, either twice daily or three times daily, is used for all the different doses. And that results in the type of relationship you see in the left graph up there.

The PK parameters are correlated with each

other. In order to conclude that one exposure measure is important for efficacy and another is not, the measures cannot be correlated with each other. You'd really like to see the type of relationship you see on the right there, where C_{min} and C_{max} are not correlated with each other. But in order to end up with that type of relationship, the sponsor would really have to collect safety and efficacy data following a mix of regimens -- once daily, twice daily, and three times daily -- for any specific drug.

In some cases the reported pharmacokinetic differences between regimens that were evaluated in different studies may be due to different PK sampling schemes, not really due to difference in the regimens. For example, consider a drug whose typical C_{max} is observed at one hour. If you sample at 0, 0.5, 1, 2, 4, and 6 hours, the C_{max} may be 50/100. But if you get rid of the one hour sampling time, the C_{max} may be 4000; and if you get rid of the one hour and one-and-a-half-hour sampling time, the C_{max} may be 3000. And there would also be a change in AUC with the different sampling schemes.

Diurnal variations should also be considered when comparing AUC values across regimens. When we compare different regimens, the AUC 0 to 24 hours is usually estimated as AUC 0 to 8 multiplied times three for three times daily dosing; or AUC 0 to 12 multiplied times two for twice daily dosing. And this estimation assumes that the PK profile is the same in the morning and the evening.

There's some evidence that this estimation is not appropriate. AUC in the afternoon may be lower in the morning, so this method of estimation would overestimate AUC 0 to 24, but we don't have data for most of the drugs.

As mentioned previously, demonstrating comparable AUC, C_{max}, and C_{min} between regimens does not guarantee that the shape of the concentration versus time profile is the same. And we discussed this graph previously.

Traditionally, C_{min} has been considered one of the most important exposure measures for protease inhibitor and NNRTIs. The literature may indicate that obtaining a specific C_{min} predicts success, but

it's really difficult to interpret the meaning and utility of that conclusion. C_{min} values can be very variable, and there will be a difference in the value reported, depending on whether it's summarized by arithmetic mean, geometric mean, or median.

For example, if you consider a representative series of approximately 70 C_{min} values, if you summarize, its arithmetic mean is 145; geometric mean, 102; and median, 121. And some individual patients may have values much lower than those summarized. It's also important to consider the time of sample collection when you consider C_{min}, because the C_{min} value may differ for different dosing intervals possibly due to diurnal variation.

The final pharmacokinetic concern I'll discuss is adjustment for protein binding. It's the unbound drug that is active. When we adjust for protein binding, can we really assume that all patients have the same fraction of drug bound to protein?

Example, consider a drug that is, on average, 99 percent protein bound. If Patient 1 and

Patient 2 both have a C_{min} equal to 100 based on total concentrations, consider that Patient 1 might have 99-1/2 percent of the drug bound to protein, one-half percent unbound, so the corrected C_{min} would be 5. Patient No. 2 might have 98 percent bound, two percent unbound, and the corrected C_{min} of 20.

For pharmacodynamics, our biggest concern is related to suppression of virus. There have been several instances in which different doses or regimens had similar efficacy to one another early in treatment, but diverged at later times. For example, efficacy may diverge between 16 and 24 weeks. Recently available data indicate that differences can even emerge between 24 and 48 weeks.

In addition to the factors I have discussed, there are a number of other considerations that complicate the evaluation of PK/PD relationships for antiretroviral drugs. These include mechanism of action. The NRGIs require intercellular activation. Thus, it's more difficult to determine the relevance of plasma exposure measures. There may be exposure measures other than AUC, C_{max}, and C_{min} that might be

important.

For example, time of a specific threshold concentration, like IC_{50} or EC_{50}. It's more difficult to evaluate PK/PD relationships for one drug when patients are receiving other drugs for the same indication, and most HIV patients are on multiple drug therapy. Response may be less than optimal if patients do not comply with the prescribed regimen.

Consumption of other agents, such as botanical products or food, may alter exposure to the drug and alter response. The prescriber may not be aware of the patient's consumption of these other agents.

Active metabolites complicate the evaluation of a PK/PD relationship. It may be necessary to include the metabolite in the PK/PD model. In situations of drug interactions, the proportions of parent drug and metabolite may change.

And finally, the relationship between drug exposure and response may be different in naive and previously treated patients due to the presence of different strains of the virus.

So if we are able to establish a PK/PD relationship for antiretroviral drugs, does it apply in all situations? Would the same model apply to all three drug classes or to all drugs within a class, or even to all populations? If pharmacokinetic and pharmacodynamic considerations make it difficult to design exposure response studies that allow the approval of new formulations or dosing regimens, we may consider whether we can find a study design that may allow more effective screening of the regimens. Such a design might allow us to weed out some failures early, and then a longer-term study would be needed to confirm the efficacy of the promising regimens or formulations.

In my concluding remarks I would like to comment on the standard of evidence needed for regulatory decisions. Under different scenarios there may be different standards of evidence needed. New formulations are held to a high standard. The new formulation may replace the previous one, leaving no room for patient management. All formulations need to be of high, well-defined quality, because they are

really the backbone of a dosing regimen.

There's more room for flexibility when interpreting drug interaction data. First, the combination may not last for the duration of therapy with the antiretroviral drug, and in many cases the drug interactions were encountered during the pivotal clinical trials. However, when two antiretroviral drugs are combined, dose adjustment recommendations may possibly be viewed as an approved dosing regimen, which may mean a higher standard is needed. And the standard of evidence for a change in dosing regimen or a PK enhancer interaction probably falls between the standards for new formulations and drug interactions.

Finally, how much uncertainty can we accept for pediatric patients? There's certainly feasibility issues with clinical trials in pediatric patients, and these patients have less treatment options. However, we want to be certain that the options we approve are well understood, safe, and effective.

When considering the standard of evidence needed for these different situations, it is important

to remember that the standard of evidence differs for regulatory decisions as compared to managing individual patients. And more details about PK/PD modeling and relationships for antiretroviral drugs will be discussed by later speakers today.

CHAIRMAN GULICK: Thanks very much, Dr. Reynolds.

Are there specific questions or clarifications for Dr. Reynolds about her presentation?

One question: What's the mechanism behind the diurnal variation that you might expect to see with different drugs?

DR. REYNOLDS: We think that there may be faster metabolism when people are awake versus when they're asleep, and that's one closed mechanism for some drugs. And it may be due to different meals. And sometimes there's actually a longer dosing interval overnight. So it's really multiple mechanisms.

CHAIRMAN GULICK: Other questions? Dr. Mathews.

DR. MATHEWS: Two quick points. One relates to sample sizes for the PK studies; and the other, you didn't mention in your otherwise very comprehensive discussion the whole issue of susceptibility of the virus in terms of interpreting or generalizing from the PK/PD relationship, and that obviously relates to the effect of concentrations. That would be highly variable depending on the susceptibility of the virus in the population studied.

But on the sample size issue, most of the PK studies that the Committee has seen over the years have relatively small sample sizes. Now, when you present an average AUC or an average C_{min}, what does the agency or the division consider acceptable limits of variation?

DR. REYNOLDS: We really look at all of the data, we don't just look at the mean values. Often we report that just because it's the easiest thing to do, but we look at the coefficient of variation, we look at the 90 percent confidence interval. And, I mean, usually the PK studies are small, so we can look at all of the individual data

and consider that in our decisions.

DR. MATHEWS: So that that range of the 90 percent confidence interval that you showed for the bioequivalent standard is what you would hope to see in evaluating PK parameters in vicinity viral context?

DR. REYNOLDS: We look at that, and that's really the standard that's used for considering no change. But in most of these cases we really don't expect to see no change, but we do use the 90 percent confidence interval.

CHAIRMAN GULICK: Dr. Yogev?

DR. YOGEV: Two quick questions. I noticed that, very satisfactory to me, that you defined pediatric as different. But for some reason pregnant women are not defined as specific. What you're saying is, it's so much different, both from safety and pharmacokinetic, that they should be defined as one of the issues that you need to see some data from, because those -- this specific population represent a unique situation, both pharmacokinetically and also from what we have today for prevention.

The other question I have is: You define

EC_{50} as efficacy. In many studies we see that the viral load media is run ten to the three over ten to the four. If it's ten to the three viral load, 50 percent reduction is almost in the variation of the method that you test. Shouldn't we put EC_{50} definition only if it's more than ten to the four of the population, and this allow enrollment of patients to studies of equivalence? Is that too low?

I notice in many studies there are even patient enroll in a thousand or less, and they are fit, in my opinion, the end product, if the end is not big, and especially over, say, pediatric or pregnant women. And I would like to hear your response to that.

DR. REYNOLDS: As far as the pregnant women, we realize that there really are not much data at all on that population. And we are starting to see more studies where they are collecting data on antiretroviral drugs on pregnant women.

DR. KWEDER: The agency in general is quite concerned about this. And while not related to this meeting specifically, we're working with the NIH.

We're cosponsoring two conferences this fall to try and generate more research interest in studying pharmacokinetics on this population.

There's a workshop in September being sponsored by the NICHD to look at study design and state-of-the-art methodology for this, and a larger one that will be the lead-on in early December for the same thing. This is not just an issue with antiretrovirals, but for drugs in general, and it covers both pregnant women and lactating women.

DR. JOLSON: Just one final comment, and it's that the division also is aware of the fact that most labels don't have any dosing information, and internally we've discussed sending letters to manufacturers asking for the availability of data. There is some data out there so that we can start to include that information in product labeling.

CHAIRMAN GULICK: Dr. Piscitelli?

DR. PISCITELLI: Kellie, what's the agency's feeling in support of accepting simulated data in support of an NDA package? I saw you present some here.

DR. REYNOLDS: The data that I presented were not in support of an NDA package. That was just the available data that we found for --

DR. PISCITELLI: In any cases would that be acceptable or useful to support something?

DR. REYNOLDS: It's possible, since we do have the Pharmacometrics Group, I mean, they have expertise in that area and could evaluate the quality of the data. So it's not something that we can rule out.

CHAIRMAN GULICK: Other questions? Dr. Murray?

DR. MURRAY: On the EC_{50} issue, I mean, I think that's just -- Kellie was just trying to define some terminology, and I don't think we've used that necessarily as a benchmark for making any decision. And I guess if you were to try to calculate an EC_{50}, I mean, you'd want to do it in a study that enrolled a range of individuals with a range of HIV RNA.

But so far, I think there's a lot of confusion around those terms. And, you know, they might be important for a ballpark kind of benchmark,

but we certainly haven't used them for a drug approval or a new formulation approval.

CHAIRMAN GULICK: Dr. Yogev?

DR. YOGEV: Just because mentioned that, can you clarify to me why we accept IC_{50} as an indication of sensitivity, not IC_{90} at least? We have a major problem in a quasi species as a whole, and we know that each human being have a lot of them, and we check the majority. So wouldn't IC_{90} represent better the population?

DR. MURRAY: Well, from my understanding -- and probably somebody else could comment better on this -- but I guess the IC_{50} might be a little bit easier to measure technically than the IC_{90} because it's on the plateau portion of a curve. And we haven't accepted any of those measurements. I mean, we think that they're useful in drug development to let you know that maybe you're in the right ballpark, and then you go and try to prove that with some clinical data. But I think it's just kind of a useful tool, and the 50 was because it's technically easier to maybe measure.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: Dr. Reynolds, thank you. Very nice presentation.

One of the things I'd just like to introduce to the Committee -- and then probably save more of the discussion for Dr. Struble's questioning of us this afternoon -- is pharmacogenetics which you didn't make mention of. But for antiretrovirals, in many ways, pharmacokinetics is kind of the expression of pharmacogenetics; how your genetic makeup and environment affects drug metabolism.

And I think there are many questions involved with pharmacokinetics that you presented that really are pharmacogenetically based, that may actually change over time in HIV patients and affect exposure to antiretrovirals. So, and I'd like to bring that up more later on this afternoon when we get to Dr. Struble's presentation.

DR. KWEDER: Kellie, I just have one question for you. It's maybe just to ask you to expand a little bit. You made the comment early on that a lot -- in many situations the types of PK data

that we have are usually in -- sometimes in healthy subjects, sometimes in patients as well.

Some of the questioning has gotten to the issue of some special populations; you know, children, pregnant women, we could include the elderly in that, different pharmacogenetic -- groups with different pharmacogenetic profiles. How much of that sort of special population data do you typically see in the applications for new formulations or dose regimen changes that you review?

DR. REYNOLDS: New formulations, we usually don't see any. I mean, the studies are usually done in men and women, but it's usually not broken down any further than that. For new dosing regimens, so far any data we've seen have been from a subset of the clinical trial, and they wouldn't really pick out just men from the clinical trial or just women from the clinical trial. So it'd really be just by chance, whatever the population is in the clinical trial.

CHAIRMAN GULICK: And just to follow up on that, what about populations with hepatic or renal

insufficiency? Are there requirements to provide data or --

DR. REYNOLDS: In order to have something in the labeling, a study needs to be done, if it's appropriate. If they know that a drug is completely metabolized, we may not need to study renal insufficiency. If we know that the drug is entirely renally eliminated, we don't really need to do a study of hepatic insufficiency. It depends on the drug, and it would really affect labeling; not really a requirement for approval, but for providing dosing instructions.

CHAIRMAN GULICK: Other comments or questions?

Okay, why don't we take a 15 minute break. We can reconvene at five of 10:00.

(Whereupon, the foregoing matter went off the record at 9:40 a.m., and went back on the record at 10:01 a.m.)

CHAIRMAN GULICK: Okay, we'll go ahead with the next presentation, which is Dr. Alex Rakowsky from the FDA.

DR. RAKOWSKY: Hi. Usually after a break it's nice to get reoriented, kind of like a mini-glass glaucoma scale.

So this is the Antiviral Advisory Committee. This is today's date. I'll let everybody fill in their own name.

Mine's Alexander Rakowsky. I'm a medical team leader in the Division of Anti-Infective Drug Products, one of the sister divisions of antiviral and the Office of Drug Evaluation 4 and CDER at FDA.

Basically, the purpose of this talk is to give a brief presentation of how the antibacterial folks have been using PK/PD parameters in various situations. It'd be nice to kind of focus in on the discussion on field today. There are various places where PK/PD has been used in antibacterials; for example, in new drug development or for approved drugs when you have a change in dosing formulation or a combination of other drugs. Also, there has been use in systemic agents versus topical, but that they all focus on approved systemic agents in this presentation.

There have also been various documents and guidances for a division, and affecting review of indications in our division through the years. The classic is the anti-infectives points to consider from 1992, the same year IDSA and FDA came up with guidances looking at various indications that our division at that time was approving. And there is some mention of PK/PD usage, essentially more for new drug approval and dose guidances.

There have been recent rewrites of the guidances for various indications, and as mentioned by Drs. Jolson and Reynolds, there is the clinical effectiveness document from 1998 which focuses more on our topic of conversation here, which again is approved drugs with changes in dosing formulation and combinations which lead to a non-bioequivalent state.

I'm not a pharmacokineticist, so I'm basically here just giving historical perspective, so please don't kill the messenger. This basically is a brief primer of PK/PD parameters using the two divisions that deal with antibacterials; namely, anti-infectives and special pathogens. And we'll have a

brief discussion of how these parameters have been used, what these parameters are, and give one example of an approval where they were used.

A real basic divide in the antibacterial world is essentially concentration-dependent drugs and time-dependent drugs. I want to start off with the caveat that many classes do not cleanly fall into one or the other, but still this is considered to be one of the basic parameters. As far as time-dependent, the major parameter of activity appears to be the time usually in serum that the drug is above the MIC for a certain pathogen. And examples of classes of drugs where this is the important parameter, the beta-lactams, such as penicillins and cephalosporins, and vancomycin.

Concentration-dependent, the examples of which are fluoroquinolones and aminoglycosides, appear to be more dependent on two other parameters: Either peak concentration to MIC ratio -- in other words, how high the peak is above the MIC -- and/or the AUC to MIC ratio. Slide.

What is an MIC? It's essentially the mean

inhibitory concentration, a similar concept commonly used in antibacterial as being the mean bacterial bactericidal concentration. The nice thing about MIC is that it's based on standardized *in vitro* work using specific preset conditions; growth media; concentrations; and for fastidious organisms, nutrient additives, et cetera. So you come up with a fairly reproducible stable number if you use NCCLS guidances for a drug-bug combination. Next slide.

The difficulty in MICs, however, is not in the reproducibility, it's in the interpretation of the MIC. Namely, what is "susceptible," what is the definition of "intermediate," and what is the definition of "resistant." One of the major issues, when deciding the interpretation, is the achievable drug levels. And this goes back to your typical ADME parameters: absorption, distribution, metabolism, and excretion. If you cannot achieve a certain drug level, doesn't matter how active the drug is *in vitro* when you're trying to define the interpretation.

Clinical data is also of great importance. And it should be mentioned that the interpretations

are defined after lengthy discussions either by a Committee such as NCCLS, or by review of clinical data by us at the FDA. And even though there is a great effort to come up with use and definitions, there still is occasional disagreement.

Let's start talking about time-dependent antibacterials. The major parameter is time above the MIC. There's some early work done in animal models, such as Bill Craig's work in the University of Wisconsin, looking at acute otitis media models. And it has been confirmed by some clinical trials that time above MIC for several classes, such as beta-lactams, is the most important parameter. But if you look at the definition of time above, it is dependent on a range of parameters; again, the ADME parameters.

You need to have a certain C_{max} achieved, and that depends on the actual patient, depending on concentration, as it were, in the case of oral from the gut, et cetera. You also have to look at the distribution of the drug, serum verus tissue, penetration into CSF fluid, and also the issue of protein binding that Dr. Reynolds had brought up.

And lastly, if you look at the time above, it's just as important to look at the half-life of the drug. And metabolism and excretion are major issues which are again dependent on the ranges depending on the individual. The MIC also has a lot of variability. It's pathogen-dependent. And for pathogens you have the sticking point of resistant strains.

And then there are other factors that need to be taken into account, such as the inoculum effect; the effect of PH on activity. A classic example is aminoglycosides in abscesses where they are not as active in low PHs, and other factors which make the MIC different in clinical practice than what you get in an *in vitro* setting.

As far as the animal and the human studies, the classic studies have shown that time above MIC for the drugs in the time-dependent category, if you have a time above MIC in the 40 to 60 percent range, this appears to be predictive of clinical success. Is this 100 percent correlation? Unfortunately not. But it is a strong predictor.

And it does vary among the members of the same class of drugs, and one of the variables that may account for this is something called the post-antimicrobial effect. When looking at concentration-dependent, again we discussed the major parameters before: the peak to MIC ratio; and AUC to MIC ratios. Animal studies have been done, and some human studies have been recently published, looking at the recent fluoroquinolones, such as Dr. Drusano's work up in Albany.

Again, you're still depending on ADME parameters. Here, since you're looking at the max achieved, you're looking at absorption and distribution. And if you're -- one of the major assumptions has always been that a serum level is predictive of other tissues in the body. But there appears to be a certain amount -- there appears to be a definite correlation of local levels, penetration, et cetera, when it comes to activity of the drug. Plus you have the local effect such as discussed before, such as PH, protein binding, et cetera. Again, clinical studies are predictive, but not 100

percent correlation.

So what are the conclusions so far? The variables are based on ranges of classic PK parameters. The work has shown good predictiveness, but not a one-to-one correlation. The MICs do vary depending on the pathogens studied and on resistant strains. And again, the majority work has been done on beta-lactams and fluoroquinolones.

The question that has come up multiple times: What is the role of PK/PD in this study and approval of antibacterial agents? And there have been two Division of Anti-Infective Drug Product Advisory Committee meetings either solely dedicated to this, or as part of the Committee discussion looking at this exact question. And it was in July of '98 and October of '98.

We had a meeting of industry in July of '98 as a preamble to this meeting, and lastly in March of '99 there was the FDA ISAP -- ISAP being the International Society of Anti-Infective Pharmacology -- workshop at which various presentations were given and discussions held regarding PK/PD parameters in

antibacterials.

In addition to the difficulties already raised at these four meetings, these other difficulties were mentioned almost every time. When you look at the models, the emphasis has been more on effectiveness and not on safety. Most work has been done with single drug-bug combinations. At least in antibacterials we're used to acute models, but for some of the more chronic use indications such as osteomyelitis, there have not been good animal studies done, so chronic use/chronic illness has not been well studied.

And in addition, one of the few divisions in the center that has a moving target. You have a susceptible pathogen one day, and the next day it becomes resistant. So resistance development, especially if these are chronic use in a patient or use-over-time in any population, will change the activity of your drug.

So is all lost? I've been pretty negative so far. But there is actually several positive impressions at these meetings. First, the PK/PD for

certain classes has been very well worked out. The models are improving greatly, and a good example of that, at ICAAC over the last few years there've been several workshops discussing primarily the improvement of models for antibacterial agents. And lastly, as can be seen in the proper context, PK/PD parameters and PK/PD data can be strong supportive evidence.

So let's give an example of how it has been used. Augmentin seven-to-one NDAs were submitted in 1994 and 1995. In these two NDAs there was a change in the formulation for adults from 500 milligrams TID to 875 BID; and 250 TID to 500 milligrams BID. In pediatrics, the divided dose of amoxicillin went from 40 milligrams per kilogram per day divided TID, to 45 milligrams per kg per day divided BID.

In all the formulations the amount of clavulanic acid stayed the same, so this was a four-to-one, 500 to 125 ratio. This was a seven-to-one, 875/125 ratio, et cetera. So with the BID dosing, there was a one-third less daily amount of clavulanic acid. Next slide.

In all settings, as predicted, AUC and half-life was comparable between the new and the old dosing regimens. The C_{max} was higher by about 50 to 80 percent in the BID dosing regimens. Again, that's predicted. The time above MIC, however, was lower in the BID regimens. On average, these regimens had ten out of 24 hours above the MIC. On average, the approved doses at that time were 11 out of 24, so there was a concern about a decrease in the time above the MIC, especially since this was approaching the cuts with the 40 to 60 percent range. And there is also concern with the one-third lower amount of beta-lactamase inhibitor activity.

The sponsor came in with strong *in vitro* data showing both a post-antibiotic effect for amoxicillin and a post-beta-lactamase inhibitor effect for clavulanic acid. Animal studies were done which showed comparable efficacy rates for the BID and TID dosing regimens.

But regardless of this data, due to concerns of the lower time above MIC and the decrease in clavulanic acid, clinical studies were still asked

for. However, instead of asking for the historical two studies for indication, one study was conducted for indication. And ultimately the NDA was approved based on the combination of the *in vitro* micro and animal work; the PK/PD data; the one adequate, well-controlled study per indication compared to the historical two; and an agreement to study, instead of BID, Q12, so as to have a more -- so as not to have a 14-hour dosing regimen for the evening dose. Overall, there's about a 50 percent decrease in the subjects enrolled compared to what would be historically required. And we see this as a good example of how PK/PD parameters have been used and will be continued to be used in our divisions as a way to kind of cut back on the number of patients enrolled.

So lastly, the conclusions are that for certain parameters and certain drug classes there is a fairly well worked out relationship. There are issues of variability in ranges, especially with the PK parameters, MICs, local effects, et cetera. And despite multiple meetings where it has been discussed whether PK/PD can stand on its own, the conclusion in

all four cases has been that supportive -- PK can be seen as strong supportive evidence, but that for the reasons and the efficiencies listed above, should not be used in lieu of clinical evidence. Thank you.

CHAIRMAN GULICK: Specific questions or clarifications for Dr. Rakowsky? Dr. Flexner?

DR. FLEXNER: I notice with the change in the Augmentin formulation, the major pharmacokinetic shift was an increase in the C_{max} for amoxicillin. I was wondering whether there was any data on concentration-dependent toxicity of amoxicillin or whether this was just a precautionary step to ask for an additional clinical study?

DR. RAKOWSKY: Actually one of the reasons for asking for the clinical study, one was effectiveness, and two was a safety concern. At the time that the NDAs came in, there was some European data looking at BID dosing with the higher C_{max}. It appeared to be a safe dosing at that time, so that was used kind of as supportive evidence as well. But that was a concern when we asked for the clinical study.

CHAIRMAN GULICK: Dr. Yogev?

DR. YOGEV: You said that MBC is a similar concept. I wonder, just because you use this example, what we call a cidal drug, there's no difference between MIC and MBC, your drug, erythromycin and the like, there is a major difference between the at least more than four dilutions. Should we look more into the MBC parameter than the MIC?

DR. RAKOWSKY: I guess I answered that in two ways. First, I agree that the MBC is very different than MIC, and it does vary depending on whether it's a static or a cidal drug. The reason I was asking -- the reason I was basically pointing that out is that for MIC -- for MBCs it's -- you can come up with more objective data, more objective reproducible numbers. And that's what I meant by them being similar.

As far as use of MBC in clinical trials, it has been discussed in multiple scenarios. For example, Dr. Reller, who is now the head of our advisory committee, is a big believer that MBC should be used for approval. But that's only the discussion, and at this time MIC_{90} is still what's commonly used

for approval.

DR. YOGEV: You know, the MIC_{90}, that's important that you mention, because the MIC_{50} is the one which usually is in the literature. The reason why is MIC_{90} is closer to the MBC, and the data, especially meningitis, suggesting that the inoculum is a major factor in the MBC -- in the MIC.

And I think that's part of the issue we need to discuss, is how you do the test *in vitro*. Because if you put what is now ten to the four, ten to the five nationally agreed -- internationally agreed for *in vitro* studies, they are way away from what you find in the CSF. And I think that's part of the problem of accepting such an entity without relating it to where you're looking for the drug to work, like in meningitis.

DR. RAKOWSKY: Yes, agreed. And actually, as far as the label's concerned, we usually ask for MIC_{90} data to be part of the approval process, not MIC_{50}s.

CHAIRMAN GULICK: Other questions? Dr. Fletcher?

DR. FLETCHER: To the amoxicillin example again, I wonder if you can comment on what was done study-wise for pediatrics.

DR. RAKOWSKY: I guess we come from a slightly different scenario, since one of the major indications for us tends to be acute otitis media. So for most of the oral drugs, we get very strong pediatric data right up front.

In fact, some NDAs are approved for pediatrics first, and then we extrapolate to adults. Rarely, but we still get the -- you know, so it's kind of like a very different scenario than what would traditionally be seen.

So for amoxicillin they actually did a full acute otitis media study. In fact, that was the first study that was done. It was probably the easiest patient enrollment, and that was where the Europeans were already using the BID regimens, so there was some historical safety data as far as that was concerned. And we have a slightly different perspective, antibacterially, because of that one indication.

CHAIRMAN GULICK: Okay, thank you.

Our next speaker is Dr. Richard Hoetelmans. And he's from the Slotervaart Hospital in Amsterdam, The Netherlands.

DR. HOETELMANS: Okay, thank you very much. And first of all I would like to thank the FDA for inviting me here to give an overview of what's been published in the literature about relationships between pharmacokinetics and dynamics for the antiretroviral drugs.

PK/PD relationships can be defined as an -- at least a finding of it, as an attempt to correlate pharmacokinetic parameters of a drug and its efficacy or toxicity. And for the antiretroviral drugs, I will focus in this presentation on the protease inhibitors and the non-nucleoside analogs. As for the nucleoside analogs, not any relationships have been found.

For the nucleoside analogs, these are prodrugs, and if you look at the plasma exposure of those nucleosides and try to relate their C_{max} or AUC or whatever to the efficacy, not many relationships

have been found.

This might be explained by the fact that the triphosphates are active and there is not a good relationship between what you find in the plasma as nucleoside concentration, and the intercellular triphosphate concentrations. And at this moment there are not a lot of data available that allow us to interpret the relationships between the triphosphates intercellularly and the efficacy, so I won't speak on this topic during this talk, but will focus on the protease inhibitors. Because for these drugs relationships between PK and PD have been established, and non-nucleosides reverse transcriptase inhibitors, for this group recently also some indications of relationships between the PK and PD have been established.

First of all, Indinavir. When you look in the literature, it turns out that Indinavir is the best studied drug in this respect, so most studies on relationships between PK and PD have been established for Indinavir in a dosing regimen of 800 milligrams TID with two nucleoside analogs. And these are some

six studies that have been published, and they all have looked at several PK parameters of Indinavir ranging from AUC minimum concentration, maximum concentration, and the so-called concentration ratio, and they've linked this to various PD parameters. Most of them are the change in HIV-1 RNA in patients after 24 weeks.

And in these studies, these authors, they all find relationships between either the AUC or the trough concentrations of Indinavir 800 milligrams TID in various populations. Most of the patients have been pre-treated with nucleoside analogs, and the HIV-1 RNA response of 24 weeks.

So some -- but not all -- studies show, in retrospective -- these were all retrospective studies -- relationships between the Indinavir PK and HIV-1 RNA response over 24 weeks. These relationships have mainly been established in nucleoside analog pre-treated patients, and reported PK parameters for Indinavir are the AUC, the C_{min}, and the C_{max}.

But these parameters were in most studies all correlated. So if there was -- if a relationship

was found for the AUC, it was also found for the C_{min} and the C_{max}. From these studies it's not easy to extrapolate which parameter is the most important one in this respect.

When you look at the use of Indinavir with either low dose or higher dose of Ritonavir, I could not find studies that show that there are clear relationships between Indinavir exposure and the efficacy, in terms of HIV-1 RNA response. When you look at Indinavir PK and the relationships with adverse effects, there was one paper from AIDS from Dieleman, and they showed in patients -- this was a case cohort study -- the patient had neurological complaints, had higher exposure to Indinavir as compared to patients with no neurological complaints.

So anecdotal data showed that the high exposure to -- that patients with a high exposure to Indinavir experienced an increased risk for neurological complaints. It has been hypothesized that the C_{max} of Indinavir is mainly responsible for the renal toxicity of this drug, but I would like to point out at preliminary data of the best trial that

compare Indinavir three times daily 800 milligram versus Ritonavir/Indinavir 100 -- 800 milligrams BID, and it appears in these preliminary data that the renal toxicity is more often observed in the Ritonavir boosted arm, which might suggest that the AUC or the time above a certain concentration is more important in predicting the renal toxicity of Indinavir, as opposed to the C_{max}. So we don't have enough data at this moment, but it might not be the C_{max} that is the most important parameter in this respect.

We look at Saquinavir. PK/PD relationships have also been found for this protease inhibitor, and have mainly been found in studies with monotherapy of the protease inhibitor, or when combined with two nucleoside analogs. In these four studies, both in naive patients and pre-treated patients, various parameters you see, and the concentration ratio have been linked to HIV-1 RNA response over eight weeks or 48 weeks or even two weeks, so the initial decline of HIV-1 RNA.

In a very recent analysis from our group, in patients treated with a combination of

Saquinavir/Ritonavir 400/400 BID, showed that we were not able to find any PK parameter that linked to HIV-1 RNA responses over 48 weeks of therapy in a cohort of over 100 patients.

So for Saquinavir some -- but again, not all -- studies show that there are, in retrospective, relationships between some Saquinavir PK parameters and HIV-1 RNA responses. These relationships have been established both in naive patients and in nucleoside analog pre-treated patients.

The reported PK parameters in the literature are both the AUC and the trough concentrations; but again, these are related to each other. And at this moment there are no clear data on these relationships when Saquinavir is used in combination with either low or high dose of Ritonavir.

Saquinavir and adverse effects in the Adam study using four drugs, amongst which was Saquinavir, there was a relationship found between complaints by the patients about gastrointestinal adverse effects and the exposure to Saquinavir over a 48-week period. So, for the adverse effects, high Saquinavir exposure

has been linked in studies with an increased risk for gastrointestinal complaints, but it is at this moment unclear which parameter is best linked to this phenomenon.

Then, Nelfinavir, if you look at Nelfinavir, there are not a lot of studies at this moment available that have looked into PK/PD relationships; and the active metabolite, M_8, has not often been taken into account in this respect. These are two studies, first of all by Kerr, et al, and they also looked at the M_8 metabolite, and they found in naive patients that Nelfinavir concentrations two hours after ingestion were related to an HIV-1 RNA response after 24 weeks.

And again, in the Adam study we found that the exposure to Nelfinavir was related to the initial HIV-1 RNA decline in the first two weeks, but we were not able to show that this very -- that patients with a rapid decline also had a better response in the long term. And as an example of what we found in this Adams study, on the "X" axis you find the exposure of Nelfinavir in patients during the first two weeks of

therapy expressed as a concentration ratio.

And what you can see here is that there is quite a large variability in the exposure to Nelfinavir which we also find for the protease inhibitors, and on the "Y" axis you find the speed of which HIV-1 RNA is disappearing from the plasma, and there was clear correlation between the exposure to Nelfinavir and the initial HIV-1 RNA decline.

So for Nelfinavir, some studies have shown, again in retrospective, relationships between the Nelfinavir concentrations and the initial or 24-week HIV-1 RNA decline, and these relationships have all been established in naive patients. In that study it was also reported that patients with a high exposure to Nelfinavir had an increased frequency of gastrointestinal adverse effects, so we were able to show that high Nelfinavir exposure has been associated with an increased risk for gastrointestinal complaints; but again, it is unclear which parameter is best associated with this phenomenon.

For Ritonavir there was one paper that's been published in AIDS and from the group -- from

Gatti, et al, and they looked at patients with gastrointestinal and neurological complaints when they used Ritonavir 600 milligrams BID, and they compared the maximum concentration of Ritonavir and a trough concentration to dose in a patient group who did not report these adverse effects, and this group found that there was a relationship, or that patients with adverse effects had higher C_{max} and C_{min} values for Ritonavir as compared to patients without complaints.

So, for Ritonavir it has been reported that a high exposure is associated with an increased risk for gastrointestinal and neurological complaints, and these associations have been reported both for the AUC, the C_{max} value, and the trough level. But again, these were all related, so it's not possible to say at this moment which parameter is mainly responsible for these associations.

Then over to the non-nucleoside analogs. When we looked into the ENCAS database, we found that patients with high Nevirapine levels during the study had a better chance of reaching a detectability for HIV-1 RNA. Over a 52-week period they showed a more

rapid decline of HIV-1 RNA after start of therapy, and the duration of response in those patients was better than patients with low exposure to Nevirapine.

So for Nevirapine, very limited data on retrospective relationships between the PK and HIV-1 RNA response both in the short and the long term have been established in naive patients, and in this study the reported PK parameter was the median concentration that was found after a random sample had been analyzed in this ENCAS study, because this study was not set up to be a study to look into PK/PD relationships. So again it's not possible to extrapolate from these data whether the value is like an AUC, or more likely a trough level is important when you look at those relationships.

This graph summarizes the results of this ENCAS trial when patients had a median concentration above 3.4 micro molars per mL. There was a hard chance of predicting which patients would be undetectable for HIV-1 RNA after 52 weeks, or which patients would not be undetectable using an ultra sensitive assay of 20 copies per mL.

Recently for Efavirenz similar relationship was reported by Joshi, et al, at ICAAC, and this group found that trough levels of Efavirenz in patients were related to treatment failure. This group looked into five different studies of Efavirenz, and they defined a trough level in patients based on an extrapolation of the sensitivity of a K-103-N mutant. This mutant would still be sensitive to Efavirenz if trough levels would be above 3.5 micro molars, and to use this threshold to divide the patients into two groups.

And it was clear that in patients with trough levels below this threshold, 63 percent showed a failure in those studies as defined by the protocols, and patients with higher trough levels showed only 21 percent of a chance of a failure. So in this study, trough levels were associated with a chance of pharmological failure for Efavirenz. So just like the case is with Nelfinavir, limited data on retrospective relationships have been established between the Efavirenz trough levels and treatment failure.

Now I would like to go further into why sometimes we do find relationships and sometimes we don't, and how this might be. In general, when we look at the PK of protease inhibitors, there is a large variability in the AUC or other exposure -- a parameter that you might look at. So when you give a patient population all the same dose of drug, you find patients with very low AUC values and patients with very high AUC values, and I don't believe that there is a big difference between the protease inhibitors, for instance, at this moment, that are available at this moment.

Now, when you look at the relationship between the drug concentration and the efficacy, in general you will, in most cases, find a curve like this: Patients with a very low concentration of the drug in the blood or at the site of action have a low chance of responding, and as the concentration increases, the chance of full suppression of feral replication rises. Now, when this is the median concentration that is obtained in the population, you will have patients that have much higher

concentrations, you will have patients with much lower concentrations. But if you look at the effect that you might see in those patients, the difference between those two groups is quite small.

So in these situations it might be very difficult to find relationships because you are at the upper limits of the plateau. And when the virus becomes more or less resistant to the drugs, the exposure to the drugs will still be more or less the same, there will still be patients with a relatively high exposure to the drug and patients with a relatively lower exposure to the drug. And in this case there will be a substantial difference between the effect that you might find in the patient, and in this situation it becomes much easier to find relationships between PK and PD.

And it might well be that in the case of single PI use where the exposure to the drugs is lower than in the case of boosted PI use -- that we are looking into this situation -- a relationship between PK and PD are more easily found than when you look into the boosted PI strategy where the exposure is

much higher to the protease inhibitors and it becomes more difficult to find PK/PD relationships in this population.

And again, it becomes more difficult to find relationships when, for instance, resistant virus is obtained. If you have highly resistant virus -- for instance, for the non-nucleoside analogs -- it is very unlikely that you will find PK/PD relationships, because all the patients will still have the same exposure to the drug; some have higher exposure, some a lower. But the final efficacy that you will find will, in both cases, be quite low, and in this situation it will again be quite difficult to find relationships.

A topic that has been discussed quite often recently is the use of trough versus IC_{50} ratios as a measure of efficacy. And I think if used, these threshold values for trough versus IC_{50} values, ratios should be established for each drug. What has been done recently is that these values for IC_{50} have been corrected for protein binding, and this is a step in the right direction. But it is also insufficient,

because many other factors, such as the penetration of drugs into compartments; intracellular accumulation, for instance.

Recently I think it's David Beck's group mainly who has shown that also protease inhibitors show very interesting intracellular profiles. They accumulate; at least some of them seem to accumulate intracellularly as compared to what you see in the plasma. Active metabolites play a role; the synergy and antagonism of other drugs that are being used; all these factors all should be taken into account when interpreting these trough versus IC_{50} ratios.

For the non-nucleoside analogs these ratios may well be, for instance, over 500 since the IC_{50} values for the non-nucleoside analogs are quite low, in the low nanogram per mL range, while the trough concentrations in the patients are more in the microgram per mL range.

For Efavirenz, you might take into account that this is a drug that is very highly protein bound. But, for instance, Nevirapine is only 60 percent protein bound. So this cannot explain why, when the

IC_{50} value for Nevirapine is very low, you still see patients -- with very high trough levels as compared to these IC_{50} values -- have failed, whereas patients with somewhat higher trough values for Efavirenz do not fail.

The protease inhibitors, I think we should realize that these required ratios may actually be smaller than one if the intracellular accumulation of protease inhibitors is an important factor, because we are looking at the trough levels in the plasma, while the actual trough levels intracellularly might be many times higher than those that are found in the plasma. So I think that these trough versus IC_{50} ratios can most likely not be used to compare the potency or durability of drugs amongst each other.

So when extrapolating from *in vitro* IC_{50} values to *in vivo* trough values or C_{max} values or AUCs, I think we should take into account many more than only protein binding, what's been done until now. It's also the accumulation of drugs, the presence of active metabolites, synergy or antagonism with other drugs that are given, P glycoprotein plays a role,

phytodiversity, and probably many other pieces of the puzzle that we do not know about at this moment.

Briefly to the topic of IC_{50} versus EC_{50}. And this has been explained earlier on. And the IC_{50} represents the concentration of a drug that is required for 50 percent inhibition of feral replication *in vitro*. And this can be corrected for by protein binding, but many other factors may play a role in the correct interpretation of IC_{50} values.

Whereas, the EC_{50} value, the effective concentration represents the plasma concentration or the AUC value that is required for obtaining 50 percent of the maximum effect *in vivo* in patients. And I think we should strive for looking more into EC_{50} values rather than IC_{50} values, because when you directly obtain EC values in patients, you circumvent the problem of extrapolating IC values to plasma concentrations, and there are many factors that we do not know at this moment how to account for.

So, conclusions, for the protease inhibitors, PK/PD relationships have been established, but not always. And I should tell, when I was asked

to prepare a review, I was quite disappointed how little information is available at this moment in the literature. I imagine that it would be much more, but it -- actually, if you look what's in the public domain at this moment, it's not a lot. It is also unclear which PK parameter should be used; either a trough level, an AUC value, or something else. And until now PK/PD relationships have mainly been found for single PI therapy, with or without nucleoside analogs, and there've been only negative results for the boost PI strategy or still no results, because this strategy is -- has just been implemented.

For the non-nucleoside analogs, indication of PK/PD relationships have been reported. Also, in this case it is unclear which PK parameter should be used, C_{min} or AUC, and these relationships might rather be explained by the presence of resistant mutants than the ratio between exposure to IC_{50} values for wild-type viruses.

Models of PK/PD in the field of antiretrovirals have largely not yet included the sensitivity of the virus that is present in the

patient as a parameter. And when linking phenotypic data with the pharmacokinetics, I think that IC_{50} values should, if they are used, rather be used in the IC_{90} or IC_{95} values, because the error that you make when obtaining an IC_{50} value is much smaller than when looking into IC_{90} or 95 values, and that EC values should rather be established than IC values. It would be interesting to know if the boosted PI strategy overcomes the PK/PD relationships that have been reported for the unboosted strategies for the protease inhibitors.

I think, to conclude, that based on PK/PD relationships, PK data can and should be used as a background for new formulations or dosing regimens, but clinical data are still essential, given the modest information that is available at this moment. And these are some people that I would like to acknowledge. Thank you for your attention.

CHAIRMAN GULICK: Thank you, Dr. Hoetelmans.

Dr. Schapiro?

DR. SCHAPIRO: Richard, thanks for the

wonderful review. You mentioned something with the dual PI therapy, there were no correlations found. Do you think that some of that may be due to the interaction of Ritonavir on the accumulation of the other protease inhibitors which comes after the drug level determination?

DR. HOETELMANS: Do you mean that the drug levels, for instance, whenever Indinavir are that high, that you are reaching the -- at the plateau of the response curve?

DR. SCHAPIRO: That Ritonavir is not only affecting to what degree you've got a certain blood level, but it also has a second effect between the blood level and the intracellular level, which therefore you lose the correlation between the blood level you have in the single PIs.

DR. HOETELMANS: It's quite difficult to answer, because if you look at the effect of Ritonavir on, for instance, P glycoprotein, the results from various groups are quite contradictory.

Some groups report that Ritonavir is very effective in inhibiting those bumps. This you might

expect, that Ritonavir increases other PI concentrations intracellularly. Whereas other groups show that with the other concentrations of Ritonavir achieved *in vivo*, it's never possible to inhibit P glycoprotein, but to an extent that it's going to be clinically relevant. So I think it's not possible at this moment to answer this question, but it might.

CHAIRMAN GULICK: Mr. Cheng?

MR. CHENG: I have a question regarding all of the studies that have shown a relationship between drug exposure and side effects. Did they also look at the relationship between body weight and drug exposure?

DR. HOETELMANS: As far as I'm aware of, no, they didn't. Well, not in those particular studies. I don't think it was clear from those studies that it was the patients with the low body weight that has more adverse effects based on maybe higher concentrations because of the low weight. No.

CHAIRMAN GULICK: Dr. Gerber?

DR. GERBER: Richard, a question that I have, you talked about a lot of confounders in terms

of why you can't interpret PK/PD. But one of them that has not been talked about so far is drug-taking behavior, which I think is a very important aspect and might explain a lot of the variables, and might also explain why we're having such difficulty finding a relationship between concentration and response. And I wonder if you want to comment about that.

DR. HOETELMANS: Yes, I agree. If you look at -- if you perform a PK analysis on patients that you admit into the hospital, you draw the blood and you know that they ingested drugs, you get a AUC value in that patient. You don't know if the values for the PK parameters that you obtained will also be obtained on the other days if the patients don't or not always take the drugs. So it is very important, I think, that we go to studies where you look at drug levels in patients as they are in real life, so whenever they come to the clinic you have a blood sample drawn. I don't work with observed intake of drugs. I think this is important in establishing PK/PD relationships in large cohorts in groups that -- well, as patients are treated in day-to-day practice.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: It seems as if -- and Dr. Fletcher and Acosta may want to comment on this -- there's some fairly big problems with antiretrovirals. One is there's a huge variability in the pharmacokinetics; and secondly, is that we don't have these same kind of dynamic relationships that we do with antibiotics in terms of peak MIC ratio or time above MIC.

And drawing from some of the bacterial data, if you take a look at some of the data from Mouton and Craig where they actually showed that for different antibiotics you have, you use different dynamic predictors, that if we're not looking at the whole picture of antiretrovirals in the patients, you can't just look at protease inhibitors, NNRTIs, NRTIs. You need to figure out if you need to measure them all, make your relationships that --

I think some of the data in the literature that says, well, there's this correlation between Indinavir exposure and reduction in viral load, but the correlations are always poor, and they're probably