Those tentative breakpoints are then used in the design and conduct of Phase III clinical trials which are meant to support safety and efficacy, and it is in the context of those Phase III clinical trials which collects more extensive clinical efficacy data that the correlation between clinical outcome and these tentative breakpoints are developed.

That activity is done within the review process of a new drug application at the FDA, so, in fact, during the review of an antibiotic, we review not only the clinical efficacy information, the basic pharmacology and toxicology, but the microbiology package includes, in fact, the proposed standardized assays, quality control information, as well as the proposed breakpoints and all of the information that is shown here to support setting those interpretive criteria.

The NCCLS is also an organization which reviews similar sorts of information, often the same package of information, and also develops interpretive criteria for new drugs and organisms.

So, the information that is considered in developing the interpretive criteria, setting these categories of susceptible, intermediate, and resistant, include the assay characteristics, population distributions of MICs for the important pathogenic organisms.

This is usually based on in vitro information that

is collected on a large number of organisms, the example that is given or proposed is 500 organisms, which represent both geographic diversity around the country. They should be recent clinical isolates relevant to the infections that are being sought, and should represent not only susceptible organisms, but if there is evidence on relevant resistant mechanisms, those should also be represented in this sample of microorganisms for which the distribution of MICs is produced.

This is often presented in tabular form or most conveniently in histograms, which it is very easy to then determine what the overall population distribution of these MICs are.

The third part of the equation are pharmacokinetic and pharmacodynamic information. That includes not only strict or simply blood levels or tissue levels, but also an attempt to look at what are the important pharmacodynamic correlates with a particular class of drug and organism.

For example, parameters such as time above MIC or AUC to MIC ratio. Many of these are peak concentration to MIC ratio, may, in fact, be important in predicting efficacy of certain drugs. These have been worked out for different classes of antibiotics. These factors are also considered in determining what are likely achievable, not only blood levels, but pharmacodynamic parameters, which are associated

rith predicted efficacy.

Finally, correlation of test results with clinical outcomes. As I stated, proposed interpretive criteria are developed in the course of drug development for antibiotics, and these are incorporated into the Phase III clinical trials, so that within an application, a sponsor may then analyze baseline MICs for the particular isolated organisms and then correlate that with clinical outcomes observed in the Phase III trials.

These are usually broken down by organism and site of infection to really get a sense of how not only the drug is performing at a specific site of infection, but what the correlation with the particular MIC and the site of infection and the etiologic organism are.

[Slide.]

To finish up this section of my talk, I just put up a list of organisms for which interpretive criteria have been established, and this is from the most recent NCCLS publication actually.

You can see that there are, in fact, a large number of bacteria for which interpretive criteria have been established. There are also clearly important pathogenic organisms not on this list, for example, chlamydia pneumonia, mycobacterium tuberculosis, to name just a few.

I think that the challenges in developing sort of

standardized test methodology and interpretive criteria really harken back to some of the issues I have talked about and some of the issues that this committee has been grappling with in terms of developing standardized methodology for HIV susceptibility testing.

[Slide.]

What I would like to move on to now is to touch on a couple of these regulatory issues, and that is how is this susceptibility information, once it is obtained in the course of drug development, now included in the product labeling, which is the source really of how we communicate all of this information about the utility of this information to the practitioner in produce labeling.

Importantly, it is also sort of the basis for a product promotion, and in that sense, these two important goals of providing accurate important information and accurate information for product promotion are very important, and need to be sort of integrated into how the approach is taken.

[Slide.]

In 1992, the Division of Anti-Infective Drug Products published a clinical points to consider document, which was titled, "Clinical Development and Labeling of Anti-Infective Drug Products."

It was quite a comprehensive document that dealt

with not only a number of general issues in the development of antibiotics, but also had a number of sections that dealt specifically with clinical trial design within specific indications, and the level of evidence to support approval of specific indications.

It provided a regulatory framework for the development and product labeling of anti-infective drugs, and while there are certain parts of that document that we have more recently started to re-review, that is, specific guidance in terms of clinical trial design, I think there are some general parts of the document which are still important to consider.

The overall goal of this document was specifically related to reporting of susceptibility testing, and the format of the Microbiology section was to eliminate advertising or other promotion that implied greater effectiveness of one compound versus other compounds based solely on in vitro microbiologic data.

To that end, one of the sections recommended a format for the Microbiology subsection. In it, it included a description of testing methodology and interpretive criteria and also a format for the listing of susceptible microorganisms.

[Slide.]

In regard to the inclusion of susceptibility

information, the reason I am sort of laying this out is because susceptibility is the converse of resistance, and the approach in antibacterial labeling historically has always been to label products for those infections due to susceptible microorganisms.

As I said, at the end of my talk I will speak briefly about the whole issue of specific resistance claims and how that has come to the fore given recent sort of clinical and scientific development.

Susceptibility information is included in two parts. There is what is often called the first list or list of organisms found specifically in the Indications and Usage section. Specific wording in the label is that the drug has been shown to be active against most strains of microorganisms, both in vitro and in clinical infections as described in the Indications and Usage section, and I will speak more about this in a minute.

The second list of organisms are organisms for which only in vitro data are available, and the specific wording for their inclusion is drug X exhibits in vitro MIC concentrations -- and this would be of a clinically relevant susceptible breakpoint based on the interpretive criteria set during the review -- or less against most greater than equal to 90 percent strains of the following microorganism, however, the safety and effectiveness of the drug in

treating infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

[Slide. 1

In regard to the first list, the first lists again are those organisms which are listed in the Indications and Usage section, and for the purposes for this document, an indication was defined as the treatment and/or prevention of infections at a specific body site due to a specified susceptible microorganism.

I think the important point I want to make here is that the indication is supported by substantial evidence of effectiveness from adequate and well controlled clinical studies. So, there are clinical data contained within the application which support not only the use of the activity of the drug at the body site, but also for the specific listed microorganism.

In general, organisms considered to be etiologic agents in at least 10 percent of the specific infections successfully treated within any particular indication may be included in that list.

Now, clearly, there are review issues that relate to this, but this is the general guideline that is provided in the points to consider document. So, again, these are organisms for which there are clinical data to support effectiveness and safety.

[Slide.]

The second list or the in vitro list, a list of criteria were developed to support their inclusion in that list, again with the caveat that there were no clinical data submitted in the application to support safety and effectiveness.

At least 100 isolates of each microorganism would be tested -- again, this is a general guideline -- that they be geographically representative throughout the U.S., that they be recent clinical isolates, represent clinically relevant susceptible or resistant mechanisms.

They should be pathogens at body sites of infections for which clinical effectiveness have been established, and this links it to the approved clinical indications for the product, and the mean MIC90 should be equal to or less than the clinically susceptible breakpoint.

[Slide. 1

Finally, the point to consider document in the Micro subsection also lays out the format for the description of the test methodology, again describing diffusion or dilution techniques, describe quality control measures, provides the interpretive criteria, which came from the FDA review, and also provide reference of NCCLS methodology, if appropriate.

[Slide.]

That sort of lays out how within product labeling's claims or descriptions of activity against susceptible organisms are described. Now, more recently, we have been reviewing or asked to review specific claims of effectiveness for the treatment of infections due to resistant organisms, and they may come in two forms - either those based purely on in vitro information or that information which may be collected in the course of the clinical development of the product.

There are examples of labels which carry information on in vitro activity for resistant organisms, for example, penicillin resistant Strep pneumo or methicillin resistant Staph aureus, which are included in the second list or the in vitro list that I have described within some product labeling.

Those will have had to fulfill the criteria that I have already laid out in terms of inclusion in that list.

[Slide.]

The second are claims of clinical effectiveness and where are we in terms of the quantity or the quality of evidence and how much evidence do we require to support claims of clinical evidence for the treatment of resistant infections.

This is an issue that we have had two recent advisory committee meetings on, and I think it is quite a

complex issue, and what I will do is sort of lay out some of the considerations that have been discussed.

[Slide.]

This again just gets back to the idea that the indication, that is, the treatment of infection at a specified body site due to a specified microorganism, either susceptible or resistant, say, PRSP, would be supported by substantial evidence of effectiveness from adequate and well controlled clinical studies, and that in general the organisms to be considered in at least 10 percent of the specific infections successfully treated may be included in the list.

[Slide.]

I think the general framework that we have developed in terms of thinking about the types of evidence we would like to see to support claims of effectiveness in these situations are laid out in the next two slides.

That is, there should be data on activity in vitro against both susceptible and resistant strains of the organism, and that there be an exploration of the relevance of the mechanism of resistance to the mechanism of action of the drug.

For example, if a sponsor is developing a product for penicillin resistant Strep pneumo, and the drug is a quinilone, in fact, the relationship of the resistance to

penicillin may or may not be relevant to the site of activity of the drug. Whether or not that bears on the observed clinical activity of the product is something that needs to be explored and developed throughout the product development of that product, and that can be done in a number of ways.

One is to look at activity in animal model systems, again, developing data on activity against susceptible and resistant strains in vitro, and also something that was alluded to in the discussion of HIV resistant strains is that information on whether resistant strains behaved differently than susceptible strains, that is, are resistant strains more or less virulent, and this could either be in animal models or is there any clinical evidence that they either are more virulent or respond differently to therapy.

Finally, the clinical information that provides a framework for assessing whether or not a product has demonstrated clinical effectiveness for the treatment of a resistant organism includes effectiveness of the product for the treatment of infections at a particular body site, for example, if you are developing a product for the treatment of penicillin resistant Strep pneumo, we need to know, in fact, that the product is effective for the treatment of pneumonia, that is, it fulfills all the

pharmacokinetic/pharmacodynamic characteristics that are requisite of such an agent.

Secondly, it is effective for the treatment of susceptible strain to the organism. That tells us something about in general the activity of that product against that genera and species of microorganism.

Thirdly, that there is some clinical data that speaks to the effectiveness of the treatment for the resistant organism in question.

[Slide.]

One of the questions, sort of a central question is how much clinical information is necessary for us to draw a conclusion, in fact, that effectiveness has been demonstrated.

Again, these considerations relate to the type of evidence that I have spelled out in the previous slide, that we would like to see a sponsor develop in the course of seeking one of these indications, that is, how related is the mechanism of resistance and the mechanism of action of the drug, what do the in vitro and in vivo data tell us on the relative activity of the drug against susceptible and resistant strains.

Finally, this issue of biologic behavior, is there any evidence that the resistant strains are more or less pathogenic than susceptible strains or are they more or less

likely to respond to therapy.

All of that speaks to how readily we can extrapolate from the large body of evidence that may be available on activity against susceptible strains to the more difficult to collect activity on resistant strains.

That is my last slide. I will stop there.

DR. HAMMER: Thank you very much.

Are there questions from the committee?

I have one or two questions. The data and the history of bacterial infections and the in vitro activity and clinical effectiveness are in a very important framework, and we have had the greatest history for that, but much of that clinical testing except for diseases like enterococcal and endocarditis and other special circumstances can be a single identified organism and a single identified antibiotic, so the clinical outcome issues are often easier as far as clinical outcome and microbiologic outcome.

I think one of the things we have been wrestling with, of course, is we can potentially deal with the in vitro aspects, but the combination therapy aspects and the clinical outcome issues are more problematic.

Do you have any comments on that as far as labeling issues? I can actually foresee that there may be for anti-HIV drugs now a resistance section within the label

that gives an in vitro description, not too dissimilar from what we see for antibacterial agents, and then there can be the clinical data, whatever it might be, in the clinical description aspect of it.

But do you have any comments on that, because this leap is a big leap as far as the clinical effectiveness side of it?

DR. CHIKAMI: Yes, I guess in general in the development of most antibiotics, we don't run into that problem. In the area in which there is most experience is an area that I really don't know well, and that is anti-tubercular therapy.

That is where I would look for most of the analogies, so I can't answer that question.

DR. HAMMER: The other question I would have -- and maybe Dr. Wong wants to comment on this -- when you think about other microbiologic categories, susceptibility testing, a lot of research, and a lot off activity, attempts at standardization, but still at least for the non-mycologist, still confusion is the area of antifungal therapy, and what progress is being made there.

Does that give us hope that other groups of organisms besides bacteria that we will be able to bring rational issues of susceptibility testing and to standards to testing and labeling? Maybe Dr. Wong wants to comment.

DR. WONG: Well, I mean antifungal susceptibility testing has been standardized, but the extent to which the standardized results have been related to clinical outcomes is really minimal.

So, in some respects, you know, the situation is similar to what we see with HIV and that we now have techniques that appear to give reproducible results, but the relationship between the results of those susceptibility tests and clinical outcomes is just in its very early development of analysis.

So, I don't know that we can draw any conclusions or analogies from the antifungal field at present.

DR. HAMMER: But we can take comfort.

DR. WONG: Right, we are not alone in not knowing exactly how to interpret the results.

DR. HAMMER: Thank you. Dr. Yogev.

DR. YOGEV: I think if you want to stay in the bacterial area, we need to look into the enterococcus as an example of a combination with so-called resistant glycoside and yet the combination with ampicillin wouldn't work, so maybe you have to look in the other one which I never saw any agency regulation is the immunocompromise, because there we have a lot of other committees, they will work together to try to decide which triple combination is better or dual combination in this population, and I think that is where

the bacteria can help us, if at all.

DR. HAMMER: Dr. Masur.

DR. MASUR: One of the things that I am not clear about is what the relationship of the FDA is to a group like NCCLS. If you are talking about establishing breakpoints or other laboratory parameters, I guess it is desirable to have an independent respected group which is establishing that for you, but is the proposal that the FDA would determine what appropriate breakpoints and techniques would be or would they defer this to some other organization, and if so, what other standard would you accept, would you accept what the commercial assays are telling you, because obviously, we spend a lot of time talking about whether those are based in solid data or not.

In other words, if you are saying you want to compare something to a breakpoint, whose breakpoint are you going to use?

DR. CHIKAMI: In regard to antibacterials, the current status is that the FDA, in the course of their review of a new drug application, will review the proposed methodology, which may have also undergone NCCLS review independently, and we will review the data to support setting the interpretive criteria.

Again, the NCCLS -- and we have representatives on the committee of the NCCLS that does set those interpretive

criteria -- will again do that independently.

DR. MASUR: Does that mean that the NCCLS might consider taking this project up? This would be quite an undertaking.

DR. HAMMER: I think Dr. Charache might be able to help us here.

DR. CHARACHE: I refuse to speak to the NCCLS, but I can perhaps add some information.

DR. HAMMER: That doesn't stop us from inferring, so please go ahead.

DR. CHARACHE: I have noticed that. It is wonderful. We can also give comfort to it is no only fungi that has standardized assay, which has to be interpreted in terms of what it means clinically, but also mycobacteria, as well, and the viral group is well underway now in terms of getting into the same pickle.

But I think the key concept here has been to develop an assay in which the answers always mean the same thing. This is like you have got a swamp, you drop piles down, you build a platform, and then you go from there to see what the relationship is between a given number and what happens clinically.

I do think that in terms of who sets the breakpoints now, the manufacturers come to the NCCLS before they start their clinical trials, and at that point, present

data which is based primarily on pharmacology and microbiology, which proposes what the breakpoints will be for that clinical trial, just as a starting place, so they can have a legitimate clinical trial based on some information on susceptibility and resistance.

The NCCLS approves or modifies the proposed breakpoints at that stage. The clinical trials are run, and then they come back to the NCCLS, and the final breakpoints are decided based in part on the clinical information that is produced, as well as the advanced pharmacological data.

The original breakpoints are set by having no fewer than five laboratories do the testing on the same clinical isolates, as well as different isolates to determine reproducibility and standardization.

So, it is not done in a single laboratory, and that is a very important point. It is done in multiple labs.

After the breakpoints are selected, every effort is made to have concordance between the FDA breakpoints and the NCCLS breakpoints. Increasingly, this has been accomplished. There are a few of the older drugs in which they are not the same, which presents major problems to drug manufacturers and equipment manufacturers, if they have two different numbers they have to worry about.

So, I think the overall process is one which it

probably is a good idea to think about right now for the viral testing and how these are set up in terms of considering your breakpoints, which address pharmacologic, as well as performance standards, and in which the reference viruses that are used to determine your IC50s are the same in different laboratories.

So, the IC50 numbers mean the same thing. Right now they can mean very different things as a function of how the method has been set up.

I think the NCCLS could be very helpful in helping to work out some of these things because they put a lot of thought into it over time. I should mention that that group is made up, one-third of industry, one-third academics, and one-third government, and the government does include the FDA and sometimes other groups that classify as government according to their scheme.

So, it has developed competency in a number of areas. Now, I think in terms of what we are seeing here, step one is to get some standardization. It doesn't necessarily mean that every company would have to use the same standard approach. It means they have to be able to translate it from one to another and say this is number means something that will have some basis in which you can talk the same language.

DR. HAMMER: Great. Thank you very much.

Mr. Harrington.

MR. HARRINGTON: I had a question about the FDA. How many patients you require in the resistance dataset as compared to the approval dataset? Is there a standard amount of clinical data on numbers of patients with resistant organism treated with the agent in order to get approval, and do you need statistical significance in that group or do you just sort of use a subjective judgment that you have seen enough patients to put it in?

DR. CHIKAMI: I think it depends on the context, which are some of the considerations that I laid out in my last slide. It depends on the context of the overall drug development. For some of the development programs that have been targeted specifically at resistant organisms, in fact, clinical trials have been targeted toward again enrolling patients with resistant pathogens.

Those are, of course, adequate and well controlled statistically powered studies. In other settings where you are looking at collecting efficacy data on resistant isolates in the course of a broader clinical trial, say, for example, community acquired pneumonia, in fact, the evidence may be much smaller.

There again, you would have to make a judgment based on again the overall context of the product in terms of its activity both at the site of infection and its

activity demonstrated against susceptible organisms which, by and large, are much more common as etiologic agents.

DR. HAMMER: Thank you.

Any other questions or comments?

Dr. Yogev.

DR. YOGEV: I think one of the dangers to accept the bacteriology as a model for what we are doing is we are dealing with a different disease, which is systemic, and not organ oriented, which most bacteria area.

One of the problems I had in the past with this issue of pharmacological versus MIC, they are related to what is achievable in the blood, and the best example is Keflex for years was thought to be very good for otitis media, to find out that it hardly penetrated over there to get that ratio.

So, while we are considering what parameters to use, we should not forget the CNS and other tissue what this virus is, and most of the bacteria are not.

DR. RAMMER: Agreed. I think this example is just the area that has been most well standardized for us to see how far off we are, and the pathogenesis of the disease puts us even further off than just the technical aspects of things

Thank you very much.

I am sorry, Dr. Jackson.

DR. JACKSON: Just one question. In terms of just practically speaking, for a given bacteria, say, pneumococcus or any other one, in terms of calculating the mean MIC90s, is there a standardized panel of isolates that is used in this area that is given to the drug companies?

DR. CHIKAMI: You mean as quality control?

DR. JACKSON: If you wanted, like Dr. Charache was talking about, if you want to talk about this is the MIC90, whether it is between laboratories or looking at different drugs, is there some sort of standard panel that has been used to define what the MIC90 is?

DR. CHIKAMI: There are quality controlled organisms set that with known susceptibility MICs to answer that specific question. In the course of development of a product, of course, we would also expect to see its activity or MICs calculated or tested against clinically relevant isolates, as well. So, it is the combination of two that allows us to look at the activity of a new product.

DR. HAMMER: I think we do need to move on. Thank you very much.

Dr. Jeff Murray will now talk to us about the regulatory issues related to HIV drug resistance testing and drug development.

Use of HIV Resistance Testing in Drug Development: Regulatory Issues

Jeffrey Murray, M.D.

DR. MURRAY: I hope to just set the stage really for this afternoon's discussion and the regulatory scenarios.

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I want to briefly comment'on what I think the role of HIV resistance testing is from our Division's perspective, again reiterate what our objectives are for Session 4, briefly discuss what I think the limitations of resistance testing are so far based on what we have heard in this meeting, what the regulatory use of HIV resistance testing has been in the past and how it is currently being used, talk about some proposed uses of resistance testing in clinical trials, and then introduce the regulatory scenarios.

[Slide.]

First, some possible products of this meeting I think would be hopefully publication of the proceedings, and I think the Resistance Collaborative Group have talked about 'doing this, and this will be very good to disseminate what we have heard here beyond Holiday Inn in Gaithersburg.

Also, if possible, to develop or start to develop an FDA guidance document or something written that can be disseminated for public comment on the use of HIV resistance testing in drug development, and then also I think that

there are maybe some possible research initiatives, so that we will be able to share from this meeting with other agencies, maybe relating to quality control studies that could be accomplished through NIH through DAIDS Virology grant or also, as was just referred to, a committee or some mechanism for developing mutational algorithms for setting breakpoints, and I think we have already got some leads on that, and then also some surveillance initiatives that CDC may have interest in.

[Slide.]

So, the role of resistance testing I think, from the Division's perspective is really to provide useful information to clinics, clinicians and patients, and have scientifically sound labeling, which would then mean scientifically sound promotion, labeling being the basis for promotion.

To potentially improve clinical trial designs both in treatment experienced patients and salvage, I think is where resistance testing could be helpful, possibly to enrich study populations for patients likely to respond, and we are just very keenly interested in surveillance issues to characterize a drug's activity postmarketing, and of course monitoring the transmission of drug resistant HIV.

[Slide.]

What we don't think of resistance testing doing is

serving as -- not being a primary efficacy endpoint, and I think HIV-RNA together with CD4 or clinical progression are the accepted efficacy endpoints, but they may help to establish a niche support for accelerated approval and indication, and they are likely to influence drug development strategies in all phases of drug development.

[Slide.]

Some considerations is that compared to HIV-RNA testing -- the Resistance Collaborative Group was kind of modeled after the Surrogate Marker Working Group -- HIV resistance testing is more drug-dependent, much like concentration monitoring, monitoring of therapeutic drug concentrations, and so mutational algorithms and breakpoints will need to be revised for each new drug approval and updated postmarketing, and, you know, one size doesn't fit all, one breakpoint is not going to fit all drugs. It is going to be very drug-dependent.

Efficient use of a way of developing this would be to do it, of course, during drug development, and to characterize the clinical relevance of genotypic and phenotypic susceptibility throughout all stages.

I think if we could do this as each drug comes out, much like anti-infectives do, it would be a more efficient way of doing it. Right now I think we have to play some catch-up with the 12 or 13 drugs that are already

out there.

[Slide.]

So, the objectives for this afternoon really are to obtain guidance on the amount and type of resistance data that should be expected of sponsors during drug development, for an NDA, and postmarketing.

How this data can be used in product labeling and indications, and how we can start using resistance testing in clinical trial designs or considering the impact of resistance testing if it is done independently by investigators.

[Slide.]

It looks like the limitations of resistance testing for HIV so far. There is still some question about the reliability of the assays, there is assay factors, clinical factors as we discussed earlier this morning, difficulty in defining resistance, and then other confounding factors in interpreting the analysis, and also the feasibility of real-time use of resistance testing in clinical trial will need to be discussed.

[Slide.]

So far, how have we used resistance testing, HIV resistance testing? It does appear in the labeling, and it appears prominently in some labels, in Warning sections, box warnings even in the Microbiology section, even in the

Clinical section in at least one label.

There have been proposals to use it for treatment indications, and I think the example from Monday for adefovir was a current proposal for that. There has been at least one case, been an approvability issue, and that for saquinavir and the Invirase formulation.

Then, it is currently, of course, being used to support clinical development.

[Slide.]

In labeling so far, I think the emphasis of the Division has been to include things in the label that emphasize high level resistance that leads to class cross-resistance, that jeopardizes the use of other drugs, drugs of the same class.

The Division has been somewhat reluctant to include statements describing lack of resistance, and that is because of recognizing the current technological limitations, the presence of resistance is more useful information than the absence of detectable resistance.

So, it seems like a double standard, but I think it is really the limitations of the data. In all of the non-nucleoside reverse transcriptase inhibitors, there is a warning regarding resistance, and nevirapine, not to pick on any one drug, but since it was the first approved, I will read what its warning is on the label regard resistance.

"Resistant virus emerges rapidly and uniformly when Viramune is administered as monotherapy. Therefore Viramune should always be administered in combination with antiretroviral agents."

[Slide.]

This was based on really pooled data from Phase I/II studies using nevirapine as monotherapy. The database was about 24 patients in which 100 percent had a greater than 100-fold decrease in phenotypic susceptibility at 8 weeks. All of these patients had one or more predicted RT mutations, 80 percent of them had it at 181. It was biologically plausible because this mutation was near the RT binding site.

[Slide.]

Resistance labeling has been used to describe really appropriate use of the drug, so as far as things that have been in the label regarding what the frequency of resistance would be, it has been described to encourage proper dosing and use of combination therapy as would occur in the Crixivan label, and it has not been used to date to emphasize that resistance develops more slowly with one drug compared to another.

[Slide.]

In the current indinavir label, there is a table that describes the frequency of resistance at 24 weeks --

this data is pulled from two studies -- showing that the frequency of resistance to indinavir is less if you take the appropriate dose, 2.4 grams per day versus less than 2.4 grams per day, or if it is used in combination with AZT.

We included this in the label because it hopefully promotes good use of the drug.

[Slide. 1

Treatment indications. The most recent example, of course, probably the only true example is adefovir where the sponsor has actually requested an indication. In this case, it was in a treatment experienced, nuke-experienced patients. It was based on the sponsor's interpretation of resistant subgroup analysis in patients with high level AZT and 3TC resistance.

Currently, there is no such indication in the label. Previous labels, you might note that there have been labels where there has been indication for treatment, experienced individuals, but it really wasn't based on resistance testing. It is sort of by default, like the previous labels, for Zerit and Hivid.

It was more so because the data didn't support first-line treatment, not because of the study result suggested exceptional activity in experienced patients or patients who were necessarily identified as having resistance to another drug of the same class, and the

studies in these cases were done in treatment experienced to fulfill the intent of accelerated approval.

[Slide. 1

As far as approvability issues, I think with saquinavir, the issue of resistance came up as a possible approvability issues. As you know, Invirase was the first protease inhibitor on the market, but suffers from poor bioavailability of about 4 percent, and a concern at the time of approval was what the effect of Invirase would be on the use of subsequent protease inhibitors, that is, after virologic failure, with Invirase, would patients still be able to derive benefit from subsequent PIs, and this question was the impetus for conducting study AZTG-333, which you heard about yesterday, where Invirase was followed by indinavir.

I think at the time of the approval, we were somewhat comforted by something that really didn't translate clinically. The resistance data that was in the NDA suggested that saquinavir selected for mutations 90, NR-48 in both in vitro and clinical isolates, and it looked like there was incomplete overlap with mutations selected by other protease inhibitors being developed at the time. That would be ritonavir and indinavir, which were selected for mutations, such as 82 and 84 and 54.

In the back of I think a lot of people's minds was

a concern regarding other polymorphisms, so that kind of based on this kind of data, you know, Invirase was approved with a label precaution, which is also now included in other protease inhibitor labels.

[Slide.]

It states, under Precautions, Resistance/Cross-resistance, "The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Therefore, it is unknown what effect (drug name) will have on the activity of subsequent protease inhibitors."

[Slide.]

I think maybe what we learned from this example is that non-overlap of mutations selected by a particular drug does not always predict lack of clinical cross-resistance. In fact, the L90 mutation appears to decrease clinical responsiveness to most all of the approved protease inhibitors including ritonavir, indinavir, and nelfinavir, and the L90M mutation was included in the DAP algorithm for the approved protease inhibitors.

[Slide.]

As far as use in clinical trial design, preclinically, the sponsors have sometimes considered resistance testing to possibly support a duration of monotherapy.

As you are aware, HIV drugs are sometimes studied

Eor short periods as monotherapy, maybe up from 1 to 3 weeks, and perhaps if your preclinical program showed a high Level resistance to a single mutation, maybe a study as nonotherapy would not be a wise thing to do.

So, resistance testing might even influence the design of the first clinical trial in HIV infected patients.

It could also be used for inclusion and exclusion criteria, and I think there is some thorny issues here, which has already been brought up by the committee. You could exclude patients with mutations to enrich patients who are likely to respond.

You could include patients with mutations to evaluate drug against resistant virus, and then you could also use resistance testing for protocol management criteria, choice of drugs or concomitant medications after virologic failures.

[Slide.]

Some other problems with resistance testing in trials, some possible limitations. Can they be conducted in real time? Are the assays -- there is a consensus that the assays are reliable enough to start using them as inclusion and exclusion criteria. To exclude patients from participation would be probably a big step.

Then, would ad lib use by investigators, clinicians of resistance testing in open-label trials, could

this lead to bias in that investigators might use resistance testing to choose part of the regimen, and this could be applied differentially across treatment arms.

We already seen differences in GART, VIRADEP, and other 3001 studies, so how resistance testing is applied across treatment arms, whether we choose to include it in trials or not, it is still, I think, a force that we are going to have to deal with.

[Slide.]

There are four basic questions to this session, and I think after lunch, we are going to try to address these questions using examples, regulatory scenarios which sometimes a specific example I think can help to tease out the issues better, but the basic questions are we want the committee to comment on the amount and type of data needed to support a clinical development program, support and initiate a clinical drug development program, the amount of data needed to claim activity against resistance isolates, and to profile a drug's potential for inducing resistance or cross-resistance within a class, and also then to comment on the amount and type of data that sponsors should be collecting postmarketing since, as new drugs are released to the market, will have to be continuously updated.

[Slide.]

We have four regulatory scenarios that you will

hear after lunch. Each has its own set of questions, and we hope that they will be able to help the committee to address the rather tough questions we have under Session 4.

DR. HAMMER: Thank you very much.

Are there questions for Dr. Murray or comments?

The only comment I would make is to emphasize -- and I will get to this in the afternoon discussion -- that refraining from any label indication about a diminished potential to engender cross-resistance, that caution should remain because I think for all the reasons you stated and as we develop more knowledge, there are direct and indirect mechanisms for cross-resistance, and would be potentially quite harmful to take a step, giving a label indication for lack of cross-resistance engenderment without a huge dataset to support that.

Questions?

Okay. This was an introduction to this afternoon. We are on time. We will break and return at 1 o'clock. Thank you.

[Whereupon, at 11:59 a.m., the proceedings were recessed, to be resumed at 1:00 p.m.1

AFTERNOON PROCEEDINGS

[1:00 p.m.]

DR. HAMMER: I would like to call the session back to order.

Open Public Hearing

DR. HAMMER: The first order of business this afternoon is the open public hearing. There are three individuals who have signed up in advance. I would ask that those individuals who come up to speak, please identify themselves, their organization for the record. Also, if you have not signed up, but have a statement you wish to make, you will be permitted to do so.

I would also ask anyone who speaks to limit their comments to under five minutes if at all possible. We have a lot to do this afternoon and need to accelerate the schedule a bit.

With that, the first individual signed up for the open public hearing is Dr. Clyde Crumpacker from Harvard Medical School.

Clyde.

DR. CRUMPACKER: Thank you, Scott.

My name is Clyde Crumpacker. I am at Harvard Medical School and Beth Israel Deaconess Medical Center. I paid my own way to this meeting. I am not being sponsored by anybody.

I just wanted to make just some very brief comments about what I think is where we are with trying to get accurate ways of measuring resistance and sort of where we have been.

I think the whole effort to develop measures of resistance to antivirals has been a very difficult one. There are only two viruses and two drugs that we have resistance data on that I think is clinically significant. That is HSV with acyclovir and AZT with HIV.

I think the clinical significance of resistance of HIV to AZT, I think was established through a collaborative working effort of six AZTG labs and the Department of Defense to use a PBMC-based assay, which we struggled a long time to develop, because we could then measure every virus that we could grow out of a patient.

I think we are unlikely to ever be able to repeat this with that same degree of rigor because of the onset of combination therapy complicating everything we do, but I think we were able to show that a high level of resistance to AZT, measured by 1 micromolar or more, did predict more rapid acceleration to death in a statistically significant way, a moderate level of resistance like 0.2 was not associated with progression.

So, I think it was a useful exercise and established for the first time that resistance of AZT and

IIV was bad.

I think that some of the things we learned may still be useful for this current era. I think standardization of a panel of clinical isolates is essential, and we have heard about this several times during this meeting, and I would just like to repeat it, that a baseline and follow-up data on a new drug is really I think key, and just to point out historically that Larder and Kemp, with only six pairs, were able to identify 80 percent of the AZT mutations - 67, 72, 9, and 15, and with one more, 41, they eventually described 90 percent of them.

So, pairs are crucial in patients who are taking multiple drugs. I think the new recombinant viral assays being so attractive because they can be done rapidly, I think that it is going to be still important to try to compare some standard panels.

I think the current dilemma about NNRTI resistance being measured by Virologic and Virco might be able to be clarified by using a standardized or a different PBMC-based assay perhaps and comparing that to the data that they are getting, as was suggested by Roger Pomerantz this morning.

The other thing I would like to address is the question of viral fitness, and I think we have heard about this in several contexts this morning, but I think we are still at a very early stage in trying to define what fitness

means, how to measure it.

I think a definition of fitness as a measure of the ability of a virus resistant mutant to result in a virus which replicates less efficiently might be a useful one in this context, and I think John Coffin pointed out, I think very elegantly, that resistant mutations may confer a difficulty or a less replication advantage to a virus compared to wild type.

Our lab in Boston has recently shown that the 74V mutations selected by ddI and the 184V mutation selected by 3TC will result in a virus which has a less processive reverse transcriptase. So, the decreased growth that occurs with these mutations, I think now has as biochemical confirmation, that the altered enzyme is biochemically different, and I think this could provide a way then to understand how drugs that are going to be developed to work on resistance virus might definitely be generated.

I think companies can help their case by trying to define biochemical alterations associated with resistance mutations to their drugs, because I think, as we heard earlier from the FDA, understanding mechanisms of resistance is a very powerful argument that a drug might be useful.

I think the best example that we have of this so far, as we have heard earlier, as well, is the case of adefovir producing a greater decrease in viral load on those

viruses that have a 184 mutation.

I think the work of Michael Miller and others to define this is the best example we have so far of a new drug that might have a niche really against resistant viruses.

So, I think the more we can understand what the virologic consequences on the replicative enzymes that viruses need to replicate are of drug mutations, I think the faster this process can go forward.

Thank you.

DR. HAMMER: Thank you very much, Clyde.

The next speaker is Francois Houyez. Is he here?

[No response.]

DR. HAMMER: The third speaker then signed up is Brendan Larder.

DR. LARDER: I am Brendan Larder from Virco.

This is kind of a last-minute thing. I just put a few slides together to really talk about drug profiling, preclinical drug profiling, because some things have been discussed about profiling so far, but a bit like resistance testing, it is already here, we are already doing it, and I thought I would like to just go through a few issues and show a bit of data just to try and put it into context, and then address some questions in a few minutes time.

[Slide. 1

The background, I think we all know about the term

new, new antiretroviral is now being developed in the backdrop of extensive resistance. In some cases we are seeing, when we survey thousands or tens of thousands of samples, 50 percent of those or nearly 50 percent of it, 215 mutation or 184 mutation, et cetera.

So, it is very obvious, and I think it was obvious from the discussions on Monday amongst the panel, that drugs that are being developed now are needed in salvage therapy to inhibit resistant strains. So, it is very clear that the determination of cross-resistance profiles as new inhibitors prior to clinical evaluation is very important.

[Slide.]

There are obviously a number of issues, and these are all the issues that we are grappling with in the middle of actually doing these studies. So, firstly, how should we choose samples to actually study and from which pool should we derive those samples? How many samples should we analyze, how are they selected? Which assay should be used to actually analyze them? How should the data be analyzed, presented, and interpreted?

[Slide.]

Just as an example of some of the work that we have done with profiling, we have profiled really quite a lot of drugs now to a greater and lesser extent. I think a primary example is this good one, and maybe can serve as

some sort of model for how these things could be done in the future.

I guess, as many people know, tipranavir is a protease inhibitor that had a suspected novel resistance profile. [Inaudible] came to us to try and see if we would profile using our database to look at a large number of isolates to see if this suspicion was borne out, the activity to tipranavir against a diverse selection of PI resistant clinical isolates was warranted.

[Slide.]

This is how we went about sample selection. We Looked for recent samples from our pheno/geno database, which currently has in excess of 35,000 samples and with a whole gamut of phenotypes.

So, we made selection actually based on the phenotype, but not on the genotype, which I think is quite important. We picked out the first, I think 100 or so samples that were broadly PI cross-resistant, and we defined that. This was just before tipranavir was approved, so we didn't include tipranavir, we didn't have the data. So, broadly resistant, cross-resistant, was resistant to 304 of the current MPIs at that time.

We also wanted to look at resistance to samples that were resistant only to one of the PIs, saquinavir, nelfinavir, ritonavir. We couldn't find any samples that

were resistant only to indinavir.

Obviously, all of the recombinant viruses, because we used the antiviral method, was sequenced, ABI Technologies confirmed the genotype.

[Slide.]

This is how we presented the data. First, the population data. I am just going to concentrate with the two data slides on the highly cross-resistant sample, that sample of 105.

The top part of this panel shows the prevalence of mutations in the protease, and it shows really what you would expect from protease inhibitor resistant sample, and shows kind of a balance. It was about 40 percent, 82, 84, something like 70, 80 percent, 90, some 48, and then a whole range of different polymorphisms or secondary compensation mutations.

If you look at the composite or the mean fold resistance of all those isolates to the drugs, this is what we found, so this confirms what we pulled out of the database, indinavir, ritonavir, nelfinavir, saquinavir, the mean fold resistance or increased IC50 was at least 40-fold, it was somewhere between 80 and 90-fold for ritonavir.

The mean fold resistance for tipranavir was 2-fold. So, this is really quite impressive and was quite nice to see in terms of trying to develop a drug that was

active against these viruses.

[Slide. 1

What I show is really all of the data. This is an easy way of looking at it. So, what we did here was to line up the fold increase of IC50 going from the most resistant, tipranavir isolate to the most sensitive, and in this case, some hypersensitivity, again, the fold increase in resistance to indinavir, ritonavir, saquinavir, sample by sample. These boxes have got numbers in them, you don't see them, but if you just look at the colors, then, the color coding is the kind of coding we have been talking about over the past couple of days, green being less than 4-fold increase, in IC50, the yellow, between 4 and 10, and the red, greater than 10.

So, obviously, the first thing that is striking is that most of these isolates that we picked out are resistant to most of the PIs at a high level greater than IO-fold. I can see some of the numbers from here. This sample is 105-fold for indinavir, 90 for ritonavir, et cetera.

The other striking thing, by lining up the samples like this, you can see there is a large degree of lack of cross-resistance, tipranavir to the other drugs.

So, we can immediately now quantitate this with a fair sample size, say 95 of the samples are sensitive 8, and this is where the percentage is now, intermediates, and only

two showed any sort of resistance.

So, we have some quantifiable number that we can put on it with a panel of isolates that we have now defined by genotype.

[Slide.]

To summarize that, I think that this study in particular highlights the utility or the potential utility of in vitro susceptibility profiling of new antiretrovirals, and maybe can be taken as some sort of model. One might think about doing this in the future.

But there are issues. The sample choice and the size of the sample is an issue, and these are really quite important issues to avoid selection bias and underrepresentation, and so we can't just hand-pick a few samples.

Finally, and this is something that we have been trying to develop ourselves, but this is in somewhat of a vacuum, standardization of data analysis on presentation we think would be useful to enable comparisons between inhibitors and between studies.

If we are talking about regulations and what companies or pharmaceutical companies are hoping to expected to do when you bring packages forward to the FDA, then, these sort of packages would be useful, but we need to be able to have some standardization, so we can make

comparisons between the different drugs.

That is all I wanted to say. Thank you.

DR. HAMMER: Thank you, Brendan. That is very helpful.

Brendan is the third and last person who signed up in advance for the open public hearing.

Is there anyone who wishes to step forward and make any additional comments?

[No response.]

DR. HAMMER: If not, the open public hearing is formally closed, and we will move on to the continuation of Session 4. The committee has been given five questions to discuss and also four clinical regulatory scenarios, I should say, not clinical, but regulatory scenarios, and what we are going to do is discuss the regulatory scenarios first and hopefully, fairly completely.

What we don't address in the five questions in our discussion of the regulatory scenarios, we will then attempt to cover briefly at the end, because it is quite an agenda and we want to try to hit this efficiently.

To kick off the regulatory scenario presentation, I would like to welcome Dr. Katherine Laessig from the FDA.

Presentation of Regulatory Proposals

Katherine Laessig, M.D.

DR. LAESSIG: Good afternoon. For the next 30

minutes or so, I will be presenting four regulatory scenarios designed to highlight some of the issues of HIV resistance testing and drug development.

The information I will present includes hypothetical claims and indications, potentially involve sections of the drug labeling, and examples of supportive evidence.

After I present each scenario, please take five minutes or so to respond to the questions posed.

So, let's get started.

[Slide.]

Scenario No. 1 involves a claim of lack of development of resistance.

[Slide. 1

The affected sections of the labeling include Microbiology, specifically, antiviral activity in vitro and resistance.

[Slide. 1

Drug R is marketed for the treatment of HIV in combination with other antiretroviral agents. Investigation of resistance to Drug R has included in vitro selection studies, involving passaging of HIV strains in the presence of Drug R. A few clinical and laboratory strains with reduced phenotypic susceptibility have been isolated, however, no consistently identified genotypic mutation has

been seen in either the lab or the clinical isolates.

[Slide.]

The Scenario No. 1 questions are: Is the failure to identify genetic mutations in the presence of reduced phenotypic susceptibility sufficient to support a claim of a lack of development of resistance?

Second. What can be concluded if there is neither reduced phenotypic susceptibility nor evidence of genotypic mutations?

Third. What type of evidence is needed to support a claim of infrequent resistance or slow emergence of resistance?

DR. HAMMER: Thank you. Five minutes to discuss this is a challenge for a single individual, let alone a committee, but what I would suggest is that committee members who wish to respond, rather than going through each question around the table, why don't you respond to one or more of the questions placed, although start with the first.

Who would like to leap in? Mr. Harrington.

MR. HARRINGTON: In answer to Question 1, no, it is not enough to failure to identify the genetic mutations, and the third question, I think it is really important to distinguish between in vitro and in vivo, and the question doesn't really do that, but I would just say you want clinical evidence of activity to support a claim of

infrequent resistance.

DR. RAMMER: Dr. Mayers.

DR. MAYERS: I think I have talked to Company X a few times.

I think that it is really important when you do these types of studies that you get the right samples collected at the time point, and there are certain drugs for which patients feel about phenotype, but I believe there actually is genetics.

One example. A company that came to this committee had 1,000 samples they looked at, but they weren't collected right, and they didn't look in the right reservoir, and Stanford looked at 25 patients who had good baseline plasma and good failure samples after they had failed with rising viral load, and with 25 samples, identified 6 mutations that were clearly selected for by that drug in failure.

So, I think that it is going to be critically important for these types of claims that there be a very good collection of samples at baseline, collection of samples of virologic failure, and a careful look at what is selected out of the genetic background by that drug, and if you saw absolutely nothing, my suspicion would be that the drug wasn't doing anything virologically, and wasn't pressing the virus at all.

DR. RAMMER: Other comments?

Dr. Pettinelli.

DR. PETTINELLI: In this kind of scenario, would the standardization of the assay per se, for example, in terms of inoculum or other parameter, would be half-full because we don't really know the reason why, there is concern what are the conditions in which the assay was conducted, and is there any way we can standardize that at the list and give some guidance.

DR. RAMMER: Are you framing a question, Carla?

DR. PETTINELLI: For the virologist. In a certain sense, you know, could that have an interpretation on this kind of scenario, is that possible.

DR. RAMMER: I think depending on the assay, certainly the inoculum size can be important. It depends I think on the potency of the agent, the target, and the virus inoculum that you are putting in, but there are certainly assays in which you can drive the IC50 one way or another by the amount of virus that you put in, so I think it is a good point about standardization.

I think the last two points raise issues about the technical background in which the data come forward, and I think that needs to be the first point of departure.

I might just comment. If we accept that, then, how do you interpret these scenarios and these questions or

how do you answer them?

I agree with Mr. Harrington. I think probably the consensus of the committee is the failure to identify genetic mutations in the presence of reduced phenotypic susceptibility does not support a claim of lack of development of resistance.

We know that patients fail on drugs, that there are resistance mechanisms that are there that you can measure fold changes in susceptibility to at least one other approved agent, and there is no controversy -- I am talking about D4T right now -- for which there is no controversy about the genetic basis of that.

I think the other aspect that comes out, and it has come out this morning, and I think we will be hearing more about it, is the issue of cellular mechanisms of resistance, particularly for drugs that are intracellularly phosphorylated anabolically, and also that can be subject to pump mechanisms.

So, I think the answer to No. 1 is no.

What can be concluded if there is neither reduced phenotypic susceptibility nor evidence of genotypic mutation? This is a slight different question, but I guess the question is deriving from if you isolate a virus in the presence of failure, is that what that question is driving at? Okay.

Then, I think you have to ask the question are there other factors which we have talked about, pharmacokinetic factors, as the drug is absorbed, is there adherence, et cetera. Assuming that the drug is absorbed and reaches a level, what can you assume by this if there is failure?

If there is not resistance by what we are classically defining, I think you would also again have to ask the technical question of how the assays were done and what they looked for.

I think, for example, has the entire reverse transcriptase, if an RT inhibitor, been sequenced, because the more we look at the right end of the molecule, the more interesting mutations show up there, and many assays don't classically, although we have extended out beyond codon 240 to codon 400 routinely, we discovered a lot there, we may discover more.

So, the issue is again what the dataset is and how good the data are, but I think the major question there may also be assuming that the drug is absorbed and that adherence is not a problem, is the drug potent enough, and it gets to the issue of lack of selective pressure.

A claim of lack of resistance relates to the first question. It may mean that you are not just putting enough pressure on the virus. So, if you have a modestly potent

drug that then claims lack of a resistance emergence, the first thing I would worry about is that you are not putting enough pressure on the drug to actually select resistance.

The other thing that should be mentioned in this, and it comes up with a later scenario, is the issue of cross-resistance. You have to be very careful. It is another reason to test isolates, not only against the agent itself, but against other agents in the same class, is that a number of agents may not select for resistance to itself, but may select permutations to other agents and the thing that has now been reported by a number of laboratories about D4T or D4T and ddI in combination that I can select for.

Associated resistance mutations and the 1.51 multi-nucleoside complex means that you need to look beyond the drug itself and susceptibility change to the drug.

And what type of evidence is needed to support a claim of infrequent resistance or slow emergence of resistance? I think the latter is easier probably than the former. I think the issues of slow emergence of resistance really relate -- we have had a number of examples of that -- it relates to the genetic barrier for the particular drug and the numbers of mutations that are really required and the frequency with which they go in and the facility with which they go in to develop resistance.

So, if you have single-step, high level

resistance, it is fast, and if you need multiple mutations to develop high level or higher level resistance, like with zidovudine or the protease inhibitors it is slow.

Developing that dataset in vitro and potentially in vivo is reasonable, I think, and can be done, and is important because genetic barriers and putting combinations together need to be thought about by physicians and patients.

The frequency with which this all happens, I think requires a fairly large dataset and is complicated by the concomitant drugs that are administered, and all the other confounding factors we have talked about.

So, in order to answer the former first part of the question, you need a pretty large dataset, probably hundreds of patients treated with different combinations studied very carefully. I don't think I could be more specific than that, but a 20-patient study would not do it.

Other comments on the first scenario? You were told five minutes. We have already gone over, but we are going to be efficient on the other five questions.

Any other comments on Scenario 1? Did we respond to a reasonable extent to Scenario 1? Okay.

DR. LAESSIG: Scenario No. 2 involves a claim of a lack of cross-resistance within a drug class.

[Slide.]

The affected section of the labeling is Microbiology: Cross-resistance, Indications and Usage, and Description of Clinical Studies.

[Slide. 1

A sponsor has conducted an uncontrolled rollover study of 30 patients who met protocol definitions of virologic failure in earlier clinical trials, and failed protease inhibitor A. Patients were treated in the rollover study with a combination regimen including protease inhibitor B. Genotyping was done prior to therapy, initially with protease inhibitor A, and at the time of virologic failure to protease inhibitor A, and that revealed a typical mutation. Results of the rollover study revealed that greater than 50 percent of the patients had a viral load below the limit of quantitation at week 24 of the rollover study.

The questions are: What type of evidence is needed to support a claim of lack of cross-resistance between two drugs in the same class? Please consider each class individually.

Would analysis of a statistically significant difference in responder rates of test drug versus control regimens be needed, or would predetermined percentage response rates in a minimum number of patients be suitable?

How should additional studies be addressed

postmarketing as additional drugs of the same class enter the market?

DR. HAMMER: Another straightforward scenario.

Who would like to start?

DR. JOLSON: Scott, the one thing I will mention for the committee to consider -- I know these sound like these are very, very hard scenarios, but even though they are hypothetical, they are somewhat typical of the sorts of issues that sponsors are asking the agency to think about in terms of where we might be heading.

So, as difficult as they may seem, they are not too far removed from the sorts of things that sponsors are starting to consider or have already asked us to consider with regard to labeling their product.

DR. HAMMER: Thank you. Also, some of these scenarios do look familiar actually, even though the names are changed to --

DR. JOLSON: To protect the innocent.

DR. RAMMER: I will start and maybe others can contribute, hopefully.

The evidence to support a claim of lack of cross-resistance between two drugs in the same class, first of all, has to start with the in vitro data that we have talked about many times, that any new drug in development needs to be tested against a panel of well-characterized isolates.

That should include, of course, isolates resistant to other members of the same class for sure. If you don't have that, you are starting from a very difficult position to make this claim, but assuming you then do have this ability -- and we have certainly seen some cases where it looked like certain mutational patterns and in vitro susceptibilities didn't look like there would be class cross-resistance, it turned out there would be.

If one wants to draw the conclusion from the clinical trial scenario or the open-label trial scenario that is listed here, what would be needed? Well, the thing is a 30-patient study in which you have a 50 percent response rate, no doubt, and a rollover study with other combination treatment makes it difficult to know without, of course, the level of resistance that was determined, the pharmacokinetic variability, interpatient variability, that may have been determined.

So, this particular study that is outlined doesn't prove it simply because there are too many other factors involved that could give you a 50 percent, i.e., a flip of the coin response rate. Also, longer term data would be needed.

But one thing that one could do is you would need to know the characterization and that you do have it genotypically, but, for example, one would need to know

whether, in fact, a 50 percent response rate is, in fact, a blunted response rate for the new drug and the particular combination in this patient population.

One could do that by looking at a comparator group, not in this particular study, but if you actually had a comparator group that had wild type virus treated with the same identical combination and controlled for basically, and both groups were controlled for their RT component, then, you would see whether in a naive population where the only differences between them were the PI-associated mutations, if you will, if you could control for that, and you got a 90 percent response rate, then, a 50 percent response rate, and here it would actually show that it is blunted.

Actually, this is familiar territory for sequential PI studies that we have seen in the past, 333 and other studies, and some of the important studies out of the Stanford group showing blunted responses to certain PIs following previous PIs.

I think the only way you can know that is either by some comparator where, in fact, the same drug in a PI mute wild type patient group gave you similar or a different response.

So, I think if it were identical to a wild type patient population, it would be evidence or at least suggestive, but even then a 50 percent response rate would

be tough.

So, I think you need the appropriate comparator group and you need to control for the mutations in the other genes and the other parts of the combination regimen. The outline that is put here does not prove it to me.

The second question. Would analysis of a statistically significant difference in responder rates of test drug versus control regimens be needed, or would predetermined percentage response rates in a minimum number of patients be suitable?

My own feeling, I think I just answered that. I don't think you can say, well, a priori, if we got a 50 percent, you know, that is good enough. I think what you need is the comparator and actually to look for whether there is a difference or not, with the right comparison group.

The postmarketing issues I think are very difficult, and I don't have a really good answer for that. The same drugs of the same class enter the market, how should additional studies be addressed postmarketing. I think without surveillance issues of (a) to know what is happening with the drug resistance in the population that are ongoing and uniformly reported, it is difficult.

I think one could ask, although I don't know how strong the commitment can be, to be able to continue similar

studies where you see response rates over time with good characterizations of baseline and follow-up isolates.

I honestly do not have a good answer for the postmarketing because the studies, because unless there is a strong commitment, standardization of this is going to be very difficult, particularly the regimens, the patient populations, et cetera.

So, one could try to initiate a series of Phase IV trials that are specifically designed to look at response rates over time with relatively standardized regimens and well-characterized populations, but that is easier said than done.

Comments on this? Dr. Yogev.

DR. YOGEV: From the scenario it seems like there is no testing of those who did not get the below level of quantitation. I think this is the most important population to approach, those who did not respond to the change that you assigned to, to see what changes are there, because both affecting other drugs and itself bringing out what you are looking for.

I, for one, think that 30 is not sufficient. I think there was a very nice example just shown to us, one of the people who just spoke recently, that out of 100 samples, you got two in a drug which supposedly would make such a claim, and it is good to know the ratio. I would be

surprised if we are going to find one who never had it, but what is important is we need to decide how many are okay and how many you cannot make that claim.

This is an important issue that needs to be addressed, and maybe part of this study which presented can give you some clue if the n will be increased and then you check all those who did not respond.

Also important is I don't see here when that happened. I think if we look in data 12 week or 24 week, it might be a little bit too early, so we need to ask for longer follow-up to see what happened, especially when you are looking at the minority of resistance, it might take time to come out that when the data changes the philosophy at 24 weeks in this era with multiple combination drug is enough.

DR. RAMMER: That is a very good point about looking at the evolutionary pattern of resistance mutations and the failures, (a) are they occurring, and (b) what are they, because we have learned that with the sequential rollover PI studies, sometimes the evolution of resistance mutations is not to the second drug, but promotes the continued pattern of evolution of the first drug, and it is a way to sort of come out with the subtle issues of cross-resistance, and that has also been shown by the Stanford group and others, so it is a very good point about the

analysis of what the mutational pattern is in the viruses that come out under treatment with Drug B.

Dr. Mayers.

DR. MAYERS: I think this points out one of the real limitations of 24-week studies. I think it is going to be critical as we study these drugs to go to randomizations that go to second round to failure, and so you look at durability of first round followed by salvageability into the second round protected by randomization, because the only way you are going to find out how good is this as a first strategy and then how salvageable are you off of that strategy.

I was trying to figure out how you could do this, and I think for this particular scenario, you could have the manufacturer have people coming out of the study and then give them two nukes or a background of nukes and your protease B versus a background of nukes and the non-nuke, a drug from a different class that is potent to try and run a comparator arm, because your problem is you are going to have the background drugs are going to be factoring in, so you have to somehow control them and then randomize.

The other issue that I think has got to be very carefully addressed is the fact that there is no standardization for resistance data.

I have seen two companies recently have a fight

over the data in which one company would have called all the isolates resistant, and the other company was calling them sensitive because they had a low number with a zero in front of it, and so I think, you know, it is really important that if they are going to get into these types of discussions, that there be baselines established for wild type, for those drugs and comparisons for your in vitro data, because it can get very confusing when two companies can have a poster up next to each other, and one company has resistance determined to be X number, and the other one is calling it sensitive in the same session, right next-door to each other, and it is just because there is no standardization of what the expected range for these drugs is with the expected reference isolates.

I think the proof in the pudding is durability of virologic response, and the issue is going to be finding a way to do a randomized comparison to a virologic response that is convincing if they think there truly is not resistance.

The way to do this up-front, if you believe it is true, is to have a randomized second round in your study.

DR. HAMMER: I would agree, of course, that we interested in durability of response, but in asking the short term virologic response question of resistance to Drug A and response to Drug B, the majority of that answer can

come in the first 24 weeks.

I think we know from several published anecdotes that the trajectory of the RNA is not going to be what you want it if there is drug resistance, and if you control for the other components of -- a single arm study, you can't do it, but if you control for other elements in the regimen, and you control for the rest of the genome besides the gene of interest, I think you can know or have a fair idea in the first 24 weeks for sure that you have got something that is active against drug resistant virus.

I think we have to have a practical look at -- we can't have every study of every aspect of new drug development and particularly some of the important virologic characteristics being 48-week studies or it will be years before we have the information.

So, you need a combination of early virologic parameters for what the question is, and then durability of response based on the other characteristics of the drug and the regimen that it is being studied in.

So, I certainly completely agree that we need long-term data, but I think that some of the virology questions can be answered quickly because of the pathogenesis of this infection.

Dr. Mayers.

DR. MAYERS: I agree, but I still think that the

true issue is how long do you go in the first round and can you salvage to the second round, and that requires a trial infrastructure at some point. Maybe it's a postmarketing look in which you look at durability and salvageability in a randomized way.

DR. HAMMER: I agree, but I just would say strategies of antiretroviral therapy over time for a patient are important to think about with drug development, but it is a distinct issue from drug development, not totally distinct, but they are overlapping Venn diagrams so that we can't -- every new drug has to be thought of strategically, but can't be studied in an independent strategic fashion over the next five years.

Mr. Harrington.

MR. HARRINGTON: Two things on the sort of the short term or the clue or the nonclinical proof that I think could be useful. One would be if they think the drug has a reasonably high genetic barrier, you are not going to bing through to resistance in two weeks.

Like the adefovir that we saw on Monday, versus placebo, you might want to actually look at a two- to four-week study in wild type versus in people that were going to take a strategic structured treatment interruption, and if the people who had the SGI had been people that were resistant to that class, you might get -- if you saw no

activity, then, you would think maybe you have some cross-resistance.

The other idea was that you might -- and we really haven't talked about this and don't have the expertise at the table -- but I don't know how feasible it is to use an animal model like the shiv monkey in some of these cases, and use sequential monotherapy to detect in vivo genetic barriers to resistance and how long they take.

You make them cross-resistant to earlier agents and then put in your new agent. You might do it both ways. I don't know how either feasible that is or how expensive it is, but it might be worth considering in cases of some classes of drugs.

DR. HAMMER: Thank you. Other comments on Scenario 2 before we move to Scenario 3? Dr. Gulick.

DR. GULICK: One of the things I think that is challenged here is even if you say okay, Scenario 2, we have shown activity of Drug B, is what is the next step, what is the control arm to compare Drug B to.

Doug Mayers suggested that you switch to another class, a non-nuke perhaps, but can you do that? I think it is going to be a challenge to figure out how you design a control arm for a true salvage study.

Most of the salvage studies that we have available right now have really inferior control arms. So, what is

the optimal control arm for a study like this?

DR. HAMMER: Best judgment.

Let's move on to Scenario 3.

DR. MURRAY: Before you go to Scenario 3, Dr. Hammer, one comment that you made was that you didn't think maybe a 30-patient uncontrolled study would make it, but some criticism that we hear is that we don't include enough resistance use information in the label.

Some clinicians think that such information might be useful and like to see it reviewed is what it is by FDA and put in labeling. So, I mean we have to kind of walk a balance. If it is not in the label, it is going to be presented, it is going to be out there anyway.

So, in considering that you might have five or six PIs to test, you know, 30 times 5, you know, it adds up as far as numbers of patients. What would you think about, is there anything about this scenario that would be appropriate in anyplace in the label?

DR. WONG: Without controls, I personally don't believe it belongs.

DR. HAMMER: My general response -- and that is why I was hesitant -- I would agree. I think more and more, and you indicated in your own talk, that we are going to have resistance data in the label, and it needs to be there. Whether we can somewhat standardize a little bit how those

data are presented, as labels have evolved, and whether we have an in vitro section and then a somewhat more variable clinical section until we get further along the line, I am not sure, but I would hope that that is where we get to.

A 30-patient study with a 50 percent response rate, 24 weeks, doesn't say a whole lot. I think the only way this could ever make it is if there is a very sophisticated virologic analysis of these patients, fully characterized at baseline, fully characterized at failure, potentially including quasi-species analysis, and that sort of thing.

But a gross 50 percent rate, I would say by itself doesn't make it, but I think a sophisticated virology study in association with it might. So, I would be slightly different from Brian, but basically, I think we are saying the same thing, you need more data.

DR. MURRAY: I guess the other thing, too, is that the comment I have heard is that people who fail one regimen, they fail for multiple reasons, and they might be a biased population. They may be less likely to respond to a second regimen.

So, if you compare them to a naive person, you might expect a low response rate because you might have selected for a group who are more likely not to be compliant with the regimen or have metabolism that would handle the

drug maybe differently than a responder. I guess a controlled study would help, but --

DR. RAMMER: A controlled study would help. I agree that that is the case. There are these clear-cut issues of cross-resistance that we can define, and there are patient characteristics that also make it problematic about sequential regimens.

There is also an unquantifiable issue. The drug exposure itself seems to be presage drug failure on other regimens, and whether that is subtle issues of cross-resistance, we don't fully understand yet. Cellular mechanisms, et cetera, I agree are there.

For small studies, though, there are enough populations, if well screened, that I think one could potentially -- if you took, for example, if it was a new PI for this case, and you had a nucleoside-experienced population, you could try to at least control for the nucleoside experience, control for the genetic background and the RT, concentrate on the RT inhibitor with a standard dual nuke or other combination regimen along with the PI, and then see what your response rates are.

It is difficult because of the combination regimens, but you have to now try to control, if you have small numbers, for as many of the confounders as possible, which would mean at least the RT inhibitor background and

the genetic background outside of the region of initial interest, but it is difficult. I think controlled trials are difficult, but they are still better than an uncontrolled, 30-patient observation with a 50 percent response rate.

It is no better than what we do just by -- with the current agents, we can get a 30, 40 percent response rate at 24 weeks with our current agents, as well, and so you are not really necessarily proving anything as far as superiority over where we are.

Dr. Mayers.

DR. MAYERS: It would certainly have to have been a trial that you designed with them up-front, having decided that there was no other way to look at the issue, because I think if you open this Pandora's box up, you are going to have a "Let the buyer beware" section at the end of your product label, and it will be quite long.

DR. HAMMER: I don't know that we really answered your question because it is very difficult. I think we all recognize that and don't have the answer. In other sessions of this committee over the years, we have never been very good at study design proposals. We can raise the issues, but we can't always answer the questions.

Next scenario.

DR. LAESSIG: The claim for the third scenario is

that of efficacy for a subpopulation with specific phenotypes or genotypes.

[Slide.]

The affected section of the labeling is again Microbiology: Cross-resistance, Indications and Usage, and Description of Clinical Studies.

[Slide. 1

Nucleoside reverse transcriptase inhibitor C appears to retain activity against zidovudine resistance based on preclinical studies.

The sponsor has proposed a study to evaluate Drug C as a part of a HAART regimen in patients screened for high level AZT resistance at baseline by a single mutation at codon 215.

[Slide.]

The questions are: Considering there are both resistance-associated mutations and polymorphisms present in HIV genes, how should mutations be grouped and analyzed in prospective studies?

No. 2. Would post facto analysis of stored specimens in treatment-experienced patients be acceptable?

No. 3. What type of evidence is sufficient to support a claim of efficacy and receive an indication for Drug C for the treatment of drug resistant virus (in this case zidovudine resistance is identified by a single

mutation at 215)?

DR. HAMMER: Another straightforward scenario. Comments? Dr. Pettinelli.

DR. PETTINELLI: Kind of general comments.

DR. HAMMER: We will take anything to start. Thank you.

DR. PETTINELLI: Why I think it will be important to such a study to have as inclusion criteria, patient to have a 215 mutation, however, think that is not sufficient, because patients are going to be treated with combination therapy and probably having the 215 mutation, they will have also other mutations to other class of drugs.

So, my recommendation is that, first, the patients should be screened, so we should really know the genotype and the phenotype of those patients at baseline even if 215 can be used as inclusion criteria.

I don't think that retrospective study or analysis of storage sample will be sufficient in this case, and I think that there are always problems with interpretation at the end. It seems to me it will be much more straightforward to do that at the beginning.

However, it will be interesting to see analysis of this data. I mean I don't know if sponsor wants to go directly into such a target study or might want to have just general information from looking at storage sample and then

decide to go into the study, because you are going directly from preclinical to clinical, so there might be some more information before doing that.

DR. HAMMER: Dr. Mathews.

DR. MATHEWS: Well, fortunately, we had a very good example of this earlier in the week where a claim was made for the product, that it was active in a certain mutational setting.

What struck me was that was a subset analysis. The sponsor selected a certain group of specimens to analyze. The agency had different criteria for selecting samples, a different definition of the response was selected. I think one was a 24-week, another was DABG, whatever. Different methods of analysis were used.

Obviously, the cleanest thing to do is to do a prospective study, and I think that is one of the points that the majority of the committee made, to examine that in an adequately powered setting where you would randomize, stratify on that mutation in that setting.

I think that these retrospective studies can be done, but the problem is that the methodology has to be stated up-front how it is going to be done, what are the inclusion/exclusion criteria for samples, the methodology of analysis, and all that stuff.

If the effect is small, as it was in the case that

was being looked at, it is going to be even more problematic.

DR. HAMMER: Dr. Wong.

DR. WONG: I agree that the best way to answer the question is prospectively, but I can well envision a set of data in which a retrospective analysis might be convincing. I thought we did not see it earlier this week, but, you know, if it is obvious and robust, then, I think it is conceivably believable. It depends on how good the effects are.

I wouldn't rule out accepting retrospective data, but they would have to be very convincing.

DR. HAMMER: Dr. Masur.

DR. MASUR: Actually, I don't have an answer, I have a question. What isn't clear to me -- and this is the problem we were dealing with Monday -- is when you are dealing with combination therapy in which this drug, which has purported activity as part of the multiple drug regimen, how do you prove that this drug had any role in suppressing in the virologic response.

You can look at genotype and phenotype of viruses down the road, but how do you prove that this one drug had activity when you hopefully have multiple drugs with activity against this isolate.

I guess I would look for clarification from

someone else.

DR. HAMMER: Dr. Mayers has his hand up, and then I think Brooks Jackson had a comment.

DR. MAYERS: I am much more comfortable with this if the company is doing it as a safety parameter, i.e., you don't get an effect. When we look at our experienced patients, you don't see a good antiviral effect, maybe you should stay away from these types of patients of our drug. I think that is a little more convincing. When nothing happens when you give the drug, that is fairly easy for people to see.

I think this does argue for the fact that the companies need to collect baseline samples on all their patients and all their studies, because I think the thing that might be compelling would be if they saw this observation, to come back to the agency and say we would like to look at a carefully selected randomized sample of patients that was not included in this analysis to see if it confirms independently of a sample size that your statisticians believe will be convincing.

Then, I think I might be compelled. On the other hand, if it is 65 patients that somebody has pulled out and done once, I am not nearly as compelled as if they went back in an took 200 patients who were different from the same study and reconfirmed it, and independent, of a sample size

that was big enough that the treatment effect was believable.

DR. HAMMER: Brooks, did you have a comment?

DR. JACKSON: Just to reiterate one of the points by Carla that clearly, a single mutation, you would clearly want to verify that with phenotypic resistance data. I think Brendan was showing or implying that that is probably the -- if you really want to show that there is resistance there, I think you have to really show reduced drug susceptibility, not just a single mutation there, which would be very important.

But Henry's point, this becomes tougher. Even if you do that and show, yes, there is phenotypic resistance there, and you do this study, how do you really -- and you do see a decrease in viral load -- how do you really know it is Drug C, I mean it is part of a HAART regimen, and then claim that it's -- and because, of course, the AZT is no longer there, and the drug pressure is off.

So, I am not sure how -- you still can say that, in fact, your drug is good against resistant AZT virus. It would probably be unethical to leave another arm with AZT on there in the presence of failure. So, it is difficult.

DR. HAMMER: I agree it is fairly complex, and I think some of the information would be potentially inferential however you define it, but if you could have an

idealized study where you are really looking just at a single key mutation.

I agree that having some phenotypic change is important, however, there have been studies to show that certain individual genotypic changes can be associated with an inflection point in the RNA response without much measurable change in the virus.

That was shown with the case 70R for zidovudine, and you can see inflections with the 82 mutation in some of protease inhibitors without much in the way of -- certainly before you got to a 4-fold change in phenotype. So, there can be subtle changes to even single mutations.

One thing to think about, though, if you could have an idealized study where you randomize on the 215, for example, or some similar mutation, is to have a regimen, have two populations, one with a 215, one without, give the same regimen, look very carefully at the slope of decline.

If that is the same and everything is identical through 24 weeks, then, I think what you are looking for is rates of escape and what those escape mutants look like later, and it gets to the longer term issue that Doug Mayers raised earlier.

But it is not clean, but if you don't put an ethical control arm in, and don't control for the viruses in the control population, you won't be able to tell.

Also, look at the Merck 035 study, highly zidovudine experienced. They did fine on ZDV, 3TC, and indinavir. So, it is also further complicated.

Henry.

DR. MASUR: In the problem we were dealing with Monday, when you have a drug which has a relatively modest effect compared to something else, how do you protect yourself from -- you could have a drug that in vitro looks great, that is hydrolyzed to an inactive compound in vivo, how do you know that your drug is really having any effect at all in vivo by doing that kind of experiment?

You are expecting a lot from a relatively weak drug, to expect to see a change in the slope of the curve.

DR. HAMMER: If you are dealing with a relatively weak drug, I agree with you it makes everything harder. I agree. I think it also gets back to -- you know, without being able to do monotherapy studies over anything more than a few days or a couple of weeks, it makes it extremely difficult.

I think the comment that Mark Harrington made about animal models and some of the possibilities there may help us. It certainly will help us with some of the mutational issues. I don't have a good answer for that because I think, you know, weak drugs are problematic from the start, and it just compounds as you go further down the

developmental process.

Dr. Mathews.

DR. MATHEWS: A thought on Henry's point is to take advantage of this notion of enrichment, which Jeff was talking about, because if you were able to characterize how many drugs in the patient's regimen were actually active, which in the studies that we were looking at the other day was impossible to tell, so that if you could either enrich up-front by having the concomitant therapies having a reasonable likelihood of activity, or analyze the mutational patterns of all the drugs, not just the agent that you are analyzing, you would be able, at least in a subset analysis, a retrospective analysis, break out the different prognostic groups a little bit more efficiently than what you could do in aggregate, just looking at the single drug.

DR. HAMMER: Dr. Yogev.

DR. YOGEV: Well, first of all, I would like to sit on your right side for next time. You are always looking to the right first. I am teasing you.

DR. HAMMER: I am fully balanced because I am always accused of looking to the left from the people on the right, because of the screen.

[Laughter.]

DR. YOGEV: I think one possibility, you mentioned to take a mutation of 215. I was wondering of a possibility

of taking a HAART with, let's say, three drugs, and then add the new drug as a fourth one to see if there is anything different in the dynamics of reducing the virus and the amount of the response.

And that necessitates you have to go to a patient with a much higher viral load, so we cannot get into this unfortunate situation that with 1 log or 1.1, you are already undetectable. So, a study can be devised that if you start with a very high number, look at the dynamic.

We have anecdotal data that if you increase the dose of certain drugs, the rate in the first week of reduction is faster, and that might be one thing that should be pursued that can give you an idea on a potent drug or less potent just because you have a control group now on the same population who has a high viral load, which can bring you this, if there is any effect, out.

DR. HAMMER: Other comments on Scenario 3?

I can't quite summarize this. We actually didn't really answer the first question - Considering there are both resistance-associated mutations and polymorphisms present in HIV genes, how should mutations be grouped and analyzed in prospective studies?

I think that is a very difficult question. It took a lot of the conversation, for example, among the best experts in the country on the RCG group to put it together

for the DAP analysis, so I think it is hard for the committee to do that.

It comes through basically consensus panels about what proven specific drug associated mutations there are that have had history by clinical isolates and site-directed mutagenesis studies and also class-relate mutations.

I think if you are going to base a trial on this, there is no perfect way to do this, but there are reasonable consensus. I mean studies have been done based on trying to look at these and make interpretations. So, as long as one is willing to disagree about some of the fine points of interpretation, you need some basis to move forward prospectively with what your hypotheses are.

So, I think there are enough consensus tables around and they will be evolving every year, and they are on the web, et cetera, that as long as this is decided upon up-front, it is okay for a study, and as long as you balance expert advice across the arms.

We answered or tried to answer the post facto analysis of stored specimens question. Probably the consensus of the committee is that if you are looking for a specific indication that it is active against viruses with X mutation, in this example, the 215, then, a prospectively designed trial with prospectively obtained specimens and tested is the right way to do it, but that retrospective

studies are not completely excluded from this although it is perhaps better to generate the hypothesis from a retrospective study and then test it, as Dr. Pettinelli said, prospectively.

Then, what type of evidence is sufficient to support a claim of efficacy and receive an indication for Drug C for the treatment of drug resistant virus (in this case zidovudine resistance is identified by a single mutation at 215)?

The answer is efficacy in the population studied, but I think the question is how you get there, and I don't think the committee really is able to really come up with a study design that everyone would agree with because of the complexities of treatment.

I think the bottom line is careful looks at virologic response and escape early on and later on are the ways to do it, and to try your best to have a comparator arm that serves as the best control you can get.

Scenario 4.

DR. LAESSIG: The final scenario is use of resistance testing in a clinical trial to enrich a patient population.

[Slide.]

Protease Inhibitor X has a somewhat unfavorable safety profile. However, based on preclinical data, it may

be useful as salvage because it appears to retain activity against protease inhibitor resistant virus. A study is proposed to look at Drug X in treatment-experienced patients.

The FDA recommends inclusion criteria based on resistance testing to demonstrate likelihood of failure to other regimens.

[Slide.]

The questions are: Please comment on the appropriateness and feasibility of incorporation of resistance testing in the inclusion criteria.

Can efficacy in the enriched study population be extrapolated for use in populations where resistance testing is unavailable?

In studies that don't incorporate baseline resistance testing to choose optimal regimens, what are the implications of independently obtained genotyping or phenotyping?

Since this is the last scenario, we got to have an extra question.

[Slide. 1

If after starting the initial regimen, genotypic or phenotypic information becomes available that indicates the chosen open label regimen is not optimal, could one or more of the drugs be changed without considering the patient

a treatment failure if the patient had not met other criteria for treatment failure?

DR. HAMMER: Can I just ask a clarification on the third question? Do you mean that someone in a clinical trial obtains genotyping or phenotyping outside of the clinical trial?

DR. LAESSIG: Correct.

DR. HAMMER: And he or she, and his or her physician have that information and want to use it?

DR. LAESSIG: Exactly.

DR. HAMMER: Just like the viral load era.

Dr. Mathews, do you want to start? You just mentioned issues of enrichment in populations. Not to put you on the spot, but --

DR. MATHEWS: The use of resistance testing in real-time, one thing I feel reasonably confident about is that whatever the evolving guidelines are for use of resistance testing in clinical practice have to match what is being done in clinical trials.

Right now, resistance testing, I mean it is just a moving target, but once these new guidelines are coming out that are saying people should have resistance testing after failing a regimen, then, you are going to have problems trying to withhold that kind of information in the clinical trial setting.

DR. HAMMER: I think the question is really what are your thoughts about up-front resistance testing as part of the study design and stratification and randomization. Is that right?

DR. MATHEWS: I think it is going to be very important to do that. The dilemma is that a lot of the resistance patterns that we have talked about and seen in the last couple of days are not well characterized, and so what decisions would you make on observing a certain pattern of uncertain prognosis.

Where I think it is most useful is what I was trying to get at earlier, was that you can reduce the heterogeneity of response and improve your chances of detecting the main effect that you are looking for by doing resistance testing and selecting the concomitant agents which are likely to be active in the regimen, and therefore the drug or drugs that you might be looking at in a factorial design, superimposed on background therapy, you would be more likely to detect an effect.

So, I think it is very prudent to incorporate baseline resistance testing at least for those circumstances where the interpretation of the results is reasonably clear.

DR. GULICK: I would agree. The heterogeneity of virologic failure that we have been talking about for the last two days, the demonstration of appropriate resistance

mutations would actually sort of narrow the failure right down to the level of actually knowing that the patient was resistant to the prior drug as opposed to non-adherent or perhaps with other PK issues.

So, it seems very appropriate to take this next step. As an observation, many of the salvage studies which will now be looked upon as the old kind of salvage studies tried to get at this point by requiring a certain amount of months of therapy and certain patterns of breakthrough.

This cuts through all that and just gets right to the demonstration of resistance. So, that would seem the most appropriate way to go.

DR. HAMMER: Other comments on Scenario 4? Dr. Wong.

DR. WONG: That is true insofar as the tests that we have really demonstrated resistance. I mean that is, you know, that is what it is, right?

DR. HAMMER: Mr. Harrington.

MR. HARRINGTON: Yes, and the other key statement was if it is clear up-front what that resistance test means, and I think for most of the resistance patterns, it is not at all clear, and it is especially not going to be clear for a new agent where you are making a guess, extrapolating from old data.

The other point I want to make is -- a couple

points. I mean supposedly we are trying to treat a virus, not a point mutation. So, resistance has an explanatory value for explaining why treatments may or may not work, but in reality, we want to know, I would think the sponsor would want to know how the drug works in a pretty heterogeneous population.

A lot of these designs disturb me because they seem to really focus on trying to make really tiny trials prove more than they can possibly prove, and I think that is a real danger.

There is a clinical need to prove utility in salvage populations, but we also -- I wouldn't think a sponsor would make very much money off of only treating these tiny niches, So, I am wondering whether they are just trying to save money by proposing all these ridiculously small, one-arm, open label studies to the FDA.

I think we need to get back to the bigger picture, which is what is the most useful information that can be generated for across the spectrum of HIV disease and how do you use resistance testing in that.

I am not sure that means you would use it in a regulatory framework all the time although that is why we are here.

DR. HAMMER: That is a very good point, and we focused in, in our discussions here, but I don't think the

scenario is meant to mean to the exclusion of having tested the drug or testing a drug in parallel in broader populations. I think that we are being focused -- and correct me if I am wrong -- on a sponsor trying to apply for a specific indication, not necessarily the only indication, but a specific indication of use in a targeted treatment-experienced population with a particular treatment experience, because the drug may have some particular advantage there.

I don't think that is to the exclusion of trials in broader populations, and I think that point is very important for us to sort of take a step back from the focus of these discussions.

Dr. Kumar.

DR. KUMAR: I think the inclusion of resistance testing and inclusion criteria will really help many of us and our patients in the salvage protocols. Many times there is a limit to how many months patients can be on a salvage protocol or on a salvage regimen before they are eligible for the second salvage regimen.

So, having this kind of resistance testing and inclusion criteria may allow us better to end all these patients instead of having patients remain on the salvage protocol for that period of time.

DR. HAMMER: Thank you.

Dr. Mayers.

DR. MAYERS: As someone who incorporates this into trials every day, you can clearly put patients on the studies with resistance testing as part of the randomization criteria. We have a 500-patient study that is doing both phenotyping and genotyping on the way on starting in December.

We have got three studies which do it on-line every day, so it can clearly be done if you set up the mechanisms to handle real-time, on-the-fly data.

The other issue I would like to bring up is if you don't do resistance testing, you can be sure that your doctors and patients are doing resistance testing if there is any indication your drug doesn't work against a certain type of virus, and if you are worried about resistance testing in the middle of your study, you probably have an ethical problem in your study design.

DR. HAMMER: I would just take exception to that last statement at this moment in time. I mean there isn't uniform access, and many patients are being managed without the availability of drug to resistance data, and there are other ways to manage patients based on their RNA change and other things, that failure can be handled clinically in some says when you don't have the finances to order a resistance test.

DR. MAYERS: The point I was making, Scott, the point I was making was that if there is a certain pattern that they can find on a resistance test, that will get them to bail out of your study, there may not be equipoise in both arms of the study for that category of patient, and maybe there is a problem.

DR. HAMMER: I would agree if there is uniform interpretation of what that meant, what those results meant.

Dr. Mathews.

DR. MATHEWS: One other point on that, if resistance testing is done up-front and as a basis for randomization, there is the possibility of misclassification error depending on when the resistance testing is done, and these are issues that we talked about already.

If it is done on drug for a certain period of time, that means one thing. If there has been a washout period, that is another thing. We see numerous examples where this can create misinterpretation of what the patterns are.

DR. HAMMER: Other comments on Scenario 4?

Dr. Charache.

DR. CHARACHE: Just on bullet 3, which asks what are the implications of independently obtained genotyping and phenotyping, and I would suggest that unless it is done in the same laboratory in which the basic studies are done,

it could not be merged.

DR. HAMMER: It wouldn't be merged, but it will be done in a different laboratory. It may or may not be done in a different laboratory. We face this all the time with viral load tests when they were not uniformly done and being handed back to patients in real time in the clinical trials, and it is a problem, but it can be handled basically because of the nature of the disease process and the clinical trial process in HIV. It is not easy, but it can be done.

Just to summarize, the appropriateness of resistance testing and incorporation in inclusion criteria, I think there is a general consensus that it is quite appropriate depending upon the objective of the study, and if there is request indication for a specific target population, the one proviso of the committee was made by Clark Harrington, I think, that we are not interested in a series of small, tiny, little indications.

We are interested in a larger indication with a clarification as to which populations the drug would work best in.

Can efficacy in the enriched study population be extrapolated for use in populations where resistance testing is unavailable?

A very hypothetical question. I think it depends really on the epidemiology of drug resistance in the

population, and that is again a moving target. It is worsening in different parts of the country. You really have to know your own regional epidemiology and the individual epidemiology of the person you are treating and the potential requisitions over resistant strain and the drug history to know whether it is applicable.

So, I think extrapolating from a small study to a larger population is difficult without the kind of larger study I think that Mark Harrington was referring to.

In studies that don't incorporate baseline resistance testing to choose optimal regimens, what are the implications of independently obtained genotyping or phenotyping?

I think it means a greater off-treatment rate. That is what it means. You have to basically power your study to incorporate that. I would agree with Doug Mayers that you need to be ready to revise your study along the way and make sure that it is ethical -- and I wouldn't disagree with that point -- if the field is changing in relation to that.

It also depends on when that resistance test is done and whether it is post of virologic endpoint, because it could be not terribly meaningful if, in fact, the endpoint is virologic failure. That endpoint is met and determined and set in the database, and then a resistance

test is done, it is not going to hurt the trial endpoints per se.

It depends what you are doing on treatment as far as continued, issues of availability of resistance testing, but I don't think that is an unmanageable issue. We have seen it many times over in HIV disease, and I don't think that is a big deal, honestly.

If after starting the initial regimen, genotypic or phenotypic information becomes available that indicates the chosen open label regimen is not optimal, could one or more of the drugs be changed without considering the patient a treatment failure if the patient had not met other criteria for treatment failure?

This is a completely unanswerable question because it really depends on the study design and the rigor with which -- and how things are defined, because if it is up-front defined that any treatment change is failure, it is failure no matter what, if is a virologic endpoint failure, which is more likely, and this is a protocol amendment in a patient who is suppressed, then, I think it is reasonable that that protocol amendment could take place and the data could still be interpretable.

Without a full study design and basic assumptions and a stat section to review, I find it impossible to answer this question.

DR. MURRAY: I think it was, let's say, of a protocol design, and not knowing the feasibility and the turn-around time for the results, you get the results back after you have chosen your testing drug X, and you add it with two other drugs, and you get the results back as the patient is undergoing a viral reduction, you get results back that say oh, I wish I would have picked a different concomitant regimen.

Would this be reasonable? I mean would you look askew at the data if, at that point, the concomitant regimens were changed, you know, while the viral load trajectory was still going down?

DR. HAMMER: You mean not the test --

DR. MURRAY: The background.

DR. HAMMER: The background regimens?

DR. MURRAY: Yes, like the nukes you would be combining with the PI.

DR. HAMMER: And you are in the specifics of the downward trajectory, that is what you are saying? That is what you said.

DR. MURRAY: Well, I would think that it would refer to maybe the time it would take to get the results back, so it would be something early on, you know, typically before the failure endpoint is looked at, like before 24 weeks, something like that.

DR. HAMMER: I would like to hear what other people think. If that issue is not balanced between the arms or among the arms, I think you are in deep trouble.

DR. WONG: I think the protocol needs to be written to take this eventuality into account. If you are really going to bail out and change everybody, obviously, that is going to have an effect unless it is specified in advance that this can be done.

DR. HAMMER: Also, I think if you are doing baseline resistance testing and then choosing, you know, randomizing on the basis of plus or minus a certain pattern, but then that information is there. It should be there before you initiate the regimens, and you should have enough flexibility in your initial regimens to adapt the background therapies to the resistance profile.

So, I would think, for example, if you used a line probe assay to look for a specific mutation, and then you also sent out full-length sequencing and randomized on the basis of a line probe, and got the full-length sequence back which caused you pause about the background therapy, you have painted yourself into a corner, and it is then better to have all of that resistance information up-front if, in fact, you think you are going to allow modifications in the background therapy and try to optimize treatment to start with.

I agree with Dr. Wong you have got to have this in the protocol up-front and try to anticipate these torpedoes coming below the water line.

DR. YOGEV: It also depend when you are getting those results, because I think this is a unique opportunity if you get it within 12, weeks, and there are no failures, to see if the phenotyping/genotyping is really meaningful to what you are testing. As of today, we don't know that genotyping is 100 percent.

It might be a unique suggestion by our committee or whatever that this pertaining to resistance, and in this specific combination, it doesn't work. So, if I get a phenotyping/genotyping down the road, I would continue the study because it is very important information for us to learn, that we don't know what phenotyping/genotyping really means.

DR. HAMMER: I agree with getting the information. The issue is really whether you would act on it and change treatments, and I think one of the caveats in thinking about this is, in fact, the results of the ABT378 first failure study, where, in fact, if they operated on that sort of information, they might not have come up with some of the interesting results we have that resistance profiling doesn't necessarily correlate with response, and it may be the pharmacologic profile of the drug is more important, or

we have to think about a different breakpoint.

So, I think it is quite complex and the best thing is to try to avoid that as much as you can.

DR. HAMMER: Dr. Mayers.

DR. MAYERS: I think, though, it is important to realize that as genotyping and phenotyping get more available and get more rapid turn-arounds, that you almost should assume that your patient coming into your study has a genotype and a phenotype, and use that data to decide whether they liked your randomization to get into your study in the first place.

It would almost be better to say would you give us your resistance results as you come in, so you would know what they had had, than to assume that people are coming in blind, because I think less and less people are coming in blind over time, and if the recommendations to the IAS that were shown this morning come in, you can assume that probably almost no one is going to come in to your trial blind.

MR. BARRINGTON: That is just not true at this time though, Doug. I mean in an ideal world, that would be the case, and I think maybe in a couple years, more people will have access, but the majority of people I know, and many of whom have private insurance, don't have that information right now, some of them do. But it is not as

easy to get as you may think.

DR. MAYERS: I realize it is not easy to get, but I am just saying that there is a fair number of people who are doing it now, and I think that fair number of people, if the new recommendations come out, that you should consider doing it, will increase dramatically.

I think that the assumption that patients are coming in blind into a study, especially anything beyond the first round, is probably flawed to begin with. You aren't getting a random population coming into those studies.

DR. HAMMER: I agree it is changing rapidly. It will change, and we may not be able to do some of the studies in a year that we could do now, but that I think has been true.

We have come to the end of the regulatory scenarios unless there is some further clarification on these that you want us to attempt.

I think what we will do is turn to the committee questions. There are five questions. As I mentioned before, particularly in light of the fact that a number of committee members have left, and others have to catch other transportation soon, we will run through these and, honestly, just try to hit the highlights of what we haven't touched on. I have also been asked to give a recap of this meeting, which we might or might not do, but in any case, we

are prepared if we have to.

Some of these questions, honestly, I think we have touched on before in the last two days, and we can move through quickly as a group.

Questions to the Advisory Committee

DR. HAMMER: The first question -- and just for the record -- is Please comment on the amount and type of preclinical resistance data sufficient to support a clinical development program.

We talked about the type of preclinical resistance data. I don't know if anybody wants to comment on the amount. I think that really relates to, for example, what size panel should be tested. That is the way I would interpret this. As far as the type of resistance data, we have talked about that repeatedly.

Does anybody want to tackle that? I don't think we really have a clear notion.

Dr. Wong says enough.

I would venture, though, that, you know, we put some numbers on other things. I think if we are talking about really characterizing a new drug, the panel of isolates, you know, it has to be laboratory and clinical isolates and well characterized on their mutational basis and their phenotype.

You are talking in the range of 50 to 100 isolates

at least -- I don't think you are talking 1,000, I don't think you are talking 10 -- on the order of magnitude, we can probably say to develop a profile for the drug.

I think it also depends a little bit on whether it is a drug that is being developed as a better drug with a good PK profile, that is more a first generation drug, and is not going after drug resistance, or if it is a drug that really is a second or third generation drug that is going after a drug resistant virus.

If it is, the ladder of the panel has to be larger.

Does anyone disagree? Dr. Charache.

DR. CHARACHE: I would just add I think that it is time for the FDA to help the various drug manufacturers by stipulating what the basics of the testing should include, and I think that can be done with the panel agreement. I don't think it is complicated.

DR. HAMMER: Dr. Mayers.

DR. MAYERS: I think the one thing that has become clear from the bacteriology field is that if they can use a standardized panel of strains and a standardized assay, especially if you are going to try and relate resistance to some pharmacokinetic parameter in the future, that it would be really useful if we would establish some reference resistance test and some reference panel of strains to look

at, because currently, every company has a different in-house assay.

They all have a different batch of 15 isolates that they pull out of their freezer, and it is almost impossible to relate the **way** they test the drugs against a clinical assay that will be done or their isolates against anyone else's isolates for any other drug.

DR. HAMMER: Other comments?

Question 2, which we have also touched on in the last day and a half.

What type of in vitro and clinical data should be provided by drug sponsors to characterize the clinical activity of an antiretroviral drug against "resistant" virus? Should different standards be required to support a labeled indication (for treatment of resistant subpopulations) as compared to that to support descriptive statements in the Microbiology section for use in resistant patients?

In your discussion, please include details such as: methods, patient subsets, number of patients, number of isolates, duration of treatment, number of drugs, definitions for assessing treatment response, etc.

I am glad there is laughter from the agency representative.

We have touched upon this a little bit and to a