phenotypic reporting.

At this time, most of the systems give fairly much the same results. A 184, you have got 3TC resistance. They all tell you that. I think the areas where there is a lot of debate is in those types of drugs I showed you in the far right-hand corner of the slide where they don't have much of a phenotype and the mutations that are associated with that low-level phenotype have not been well worked out. And so there is a lot of debate, for example, on whether something is D4T partially resistant or susceptible resistant.

But I think for most of the major drugs, there is a growing consistency across the reporting formats.

DR. McCURDY: That would seem to me to be one of the major potential barriers to switching from so-called class III to class II is how one deals with new changes as they come down the pike.

DR. BOYLE: Quite frankly, that is probably the easiest solved problem if there was a barrier. All it would take would be the desire of industry to get together and do it because the data is there.

DR. McCURDY: So?

DR. HOLLINGER: If there are no questions right now for Dr. Mayers, I think we will go on to Dr. Murray who is going to speak now.

CDER Perspective

DR. MURRAY: I am Jeff Murray from the Division of Antiviral Drug Products from CDER, Center for Drug Evaluation and Research.

[Slide.]

I am here today to kind of give you what the CDER perspective, or our division's perspective, is on the current strengths and weaknesses of resistance testing and why we are interested in this and, hopefully, to give you some assurances that it is not only the assay companies that develop, figure out what is important as far as genotype and phenotype but, really, a lot of the work goes on during the development of the drug.

[Slide.]

What we are not going to use resistance testing for is as a basis for approval. This is just to go over the division's current recommendations for approving antiretrovirals. We have accelerated and traditional. Accelerated is an earlier approval for drugs that show some meaningful therapeutic benefit over existing options or can treat patients who are intolerant or have failed existing options.

For accelerated approval, we base it on 24-week changes in HIV RNA. For traditional approval which, up until about two years ago was just based on clinical endpoints only, it can now be based on 48-week changes in

viral load or HIV RNA. Our preferred endpoint now is a proportion below the assay limit which is 400 or, now 50, or time to virologic failure above and assay limit.

As I said, resistance testing will not change primary study endpoints but we see it as important information on how to use the drug much as information on how to use a drug for renal impairment and that sort of information, how to characterize a drug.

[Slide.]

Our interest is that we think monitoring prevalence of resistance is crucial. Doug showed you that the prevalence of transmitted HIV that is resistant to current drug seems to be increasing. We think that it provides very useful clinical information in the label much as other drug-interaction information, other safety information and dosing information would.

We think that including the information in the label will not only help clinicians use a drug but would stimulate further research in defining clinical resistance and assay development. We are interested in it to provide a level playing field for drug sponsors so that a standard or kind of routine set of data describing how their drug affects viral mutations and susceptibility.

So we see the need for a level playing field and to aid in negotiation of fair and balanced promotional ads

which might use resistance data to promote their drug.

[Slide.]

For instance, a hypothetical example is a drug sponsor might say, "Use our drug, Drug X, first because there is less drug class cross-resistance after failure on Drug X compared to if you start with Drug W, or Y, or Z." Sometimes, this is just the supporting data. It might be just from a retrospective analysis of patients pooled from several studies and there might be less than 50 patients.

So we want to try to have a more uniform standard of resistance data submitted so we can figure out if these sorts of label claims and characterizations are valid or not.

[Slide.]

We are so interested in this that we are going to host and advisory committee meeting--it is more like a workshop--to cover the following issues in four sessions. We are going to dedicate some time to performance characteristics and limitations of the currently available both genotypic and phenotypic assays.

Session 2, we are going to evaluate the relationships between HIV resistance testing and treatment outcomes. So we will go over some of the same data that Doug Mayers just summarized. We are going to talk about practical considerations for the use of resistance testing

and clinical trials in drug development. In the fourth session, we are going to talk about potential roles of resistance testing in drug development.

The purpose of this meeting, really, is to get feedback on how much, what type of data would the committee think is necessary for us to fairly characterize resistance data in the label knowing that this can be pretty important for promotional claims.

[Slide.]

There are a lot of available assays commercially. This is not a comprehensive list but these are some of the assays, genotypic and phenotypic, that are being used in clinical trials and that physicians are also getting a hold of now using it as a research tool to make decisions on their patients.

There are probably more available genotypic assays. Some use PCR amplification and sequencing techniques and some use hybridization and there are pluses and minuses to either of those. There are probably less available phenotypic assays. The ones that are more commonly used would be the recombinant viral assays where, as Doug said, where the RT and the protease gene are inserted into a lab-type strain or a backbone, and then there is a cell-culture step.

[Slide.]

This is from the Hirsch paper that you should have received as background. Just some relative advantages of genotyping versus phenotyping is availability, quicker results, cheaper, technically less demanding and actual mutations may proceed phenotypic changes so you might get a jump on some important information.

For phenotyping, there are some advantages to that, so that is what we usually think about from the antimicrobial paradigm. It is a direct measure of susceptibility. It is clinically familiar. You have break points and it takes into account increases and decreases in susceptibility in combination therapy because some genotypic mutations--not all genotypic mutations are bad. Some of them actually can increase, perhaps, sensitivity to other drugs.

[Slide.]

Some relative limitations; this is just kind of the reverse may of the other slide. Genotyping is an indirect measure of susceptibility. Certain mutations may not always correlate with a change in phenotype. With thirteen drugs and lots of different mutations, sometimes expert opinion is required for interpretation, as we talked about.

Both assays could be very insensitive for minor species. And then I mentioned the effect of sensitizing

mutations. For phenotyping, its limitations would be restrictive availability, a longer processing time, technically a bit more demanding, clinically significant cutoffs not defined for all drugs and, again, insensitive for minor species.

[Slide.]

Our division thinks that probably the major limitations of the assays are not so much the clinical correlations but the analytical limitations. I think this was true with HIV RNA is that we were very anxious for the assays to get reviewed and approved by CBER so that we could know what the lower limit bounds, what the limit of quantification and the variability of the assay so that we could use it.

In fact, for HIV RNA, the clinical correlations that eventually supported a prognosis indication, we saw those clinical trials maybe a year or two before, so we felt pretty comfortable with the clinical correlation of the HIV RNA test even before it was approved for the indication of monitoring.

Likewise, where I think these genotypic and phenotypic assays which are probably several magnitudes of order more difficult analytically than just an HIV RNA test, we think that it is the analytical limitations that really need to be focused upon such as amplification sensitivity,

how high does the patient's viral load have to be to pick up new mutations, analysis sensitivity--what proportion of minor quasi-species can be detected. 20 to 25 percent is an estimate--reproducibility and quality control--is it reproducible between labs, between different people running the labs.

Also, interpretation of results is a problem. There are complex mutational patterns for phenotypes. we don't have break points for all the drugs. So that still is a limitation as well. Another limitation of the assays is that, at this point, they are a bit technically demanding and they is a turnaround time and cost associated with that.

[Slide.]

Other considerations; clonal versus population sequencing. Are resistant mutations all on the same genome? Clonal methods be much more technically demanding so this is something that maybe needs to be addressed. Studies would indicate that, for the most part, they are linked on the same genome. Are plasma samples good enough or should we also be looking in other viral reservoirs, lymph node, gut. Of course that wouldn't be feasible for clinical use.

And then other considerations are timing of when you get the sample because if you are off a drug, quite often, you will see reversion to wild type.

[Slide.]

Reproducibility; I think this is data from Schuurman et al. This was recently presented at a resistance conference in San Diego. There still is some problem with correct calls of genotype between labs. In five samples that were sent to 60 labs with results reported from 33, the labs were pretty good at making correct calls for 100 percent wild type with reverse transcriptase. They have a perfect record for that and, for protease, about 94 percent correct calls.

If they are 100 percent mutant samples, about two-thirds of the calls were correct. But if they were viral mixtures of 50 and 50 percent for RT and protease, the percentage of correct calls was less. So I think, clearly, there is room for improvement in lab-to-lab reproducibility for viral mixtures which is what we are very likely to see in the clinic.

But, again, this is a technical limitation.

[Slide.]

As Doug showed you, I think the evidence supporting clinical relevance is that there are two prospective studies. There is no completed prospective study for phenotyping but there are some ongoing. And there are several retrospective studies.

As far as the retrospective studies, some show predictive value of certain mutations at baseline and how a

patient will respond. Others show the more gross associations that show a relationship between the number of mutations and outcome and the number of sensitive drug classes available but not, perhaps, specific mutations and outcome were seen in the retrospective studies.

[Slide.]

So for the prosecutive studies, two of similar design. Again, the difference between viral-load response at 3 and 6 months for GART and VIRADAPT, respectively, was about a half a log. So it is very similar. For GART, it looked like each sensitive drug added about a 0.28 log reduction.

Criticisms have been the expert opinion in GART but, as that was not seen in VIRADAPT, it seems to allay concern related to that criticism. Shorter-term follow up for GART; that was three months. But VIRADAPT had a longer follow up so that helps. In the VIRADAPT study, there were more zidovudine mutations in the control arm which might have made a difference but that didn't seem to be a problem in GART.

So, as in drug approval, we do two studies because no study is perfect, but these studies are pretty much complementary and I think help to confirm the results. I might say a half a log difference in HIV RNA we do think is clinically significant. If this were a drug, it would

probably confer a clinical benefit in terms of decreasing morbidity

[Slide.]

As far as retrospective studies, I think Doug mentioned most of these, the Zolopa and Deeks study. What I might say is that not all of the retrospective studies necessarily showed the relationship of a specific mutation but with the number of mutations, perhaps, and treatment outcome. This is just because in these studies, it is 50 patients here and 50 patients there tested so they might have not had power for each individual's specific loci.

[Slide.]

Also, as Doug suggested, even before the prospective studies and the retrospective studies looking at baseline mutations and eventual treatment outcome, for zidovudine, in ACTG116 and 117, there was a definite correlation between the presence of zidovudine mutations and clinical outcome. Both the risk of disease progression and the risk of death was increased in patients who had both the 215 and a 41 mutation associated with zidovudine.

This also correlated with the phenotypic susceptibility; those who had 215 and 41 versus wild type had about a ten-fold decrease in the in vitro phenotypic susceptibility. So it really kind of pretty much hangs together for zidovudine.

Also, for the non-nucleoside reverse-transcriptase drugs which do lose their susceptibility sometimes after one--may times after one mutation. In the current nelvirapine immune package insert, resistance issues come up in the warning and the indication section based on data from 24 patients in phase I/II trials. It should be 100 percent of patients had a greater than 100-fold decrease in susceptibility at 8 weeks. This is when nelvirapine was being used as sometimes monotherapy or only dual therapy not the way it should be appropriately used.

All of these 24, with decrease in susceptibility of greater than 100-fold, had one or more characteristic mutations. The mutations are listed there, at 103, 181, 188, or 190. 80 percent of them were at 181. As it turns out, the 181 is in the RT binding site of the drug. So not only did this fit with the virologic outcome, it fits in how we know this drug is interacting with the enzyme. So it has near perfect biological plausibility.

[Slide.]

Other correlations between genotype and phenotype. Virco has a good, large database. I guess this was presented at the San Diego conference of 7,000 samples or, perhaps, more that show good correlations between genotype and phenotype for many drugs including 3TC for the 184 mutation and for multiple zidovudine mutations and for

several protease-inhibitor mutations, particularly for nelfinavir.

Other retrospective correlation between genotype by Harrigan et al., also presented at the same conference, showed strong correlations between genotype and phenotype for many antiretrovirals except for, in his study, 59 patients. Less for abacavir and D4T which had moderate correlations and lower correlations for ddI and ddC. I think Doug brought up the fact that there are certain drugs for which I think it will be harder to maybe correlate a genotype and its relationship to treatment outcome.

It is more a characteristic, I think, of the drug rather than the assay.

[Slide.]

There are a lot of experts and panels who get together frequently to decide how genotype correlates with treatment outcome, and to devise these panels to be used in clinical trials and for clinical use, mostly based on consensus opinions of the experts, as you saw a table similar to what I am talking about in the Hirsch article.

It is based on literature abstracts, data from industry and academia, like the IDSA consensus algorithm. The GART and the VIRADAPT used a similar algorithm. And then a resistance collaborative group which is a group made of academia and industry and government has also come up

with an algorithm for defining genotypic resistance.

These will be modified and are diligently worked on by a lot of different hard-working groups to define these relationships.

[Slide.]

As Doug mentioned, proposed clinical use of HIV resistance testing will be, of course, crucial to monitor the prevalence transmission of resistant virus. It will probably be used more and more in adult-naive patients, especially in high-risk areas or high-risk groups for resistance such that you might consider starting them on different regimen if they had got infected with a resistant virus.

The problem here is that wild type tends to outgrow resistant virus in the absence of drug pressure. For use in pregnancy, especially in naive patients in high-risk groups. Also in the treatment-experience patients to help protect vertical transmission. It is a little controversial at this point.

Probably the biggest use of these assays now, kind of by clinicians who are getting them, are after first virologic failure to help guide in the selection of second-line treatment and, in subsequent virologic failures, to try to put a new drug regimen together when you have failed several.

The problem is that we are kind of limited by the number of drugs we have on putting new drug regimens together because of cross-resistance. Again, if you are taking the sample when you are not on drug, you could come up with the wrong conclusions, perhaps.

[Slide.]

So I think our division's conclusions would be that knowledge of genotypic data appeared to affect treatment outcome in two randomized, controlled prospective trials. The effect in HIV RNA was of the magnitude that would potentially support a drug approval.

Retrospective studies also have shown associations between genotype or susceptibility in treatment outcome although some of the retrospective studies showed more gross associations. Zidovudine mutations have been shown to be prognostic for clinical progression.

[Slide.]

Clinicians desperately need guidance in selecting second-line regimens. However, I think the current limitations mostly in assay analytic sensitivity, specificity, reproducibility and lack of clinical correlations for some drugs prohibit recommendations for routine monitoring of individual patients for all drugs.

Another conclusion is monitoring prevalence and transmission of HIV resistance to HIV is crucial to the

whole field. Compared to HIV RNA testing, HIV RNA resistance testing is drug specific, much like therapeutic monitoring of drug concentrations. Mutational algorithms and breakpoints will need to be revised for each new drug that enters the market.

Really, an efficient use of resources would be for the antiretroviral drug sponsors to characterize both the clinical relevance of genotyping and phenotyping susceptibility in the context of drug development because you don't have mutations if you don't have the drugs.

Really, I think the best and most convincing data could come from the randomized, controlled clinical-trial setting. So if this could be folded into drug development, we could have information by the time the drug hits the market on how this could be used and what resistance testing means for that particular drug.

That's all of my comments for today.

DR. HOLLINGER: Any questions of Dr. Murray?

DR. McCURDY: I was a little bit concerned about the report of the variability between laboratories in detecting subpopulations and so forth. I was disturbed by a couple of things. One as the variability and the other was that approximately half of the laboratories that were involved in this did not reply or did not provide data.

I was wondering what kind of assurance does one

have that these tests are likely to be done well in the laboratory. Is this something that may be regulated or is regulated under CLIA or some other way to be sure that once the tests are approved, as class whatever, they are actually going to be done well?

DR. MURRAY: I don't know if I am the person to answer that question. I used that information from an abstract to just illustrate a point of where I saw the limitations. I thought technical and quality control were a big part.

There might be somebody else who could better answer that question. I know that certain assay sponsors have looked at CLIA certification and that sort of thing. As with any test, it is a very important thing to iron out. Probably most of our discomfort with using HIV RNA was not its relationship to clinical outcome which I think has the most impact for the decision you have to make today, but it was with the more technical aspects of the assay; can it really measure what it is saying it is measuring.

I think if those areas are controlled, the clinical use of the assay will fall in place as it is defined in clinical drug development and as it is defined in the clinical setting among the experts.

MR. WILSON: One the issue of CLIA control, I think you would have to refer to HCFA, generally who

controls the CLIA regulations. Typically, there is a reimbursement in CLIA control over tests which are approved or cleared by the Food and Drug Administration. You would have to talk to them specifically about how that applies.

The second point that I would like to bring up is that, as part of a premarket review process, be it a 510(k) or a PMA, we would typically ask for three or more sites to run the test and then have, for example, certain types of controls being run concurrently to make determinations as to how well the instructions for use are written, how well known positives can be recovered, et cetera.

The point I wanted to make is that whether it is voted as a class II or a class III, those types of evaluations would be embedded in either premarket approval process.

DR. BUCHHOLZ: I was about to say something although not what Len said. It seems to me that as we talk about a number of things that we have discussed this morning--we have hit clinical acumen, we have hit promotion and claims, education of physician, labeling content, adequacy of performing, testing, QC--that there is a blurring here of things that I think would be issues whether this is a class II or a class III.

I think it is very confusing for the panel to have the information that has been presented which, in fact,

blurs these distinctions and really gets us into an area that I don't think we are being asked to make an assessment about.

I think we are being asked is this a class II device or, in fact, should it be a class III device. But whether physicians can use it adequately or whether there is CLIA testing and compliance, it seems to me that should be an issue for these products, whatever classification it is.

So can I just ask you to help me understand and, perhaps, help some of the other panel members understand what our charge is here because it seems to me we are being presented with information that is far more than we need to make the assessment I thought we were being asked.

DR. HOLLINGER: I think you are right. To me, I understand we are being asked whether this should be reclassified since it would ordinarily be classified as a class III just because there is no predicate test available or anything, an equivalent test that they can compare it to. This will be classed as a class III and they are asking if it could be now classed into class II for a variety of reasons, primarily the one that premarket approval is not being required, although we have learned that they could ask for clinical trials also and make it as stringent in class II as it is in class III.

Is that correct?

DR. DAYTON: Yes; that is absolutely correct. We wanted you to see the science today so that you would have an idea for what is out there. If nothing were known about these, it would be a very different story. So we are asking you to realize that an awful lot is known out there and that we can make good judgments based on that.

As I said, it would be a very different story if there were no track record of clinical and scientific data.

DR. HOLLINGER: I am going to call on the committee here, but just to give you some idea of where we are going here in terms of this, in terms of your questions, and so on. We still have an open public hearing of which there are at least four people who have asked to speak, mostly from companies involved with these products.

So we are going to do that, but I want you to sort of understand this because we will probably take a break right after this here for about fifteen minutes and then return for the open public hearing.

DR. NELSON: One of the things that confuses me a little bit is the fact that this isn't actually--if you look at it technically, it isn't one test. What we are looking at is that there are dozens of different genotypes, some of which the association with an outcome or clinical application is clear and has been well--and there are others where it is very fuzzy in which the data are not clear.

So it is a little different. Maybe that is why it is a device. I don't know. But it is different than the question we are often asked.

DR. HOLLINGER: I think that is why they have called these HIV mutations test which is going to be the name, I suppose, of what you are doing.

DR. DAYTON: Or something like that. But, in general, most of these sequencing assays, in particular, will look across and entire region and give you a sequence. So, in a way, they are all looking at the same thing, basically. But then, for each of the individual codons, then there is a distribution of knowledge.

DR. NELSON: But I mean for some tests where the meaning of a result isn't clear, let's say a codon is identified and, with regard to this drug, you don't know what it means. The FDA would not allow that--or there would be a different report or a different standard.

DR. DAYTON: You would have a claim-specific issue.

DR. NELSON: Right.

DR. BOYLE: I am confused, and I am confused because I took away from this excellent presentation three points that don't seem to quite add up to me. I would like to find out which of these I am wrong on. It looks like that what is being presented is that the data on drug

resistance is critical to the optimal management of HIV. The data that is presented seems to be very clear on that point.

Secondly, genotyping and phenotyping analysis from HIV drug assays can provide that kind of information for optimal management. Of course, the converse side is if it is done wrong, then it is worse than random. Basically, the information is critical.

The third piece, though, seems to be moving this type of thing that is life-sustaining from class III to class II classification, in looking at these comparisons, the main difference is that clinical data is not always required in class II but in class III, you have to have clinical trials.

Having convinced me how important this is and how the tests have to be done right or you basically are in serious trouble, why are we proposing not requiring clinical trials for a particular test or test kit?

DR. DAYTON: First of all, we don't know that wrong results are better than random. It may actually not be the case. It may be equal to random. And then our essential approach here is is there enough information in the literature to say that these things are useful. Actually, we see two studies, the GART and VIRADAPT, are saying, actually, in practice they are useful.

And we have seen, particular for AZT, evidence where individual mutations are quite well validated. So we have to come back to that point. I think those are the key points to keep coming back to.

You don't want to get off on the tangent of saying, "Well, this is all very complex science and it isn't all worked out." That is true, but it is not a barrier to getting something out there that is useful.

DR. BOYLE: Then is this the equivalent of approving a class rather than a drug?

DR. DAYTON: No; you are not approving anything. You are not approving anything. You are just classifying it. We are not here to approve any particular individual test. We are just categorizing at what level we regulate them.

MR. WILSON: Maybe I can help here. Number one, these products have not been approved or cleared by the FDA. In the regulations, there is a section that describes what is to placed in the package insert. In the package insert, there has to be adequate directions for use in detail. Now, I am going to assume that because these tests that are out there that are being used as home brew haven't had this level of scrutiny and that is why we have an FDA to evaluate these things.

So, oftentimes, we will review the package insert

procedures or interpretations, et cetera. This is not going to run clearly by technologists at a reasonable level of competence, et cetera. So a lot of times--all the time, to the level of the state of the art, these types of issues get cleared up. So I think what you are seeing is that we have a new test coming into being used, and this kind of happens routinely. It is not all organized and standardized as well as it could be two years from now, but the idea is in a premarket review, the labeling requirements for the 510(k) are the same as the labeling requirements for the PMA.

The other point I would like to make is that, as I had stated in my slides earlier, a special control could be additional labeling. And what I was hearing from the presentations is that there is some difficulty interpreting results.

The committee can take the position that if they elect to vote for a class II, that is special-labeling consideration should be made. Let me give you an example, but it is up to the committee. It may be a boxed warning that states that the interpretation of such results need to be carefully considered by physicians who are engaged in whatever, or it could be in a section called the limitations of the procedure. It doesn't have to be a boxed warning.

There could also be recommendation by the committee to have some pretesting of some of the labeling,

some of the instructions or some of the interpretations as part of the review process to better insure absorption by the physicians who would be using this test.

What would happen in that type of a situation, we would get a study-design proposal for the interpretation and it would be known correct answers, and how absorbable is this information. And the manufacturers then would modify the labeling to control that.

So this kind of thing can be controlled under class II classification.

MR. DUBIN: I think one of the problems is for those of us that have had a lot of experience with AIDS drugs, this is not a new picture because, really, from '93 on, this issue is coming up before other committees quite regularly. I think in the BPAC, we don't face this kind of issue very often where something needs to go to market in a rapid way that might directly impact care in the way we are facing.

I think, from our perspective, that is the core of the issue and it is the context with which we need to look at within. I think, John, you are right, we are looking at--and you said the same thing--we are looking at a body of tests. We have better handle on some, on some we don't.

I think, from our perspective, reclassifying this will put more flexibility in the clinicians' hands. As I

said earlier, our experience is that that is a necessary tool right now. Certainly, I can only speak for hemophilia, but I also chair California's--just finished as Chair of California's HIV AIDS working group. The resistance issues are coming right to the fore in every community and everybody is concerned, as they are about side effects. That is why I raised the issue of postmarket and our concerns there.

So I think this is critical and it is important to get this into clinician's hands. My concerns, and I think they can be addressed--I think some of them just were. I think we, as a committee, can set some labeling standards to educate physicians because I do think--Mary, you said something really important that is our experience, too. Some of our clients are with Dr. Gottlieb in Los Angeles or some very well-known--and then we have got clients in rural areas who are with hematologists, who are busting their butts to stay on top of this.

But it is difficult. It is not their area. I think the second thing you just said that is important is the review process of the labeling considerations. Let's say you all decide to start with a box insert. I would like to see, personally, some review written into that so if you all discovered that the doctors weren't really absorbing that, maybe you would go to another way of getting that

information across.

But I do think that is important. I do think this is evolutionary. And I do think it is important. I certainly support reclassifying this because of our experience. We discussed this at length within our medical team and a lot of our people who do a lot of Washington work. We think this has got to happen but we also think that it has got to happen the right way.

And that is why I raised my earlier concerns about postmarket and some difficulty because postmarket is a big job. In some areas, it seems to have been more difficult for FDA than others. Now, I don't have a lot of experience in devices. I admit that. I have heard, repeatedly, that is the strongest part of the agency, actually.

Regardless of my concerns, though, I think this is important to do and I think it is a little more complex than you were saying because I don't think it is so cut and dry because I do think we need to look at labeling considerations and ways to insure that the information needed to go with these tests to the clinicians because the top clinicians are going to know how to deal with it and they are going to understand the limitations and others aren't.

DR. DAYTON: If you remember the questions we proposed, whatever decision you make, you have an

opportunity now to suggest specific additional controls for labeling requirements.

MR. DUBIN: That is what I am talking about.

DR. DAYTON: And also when the draft guidance document is publicized, there will be an opportunity for public contribution to that. So there are at least two opportunities that we identify to do that.

MR. DUBIN: I think if we look at it in this kind of broader context, it is a little different than we normally do, it is not so confusing. And there is a way through this that I think the committee can make some good recommendations and, just to underline the one part, and build in certain reviews to insure that there is an ongoing review of certain aspects that we have concerns about.

DR. FITZPATRICK: The essence that I understand of what we are going to do is accelerate the time line--

MR. DUBIN: It is fast-track.

DR. FITZPATRICK: --that FDA is required to review these things and impose the same restrictions and structure that they would to bring it to market under a class III. And that doesn't appear to be a bad thing. And we have the opportunity of putting those restrictions now and that seems what we should be focusing on.

DR. BUCHHOLZ: I am a little concerned that there was an impression left in the asking and the response to an

earlier question about a class II device and a 510(k), that there was no clinical data required. I work for Fenwal Laboratories which makes blood-collection and processing equipment. We deal mostly with device applications.

I have sat here for a while trying to think of a 510(k) submission that we have submitted that we have had not had clinical data. I can't believe that we are that different from the typical device that CBER regulates. So I would like to ask somebody what is the percent of 510(k)s that have clinical data because I think it is very valid concern if the level of scrutiny here is significantly less between a 510(k) and a PMA.

But, at least in our experience, there is clinical data that is routinely required.

DR. HOLLINGER: Does anyone know that information or, Len, can you give maybe just a little bit of a hint?

MR. WILSON: I will do my best. I don't think that the statement is incorrect. I think what the question really is for the table here is what type of clinical data. For example, in this particular instance, we were looking, as Dr. Dayton described regarding known panels of samples, some retrospective testing, some repositories.

That would be, in a sense, clinical data as opposed to a full-blown prospective clinical trial. So what we were looking at here was trying to get some testing

validity with some real samples and some analytical testing. That is kind of where we were coming from, if that gets to the point.

DR. MITCHELL: I had a couple of clarifications. One is about the drug resistance assays so I would assume that that would apply to both the phenotypic as well as the genotypic tests; is that correct?

DR. DAYTON: Well, we are actually just bringing for the classification of the genotypic assays in this meeting. We are not bringing forward the classification of the phenotyping assays. Phenotyping assays can be used in direct clinical situations. That is what we are discussing right now. But there are also phenotyping assays that are done in vitro to validate the genotyping assays.

So, at the moment, we are only discussing the classification of the genotyping assays in direct clinical use and we are not addressing the classification of the phenotyping assays in direct clinical use.

DR. HOLLINGER: That was clear to me, either, Mark. I am glad you asked that.

DR. MITCHELL: The second question I had was about the minor typing. I guess I am very concerned about minor types because, obviously, once you treat the major type, it is going to be replaced and that is going to be the new major type. So I am very concerned about the sensitivity of

the tests and picking up minor types.

So I am assuming that one of the things we can do is ask for some level of minor type that a test would be able to pick up.

DR. DAYTON: Absolutely. It will probably be in the neighborhood of 25 to 30 percent of the overall species. Yes; the ability to pick up a minor type is a major concern. But, of an even larger concern is, even if you are only able to pick up major types, is that of clinical benefit. I think the answer is yes.

But we certainly are concerned about minor types and we will ask sponsors not only to claim or what is the lowest percentage of a species that they can detect, but also to titer through that so we know just how quickly assay performance deteriorates when you go below what they claim.

So we are concerned about that.

DR. MITCHELL: My next question, then, is do they even know--I mean, is it easy to characterize a percentage of a type. Do we know whether the major type is 60 percent or 95 percent.

DR. DAYTON: You can do that in research settings. So you could certainly do that on spiked samples. You can do that in panel type specimens where you can make multiple subclones and multiple sequences of each of those clones so that you can identify what the swarm is.

So, yes; you can do that in a research setting.

DR. McCURDY: I have a certain amount of objection to the implication that we might reclassify this to get it out faster. I think it ought to be gotten out right and, if it is a right to have it a class II with the appropriate kind of controls, and I am currently tending in that direction, then that is fine.

But I think the idea of getting it out faster by reclassifying it is not the right way to go.

DR. FITZPATRICK: I don't think it will necessarily mean, by reclassifying, that it would go out faster but it requires the FDA to review it faster.

DR. STRONCEK: I may come from a different view. I think this makes a lot of sense. I have worked with HLA, the field, and we do genotyping. When you are on the cutting edge, manufacturers don't make the kits. You make them in-house in laboratories.

I assume that Dr. Mayers' tests were developed by himself. He orders the primers. He orders all the reagents. So this field is going to progress. Now, he has published this data or he will. He is showing it is effective. So now we are in a situation where we have an effective test but we need lots of clinical trials to show that it works. And there are no commercially available tests to further the field.

So manufacturers can't sell these tests to make them widely available until they go through the FDA. So the field is in a situation where commercial tests are not available to have the field progress, yet there is data in the literature, peer-reviewed literature, that says it is effective.

So I think it makes perfect sense to go this as a class II based on the data in the literature but then, as you are proposing, to closely monitor the kits that go out to make sure--to try and do some premarket evaluation as best you can and then to try to monitor them afterwards.

This is going to be a very fast-moving field, too, so it is very important to have a structure where you can change things quickly. I think what you are proposing will do that.

MS. KNOWLES: I would support a change from class III to class II based on having strict controls, the standardized reporting form, close postmarketing monitoring, and then Dr. Murray's last comment about including some of the issues of testing in the pre-drug development.

DR. MACIK: I kind of look at it, too. Two reasons get you into class III; either it is a life-or-death-type experience or there is no predicate device. One of the things here is that it will help management, but the bottom line is that you are still going to be looking at

viral load and you are going to be looking at CD4 count.

So if this test told you something wrong, you know about it. At best, it gives a running leap at the right guess, but there is still a good follow up to know whether that test gave you the right answer and it is no worse than where you were before if you didn't use the test.

So, in my mind, it really is--clinically, it has a good backup. I think, from that standpoint, would make me want to put it into a class II type category.

DR. HOLLINGER: I think Dr. Gutman, who is the Division Director of the Clinical Lab Devices at CDRH wants to say--

DR. GUTMAN: I just want to clarify. I realize there are a lot of very complex issues on the table and I have absolutely nothing to do with the product line at all, so I am absolutely free to speak, although, obviously, the decision you make would be of interest to folks over in the devices area as well.

I just wanted to clarify that when we look at the scientific review process, which is quite complex and possibly multilayered here, that we feel quite comfortable, frankly, in carrying the exact same rigor of science between the PMA and the 510(k) program, that we have no difficulty at all if we think appropriate clinical information is necessary to characterize a product to have immensely

at

complex and intense reviews and requirements for manufacturers in the 510(k).

It sounds to me, as an outsider, that there are very complex clinical issues to be dealt with in the context of the guidance that would be developed to support this, the special controls to support this and that there, in fact, might be various approaches to different analytes within the context of that guidance.

Although I realize you might shy away from trying to provide administrative relief, it sounds to me, again, as an outsider, that what this division or this group is saying is that they do have a fair amount of scientific knowledge to draw from, that they do understand the questions of safety and effectiveness that they would like to apply to this product line and that they think they can do good scientific review on your behalf and the public's behalf in the context of the more flexible 510(k) program.

From my perspective, we have lots of experience doing this and we do everything we can as we move across administrative paths to preserve scientific thresholds. We have done this with--the closest that I think in our shop to this product, the scary product, was tumor markers and we downclassified a variety of tumor markers because we had such a rich literature and methodology and experience and statistical methodologies to draw from.

I think what we have done in that case is serve the public well because we have made it easier for us and for sponsors to bring out a wider array of tumor markers and to improve choice.

I realize there are a lot of complex issues but I just wanted to assure you that whatever decision you make, this group--I know and love this group. This group isn't going to sell the scientific product short.

DR. HOLLINGER: That is probably not a good example about tumor markers. I will tell you that they don't have a lot, sometimes, of clinical application and we do spend a lot of time with AFPs and CEAs and CA125s with high values that don't have much meaning at all. So I am not so sure that clinical application would not have been very useful there.

Just from my standpoint, I will say, so far, I sort of share initially what Mary brought up here. We have no data. There was one study here which is the GART study. We don't have the paper to look at. There are some major issues about its utilization.

I don't think there is any question that resistance does make a difference and does make a difference in terms of treatment. The question is whether the data is there to tell us if the tests are going to make a difference in the management of these patients over and above what we

have today which are CD4 count and HIV viral loads and so on.

While it may, and the data looks like that, there are some really difficult issues that have not been addressed. Certainly, the question is, in class III, at least you are required to do a PMA evaluation whereas we have to accept the fact that it may be asked for by the FDA but it is not a requirement.

So, right now, at least from my standpoint, I am looking more at this not to reclassify but I am going to be listening to what others have to say here plus the other material that is going to be presented in the open public hearing.

DR. BUCHHOLZ: I think one thing that the committee may not be aware of with a class III device--I mean, I think there is general agreement that it takes much longer for regulatory review and approval of a PMA-type device or a class III device. That is a double-edged sword because I think the regs read something that you are required to file a submission, be it a 510(k) or a PMA, if you have a significant change in an existing product, a significant change that impacts safety or efficacy.

I know from personal experience that Fenwal has had some situations where we find a problem in the product that is marketed and we say, "Oh; well, we want to fix

that." We are perfectly willing to implement that change. I think any reasonable reviewing group would say, "Yeah; it makes sense to fix that. That is an unforeseen problem."

Yet, with the PMA situation, we may go through a year or more of putting the file together which takes longer than a 510(k) and also getting that regulatory review and blessing to make that change when it is a change that improves the product, that enhances safety, that enhances efficacy.

So that is a double-edged sword in terms of the PMA process in that it can significantly lengthen the period of time simply by virtue of the more complex review that it takes to implement good things in an existing product.

DR. HOLLINGER: Can I have one more response from Dr. Chamberland and then I think we are going to take a break. I think people need a break for a minute. And then we will come back. So, Dr. Chamberland?

DR. CHAMBERLAND: I guess I have just been trying to put together everything that I have heard presented formally and then the discussion so far among the committee. At least, I hope I have this right. If I don't, somebody correct me. But what I have heard is that FDA is asking us to--they feel that downclassifying these types of tests from a III to a II is okay for two reasons. One is that there is a body of performance data out there about these assays. It

tells you about how good sensitive-specific reproducibility--the data may not have been derived in the traditional clinical-trial approach, but they feel that there is adequate data out there to address it.

The first conclusion, though, on Dr. Murray's slide said that the knowledge of this genotypic data--and this is the second reason that FDA gave us, at least what I heard, why they felt this downregulation or downclassifying was indicated was that there was a benefit "to public health," that clinicians need this kind of information.

The first conclusion, in Dr. Murray's talk, that knowledge of genotypic data appeared to affect treatment outcome in two randomized prospective studies. I think, for me, that is--my gestalt tells me that that is probably true. But I don't think we, at the committee, have the amount of detailed information to have a sense that data from these two trials is readily generalizable to the larger field of practicing clinicians.

I think that your ability to generalize really depends on how these patients and physicians were selected for both of these prospective trials and, secondly, the kind of information that was presented to the clinicians, how these genotypic test-results data were presented.

In looking at the Lancet article, it seems like the physicians got information about--and this was the

VIRADAPT trial--they got information about what the mutations and the codons were which, for most clinicians doesn't mean, necessarily, a whole lot. You know, V75T. But they also gave the clinicians information on the drug, then, that they would not suggest you choose, that there was some interpretation to these data.

So I think the question is still out there a bit on the utility, the usefulness, the public-health benefit of these tests. I think it really rests on how the information is presented to clinicians in a way that they can use on a day-to-day basis that is interpretable.

So I have some reservations about the statement that we have two prospective studies which appear to demonstrate that knowledge of genotype impacts significantly on clinical coursing in the patient because I think there are only two, the selection of the physicians to participate in the trial is not clearly outlined, and then I think it made a big difference on how the data on genotypic results were presented.

DR. HOLLINGER: We are going to take a break and then we will come back to other discussions later on.

[Break.]

DR. HOLLINGER: We have four speakers in the open public hearing who--four companies have asked to speak and their representatives. The first one is from Visible

Genetics. That is going to be Dr. Curtis Scribner.

Open Public Hearing

DR. SCRIBNER: My name is Curt Scribner. I am here presenting on behalf of Visible Genetics. They were rained out because the planes weren't flying from Toronto last night so I am here to present their information.

[Slide.]

Visible Genetics is developing a true-gene HIV I procedure which comes as a complete kit. The first few sections up here are all done using standard laboratory-based criteria. Then there is a bidirectional sequencing of the material presented her, separation by electrophoresis, analysis by our gene objects, a computer system with, then, the report that comes in.

[Slide.]

The report comes out initially looking like this. Unfortunately, this is the fax because this got taken care of by Floyd as well, but we see that we have resistance with the protease inhibitors, the non-nucs and the nucs, with a further report here with these two pages of exactly what kind of information we have seen and the scientific basis, the literature basis, upon which we have made these decisions.

These decision-tree recommendations--not determinations, but recommendations--of those drugs which

may not be useful are based on a scientific committee which meets on a regular basis to evaluate all scientific data and put them together.

[Slide.]

However, for Dr. Chamberland, of course, we always put this together which shows definitively the types of mutations or changes that are demonstrated in our process.

[Slide.]

Performance of any kind of a kit is vitally important. These are the types of studies which are already ongoing which you are going to be looking at. We have taken collection of plasma from nine people with viral loads from anywhere from 1300 to 300,000 which have now been aliquoted in a blinded fashion and will be separated and sent to multiple sites for validation looking at site-to-site, day-to-day, technician-to-technician to make sure that the sensitivity, specificity and reliability of the test are adequate and important.

We have a multicenter study already going for reprodicibility and accuracy and we are concurrently working on the freeze-thaw studies using multiple viral-load samples to make sure that we understand the differences or the problems with freeze-thaw, a difficult problem, as we have already known from the viral-load PCR testing.

[Slide.]

Interfering substances, of course, are important. These are the types of things we are already looking at, other pathogens, including viruses, biochemicals, including drugs, and with the antiretrovirals. We are looking at mixtures to address the question of what is the sensitivity looking at a mixture of wild type versus resistant, and we are using various ratios working from 100 percent wild type down to 100 percent mutant.

We are as concerned as you are with the NVA II study. Since there are sixty sites around the country, apparently, which are doing this, we believe that is vitally important that this information be readily available and published for people to examine.

We are doing plasma-extraction studies as would be necessary depending on the type of plasma that would be needed and anticoagulants. Everyone has understand the limitations of heparin. There are multiple other anticoagulants which are also available, each of which will be determined.

[Slide.]

Our clinical trial is base on search. It is a twelve-month, prosecutive controlled study. It is ongoing using 300 randomized subjects. The randomization in this case will be to those people who will have the genotyping provided and those who will not.

We have almost completed enrollment into the trial. The basic difficulty is that, as you all realized, this type of testing is already readily available in the United States at the present time through the home brews through several large clinics, through several large laboratories.

All of the subjects have had pre-treatment and are failing. The primary endpoint is fixed at 24 weeks and we will examine the change in viral load from baseline and then carry it on out to one year.

[Slide.]

At the same time, we are looking at the studies, both GART and VIRADAPT, which you have heard today, with the reanalysis of all of their samples looking at the ability of our device to find the same types of mutations or changes in the clinical trials so that these data could be used by reference in our application.

[Slide.]

Also part of the PMA submission--I say PMA submission with the understanding that it is our assumption it might take as along as 18 to 24 months in order to get these types of final rules finally completed. We will have more than 400 assays performed at greater than eight sites looking at the device characteristics including reproducibility.

Clinical utility will have at least 400 assays looking at the various samples that we have already talked about before, done at two to three sites to make sure that we can have good reproducibility.

I also have three comments that I would like to add based on what we have seen before. We have not, of course, seen the guidance document that has been presented to you in incomplete draft form but we have serious concerns about the use of genotyping with clinical validation if the IC50 or IC90 in an in vitro process is greater than eight-fold.

It is very difficult to find these patients. We would very much welcome suggestions on the appropriate clinical methodology to treat these, to find these, patients and to have appropriate reproducibility for those studies.

We also would like to point out that it is very difficult to do studies right now with a randomized process. With the availability through the large clinical laboratories of unpublished genotyping testing, it is difficult for a person in a clinical setting to decide whether or not they will use genotyping since it is readily available commercially.

We find that it would probably be almost impossible to do clinical studies after approval based on the fact of having an approved or cleared test already in

place. That is a subject you might want to keep in mind.

Finally, we want to note that the Visible Genetics Organization is in the process of enrolling a clinical study to address the issues that we had talked about before of reproducibility across populations as well as reproducibility of looking for new genotype changes by enrolling up to 30,000 people over a long period of time such that this would form the basis for evaluation of new genotypes that would be reported.

Thank you very much.

DR. HOLLINGER: Thank you. We appreciate it.

Just so the speakers will know, I am going to limit you to seven minutes. Just so you will know that ahead of time so you can get to the critical issues.

The next one is from Innogenetics, Michael Ussery.

MR. USSERY: Thank you. We appreciate the ability to speak to you today. Since we are not actually talking about approval of our specific test, I am not going to go into great detail. I have provided copies of the few slides that I have brought with me and there are a number of papers in the open literature about the performance of our test.

[Slide.]

The line-probe assays, as were mentioned before, are quite different from the sequencing-based assays. There

is an amplification step and then there is a reverse hybridization with lines on a nitrocellulose strip. Where we are looking, on each strip, there is a mutant and a wild type oligonucleotide that will provide a line for either mutant or wild type or, in the case of mixtures, for mixtures.

There are some advantages and disadvantages to this kind of approach. It is rapid. It is very cheap, relatively, and it is very good at picking up mixtures. We have clinical data that shows an ability to pick up 5 percent mixtures, readily.

Sensitivity; the studies that we have so far, routinely, we can detect 500 copies per ml and we have, down below that, at even 50 copies per ml, we can detect about half of the samples and give you a readout. But, anyway, that data would be provided in either our PMA or our 510(k).

I wanted to comment on just a few of the issues that were raised from an industry standpoint. Dr. Murray mentioned that a lot of the data on the clinical relevance of specific codons is not going to come from the diagnostic companies. We provide our tests to the pharmaceutical companies in their clinical trials and we would, of course, agree with the FDA that this clinical utility of a particular codon has to be established, but most of that data will come from the pharmaceutical companies in the

course of approving a drug.

They are asking for quite a bit of this information and I think we would fill in the holes and the gaps where they were necessary.

One of the things that I did want to mention. This is our reverse-transcriptase strip. There is another strip on the next slide for the protease mutations.

[Slide.]

The other thing I wanted to mention was a little bit of the real-world situation in terms of trying to plan well-designed prospective trials. We have, at least from experience recently with a well-designed, randomized prospective trial, similar, in some ways, to the GART and VIRADAPT, with our test that the IRB at Johns Hopkins said was really no longer ethical because of the results of those two trials.

There are certainly other kinds of clinical-utility data that we can gain and I think that what we hope to gather from this process would be a better definition from the FDA of what studies we really need to do.

But the concern there was that, even though these tests that are home brew are not being reimbursed, if we are actually going to do the test in two different arms of patients, then, at this point, they feel that the relevance of the testing information is so important that we have to

let the doctors know. We can have a group of doctors that would not know the outcome of our test even though it is, as of yet, unapproved.

So that makes some kind of randomized prospective trials difficult. There are other kinds of performance clinical trials that certainly need to be done and we hope to work with the FDA as I am sure all the other sponsors do in defining what exact trials would be acceptable and we are supportive of this proposed change.

[Slide.]

I just wanted to mention a few pieces of information that apply to all the resistance tests that the different manufacturers are talking about, not just ours. There was data that was mentioned by Doug on the GART trial. I think this just really goes to the issues of risk/benefit, of allowing these kinds of tests on the market a little sooner.

If you looked in that study, the patients that did not-their management was not based on GART, they refused fewer drugs that were active against the strain of HIV that they were infected with. So, as a corollary to this, they were exposed to toxicities of a higher number of drugs which were inactive against their virus strains and, thus, had little or no clinical benefit to add to their management.

The fact that these patients were treated often

with only two active antiretroviral drugs and, in 10 percent of the patients, only one because they didn't have the genotypic data, makes these patients even more likely to rapidly develop resistance to those few remaining drugs that they were susceptible to.

I think that that is an important thing to keep in mind. One of the observations was made that the genotypic data will not be looked at by clinicians alone. There will be CD4 and viral load data and that can serve as a check in case there are some wrong calls made in genotyping.

[Slide.]

Finally, I just wanted to mention a study that was reported at the San Diego workshop looking at the VIRADAPT study from a pharmacoeconomic analysis. It was interesting that even in these short studies that there still was a significant trend towards a reduction in the cost of antiretroviral drugs in the genotyping arm and that the cost of genotyping--in this case, it was by sequencing which is, maybe, somewhat more expensive than our test, but, anyway, that cost was offset by the savings in antiretroviral drug costs. I think that is also important for the management of our patients.

I think that is all I have today.

DR. HOLLINGER: Thank you.

The next speaker is Tony Lam from Applied

Biosystems.

MR. LAM: My name is Tony Lam from Applied Biosystems and PE Biosystems.

[Slide.]

Before I start, I want to point out one thing, that the PMA also has the requirement of manufacturer information submitted and also a preapproval for quality system inspection. So these are additional to just the time line that you have to submit the 510(k) which is going to be a lot slower and a lot of time to get ready.

[Slide.]

This is our product. Our product is basically a genotype system with sequencing-based HIV genotyping and utilizing PCR sequencing and software technology. It is an RNA assay to give you nucleotide sequences of DRT and the protease gene in the HIV of the patient. The genotype is, actually, compared to a known HIV antiviral drug resistance mutation on a public database.

Two reasons that the downclassification is that the background is that the HIV drug resistance has been identified with treatment already, failure already, and the patients and all the other parties are actually using it regardless of approval. But in the absence of a cleared product, cleared HIV product, will make sure that the inconsistency is still going to be there and the delay would

also create a public-health risk of substandard testing.

[Slide.]

So the technology is very commonplace now and the main thing is the intended use should be falling under the purview of the Food, Drug and Cosmetic Act but not the Public Health Service Act. The reason is that this is to provide guidance to physicians not used as a blood-banking diagnostic as a primary test.

[Slide.]

To compare class II to class III, will require flexibility from the regulatory agency. And, as I mentioned before, class III also needs manufacturing data and, also, a preapproval inspection plus all the other 180-days and all that long kind of review.

The class II is a lot more flexible as a lot of people have already mentioned. It will give you a lot of flexibility and have fast approval process and it is easier to update for improvements and changes.

[Slide.]

We have an any for this. CBER has already accepted a concept of a similar HLA device. I put them next to each other. The first point is it could be validated by an outside academic consensus group similar to the HIV which has already a public database compendia and independent peer review.

And then the new information will be incorporated in diagnostic labeling claims without any more submissions. This should be the same, that the database is continually updated with new resistance, mutation resistance.

[Slide.]

We should focus on analytical performance because 510(k) or PMA, at this point, is lacking a standard and what should be done and how should it perform. The 510(k) proof of performance should use some panels, but not very many, for mutation and then it will be the same for the new mutations. It should not require a lot of data and isolets.

The benefit will be that it will avoid delay in the process in clinical access for this kind of information and also to avoid expensive large-scale clinical studies which are not necessary.

[Slide.]

Also evidence of analytical performance is there is an ongoing database which will enable the incorporation of new resistance data. This will be continuously updated and improved by the independent peer review and not based only on the submission of on PMA from one manufacturer, limited resources.

[Slide.]

Again, more analytical performance. And, if it is available in a fast, short time frame and it could be used

by the pharmaceutical companies for their antiviral drug develop. And it reduces inherent available and unknown performance of home brew.

[Slide.]

Another important point is to adopt a standard or guideline. Right now, the HIV Resistance Collaborative Group has already drafted a proposal which provides clear, and a key word is, technology consensus because that is what we don't have at this point. So we have an analytical performance to validate the assays for the 510(k).

This is consistent with the FDAMA Congressional mandate that the FDA should favor consensus guidelines. Together with the use of this public database and the guidelines will protect public health.

[Slide.]

If we don't downclassify, it will result in delayed use of the clear products and then encourage home brew, create a public misconception that FDA is raising high hurdles for approving products and delay patient access to more effective existing and new antiviral therapies.

[Slide.]

In summary, it is low technology risk because it becomes commonplace and the intended use is not a stand-alone but guidance and not diagnostic. We require flexibility from regular agencies to serve public health,

interests. We should focus on analytical performance and then make use of the public database compendium and adopt or create a consensus guideline by the FDA so we could use it for clinical validation as basis for a 510(k) clearance.

[Slide.]

So this, basically, will end up as a Tier III which is identical to the technical and scientific requirement of the PMA and the FDA could still exercise appropriate oversight.

Thank you.

DR. HOLLINGER: Thank you.

The last speaker is Brendan Larder from Virco.

MR. LARDER: Thank you for the opportunity to speak here. Virco is not actually a kit manufacturer. We are a service-based company and we provide both phenotyping and genotyping in the U.S. and the rest of the world.

[Slide.]

The reason I am here is really to make a few comments about interpretation which, I think, is quite appropriate, or interpreting genotypes, is quite appropriate considering some of the discussion earlier this morning.

[Slide.]

By way of background, and this has, obviously, been touched on quite a lot this morning, that phenotypic testing is complex and it requires specialized central labs,

specialized equipment and well-trained scientists. I don't think anybody really thinks that phenotypic testing is ever going to become a kit-based assay. I think it would be very difficult for this to happen.

As such, this is now regulated in the U.S. under CLIA, the CAP and New York State's regulations which we adhere to. That actually puts a lot of the validation and regulatory processes in place in the actual lab and is quite exacting and demanding.

Obviously, genotyping assays, as we have heard, are more amenable to kit-based formats although, again, they are being used by centralized labs, so-called home brew. But these also are regulated and can be regulated by CLIA. I would just like to point out that the Rob Sherman study, those 30 labs, most of those labs were academic labs that weren't carrying out genotyping under CLIA regulated conditions.

But the real crux, I think, is relating complex genotypes to phenotypic resistance. This is really quite difficult. Doug Mayers touched on this as did Jeff Murray. Really, to interpret genotypes in a sensible and informative way, these large phenotype-genotype databases really should come into their own in facilitating interpretation and enhance the value of the genotypic testing.

[Slide.]

Just as a quick overview, these are the assay principles of the assays that we carry out at Virco and by LabCor for providing the testing in the States. ABI-based sequencing, computer analysis an interpretation, which I will touch on a bit later to give the Virco genotyping report. And then recombinant virus assay for phenotyping where a PCR fragment is recombined into homologous virus. The available virus is grown up, titered and tested against drugs. That is the antivirogram report.

[Slide.]

This is the antivirogram. You can see it can give a fairly simple and direct readout of phenotypic resistance. This shows the drugs tested, the panel of drugs tested, all in one test. This shows the assay range and sensitivity to each drug is where the blue dot is.

Just, in summary, you can see red for resistance, green for no-resistance, et cetera, so it is very easy to read off. These values are based on cutoffs of around about for intermediate resistance or resistance greater than four-fold or ten-fold.

[Slide.]

When we come to genotypes, and I think you have seen lots of mutations already today so I won't, obviously, dwell on this, but the list of mutations is enormous. This shows nucleosides, non-nucleosides, protease mutations.

This is not exhaustive. The problem is the more work we do, and the more samples that we analyzed, and we have analyzed thousands and thousands, the more mutations you come across. So interpretation become a real problem, particularly since they are not seen singularly but in complex mixtures.

[Slide.]

This is some data that we presented at the San Diego meeting a few months ago on samples from routine testing greater than 5,000 samples, just showing the percentage, for example, 215 mutation and 50 percent 184 mutation, non-nucleoside mutations, protease-inhibitor mutations. There is a lot of resistance out there and, as more people get tested, we find more mutations and more complex patterns of mutations.

[Slide.]

Other examples here are new mutations that we can find, again, using database-type analyses, again some work we presented. This was quite a surprise but when everybody says, "Yeah; we know what 3TC resistance is, it is the 184," well, actually, that is not the whole story.

We found here that, in the absence of the 184, there are quite a substantial number of samples from patients that show phenotypic resistance to 3TC. This is due to what we consider polymorphisms in a background of AZT mutations. Without having this consistent back reference

phenotype to genotype, we will never discover this sort of information.

If we just look at the genotype, we are really kept in the dark.

[Slide.]

Again, if just concentrate on individual mutations, and this is just an example for non-nucleosides, again we can make some probably wrong decisions. So, for example, a common non-nucleoside mutation, 198A, phenotypically, the virus is resistant to nelvirapine but susceptible to the other non-nucleosides.

You can see, as we get more complex mixtures of these mutations, sometimes you can see resistance to all three, sensitivity to one here or another here by phenotypic testing.

[Slide.]

One of the answers that we feel is really to direct comparisons with genotypic and phenotypic databases; our database at the moment--actually, this is a bit old--has more than 15,000 genotypes and over 30,000 phenotypes with all the drugs. What we do know is we don't depend on algorithms because I think algorithms, once you establish algorithms of what mutational patterns might mean in terms of phenotype, it is a static thing. You need something that takes into account that everything is changing all the time.

So this database continues to get updated with genotypes and phenotypes. Now, through the software that we developed, we can input a sequence. The software can recognize complex patterns of mutations and scan the genotypic database and find matching samples that match and then, with all the samples that match with the same patterns of mutations, pull out all the phenotypes and then condense that down into a relative risk, if you like, of a virtual phenotype and to say what percentage of these phenotypes were resistant, what were intermediate and what were sensitive in terms of this original sequence.

So what we have done is taken the sequence and turned it into a phenotype through this database matching.

[Slide.]

This is the kind of report that we soon will be launching as our version II report. It is fairly similar to the antivirogram but shows mutations. This is just genotyping information. It shows drugs. That interpretation, via distribution of matching phenotypes from the database, showing how many matches there are--some of these are about 8,000 and some are a few hundred--and then showing distribution so you can quickly read this off, easily read this off, saying, "Well, there is a large amount of resistance of red here so the virus is likely to be resistant to this drug via this pattern recognition of

matching the genotype with the phenotypes in the databases."

[Slide.]

The other thing I should say, and I think this is important for the committee to consider, that the phenotype/genotype interpretation, the interpretations on algorithms can be tested and they should be tested statistically.

This shows a little bit of data where we took a whole bunch of phenotypes where all these viruses were phenotypically resistant to the protease inhibitors. We ran the sequences through our database and said, "What is the prediction just from the sequence, for each of the four proteases that we looked at showing that, in most cases, there was a high level of good prediction of high-level resistance just by taking the sequence and saying, "How do they match and what sort of phenotypes do we see?"

You can apply statistics to this and I think that should be done in terms of interpretation. It is really essential. If people are saying we have an algorithm or system for interpretation, then it should be tested statistically.

[Slide.]

Just to conclude, I think everybody is in no doubt now that there are numerous different combinations of specific mutations that are frequently seen in routine

clinical practice. Somehow, predictable phenotypes, 184 3TC resistance--some have less predictable phenotypes or, in fact, are not even known at the moment.

What we are trying to work towards--we are not making kits but we are trying to enhance the interpretation of genotypic information through use of a large relational phenotype-genotype database which enables us, now, to generate these virtual phenotypes that can be derived just from the sequence, comprehensive sequence, data.

We feel now that this is really going to be a valuable tool in helping genotypic interpretation.

Thank you.

DR. HOLLINGER: Thank you very much.

Let me just find out, is there anyone in the audience, before we close the open public hearing--does anyone else need to respond or comment?

If not, then I am going to close the open public hearing. I am going to ask Dr. Tabor to make a few comments here and then we are going to open it up for the committee discussion on the question.

DR. TABOR: We have been spending the morning discussing an issue that has become more and more complex as we have heard more and more presentations. I would like to try to clarify some of that for you, perhaps reiterating some of what I said before.

What you are being asked to do, as a committee, is not to rule on the approval or disapproval of any particular product but to give an opinion on an approach, in a regulatory approach, to a certain category of product, the genotyping assays for mutation detection in HIV.

We are only talking about the genotyping assays at present and that was what was in the public announcement and that was the intention of the FDA in bringing this to you at this time.

What we are talking about whether something that, in the absence of your acting, would be a class III device requiring a PMA, a longer review time, essentially mandatory levels of clinical information. We are asking you to decide whether the category of device can be regulated as a class II device.

We can still ask for as much clinical information as we want of a class II device. The difference is on the impact, or the potential impact, in the health of the patient and the public safety. So, if we have an application that we decide--let's just say that you say it can be a class II device; if we have an application that deals with well-known genotypes with well-known associated mutations, we can ask for less clinical data than if we have an application that is dealing with new mutations or areas that are not as well studied or as well known.

We can ask for the same amount of clinical information if we want as we would ask for a class III. It is just that it gives us the additional flexibility, if we are dealing with something that has minimal direct impact on the patient health and where there is a lot of information available already.

With the issue of genotyping versus phenotyping, you have heard a lot of really good data and you have seen how extensively both areas have been studied. All we are asking you to look at today are the genotyping tests. We will come back to you at another BPAC meeting in the near future to ask you the same question with regard to the phenotyping test.

So I am asking you to set aside a lot of the scientific information you have heard and, certainly, I am asking you to set aside the specific information about specific tests that were heard in the open public hearing and save some of that information for the next meeting, and only decide, at this point, whether the genotyping assays can be regulated as class II devices because, otherwise, they will be regulated as class III devices.

DR. HOLLINGER: Thank you, Ed.

I am now going to ask Dr. Smallwood to read the charge to committee.

Charge to the Committee

DR. SMALLWOOD: The Blood Products Advisory Committee is sitting today for this issue as a medical-device panel. This is permissible under the charter of the Blood Products Advisory Committee which states that it allows the committee to sit as a medical-device panel when there are such issues which would involve classification issues and the setting of standards as this discussion today.

I know you have heard a lot of information regarding this. What I would like to do is reiterate the salient points of procedure to assist you when you are making your deliberations on this particular topic.

As has been explained, we are asking you for a recommendation for reclassification from class III to class II. You have heard the definition of a class II. I will just state, again, the devices which cannot be classified in class I because the general controls, by themselves, are insufficient to provide reasonable assurance of the safety and effectiveness of such devices but for which there is sufficient information to establish special controls to provide such assurance.

Examples of special controls include performance standards for which you have heard postmarket surveillance, development and dissemination of guidelines. They may include clinical data on a 510(k). They may address

labeling content regarding indications for use, instructions for use, contraindications, warnings, precautions and adverse effects. Also, design controls.

It is discretionary that FDA may find it necessary to implement other controls to protect the public health or provide the safety and effectiveness data.

What we need from the panel, essentially; a recommendation for reclassification of the devices that are the subject of this panel session. These recommendations may include a summary, or summaries, of the reason for the recommendation and a summary of the data upon which the recommendation is based and identification of special controls for class II which have been presented to you in the concept memo.

What will follow after these deliberations and your recommendations will be a decision on the appropriate class. Obviously, FDA has presented their concept and their thinking regarding this. There will be published a public notice of panel recommendation to reclassify these devices.

There will be a review of all comments and, finally, there will be a published Federal Register notice of reclassifying these devices. All committee members were provided with Form FDA 3428 which is entitled In Vitro Diagnostic Product Classification and Questionnaire.

I know that it may seem overwhelming to you but I

hope that I can help you in making it a little easier. Essentially, questions 1, 2, 3, 4, 5 and 7 would pertain to these deliberations. I believe that after you have engaged in the discussion here and have decided what your recommendation will be that you will be able to easily complete this form.

As has been mentioned before, if there are any particular special controls that you feel should be implement or that you may recommend, please include these on the form.

You also have a supplemental data sheet and that is only needed if you have additional information that cannot be filled out on the first form, FDA 3428. After completion of this form, I would request that it be mailed to me not the address that is on the form after this meeting within two weeks.

If there are any further questions, you may contact me regarding this after these deliberations.

Thank you.

DR. MACIK: Very quickly, what is the generic type of device? What are we supposed to call this?

DR. HOLLINGER: Do you want to call this HIV mutation test for right now?

DR. DAYTON: Why don't you call it HIV genotype drug resistance test.

DR. SMALLWOOD: I believe Mr. Wilson had displayed a slide which indicated how these would be described.

MR. WILSON: That is a proposal, so I would defer to Dr. Dayton's language.

MR. DUBIN: How about HIV drug resistance assay test/genotype.

DR. DAYTON: That's okay. The key words are genotype and drug resistance and HIV.

MR. DUBIN: And they are all there.

DR. SMALLWOOD: Are there any further clarifying questions that I can answer at this time?

DR. HOLLINGER: Thank you, Linda.

Committee Discussion and Recommendations

DR. HOLLINGER: I am going to now open this up for committee discussion but, Dr. Mayers may have to leave. I would like to ask, first of all, if there are any clinical questions that you would like to address to him regarding any of the studies or what your thoughts are or anything like this before he has to leave.

DR. MAYERS: Dr. Hollinger, I have rescheduled his afternoon.

DR. HOLLINGER: He has rescheduled his afternoon, but we could still ask him the questions anyway.

DR. TUAZON: Doug, in your opinion, for what percent of AIDS patients would this test for clinically

useful?

DR. MAYERS: Over the course of their illness? Essentially all of them on multiple occasions. It has been shown, I think for newly infecteds, this is clearly becoming increasingly important. The French ANRS has actually made a recommendation to their government that newly infected patients with less than one year since their seroconversion should all have resistance testing done.

If it is more than one year, they are recommending not doing the testing because their is a very low rate and because of the concerns of back reversion that Jeff Murray mentioned. But, then, subsequently, I think it is going to become the practice to provide additional data as you try and find late rounds of therapy.

DR. TUAZON: I think, eventually, you probably would need this information because if the transmission of the newly infected ones will be infected by resistant strains, then you would need this in your primary management of patients.

DR. MAYERS: The fundamental problem is that, when we checked our clinic at Henry Ford Hospital in Detroit, 48 percent of our patients have seen at least two PIs in the non-nuc and have positive levels of RNA. So right now, there is a huge population of patients with multi-drug-resistant virus potentially going to transmit to the next

generation of patients.

DR. NELSON: I think that I agree with Dr. Mayers. I think that this will be extraordinarily useful data to the practicing clinician. One of the concerns I have, and I don't know if it really relates to the class II versus class III issue, is I see the possibility of some abuse because of the fact that it is a gene, or two genes, that are being--or segments of the gene that are being analyzed.

Data could be reported on a genotypic variation or mutation to which there is not good clinical relevance. I could even see a scenario where a pharmaceutical company that had developed a new drug, or had a drug, was also doing resistance testing and was using this for commercial gain or what have you, not necessarily for patient benefit.

The issue is there are some genotypes described by Dr. Mayers that are clearly related to AZT resistance, nelvirapine resistance and individual or combinations of drugs. But there are others in which the data are unclear.

I guess my question is how will that be regulated? Will that be on the brochure of the product insert or will the company that is doing the genotype testing can only report genotypes to which there is some scientific data to back up its importance? How will that occur?

I can see where it could be regulated by FDA whether or not there was a class II or a class III approval

process. I don't understand that issue very well.

DR. TABOR: I think your point is a good one but I really think, at this point, we ought to really focus on whether this should be a class II or a class III device and then go on to the special controls that the committee would like to see because that is what we really need to accomplish today.

DR. NELSON: To simplify my question, is my concern relevant to the class II versus class III, or is it a secondary issue?

DR. DAYTON: It will be handled adequately and in either class II or class III. Yes; the assays will make occasional errors but, on average, they already seem to be doing better. But class II or class III, we can handle that equally well.

DR. HOLLINGER: Doug, I have got a couple of questions on this issue. I know you have a conflict of interest here because this is what you really are interested in. You are also the expert in the area. You got to have both ways.

There was a thoughtful editorial by Judith Faloon on the Lancet article. I hope you have read it. Without putting you on the spot, she makes some very interesting observations like there are no clinical outcome data and few data correlating baseline genotype with viral-load response.

She talked about several other issues about this and the data.

Do you believe, at least right now, that there is enough clinical data--and I know what we are talking about, but this has to do with the classification of III and II because III requires premarket approval. It requires clinical data before it is approved. It is a longer process but it does require--we vote on a lot of things that later on we say, "I wish we had done that study and got the information because we will never get it after this."

So I would like to know whether you think there is sufficient evidence under these two things, with small numbers of patients in each one of these studies and with the data and with the questions that we brought up about compliance and other things, which you don't have the data on yet--but give me some feeling about where you are with this and some of her response, if you would.

DR. MAYERS: I think, to a certain extent, it becomes is the glass half full or half empty. In this particular instance, I think the glass is probably about 80 percent full. I do not believe that you are going to be able to get clinical-endpoint data for this issue in a similar way that drug development is having trouble getting clinical-endpoint data anymore because your original test and the clinical outcome are going to be so far apart that

their relationship will be vague even when you do get the outcome.

I personally have the same problem that the Hopkins IRB had in that knowing that I can get a patient that is twice as likely to be undetectable with the test as they are without the test, I have problems taking them against no test anymore whereas if I take a genotype against a phenotype, I think that is a very doable trial, but I think the sample size approaches that of the infected population of the United States, so I am not sure that that one is doable either.

I think with the data available, we know that we can manage patients more effectively in the short term with the data than without it. I think that the concerns the committee has expressed about both quality control for testing and standardization of interpretation are both very valid concerns.

To my mind, I think that making the companies prove that they can detect the mutation accurately and consistently and, if they market a kit, that that kit gets the same mutation no matter who does the assay is a very reasonable requirement of any company.

I might suggest, from having listening to this discussion, that, perhaps, it might be useful, since I don't think any of these companies want to prove that a mutation--

they have to and individually prove that their mutations that they can detect with their kit are clinically relevant--it might be very useful for the FDA to consider having an expert panel that actually meets for them to decide what mutations have reached that level in which they are comfortable with it and what mutations have not because then the issue becomes does the company measure the mutation accurately.

If the company measures the mutation accurately, that would be the basis for what the company would have to do. What mutations does it cover could be addressed more globally by has this mutation reached a level of validation that the FDA is comfortable saying if you can detect it that you can report it as having this meaning.

So you might have to break the process in two. I am not sure, but that is my own personal opinion, though, Blaine. I think we are to the point where we can use it and use it usefully and it gives useful information. There are some areas of greyness. Some of them may be resolved and, quite frankly, some of them may never be resolved.

DR. HOLLINGER: You feel that outcome would be beneficial--might be--if you could do it long enough, even more so than what we currently have available.

DR. MAYERS: I think that the outcome gets better if you can do repeated measures similar to those done by the

VIRADAPT group. If you can repeat the test on multiple bases, you can--but I think the bottom line is, in 1999, with the drugs available to the clinician, that, right now, you are going to hit a wall and it is about 30 percent of your patients.

When you hit that wall, you cannot break through it no matter what test you use because we just simply do not have the drugs to bring those patients' virus under control.

DR. HOLLINGER: Thank you.

DR. McCURDY: I think he put it fairly succinctly in my thinking on this. I think there is very little question that the technology can detect mutations. So the issue is does the individual test kit detect the mutations that it says it does. This is solvable on review, I think. The interpretation of it is also a very difficult one although there appear to be, from the presentations, some mutations which are pretty commonly, or almost universally, associated with resistance.

I think that this can be taken care of in the labeling and relabeling if new mutations come along. The idea of an expert panel dealing with mutations that do cause resistance or multiple mutations that cause resistance is a good one and it is analogous to what both Dave Stroncek and I have referred to in the HLA--the designation of certain HLA class I and class II alleles.

So I think that it is reasonable to reclassify this to a class II device and that it can be managed with the controls that have just been mentioned here and that can be put in place by the agency.

DR. HOLLINGER: Thank you.

Other comments before we put the question up on the screen? All right; let's put the question on the screen. The question is, if we could make the amendment, then to this question, because you want to say genotype; right?

DR. DAYTON: Yes.

DR. HOLLINGER: If I may, I am going to make a recommendation that we change it to, "Does the committee support the reclassification of HIV genotype drug resistance assays from class III devices to class II medical devices?" I would like to vote on that change, if you will.

All those in favor of that change, raise your hand.

[Show of hands.]

DR. HOLLINGER: All opposed.

[No response.]

DR. HOLLINGER: Any abstaining?

[No response.]

DR. HOLLINGER: With that change, then, we will have a vote on this. All those who are affirmative with

this or want to vote yes to have this change, reclassified from class III to class II medical devices, so indicate by raising your hand.

[Show of hands.]

DR. HOLLINGER: Those opposed?

[One hand raised.]

DR. HOLLINGER: Abstaining?

[No response.]

DR. HOLLINGER: Would you please read the results.

DR. SMALLWOOD: The results of voting for question No. 1 as modified, and I will read the question as modified; "Does the committee support the reclassification of HIV genotype drug resistance assays from class III medical devices to class II medical devices?"

The results of voting; 13 yes votes, one no vote, no abstentions. At this time, I would ask the recommendation from the industry rep.

DR. BUCHHOLZ: I vote yes.

DR. SMALLWOOD: The consumer rep left. However, she did leave her vote which I will read. Her recommendation was yes for genotype assays to be reclassified to class II. And she did have a commentary; "with strong recommendation of standardized reports as part of the controls and close postmarketing monitoring, and also to include the statement coming from Jeff Murray's last

point of using genotype/phenotype testing in new drug development."

DR. HOLLINGER: Thank you, Linda.

Now, we have the hard part--maybe the easy part. Now, let's have the second question because we are not going to deal with the third. The second question is, "If the answer to No. 1 is yes, what additional special controls or requirements, if any, does the committee recommend?"

I know we have had several made here already that can be gleaned from all this data. But, specifically, would somebody like to make some comments on this?

DR. MACIK: I think the easiest way to address that is to look at the form where it says "controls," and just vote on each of those and then add in anything that is left. For example, it starts out with postmarket surveillance. Maybe we could vote on each of those and then add in anything else that was extra.

DR. HOLLINGER: I don't think we have to vote on this. I think, mostly, and correct me if I am wrong, but I think you are asking for information, Andy. But can you please help us?

DR. DAYTON: Somebody correct me if I am wrong, but my understanding is that you have to vote on a), classification, which you have done, and special controls. In this case, we would propose that special controls would

be postmarketing surveillance such as you have just identified and the formulation of a guidance document the highlights of which we have discussed.

So if you feel that the discussions are such that we will know what to put in the guidance document and we know what to put in postmarket surveillance, you could vote to accept those as is, for example. Does that clarify the situation? And there might be more.

DR. BOYLE: Would the guidance document include performance standards and testing guidelines?

DR. DAYTON: Oh, yes. I didn't go into that because that was assumed, obviously.

DR. HOLLINGER: On the form, just as you know, if you all see 3B, they talk about postmarket surveillance, performance standards, testing guidelines--that is the guidance document, part of that--device tracking and then other.

First of all, do the members all feel that at least the first four, the ones I read--not the other, but the four--

MR. WILSON: Not device tracking.

DR. HOLLINGER: Sorry; what is device tracking, anyway?

MR. WILSON: Device tracking is where you would track the individuals individually who the device is used on

in the event that there has to be a follow up to the company.

DR. HOLLINGER: Okay. End users. So the three. does the committee at least certainly agree--and I would just ask you for a quick vote at least on the postmarket surveillance, performance standards, testing guidelines or guidance document, if you will.

All those who certainly agree that those are some of the special controls, raise your hand.

[Show of hands.]

DR. HOLLINGER: Any opposed?

[No response.]

DR. HOLLINGER: Any abstaining?

[No response.].

DR. HOLLINGER: What about the "other."

MR. DUBIN: Labeling, because I don't see labeling listed in this breakout so I think in the "other," we should talk about labeling.

DR. HOLLINGER: How do you mean labeling?

MR. DUBIN: One of the things we talked about earlier is in terms of how the information flows to physicians. If you kind of juxtapose an infectious-disease doctor who is on the cutting edge with a hematologist treating hemophilia who is treading water to stay on the cutting edge, it seems to me it is important that FDA have

some sense of how to ascertain how the information is being taken in and used. That could be done in a labeling environment and a review of that, some kind of outcome assessment, that lets you know that information is being internalized. That is what I am suggesting.

DR. DAYTON: We certainly are open to suggestion for labeling. Many of these things we normally would handle in any labeling procedure. Probably the best thing, if you want to focus on labeling which, of course, is a reasonable thing to do, is try to focus on things that we might otherwise not normally do.

MR. DUBIN: You would do everything that I just articulated?

DR. DAYTON: What would be the list, then?

MR. DUBIN: Labeling in terms of the information needed by physicians using the test, understanding that there is quite a gradient between physicians in terms of understanding.

DR. DAYTON: Oh, yes.

MR. DUBIN: And some type of outcome review of that labeling so you know if it is being internalized out there in the world.

DR. DAYTON: That is a tough one. We could do that.

MR. WILSON: In other words, this would be voted

on as a special control and, in the premarket review of the product, as part of the 510(k), we would be asking the companies to evaluate the reports in terms of how the physicians interpret them appropriately.

MR. DUBIN: Absolutely.

MR. WILSON: If they are getting it all wrong all the time, we will not clear the product.

MR. DUBIN: Right; that is what I am talking about.

DR. HOLLINGER: I'm sorry. Excuse me a minute. Linda needs to read the response to what we voted on just a minute ago.

DR. SMALLWOOD: This is for clarification so that everyone will understand the action that the committee just took on their last vote. There was a unanimous vote for additional special controls or requirements. What the committee included in that vote were postmarket surveillance, performance standards and testing guidelines.

DR. HOLLINGER: Thank you.

MR. DUBIN: They were going to answer. He was in the middle of answering.

MR. WILSON: We did not make a recommendation, although the committee can, relative to performance standards. Performance standards are, for example, voluntary or involuntary national and international

standards that would apply to various elements of the performance characteristics of the product.

There would be none existing for this type of product currently. It takes an extremely long period of time to develop standards. In lieu of that, what FDA does in term of develop criteria for the clearance of the product, is embed some of that information in the guidance document.

So what would happen is that if the committee were to approve the performance standards, none exist formally so we would not be able to apply that. Maybe if some become available, the committee can recommend, if available. But none exist currently.

The safety and efficacy is largely going to be framed out in the guidance document.

DR. CHAMBERLAND: Is it standard procedure for the FDA to have the BPAC review draft versions of the guidance document?

MR. WILSON: If the guidance document were to be available, we would have provided it to you. It is still under development. Lots of things are moving very quickly. However, the process of the approval of the guidance document would be to publish it in the Federal Register. We could certainly provide that to the committee selectively, also. Comments can be made on it. They can be made by

anyone who reads the Federal Register.

We are obligated to review every one of the comments so that you can get your input in as everyone else.

DR. CHAMBERLAND: I think that is somewhat what I am personally struggling with which is it is hard to know if additional special controls are needed when the postmarket surveillance and testing guidelines have not been spelled out in a very detailed way. So it is hard to know where the gaps might be.

DR. HOLLINGER: I agree with you, Mary. You have got a document. We haven't seen it. I think that what I would like to see, at least right now, is at least for us to express what things we ought to do. And they can take them as recommendations, not necessarily voted on.

We have discussed this throughout this session today. Then we can see where we are going to go from there.

MR. DUBIN: We were still on labeling. I don't want that to get lost. I don't want it just hung out there. That is the one we didn't vote on.

DR. HOLLINGER: Tell me what--

MR. DUBIN: FDA just made a proposal back that sounded decent.

MR. WILSON: The "other" on the box is what we-- normally, 510(k)s are obligated to have labeling consistent with 21 CFR 809.10. So you already get labeling.

MR. DUBIN: I understand that.

MR. WILSON: What we would be asking for here is what we would call "special labeling."

MR. DUBIN: That's right. That is what I am talking about.

MR. WILSON: That would be at the direction of the committee on some of the interpretational issues that were discussed earlier. You could make that recommendation to us and then what would happen is that, based on those recommendations, we would exercise that in the review process.

MR. DUBIN: Right. I think what we were suggesting was twofold, in terms of labeling and them some review of the doctors are internalizing that labeling because there is such as gradient between people who are practicing infectious disease in HIV AIDS on the cutting edge and people who are not.

That is not to make a negative statement about--it is just the truth of what is out there.

DR. TABOR: I think we want to be careful not to get too bogged down in details. I think, as Dr. Hollinger suggested, you can make a group of suggestions that we would take into consideration in the review of specific products. The question that is up there, question No. 2, is asking about specific special controls or requirements.

I think some of what you are suggesting are in the category that Dr. Hollinger was referring to which is discussion items that we should take into consideration during the review of these products.

Here, you are talking about something that would apply to every class II device in this category.

MR. DUBIN: Let me back up and try to be clear. The question gets asked is is this dangerous. Obviously, this does not pose a direct health risk. However, if this test is used incorrectly to inform--used diagnostically and it is not used correctly and the diagnosis is misdiagnosed, I think we would all agree that could cause some problems for the patient, and the doctor, as well.

So I don't know if we are just lost in the part of this that is just loose recommendations. I think there has been expressed some serious issues about labeling at this table. I have been hearing them. I don't want to just write it off as "other."

DR. HOLLINGER: Dr. Boyle, do you want to respond, also, to this?

DR. BOYLE: Just in that it may not be a labeling issue so much as what has been said is that there is an interest in a standard for interpretability of the assay findings for the average user. That is a separate issue. That is one issue that has come up here and it would be one

thing that I would put on the table.

DR. TABOR: I think that is the kind of thing we want to hear and to take into consideration.

DR. HOLLINGER: Because the question is, if you are out there--what is "partially resistant" going to mean? Does that mean you jump in and you do another--for the general clinician that is out there who sees something that says, "partially resistant," or an AZT that says, "resistant," do they stop their medication? Do they not? Should there be guidelines for that kind of thing?

Let me see how you perceive that because that is what is being asked here in two places about interpretation and what the FDA needs to, then, sort of generate in their guidance document and other things as it relates to this because it sounds like it is a pretty important question.

DR. MAYERS: As I sort of said earlier, I am not sure if the FDA is going to invite me back, but I think this really comes down to two issues. One issue is a technical issue which is can you measure a mutation and, when you say the mutation is present, is it there. I think that is a very reasonable expectation for the companies, to prove that they can measure it, to prove to what level they can measure it, to prove what is the reproducibility of their product is. I think that is a very reasonable standard.

DR. HOLLINGER: It is it relevant.

DR. MAYERS: I think it is very relevant.

DR. HOLLINGER: I mean, and is the mutation relevant.

DR. MAYERS: But that is where I don't think the company should have responsibility. I think that there should be some standard place where--and I think that CDER is probably a better place than CBER, quite frankly, because I think it should be part of the drug-development process.

I think the company should, as part of their package when they submit, find out what mutations cause loss of activity of the drug and what mutations when someone enters the trial caused their drug not to work and what level of resistance causes their drug not to work. This should be part of the approval process for a drug.

As part of the evaluation of that drug approval, that part of the package should be looked at. So I think there should be someplace, somewhere in the system, in which we say, "When you have a 184, we have validated that this is associated with this, this and this. When you have a 215, we have validated this, this and this."

That should not be on the back of each strip manufacturer and each sequencing company. What they should be able to prove is, "I have got a good product that gives me a good sequence. When I report the sequence out, the sequence is clean and you get the same result if my tech

does it, your tech does it or somebody else's tech does it."

But then, I think it probably is a good idea because of the issue about politically interpreting results to have some group which has some vested authority which says, "We believe this has reached a level of validity that, once you have proven you can measure this mutation," and for a strip manufacturer, they are going to have to prove they can measure 184 in that strip.

For a sequencing person, that is a little bit different. They are going to have to prove they can get a sequence that is clean across the whole stretch. But, once you have got that, it goes across all the manufacturers. If you find a 184, it counts no matter who finds it, by which technology, it has the same interpretation.

So I think it might really be better to split the technical validation of an assay, which I think is a very strong--something that the company should do--from the interpretative result of that assay which, I think, also needs some sort of controls placed on it.

But I think it should go across the whole system. If you can find it, it counts.

DR. McCURDY: Blaine, I was going to suggest that we recommend a consensus designation or determination of new or resistance mutations. There are certainly, now, a number of consensus--and exactly how that is done, but I would

second what was just said that it needs to be done and it should be done by some type of consensus group in or out of the government or whatever.

It is part of the situation with the kits because the kit manufacturers may make, or want to make, labeling claims that they can detect mutation X which is a resistant mutation. They need to be sure that that is consensus resistant mutation.

DR. TABOR: Paul, I assume you are using the word "consensus" in the literary sense and not in the molecular-biology sense. If I am right, I think you may be placing too much of a constraint on the review process. I really think that, in a changing field like that, the reviewers need flexibility to make their own decisions as a group based on whatever expert opinion they can get at the time.

I certainly don't think we want to set up committees or advisory groups to determine what are resistant organisms and what are not because it is a changing field at all times.

DR. McCURDY: I think I am using the word "consensus" more generically. I think that it should not be something that is reported once in the literature or at a meeting or something and then immediately leapt upon by everybody. There ought to be a certain amount of confirmation that a given mutation is responsible for. This

could be done in the review process.

DR. TABOR: I think this is just part of the review process.

DR. HOLLINGER: It could be like an NIH consensus conference. Are you talking about something like that, Paul?

DR. McCURDY: No.

DR. HOLLINGER: Nothing like that?

DR. McCURDY: No; no, I was not.

DR. DAYTON: If I could address this point in particular, I did mention this when I was reviewing the highlights of the guidance document--in the guidance document, we are trying to lay down requirements for just how much validation we need to see in the literature.

I gave you an example of, for instance, if we see a certain change in the IC50 or 90, we may or may not accept that as prima fascia evidence that it works. The point is that that is going to be a major focus of the debate on the guidance document. So, if you trust the process, the guidance document will provide an answer to that.

DR. HOLLINGER: Is that okay?

DR. McCURDY: Yes; I think that is--

DR. FITZPATRICK: The guidance document and the review process can focus on that, but when we started doing western blots for HIV for diagnostic and clinical samples,

there was a great deal of difference in the interpretation of that western blot. It took consensus and standardization before we got the same answers from the same laboratories or we diagnosed patients the same way based on the western-blot results.

This test seems to be in that same stage of development to me. We can validate the test and we can know that the test is providing us the right codon, but we need a way for everyone to interpret those tests correctly. I think it is going to need to go beyond the review process to get that.

DR. HOLLINGER: I am assuming, Dr. Smallwood, that since we were all given one of these copies here that, literally, I mean, basically, we can put down what we want to under "other." It doesn't have to be a consensus for this, so I presume, Corey, that this is an opportunity for you to write in--there is a supplemental sheet. I guess, if you want to write four or five pages, you can do so.

But I think that is important because these are issues that they would want to speak do.

Are there any other issues before I bring this meeting to a close?

DR. STRONCEK: I have a question on question 4. It is addressed to device II and III. Are there any suggestions on what we should consider if we check that

answer off, 4A?

DR. HOLLINGER: About the performance standards?

DR. STRONCEK: Yes.

DR. HOLLINGER: I think what he was saying is they don't have any performance standards.

DR. SMALLWOOD: Right.

DR. HOLLINGER: But I don't think that he said that they would not be useful if they had them.

DR. SMALLWOOD: Essentially, they do not exist. That is what was stated by Mr. Wilson.

DR. HOLLINGER: Thank you, Linda.

DR. BOYLE: My form, 7A, do we have to restrict it in terms of who uses it? I am not sure what the intent there is.

DR. HOLLINGER: Could you explain that, maybe just to those of us who are not--

MR. WILSON: Restricted equals by a prescription. That is the short interpretation. There are very few restricted devices that are in distribution.

DR. HOLLINGER: Unless you wanted to have a prescription, you would answer "yes" on something like that.

MR. WILSON: Correct.

DR. STRONCEK: No; you would answer "no."

DR. HOLLINGER: Okay. No; you would answer "yes." The answer would be yes. If you want prescriptions on this,

then answer "no."

I want to thank this committee again for all their hard work, as usual. Everybody was prepared and came and we appreciate it. We are not going to have a meeting in December. The next meeting will be in March or June? Linda, do you have the times so we can mark it?

DR. SMALLWOOD: The next regularly scheduled meeting is tentatively for March. It will generally be the third week in March, that Thursday and Friday, pending availability of appropriate facilities. The meeting following that would be scheduled for June and then September, accordingly. We will talk about whether there will be a December meeting in the Year 2000.

DR. HOLLINGER: Thank you all very much.

The meeting is adjourned.

[Whereupon, at 1:13 p.m., the meeting was adjourned.]

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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.

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