fair extent as to again if the indication is going after drug treatment experience, drug resistant population, the bar is a lot higher than if you are doing a general "population" and then perhaps retrospectively looking at subgroups.

Would anyone like to sort of describe this further? I am not sure we really can.

Dr. Charache.

DR. CHARACHE: I would say it depends.

DR. HAMMER: And we all concur with that, I think.

I think we have given you guidance on this. If we can move on.

Question 3. What type of in vitro and clinical data should be provided by drug sponsors to characterize an antiretroviral's ability to induce resistance and cross-resistance?

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.

We also touched upon this I think in the scenarios about resistance and cross-resistance.

Would anyone like to add to this, because we have really talked about this. Certainly, I think everyone is in agreement that the lack of ability to induce resistance or

cross-resistance, the bar for that claim is very, very high. The issue of a little more slowly developing resistance, I think can be made based on genetic barriers and the mutations that come in, in vitro and in clinical isolates.

The clinical trials have to be well designed to really assess failures on treatment when they are in salvage regimens to really start looking at the issue of cross-resistance to other agents in the class.

I am not sure we can be more specific.

Dr. Pettinelli.

DR. PETTINELLI: Just as a general statement, however, I think it will be important to be able to evaluate all the drug available in the specific class. The recommendation will be really to look in terms of cross-resistance all the available agent.

DR. HAMMER: I was looking at Dr. Stanley's comments to me to see if there was something to add.

Did anyone else want to add to Question 3?

Dr. Mayers.

DR. MAYERS: I think that the in vitro data can clearly can tell you drugs you don't want to randomize to the patient the next time around, but I don't think in vitro data necessarily helps you for activity, so that I think that it would be very useful if there could be some mechanism developed for the companies, where there appears

not to be cross-resistance, to arrange to randomize the next round off their large Phase II's into those classes of drugs to get that answer, because right now we are really not getting the randomization until the next round of the patients, and the next round cleanly for these drugs, so that there is a lot of claims based on in vitro data, and that there is very little true efficacy data, which I think is the gold standard here.

DR. HAMMER: Although there is sequential selection bias in such studies.

Dr. Mathews.

DR. MATHEWS: One thing that we haven't really emphasized as much, although Trip made a comment that I think is important, is that the resistance and cross-resistance information I don't think can be a substitute for the treatment history, the previous treatment history, because of all of the problems, and cross-sectional looks at resistance.

So, collecting and analyzing the treatment history in conjunction with the resistance data, I think until we get further information validating the resistance data, it is going to be very important.

DR. HAMMER: Although I would mention one. It is only one study, and it was a relatively small study of Mike Saag at ICAC, 71 patients -- and I think the resistance

testing was done retrospectively, but in a multi-variant analysis, phenotypic testing, when that was included, antiretroviral treatment history was no longer a significant predictor. However, it was just a single study, and it was only 71 subjects. I think the point is very well taken.

The next question, we really should try to spend some time on, because this is important. It has come up, and it is really where many of the issues of resistance and cross-resistance have come out in academic and company studies.

The fourth question is: What types of postmarketing evaluations regarding drug resistance/cross resistance should be conducted?

This, we really haven't wrestled with, and it is an important issue because that is where the larger numbers are treated, and these issues come out.

Dr. Pettinelli.

DR. PETTINELLI: Just one comment. After accelerated approval, I think that some of the patients are being followed up for a longer term, and I believe it will be essential to also evaluate those patients in terms of their genotypic/phenotypic profile.

DR. HAMMER: Also, I would like to read into the record Dr. Stanley's comment on Question 4.

"There should be a plan up-front to continue to

monitor certain subsets of patients for development of resistance or cross-resistance. For instance, a sponsor could establish an agreement with certain clinicians to perform genotyping and phenotyping on any of their patients who go on the drug and who then fail."

I think there are a number of research groups, practice research groups and academic research groups and others who would be even more than happy to participate in such studies.

That last comment is my editorial comment.

Dr. Charache.

DR. CHARACHE: It would probably be important to also test a subset of those who did not fail, so you can better interpret some of the changes.

DR. HAMMER: You mean at baseline, because at least with the current techniques, we can't amplify the virus in those who succeed by our most critical definitions of success.

DR. CHARACHE: You are absolutely right. Take it back.

DR. MURRAY: I have a question regarding maybe -- well, I don't know, since Dr. Stanley made it, I don't know if anybody can answer this -- so, a company does some postmarketing surveillance, it is not going to be controlled, what do we do with the information? What can

:hey say about it?

DR. HAMMER: I don't have Dr. Stanley's cell phone number. In Phase IV data, I think what you can try to do, and I think what she has indicating, is to really set up a number of cohorts of reasonable sizes where although it is uncontrolled information, you have got data on treatment experience, treatment history, follow-up information, and marker data, and try to make thoughts about really, and then be able to grab the isolates and study them.

So, I think that the cohort information that one could develop through these sorts of things, it wouldn't take more than perhaps several hundreds of patients really, can be quite valuable.

So, it is uncontrolled, but it is really the length the follow-up and the completeness of the dataset and the virology analyses that can correlate, that would be of greatest use.

DR. MURRAY: And label-worthy?

DR. HAMMER: Potentially label-worthy, but we would already be in Phase IV, so this would be an amendment to the label rather than a primary indication. I would think that that kind of data would be supportive information, and, yes, could be label-worthy because it may be supportive of the smaller dataset that says a drug is helpful in a certain population, or it may actually modify

the label to back off.

Dr. Yogev.

DR. YOGEV: I was just wondering if this is not the time to think about the clearinghouse, like we have immunization, an agency, you said. Because we are going to do more and more often, as clinician, to identify for ourself why the patient failed, we should have a place where we can send those results to be verified or whatever, and that is how you can collect them there.

A company now, for example, are following pregnant women who are receiving their drug to see if there are any side effects, and that is how they will change or at least inform the rest of us. I think because it is so complicated, and because we are individually doing it, we need a place maybe to think about it, it will be part of the postmarketing, to have a place to send those, which we identify resistant as the reason for the failure, to send over the accumulated data.

DR. HAMMER: It is a good idea, but it just seems like an overwhelming undertaking if we have 30, 40, sometimes, in some populations, 50 percent failures of treated patients. The sheer numbers are extraordinary, and if one doesn't control for the data that is given, and it's passive acquisition, I would be concerned about really what conclusions could be drawn outside of the kinds of cohort

populations that are being described now. The numbers are just overwhelming as far as failures in this country on antiretroviral therapy.

DR. YOGEV: I was not talking about the failure per se, I was talking about an investigator tested, found out they are resistant, to have a place that will collect them, because then you find out suddenly that there are 300 cases, nobody knows how much, because the cohort might be very difficult to follow, because over there they investigate all the failures. All I am talking about is collect the resistance, verify them, and then you know what you have.

DR. HAMMER: That is a good point. I think we have actually a little bit of handle on that from the two commercial groups that are doing phenotyping, have put out some very impressive information that have helped evaluate, that is selected by obviously what they receive, but it gives you an indication at least in patients who are failing and getting resistance testing what it looks like. So, that could be taken further in a more independent fashion I think is what you are suggesting.

Other comments on Question 4?

Question 5, which I think we can deal with very quickly, is: Please comment on the feasibility and limitations of incorporating "real-time" HIV resistance

testing in clinical protocols.

I will ask Dr. Mayers to answer this in three words.

DR. MAYERS: It is doable. I think that actually real-time resistance testing costs the same amount as post-hoc resistance testing, if you define what you want to test, and I think that actually there is a real utility to the industry to collect baseline samples to look at the resistance in their failure patients in their early studies to understand whether their drug is working and how it fails to tailor and design their Phase III studies.

So, I think it is of great utility to the company, and it is a reason for the patient to stay in the study because they are going to get some data back that is potentially of use to them.

So, I think that this has real utility in understanding your drug's success and failure and designing your Phase III studies and helping to manage your patients when they fail the study. I personally don't see a drawback to introducing this if you have a plan set up of evaluations for your drug. Doing it real-time just gives real-time data rather than data a year down the road.

DR. HAMMER: Dr. Mathews.

DR. MATHEWS: Several times this issue has come up about doing resistance testing in people that are succeeding

on therapy and how it is not feasible. I just wonder what your thoughts are on looking at the idea of periodically withdrawing therapy even on trials to sample rebound virus, and see what the mutational patterns are.

DR. HAMMER: It certainly is feasible to do. I think there are issues of safety. One has to decide what you are doing that for, and to me, there are issues still of safety. Within a clinical protocol, it is not unreasonable, but given the fact that you are re-seeding targets and you may drop your CD4 count, it is a bit problematic to me, although obviously, it needs to be studied further.

Mr. Harrington.

MR. HARRINGTON: TAG co-sponsored a workshop on this topic in the summer, and Dr. Miller was there. I think there is going to be plenty of protocols that are going to be looking at structured treatment interruptions in the suppressed and unsuppressed, and first line and salvage population.

I think we might get some answers out of that, and I would think it probably wouldn't be clinically ready for prime time other than in the context of a study that had a good hypothesis behind it.

DR. HAMMER: I think Chris's point is it is a good way to get an isolate approximate to the regimen to see what it looks like. I think we will get information about this

at the Retrovirus Conference and subsequently.

Other comments?

Dr. Gulick.

DR. GULICK: One thing that has been said before should be restated is that the use of resistance testing on study should, at the very least, be up to where the level of where clinical care is, as we have learned from viral load and the use of real-time viral load testing, which suddenly became really the only way to do it, because that is what was being done in the community. The same principle probably needs to be applied here.

DR. HAMMER: Does anyone on the committee see that there is a real block to the feasibility of real-time testing in the setting of drug development and clinical protocols?

Dr. Jackson.

DR. JACKSON: Maybe Doug could comment, but I agree the utility is clearly there for a number of reasons, but in terms of the feasibility, obviously, you need to get a viral load, as well, at the same time before you waste your time trying to amplify something that isn't there, but what has sort of been the range of turn-around times that you have been able to achieve in real-time for these protocols?

DR. MAYERS: We are turning them around in about

10 days right now on average.

DR. JACKSON: On average.

DR. MAYERS: On average. The problem is if everything amplifies right for you the first time, it's a three to five day procedure.

DR. JACKSON: But when they don't --

DR. MAYERS: It can be ugly, and we do go to back-up primers and back-up to get sequence.

I think that the way we are doing it in the CPCRA, which I think is reasonable, is we bring the sample in, we do a viral load. As soon as the viral load hits the cut point, you send the sample in for sequencing. Since it is the same labs, that is a fairly rapid process, and it can be done out of the same vial of plasma.

It is feasible if you are set up to do it. I think that the new technologies, especially the rapidly improving ability to put it all together quickly and check it, what used to be eight hours of somebody's day is now significantly shortened.

But the turn-around times, I think in the next year are going to be 96 hours, you know, five to seven days is going to be expectation, five to seven working days will be the expectation of getting this data back. It is getting faster and faster. The technology is getting better.

DR. JACKSON: Although obviously, there are always

problems that take sometimes longer, two to three weeks even, and, of course, that is in the laboratory. Our experience with viral load testing, of course, the real delay is getting the specimens from the sites with the correct labeling and everything else.

So, I think it is important for sponsors or investigators, in designing trials with real-time testing, that if there are randomization points, that we have to be very realistic in terms of how much time is really necessary to do real-time testing, taking into account all these factors.

DR. MAYERS: If you are asking from when the blood is drawn to when the result goes out to the field, right now it is taking us -- because we ship weekly and there is an average of six days between the blood draw and actually getting it to the lab -- it is a 13-day turn-around time from the shipment of the sample coming in to it going back out to the field, and it is probably on the order of 21 to 24 days between the sample being drawn, the viral load and the genotype getting back in the current system.

I think that you may not, people may not be willing to wait that long, you are right. On the other hand, I think that if the issue is, is it worth the company getting the data on a real-time basis, I think it actually has pragmatic utility to the companies.

I have a little more concern actually about the issue of doing genotyping on the way in for a drug where I don't know what its responses are going to be, because you are presuming you know how the drug is going to work before you have ever put it into people, and that is a limitation.

If you assume that you know what is going to happen before you do the study, you can limit yourself from finding out data that is very useful. So, I think I am a little less comfortable unless there is 100 percent resistance between the two drugs.

In my early, first-time failure studies I am going to limit the patients until I get some data to support that knowledge. I think you can prejudge yourself out of utility unless you at least do a little clinical data to make your decisions.

DR. HAMMER: I think we can rely on the sponsors not to do that. We will have their drugs before they have adequately tested them.

Dr. Jolson.

DR. JOLSON: I had another feasibility question. Maybe Doug could answer it.

We are often criticized that our requirements are burdensome, financially burdensome, particularly for smaller companies. What we are talking about I think at this meeting involves more testing than is currently being done

in clinical trials.

What would you -- and this is just an estimate -- the incremental cost is when you consider doing at least baseline resistance testing on most trial participants, and then resampling again at the time of failure, how much additional cost should we be anticipating that will be incurred?

DR. MAYERS: Phenotype and genotype together?

DR. JOLSON: Well, maybe you can tell me for each one.

DR. MAYERS: It is running about $385 to 400 -- around $400 a sample, a little bit less, for genotyping of the protease and RT gene. The companies are just establishing pricings for phenotyping, but my understanding is it is going to be in $750 to $900 range.

So, you are probably adding about $2,500 to that company for that patient who fails. For the ones who don't fail, obviously, not as much money. On the other hand, my counter to that would be that if you don't do this testing, and you go into your Phase III program, you are going into your Phase III program blind, and what is the cost of doing 1,000-patient trial in the wrong patient group because you didn't have the data to select the right patients for your large studies.

By investing up-front in your Phase I/II program,

and looking at where does my drug work best in experienced patients, how does my drug fail in inexperienced patients, that allows you to design a Phase II/III program that efficiently targets your drug to the right patient groups.

DR. YOGEV: Do you really need both of them? We just thought that it's so nicely correlated, it would be enough, the genotype only, for example, in Phase I/II.

DR. MAYERS: I think in Phase I/II, you are going to have to get both data, because it's a new drug. You don't know what the relationships are.

I think that you can then, once you have enough Phase I/II data, make an efficient strategy as to how you are going to go beyond that, but I really do think, in Phase I and II, it pays off to invest the money in those patients.

DR. HAMMER: I would agree.

Dr. Jackson.

DR. JACKSON: Getting back, if a company is going to make a claim about resistance, and efficacy against resistance, I think you have to have phenotypic resistance data.

DR. HAMMER: That makes sense, internally logical.

Are there other comments on Question 5?

Since we are running ahead, I have been asked to recap this meeting, which I think is just a slightly daunting request, but at lunchtime I put a few slides

together and I will try quickly to do that. I think this is intended really for the potential sponsors in the audience. I would say that, in advance, that any comment I am going to make has not been vetted with my colleagues here, it is really personal sense of this, and is somewhat generic. The details need to be worked out, I think, as each drug comes through development, but maybe it will create a summation for this meeting.

Recap and Summation of the Meeting

[Slide.1

DR. HAMMER: First, I think the first important thing at the recap is I think thanks should go to Heidi Jolson and Jeff Murray and their colleagues for putting this meeting together.

I think I can speak for the committee that it has been a privilege to participate and particularly to hear the wealth of data that has been presented, some of it, and a fair amount of it, for the first time in this venue.

I think and I hope that we can look back at this as a turning point, if you will, in the resistance field in HIV drug development, much as the RNA Symposium was the turning point for drug development in clinical trials, as well.

[Slide.]

So, I started the meeting recap with a non-

controversial question and answer, which I think is at least where we should start.

Does resistance testing have a role in drug development?

I think the consistent message from the group subject to disagreement here is an emphatic yes. It not only does, but should have a role.

[Slide.]

I think there is also general agreement that both genotypic and phenotypic testing are important. I think it is also well to remember that we get wound up in specific assays, but that no single assay, genotypic or phenotypic, has been individually discussed or should or can be recommended.

I think there are pros and cons to each of the assay and the formats. The technical and interpretive limitations have been well outlined, particularly in Doug Richman's talk, and that, as everything else in science and development, you need to choose which assay is most appropriate to answer the question that is at hand.

I think whether you are doing genotyping or phenotyping and which platform you are using and which assay you are using, you need to think about what question you are asking and what answers you want.

I also think in relation to NDAs that come in, and

certainly data that is seen by this committee, that validation data for any assay that is used needs to be provided. This can be more easily done, obviously, if there is a well validated commercial assay, but I think for in-house assays, we need to know really what their performance characteristics are.

I think the agency will demand that, and as we have talked about, standardization is going to be increasing important. It may be externally imposed, as well.

[Slide.]

So, yes, I think NDAs should include resistance data. They already do essentially, at least the ones that this committee has seen in the more recent times, and that is not going to change.

There is an issue of what level, I think, and it is termed at sort of the minimal level, and again I say this as personal. This is not committee-wide, this is not the agency, this is just me from this meeting.

At the preclinical level, I think we have talked about this, that at the minimum, we want to see drug passage studies where passage in the presence of drug with genotypic and phenotypic characterization of mutants is performed, and then the testing of the significance of those mutations, there would be a site-directed mutagenesis.

For companies that have been well involved in

this, this is old hat. For companies that are thinking about getting into this area, this may not be so old. But I think it is important, and again, in the era of non-monotherapy, the in vitro data and trying to characterize mutations and what they do in vitro, and potentially, as we talked about in some animal studies, but certainly in vitro, it is going to be important because the clinical data will be increasingly complex.

The second minimum characteristic is to test the drug against a panel of well-characterized isolates. We talked about this a lot. What we haven't really wrestled with is what the size of that panel should be. I threw out a number, I think somewhere between 50 and 100 isolates is what we should think about, laboratory and clinical strains, and certainly if you are looking at an agent against drug resistant mutants, you are looking at a panel closer to 100 or more.

I think in the open public hearing, the data on tipranavir is sort of an illustration of sort of what a panel of 100 or 100 isolates can tell you of highly resistant isolates against a new drug.

[Slide.]

On the clinical side, minimally, one needs to characterize the escape mutants on therapy, and the group lacked a lot of consensus on this, it is the issue that

resistance is not the sole reason for drug failure, and to make sure that the confounders of failure are taken into account when looking at the escape mutants on therapy.

So, PK substudies and adherent substudies within larger trials are important to try to pin down what is the cause of the failure, and it may not be just one issue. It may be more than one issue.

The other issue, at the minimum, is depending upon the prevalence of drug resistance in the population, and this drives to Susan Little's presentation. You may need baseline characterization of the population that you are studying even if you are not particularly going after a drug resistant population as an indication, if you are testing that drug in New York, San Diego, San Francisco, et cetera, you may in the next few years need to really at least sample that population to know what you are doing.

Retrospective resistant studies, I think are still acceptable, but obviously, our notions are changing, and there will be an increasing emphasis on pressure to look at prospectively designed studies that bring in resistance testing even in drug development that it not going after a specific indication for an experienced population, because even in naive populations, this will have, in areas where there is a lot of drug penetration, will have an impact on response.

[Slide.]

At the next level, not the minimalistic level, but the next level, for drugs with potential activity versus drug resistant virus and for which a primary indication for treatment of patients with resistant virus is sought, characterization of those patient up-front, genotypically and/or phenotypically, is important, and then to test for activity in combination regimens.

This slide was made at lunchtime, before the afternoon discussion, so this was already covered. This is a question mark because no one really has the answers for what the right comparator regimens are. You can just do your best.

I think you do need comparator regimens, and you need to try to control for as many factors as you can virologically and otherwise and regimenwise to try to come up with what those treatment responses are in those patient populations.

Again, the confounding issues need to be taken into account. One needs to think about not just up-front, randomizations based on drug resistance, but also strategic trials, i.e., looking at patients who fail on regimen A, and then using a new drug and a new combination to rescue those patients strategically. So, that is the use of resistance testing in the midst of a trial in more of a strategic

fashion.

Then, the RCG analysis has brought up with us the issue of uniformity of analyses, and this is not for me to really state one way or another, but I think the committee over time is helped by sort of looking at data that is analyzed perhaps primarily in one way, but more uniformly in another way, and it was very helpful to see the RCG analysis, and I imagine discussions will go on with the agency and sponsors about how to sort of put forward their clinical resistance information and drug activity information in the packages that are submitted in much the same way that endpoint issues were discussed when RNA became the primary endpoint, both for accelerated approval and for most traditional approvals.

So, I think this needs to be discussed more at the agency sponsor level, but the committee looks at this with interest.

[Slide.]

There are a number of secondary gains from this meeting, which I hope, in fact, will occur. The first and most important is despite what happened at the beginning of this week, I would hope that there is strong encouragement for the further drug development and treatment-experienced patients, and the presence of drug resistance testing and its prevalence in trials and in clinical practice is going

to drive this, and I hope this meeting helps that.

We can hopefully facilitate more collaborations among industry, academia, and government. It is the only way we are going to develop the data. We need the drugs, we need the assays, we need the clinical trial design, we need the patient populations that bring all these groups together.

The RCG effort, I think was a beautiful example of the way these three groups came together to analyze their data in a record-setting time frame.

We talked about standardizations, and we need to move toward that. We are recognizing the issues that are involved in that. It is not antibacterial therapy. I think that helps us strongly to say what might be a reasonable Holy Grail to go after, but we are far from that, but we can standardize in certain areas as far as panels of isolates, the assays that are used, validation criteria, et cetera.

Obviously, through all this, we are going to get smarter, and most importantly, this is going to increase the pressure to improve access to resistance testing for populations in this country and elsewhere, a very important side effect.

[Slide.]

I thought the way to end really was to talk about -- you know, we talked a lot about what we don't know and

what we need to know, so I thought it was important actually to try to organize or at least put some thoughts forward about where current research and future research should be going in the resistance field, which directly drive to drug development, as well, although not specifically or uniquely.

There are four areas to consider. One is the epidemiologic. I think it is clear from the presentation this morning that we need increasing data and ongoing studies about the prevalence and transmission of resistant virus. There are some, but we need better studies about the cost-benefit of resistance testing to prove to third-party payers that if you stop wasting drugs or expose patients to toxic drugs that they won't succeed with, that, in fact, resistance testing can be cost effective.

[Slide.]

The long list of current and future areas of research is on the clinical research side, and we saw some of the prospective studies that are currently going on. We need to really think about whether it is phenotypic testing, genotypic testing, or both, the most expensive option, and it won't be this, but whether it be one or the other, or virtual phenotype, so called, or whatever, we will know in the course of the next year, year and a half.

The role of resistant testing in primary and established infection and, really, how widespread that

should be in our population needs to be determined, and how it improves outcome.

The further definition of the role of testing and treatment failure. I mean I think there is still debate despite what recommendations may be forthcoming about whether a physician's best guess and treatment history and RNA trajectories may be just as valuable as an expensive resistance test.

We have talked about assessing relative contributions of resistance, adherence, and the pharmacokinetics to treatment failure. The best thing about the attack on resistance is to prevent it in the first place, and this means good drugs, good regimens, intelligent treatment choices, which we don't talk about too much, we assume this probably too often.

We talked about this, and this is very important - the long term benefit of resistance testing. Those are data we did not see in the last two days, and hopefully we will see over the next couple of years.

We also talked about the fact that we don't know what the relationship of an IC50 or an IC90 or 95 is to the in vivo activity of the drugs, and one clearinghouse we do need is the knowledge base of achievable drug levels and the determination of whether peak trough, area under the curve, or whatever, is the best measurement, the pharmacologic

correlate of response.

This is going to be helpful particularly if we get into therapeutic drug level monitoring.

It has been brought up a couple of times that individual drug susceptibility may not be as helpful as looking at a regimen score of susceptibility at least in clinical trial assessments of success. That is a little bit more difficult on an individual patient basis.

[Slide.]

The pathogenetic side we didn't talk about too much, but this is going to drive the rest of the field. The dynamics and the relative fitness of viral subpopulations in relation to strategic treatment interruptions and drug recycling will help us, I think, in knowing what to do in salvage therapy, and will also help us in trying to think about interesting trials with new agents for salvage.

Rich D'Aquila touched on this, the importance of resistance mutation interactions. We have a number of them. Some have been tried to be exploited in therapeutic interventions, but we really haven't exploited this to the full degree that we can.

There is a very important issue about the evolution in latent reservoirs and compartments. The compartment issue was talked about. We know that there is virus in latent reservoirs. Some individuals have evolution

in their envelope. To date, there has been very little evidence of evolution in RT and protease, but the numbers of overall patients that have been studied is relatively small, and if you are evolving an envelope, it is I think only a matter of time before there is evolution in RT and protease even in these very low level infected reservoirs.

The cellular mechanisms of resistant and particularly the most recently described MRP4 with PMEA and some of the nucleosides is important.

The role of protease cleavage site mutations, Doug Mayers brought up, and we have talked about natural polymorphisms and what is a polymorphism and what is a drug resistance mutation, and that debate has been going on for a couple of years, but I think one of the key issues now are these low level changes in susceptibility in recently infected individuals, again Susan Little's data, and really what that means clinically is a 4-fold change or a 6-fold change or an 8-fold change, and susceptibility to an NNRTI in a naive population important, and we honestly don't know the answer to that, and these are recently accrued data that we need to investigate through treatment response studies.

[Slide.1

Lastly, there are technical issues, and we talked about this, I think on the first day.

We need improved detection of mixtures because of

the fear that a low level mixture, a low level subpopulation will arise quickly when we start a new regimen. The amplification issues I think are going to take care of themselves. I think we will see technical improvements that will be very consistent at 1,000, increasingly consistent at 500, and potentially down to full levels of detection.

The different subtype issues has been raised with certain types of assays, for example, the chip technology has not performed particularly well with subtype issues, so this always has to be looked at, particularly as subtypes circulate around the world and as drug hopefully circulate around the world.

Then, the data analysis interpretation both at the clinical trial level, cohort study level, and individual patient level is a huge issue in really handling these data, not only in a physician's office, but in a clinical trial's operation, as well, and for the agency.

Some of the issues that are going on with relational database development are going to be very helpful there. Again, we talked about we are only as good as the assays. The information that is produced is only as good as the assays that produced them, so the quality assurance issues need to be tackled, and this can be done in a number of ways - through external groups, through quality assurance programs like the BQA program that was mentioned through

DAIDS, and others, but that needs to be also brought to play.

So, that is sort of the future, and I think a lot of this relates to drug development, so these issues of research are relevant.

On that note, those are my recap comments. I would like to actually give the committee a chance to add anything they would like to since I didn't have a chance to vet this with my colleagues except that I think they knew by inference that I was going to make this mercifully brief.

Dr. Jolson, is there anything else that the committee needs to tackle?

DR. JOLSON: Well, I certainly wouldn't dare ask you any more questions. In fact, the committee has just been incredibly diligent to work through all these questions, and when we started off the meeting, we called it a workshop, and hopefully, you understand why the emphasis was on the work, not on the shopping part of it.

I just really want to one more time thank everybody for their thoughtful input. I want to thank the speakers on both days who just did a wonderful job providing really important background information for the committee's deliberation.

Yesterday, I acknowledged the RCG, but I would also like to reiterate our commitment to an effort like

that, that brings together industry and academia with the government and other interested groups.

I want to acknowledge everybody on our side who just did a tremendous job putting this workshop together. We really do see it as a milestone, as you were mentioning, that it really is a very public statement for us that we are seriously concerned about the issue of development of resistance to current and future antivirals, and we do want to see the field move forward, so we can provide better information and product labeling.

We saw these two days as an initial step towards those goals. So, I just again want to thank everybody for their hard work and their contribution towards that effort.

And thank you for chairing a meeting that ended on time. That really met our goals.

DR. HAMMER: Thank you. I would just like to thank my committee members and guests, and thank you and also once again thanks to the audience participation and particularly to the speakers, who I think did a fabulous job in updating us on a state-of-the-art fashion.

With that, the meeting is adjourned. Thank you.

[Whereupon, at 3:15 p.m., the meeting was adjourned.]

- - -

CERTIFICATE

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

ALICE TOIGO

B

C

D

E

F

G

H

J

K

L

M

N

O

P

Q

R

S

U

V

W

X

Y

Z