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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

64TH MEETING

VOLUME II

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at

C O N T E N T S

P R O C E E D I N G S

Introductory Remarks

DR. SMALLWOOD: Good morning and welcome to the second day of the 64th meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary. Yesterday, I read the conflict of interest statement. It also applies to today's meeting.

This morning, the Blood Products Advisory Committee will be sitting as a medical-device panel. You will hear presentations that will describe the role of a medical-device panel. For this purpose, we have asked consultants to join us today in this deliberation who will be sitting as temporary voting members.

I will introduce those consultants to you. They are Dr. Carmelita Tuazon. Would you please raise your hand, Dr. Tuazon. Dr. Paul Edelstein. And Dr. Roy Gulick. We understand that, because of the weather, that some individuals have had difficulty in getting here. We are assuming that they will be coming since we have not heard that they are not.

We also were to have join us, as a guest of the committee, Dr. D'Aquila who advised me that he was unable to attend today.

The Chairman of our committee is Dr. Blaine Hollinger. Dr. Hollinger, would you raise your hand,

please. For those of you who were not here yesterday, I will just quickly run through the committee and give myself a memory check here.

Dr. Gail Macik, Dr. Richard Kagan, Dr. Mary Chamberland, Dr. John Boyle, Dr. Norig Ellison, Dr. Michael Fitzpatrick, Ms. Katherine Knowles, Dr. Donald Buchholz, Dr. Joel Verter, Dr. Mark Mitchell, Dr. Jeanne Linden, Dr. Paul McCurdy. We also have Mr. Corey Dubin. I don't see him here this morning but I assume he will appear.

Are there any declarations that would need to be made before we proceed with this meeting concerning any conflict of interest or any perception thereof?

Hearing none, then we will follow the agenda as closely as we can. We have a lot today. We will try to meet the time frame that has been established if everyone will cooperate accordingly.

At this time, I will turn our meeting over to our Chairperson, Dr. Blaine Hollinger.

DR. HOLLINGER: Thank you, Linda. We will stick within our time frame, hopefully, today. This is, I think, an important meeting today as we sit as a medical-device panel for reclassification of HIV drug sensitivity assays. This is, of course, an important issue, also.

I think it is going to be an interesting morning. I hope you have all looked at these forms. Mary Chamberland

said that she has been in government a long time and she said it took her six hours to fill it out. OMB says one to two hours, but--I told someone that that means that we all get a royalty of about 5 percent on anything that is produced.

So, we are going to start this morning with an introduction and background. Andy Dayton is going to start us off today and then we will go to an overview of the device reclassification. Then we will have a presentation of the problems and issues associated with this.

Medical Device Panel Reclassification

of HIV Drug Sensitivity Assays

DR. DAYTON: Good morning.

[Slide.]

Today, you are going to be asked for your recommendations as to whether or not HIV drug resistance genotype assays should be reclassified as class II medical devices rather than class III medical devices.

This is a timely issue because downclassification would foster rapid and simplified regulation of numerous, currently diverse, HIV genotype assays and this would facilitate antiviral drug studies and, ultimately, accelerate physician access to information useful in the management of individual HIV-infected patients.

I am going to give a very short presentation of

the regulatory considerations. My presentation, in general, will give you a general overview of basic regulatory and technical issues involved today. Following my short presentation, Len Wilson will present a more detailed and comprehensive review of the regulatory issues.

[Slide.]

After that, I will give a brief overview of the scientific and clinical issues and then Jeff Murray and Doug Mayers will present more-detailed summaries of the relevant clinical and scientific literature. After the presentations on regulatory and technical issues, there will be an open public session and then a session for committee discussion following which you will be asked to make a recommendation on the classification.

I want to emphasize at this time, as you have already been told, you are sitting as a classification panel. We are not requesting you to vote on approving or clearing or licensing any product. We are asking you to decide at what level we should regulate HIV drug resistance genotype assays. What I mean by this will be explained during the course of this session and I believe you have also had an introduction yesterday as to the various classifications available.

[Slide.]

Currently, there are no FDA-approved or cleared

assays for the assays for the determination of HIV drug resistance. Given this, HIV drug genotype drug resistance assays, by default, are class III medical devices requiring premarket approval.

An option exists, however, to classify such devices into class II, or 510(k), when general controls and special controls exist to insure the safety and effectiveness of the device. It is FDA's view that adequate special controls can be provided by adherence to a guidance document containing recommendations for study designs, reagent characterization and performance characteristics--for instance, reportable range, sensitivity, precision, specificity, stability, et cetera--and by completion of postmarketing surveillance studies designed to evaluate the correlation between predicted and observed viral phenotypes in a clinical setting.

[Slide.]

These are the questions that we are going to asking you at the end of the presentation and, of course, you are welcome to alter them as you see fit. Does the committee support the reclassification of HIV drug resistance assays from class III medical devices to class II medical devices? If the answer to No. 1 is yes, what additional special controls or requirements, if any, does the committee recommend?

If the answer to No. 1 is no, what additional specific criteria does the committee recommend to allow future reclassification as class II devices?

[Slide.]

The science involved can be quite complex and, certainly, much desired information is incomplete. However, we urge you to remember that the key issue is not whether or not all the scientific information is complex or whether all the scientific questions have been answered. The key issue is whether or not you believe we can identify special controls which will guarantee reasonable efficacy without requiring the completion of full-blown, traditional clinical trials before marketing.

In the next presentation, Len Wilson will focus on this issue from a regulatory perspective.

Len?

Overview of Device Regulation

MR. WILSON: My presentation today is to take the committee through the regulatory pathway to classify medical devices. Why do we do this? Because the law says we must classify medical devices. So we go through this exercise periodically as new products come up or we want to change the regulatory classification of existing products.

In the past five or so years that I have been engaging in reclassifying devices, this committee has voted

on a number of them, sometimes classifying up from a I to a II, sometimes classifying down from a II to a I, et cetera. So there are no surprises in this process.

With that, what I would like to do is have the first slide and essentially start out.

[Slide.]

What we are trying to reclassify here an HIV mutation test. An essential proposal is that the HIV mutation test can have a reasonable assurance of safety and effectiveness when regulated as a class II medical device. Class II medical devices, as I will discuss later, have some requirements associated with them. One of the requirements is having a special control.

The proposal here today is that the FDA would develop a guidance document for the content of the 510(k) filing, the class II medical-device filing, which we would review and we would clear if the manufacturer provided sufficient information to assure the safety and effectiveness of the device.

And then there is an additional special control that we are proposing, postmarketing surveillance. This would be used, as Dr. Dayton described, to do some follow up. I want to emphasize that the postmarketing surveillance component of a special control here is not intended to be the basis for the approval of the product, approval or

clearance of the product.

The postmarketing surveillance is intended to answer some unanswered questions or some prospective concerns.

[Slide.]

What I will be talking about are, basically, three topics. Is the product a medical device? If so, who regulates it within the Food and Drug Administration? And, into which regulatory class should it be assigned?

[Slide.]

Is the product a medical device? According to the law, if a product is labeled, promoted or used in a manner that meets the following definition in Section 201(h) of the FD&C Act, it will be regulated by FDA as a medical device subject to premarketing and postmarketing controls.

[Slide.]

A device, by definition, is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article including a component part or accessory which is--

[Slide.]

--recognized in the official National Formulary or U.S. Pharmacopeia or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease in

man or animals or--

[Slide.]

--intended to affect the structure or any function of the body of man or other animals and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent on being metabolized for the achievement of any of its primary intended purposes.

[Slide.]

So now we have established that this type of a product would be a medical device. The next question is how would it be regulated by the FDA, either by the Center for Biologics or the Center for Devices, the Center for Biologics Evaluation and Research, the Center for Devices and Radiologic Health.

The Center for Devices and Radiologic Health regulates most of the medical devices that are in commercial distribution in the United States. In 1991, there was an intercenter agreement which was issues between the two centers. In general, CBER has the lead for regulating medical devices used or indicated for the collection, processing, storage or administration of blood products, blood components or other analogous products.

So, for example, this empowers the Center for Biologics to regulate those test kits which are used to

screen blood donors.

[Slide.]

But it also states that CBER also regulates in vitro tests including diagnostic tests and any other medical devices intended for use in dealing with retroviral products. So this particular product that we are talking about today is a retroviral product, so the Center for Biologics has jurisdiction.

[Slide.]

I wanted to underscore, also, even though we have jurisdiction over this product, we use the same sets of regulatory requirements that are dictated by the Food, Drug and Cosmetic Act which the Center for Devices uses. So we are using the same sets of rules, here.

[Slide.]

Devices are classifying as required by law into one or more of three categories, or classes, depending on the regulatory controls needed to provide reasonable assurance of safety and effectiveness. This would be class I, class II or class III.

[Slide.]

A device is automatically, by law, in class III if it was not on the market before May 28, 1976. This was the date at which the Medical Device Amendments to the Food, Drug and Cosmetic Act were passed establishing medical-

device law and regulations. Or if no predicate device exists; in other words, FDA has not cleared a 510(k) for the same device. So a predicate would mean, in this particular situation, has the Food and Drug Administration cleared an HIV mutation test or viral-resistance test before. Is there something that we can compare against?

And the answer is no. So, by default, as we move down, it would be in class III in the absence of formal classification. However, there is an option where the FDA can classify products into some other medical-device classification.

[Slide.]

So the steps, in general, to classify a medical device are found in the regulations, 21 CFR 800 through 899. It can be initiated by FDA or a sponsor. In this particular instance, FDA is bringing it to the committee. A sponsor would mean someone who was petitioning the FDA who would be trying to get a test kit approved or cleared. They can petition the FDA and say, "Gee; I would like to have this regulated as such-and-such as class." And then we would go through this same type of a cycle except it is coming externally.

We would obtain a recommendation from an advisory committee, this committee. Based on that recommendation, we would publish, in the Federal Register, for comment, the

outcome of the committee's deliberations and vote and then get some comments, make potentially some changes, and then publish a final rule.

Once that final rule is published, into the CFR would appear, once the administrative processes are completed, a section that would be entitled, for example, HIV Mutation Test. It would have a number and then any sponsor who comes to the Food and Drug Administration to get a test approved or cleared, they could cite that as a predicate and they could file, in our proposal, a class II--it would be regulated as a class II and they can file a 510(k).

[Slide.]

In the regulations, the committee should consider, in determining safety and effectiveness--and this is something that you may want to tag on the slides that I gave you--you should consider the persons for whose use the device is intended, its conditions for us, probable benefit to health weighed against risk of us, and the reliability of the device.

[Slide.]

Which regulatory classification are we attempting to vote on here? Well, all medical devices, as stated earlier, are classified into three classes. Class I, general controls are sufficient to assure the safety and

effectiveness of the device. Class II, general controls are insufficient to insure safety and effectiveness of the device so special controls are added on top of the general controls in order to insure safety and effectiveness of the device.

Class III devices are those where general controls and special controls are insufficient to insure the safety and effectiveness of the device and premarket approval is required. That would be a PMA, a class III. In general, a premarket approval application, which I will touch on later, essentially, there would be clinical trials associated with it because the answers for the safety and effectiveness of device could not be assured by general controls and special controls.

I will walk through what these controls are.

[Slide.]

What are general controls? General controls, which apply to all medical devices, are registration of the manufacturing facilities. We need to know, at FDA, where the product is being manufacturing. The manufacturer is required to have a medical device listing, what products are being manufactured there.

These two bits of information are used so that FDA knows where to inspect on its periodic inspections. These products are routinely inspected on a periodic basis for

their compliance with good manufacturing practices or what we now call QSRs.

There was a revision to the good manufacturing practices. Good manufacturing practices are those sets of rules by which manufacturers produce products in a clean environment, have quality control, et cetera, et cetera. Again, these are listed in 21 CFR 800.

Recently, within the last two years, the good manufacturing practices section has been revised and upgraded. They are now termed QSR, quality system regulations. The important point here to consider is that they have been strengthened considerably. However, in class I products, design controls, which I will explain in a moment, are not required, in general.

Class I general controls also include labeling requirements to make sure that there are adequate instructions for use, et cetera. For a class I, a submission of a premarket notification also known as a 510(k) is required. It is also important to note that certain general controls can be exempted, also. That could be done by the Food and Drug Administration as well as by a committee vote.

For example, some products we may exempt the need to file a 510(k). This committee voted on such a situation several years ago where we dropped the requirement for a

510(k) for copper sulfate for use in determining hemoglobin in blood donors.

[Slide.]

Some more general controls; record keeping and requirement for repair, replacement and refund when defects are found.

[Slide.]

Some examples of class I devices; heat-sealing devices to crimp blood collection tubing; alanine aminotransferase tests. This is a clinical-chemistry test and you can see the it has an asterisk. This, in fact, has been exempted from filing a 510(k). So all the other general controls apply, but they are not required to file a 510(k) to get premarket clearance. An ammonia test system; iron-binding-capacity test systems.

The 21 CFR 862 is that section which is listed in the regulations and I will show you an example of what you would have in this particular situation for HIV mutation tests as we move towards it.

[Slide.]

Class II; general controls are insufficient so, therefore, you would need special controls. Now, special controls consist of, for example, a guidance document. And I have bolded that because that is what FDA is proposing. A guidance document would basically have the content of the

510(k) submission spelled out. There would be some clinical data if indicated. There would be contraindications, warnings, adverse effects, et cetera.

Now, I want to draw attention to the committee that, in August of 1989, FDA issued what we called then a points-to-consider document. But it is essentially a guideline for manufacturers as to what to submit for a product-license application for a blood screen. This is, conceptually, what we are looking to produce here for this particular product. Dr. Dayton will go into that in more detail.

Another special control can be a performance standard. Are there voluntary standards or international standards that can be applied to this type of product. What FDA would do, then, is we would recognize it by rulemaking, notice, comment and rule, and that would be the special control for that particular device if voted on by the committee.

[Slide.]

There could be special labeling, some restrictions, some additional information that would be imbedded into the labeling that wouldn't normally occur in a medical device because there is some greater concern that has to be mitigated.

Patient registries; sometimes, patient registries

are necessary to track particular devices, how they are used, because there could be a problem with them that we would have to get back and notify the patient. Again, I am bolding here postmarking surveillance to answer unanswered questions once the product does get into the marketplace.

It is important to note, going back to the GMP part, the QSR, design controls are required for class II medical devices. Now, what are design controls? The short answer is that design controls are part of the manufacturing process where each product has a set of controls placed on top of it where design input, design output, verification and validation of all the manufacturing processes are tightly controlled.

This is a new concept because FDA has determined, over the last decade, that failures of medical devices consists basically of two types. They weren't manufactured according to the instructions. The other type is they were manufactured according to the instructions but there was a design flaw and the product didn't work.

The objective here of design controls is to insure that the design of the product has been adequately challenged and it insures that the manufacturing process, as well, can be conducted with integrity.

[Slide.]

Examples of class II devices; an empty container

for the collection and processing of blood, transfer bags, a quality-control kit for blood-banking reagents. The controls that are used relative to CLIA, positive and negative controls for HIV tests, hepatitis tests, are regulated under this regulation. And they are classified as class IIs.

CMV serological reagents; the CMV test kits which are used electively to screen donors are regulated as class IIs. Lectins and prolectins used in blood banking are regulated as class IIs. However, we have recently exempted them from filing 510(k)s because the safety and effectiveness could still be assured without doing that.

[Slide.]

Class III; general controls and special controls are insufficient to insure the safety of the device, so premarket approval, also known as a PMA, must be filed. There is an alternative to a PMA called a PDP, a product-development protocol, but it gets you to the same place.

The main issue here is that clinical trials are required to insure the safety and effectiveness of the device.

[Slide.]

Some examples of class III devices are HIV home-collection test systems which are sold over the counter in pharmacies; HIV tests for prognosis; and HIV tests for

monitoring. These would be the viral-load types of tests.

[Slide.]

I tried to put together a compare-and-contrast chart for class II versus class III. This is not all-inclusive, but I think this hits the major points. Class II, general controls; class III, general controls. Class II, special controls; class III, special controls, if necessary. Class II, clinical data not always required. We do have the authority to ask for clinical data in a class II medical device. It is generally not done, but we do have the authority. With a class III, clinical data is always required.

QSR design controls are required in both. We have a postmarketing order option. In other words, we can say to manufacturers, "You need to do some follow up to answer some unanswered questions." Both classes are required to report, under medical-device reporting, if there is a failure that could cause serious injury. They have to report that to the Food and Drug Administration.

A difference with the class II is that there is a 90-day review cycle. 510(k)s have a 90-day review cycle. PMAs or class IIIs have a 180-day review cycle. The reason for that is that the content of the class III PMA is generally more detailed so FDA is allowed more time to conduct the review.

As I stated earlier, class II products have periodic QSR inspections which are conducted by the field investigators. For a class III device, there is a difference. There is a preapproval inspection and then periodic QSR inspections are conducted. So, with the class III, there is basically a GMP inspection of the plant or QSR inspection of the plant prior to the approval.

[Slide.]

So, which regulatory classification are we looking at here? Well, in the regulations, Chapter 1, 12 CFR 866, immunology and microbiology devices, subpart D, serological reagents. The proposal would be that, in Section 866, and a number would be assigned, there would appear an HIV mutation test.

[Slide.]

This is what it would look like, actually, in the regs. Mutation-detection reagents; a, identification, HIV mutation-detection reagents are devices that consist of ligands use to identify mutations in the HIV genome in infected individuals. The identification of mutations aids in the clinical management of HIV-infected individuals.

We used the term "ligands" because we wanted to have flexibility whereby this could be done by nucleic-acid testing or, potentially, by other means, serological and the like. So we would have the regulatory designation that we

would be able to use for some variance on the same theme.

[Slide.]

The next part of the regulation would basically be which classification is it. It would stated that it is a class II and special controls are required.

[Slide.]

So the FDA proposal is that an HIV mutation test can have a reasonable assurance of safety and effectiveness when regulated as a class II medical device and the special controls proposed consist of a guidance for the content of a 510(k) and postmarketing surveillance.

With that, I would ask Dr. Dayton to resume to spell out the concepts associated with the guidance document and the postmarketing surveillance.

DR. DAYTON: Do you want to take some questions now because we are going to on to the sort of technical and scientific issues.

DR. BUCHHOLZ: I wonder if, for the committee, you could indicate the actual time for the review as opposed to the statutory or guidance times for a 510(k), for a PMA and for a supplement to a PMA, say, an average over the last couple of years, just to give us a feel for how long it takes if, for example, one wanted to make a change in a product that was a PMA product, how long it would take to make that change as opposed to a product that was a 510(k)

product.

MR. WILSON: You have asked a number of questions there. I will do my best and, if I slip on one, please--I don't have the actual review times with me, but let me try to help answer that question. For a 510(k), when the manufacturer supplies that submission, we are obligated to review it within 90 days.

There is a device action plan that CBER is now fully engaged in and the effort is to make that date on all medical devices that are filed under 510(k). If the manufacturer does not provide sufficient information to allow us to make a determination of substantial equivalency to a predicate, we would write a "more information" letter.

Now, it is up to the manufacturer how long the manufacturer responds. There is a statutory requirement of 30 days an we have the option of actually withdrawing it if they don't respond. I can tell you that many manufacturers have taken a lot more time than 30 days to respond.

We try to be reasonable and flexible, particularly when products that we think are a benefit to public health, are valuable to the market. When the manufacturer does respond to the additional information with the 510(k), the time clock is reset. It is another 90-day review cycle. Now, we do our very best to review those products as efficiently as possible, but we do have the authority to do

that.

I think, to try to answer your first question, a fair number, maybe half or more of the 510(k)s that CBER reviews, take more than one review cycle to get clearance. So you are talking approximately six months beyond. The regulatory requirements for making changes in a 510(k) are somewhat different from those for a class III medical device. And we spell that out in guidance. CDRH has done a great job of articulating it.

It leaves the decision to the manufacturer. It is essentially if there is a new intended use or if there is technicologic change, they are required to file an additional 510(k). In other words, they would have to wait to make those changes. So that is the 510(k) side of it.

PMAs, we have a statutory requirement of doing the review within 180 days. Depending on the type of response that we get, we can reset the clock on a deficiency letter to an additional 180 days. I would say, in most instances, in CBER-regulated products, we do not have many products that we have approved under class III under one review cycle.

Making changes to a PMA product, more stringent rules are required. So, therefore, a supplement would need to be filed in many instances. The supplement would have a 180-day review clock on it.

Did I capture all your concerns?

DR. BUCHHOLZ: Thank you.

DR. HOLLINGER: The real asset here, somewhat, is the assurance of safety and efficacy between these two classes, II and III. Can you give us some more information about what you really mean by safety and efficacy, how these really differ between II and III in terms of classifying something? Maybe some examples, even.

MR. WILSON: I think the best example would be where we have apheresis equipment. Apheresis equipment, in fact, has two regulatory levels associated with it, a II and a III. Class IIs are those which the technology is by centrifugation. Class IIIs, which are intending to downclassify to II but, to try to answer your question, is by filtration. So separation of the blood components are performed by a different technology.

The centrifugation has less of a concern relative to the product produced--the platelets, for example--than the filtration. The concern with the filtration was that there would be membranes that would potentially capable of activation platelets, so there were additional issues of safety and effectiveness that would be of scientific concern so that, at the time when those products were--back, approximately ten years ago, when they first came to the marketplace, they were class IIIs.

It was found that, with the data presented to a committee back in the 1980s, that those instruments by centrifugation were found to have sufficient safety and effectiveness regulated at the class II level.

Recently, some data has been presented to the committee whereby we have got enough information now. What is enough information? It has been out on the marketplace for a period of time. We have looked at the MDR reports, the medical-device reporting, and found that the problems are not serious and, therefore, we feel that the lower regulatory controls would provide us safety and effectiveness.

There are some advantages and disadvantages to which regulatory class a product is in. There are some requirements that manufacturers have to follow--annual reports, for example--with a PMA and the like.

Am I helping you here? That would be, for example, where we had safety. Effectiveness, I am stuck here. If I could try to roll the two of them together where the platelet is performing, when separated by filtration, as well as when separated by centrifugation.

As you can imagine, there was a lot of detailed analysis to determine platelet function and the like. And it was determined that yes, the platelets were not compromised and the equipment could be felt to be

substantially equivalent.

DR. HOLLINGER: You have placed HIV tests for monitoring and for prognosis, the NAT test, as a class III device. I think that has something to do with what we are talking about here. I would like to know, if you can, in the short term, tell me a little bit about why you decided that that should be a class III device for both prognosis and monitoring.

Some of those systems are very much maybe what we are going to be discussing here today with this test.

MR. WILSON: I can give you the short answer. The short answer is that when we first were reviewing HIV monitoring, viral-load type tests, we did not have anywhere near the kind of information and knowledge base that we have today for genotype testing. Again, that would be the short answer.

I think that Dr. Dayton will be providing you those distinctions as he continues with his talk.

DR. MACIK: You talk about if you are going to make it a class II that you would look, perhaps, at putting on postmarketing surveillance. What does that mean an what weight does that carry if you take it out into the market and you are watching it and something comes up. I did not go clinical trials as a phase III. You put it out as a phase II.

You are really allowing your postmarketing surveillance to be your clinical trials. How can you bring it back? How do you get it if we let it out there ahead of time?

MR. WILSON: Very good question. First of all, the postmarketing-surveillance order can have a number of different requirements, not necessarily those constituting a clinical trial. Again, the idea here is that the postmarketing surveillance is not intended to be the basis for approval. That would be backwards; we clear the product and then we will find out if it works.

No; that is not what we are trying to do here. What we are saying is the product is clearable with what is provided to us. And then there are some logical additional unanswered questions that, from a public-health point of view, probably should be evaluated. So the postmarketing order would be structured on that.

Again, Dr. Dayton would be providing you with where we are headed with that.

Let's say something goes terribly wrong. We have several regulatory options here. One is an inspection of the facility to determine problems with--complaint handling, to see if there are a number of problems there. We also have some, by law, ways of dealing with products that are not performing; they are either adulterated or misbranded.

So there are compliance mechanisms to control that. I think that, if, over a period of time, it becomes evident that a product has problems that were not foreseen, it could be brought back to the committee and we could present a proposal to upclassify it to the III.

Also, as I said earlier, FDA could propose to the committee. Sponsors could also do the same thing. So there are some regulatory remedies. You are not in II forever, if you vote for a II. But we are trying to look at our knowledge base of dealing with guidance documents, dealing with what we already know about these types of tests and the technology and we feel, at least at this point, that a class II would give us reasonable assurance--the law says "reasonable assurance of safety and effectiveness."

DR. FITZPATRICK: You mentioned that you don't have to do full-blown clinical trials. So that implies to me that FDA would, then, open the door for the manufacturer to submit data from clinical use that was not part of a clinical trial, which they don't do in some other instances. Is that what you are saying?

MR. WILSON: That could be a part of the postmarketing-surveillance order. Again, I think Dr. Dayton would be able to frame out where we are, what we are proposing with that.

MS. KNOWLES: I think that I recall that even FDA

recalled a home-collection test kit for HIV that was in III at one point in time in the last two years; isn't that correct--because it did not perform?

MR. WILSON: There was a home-collection test which was classified as III that there was a problem associated with some labeling and it got relabeled on the pharmacy shelves and FDA took action, basically, because there was a violation. That got corrected.

MR. DUBIN: Early on in the year, our organization had met with Commissioner Henney. One of the things we discussed was postmarketing surveillance in terms of AIDS drugs because we had concerns. We had all supported fast track but we thought fast track was getting a little out of hand.

What was conveyed back to us was a resource issue, that what we were talking about would involve a lot of FDA resource in terms of both people power and dollars, and there were some questions. So I think my question is, in terms of undertaking this and managing it in a postmarket climate, does FDA have the resources and the people power to be able to do that and stay on top of it close enough to insure that we don't have some of the problems we are seeing with AIDS drugs.

MR. WILSON: I can't always predict the future, but I think that the tools that we have are structured to

enable us to assure these types of orders and maintain the integrity. For example, for postmarket studies, it would be a postmarketing order, the obligation of the manufacturer to do X, Y and Z.

A lot of times, we will have reporting requirements periodically over a period of time. I can tell you first-hand, if we don't get the report, we call them up and say, "Where is the report? You are obligated." We put it in writing. We send it out and, if we don't get it, then we have several other options. Directed inspection; the reviewer can propose, because the manufacturer has not responded to the Office of Compliance, we would like to have a directed inspection to the firm. This can be done on a priority basis depending on the particular product involved or health issue.

In many instances, and I have triggered them myself, within a week or two or three or sometimes overnight, we can have inspectors into the plant. They know what the problem or the concern is and the headquarters is often on the phone on a daily basis with the inspectors because they are not the headquarters reviews and they will need a little bit insight. We have got a very good working relationship in that regard.

Does the help to answer some of the concerns?

MR. DUBIN: Yes.

DR. TUAZON: I know that the genotyping and phenotyping assays are being used clinically right now. What regulatory measures do we have on those used at the moment?

MR. WILSON: There are no cleared or approved tests by FDA. The products I assume you are talking about are those that would be generically identified as "home brew?"

DR. TUAZON: They are really done by the labs do our routine testing for HIV patients.

MR. WILSON: Right. But the actual reagents, themselves? They build the test themselves?

DR. TUAZON: These labs that we sent through the medical centers are sent through diagnostic labs like LabCor or Quest Diagnostics.

MR. WILSON: There is--and this can get a little bit complicated so I am going to try to give a short answer but there is a regulation called the ASR Rule, analyzed specific reagents, which has requirements for some home-brew types of products. I guess I can say that, with the outcome of this vote here, that may have some effect on the regulation of those types of tests.

But the objective of that would be to level the playing field. I think it is important to bear in mind that--I think all want good-quality tests of high integrity

that have the reliability, et cetera. Whether it is a home brew or whether it is regulated by FDA as a normally distributed commercial product, it should work well.

So we have got two arms for regulation, one for the home brew and the other for traditionally commercially distributed products.

DR. HOLLINGER: Thank you, Mr. Wilson.

Dr. Tabor?

DR. TABOR: Just in further answer to Mr. Dubin's question; provided there is no negative impact on the public safety, the use of the 510(k) mechanism is resource saving for FDA because a lot more FDA human resources have to go into the review of a class III device than a class II device.

DR. DAYTON: Let me elaborate on some of the questions that Len just answered and, in particular, let me start with Dr. Hollinger's question about special controls and how you would choose between class II and class III. Let, of course, gave a very accurate answer but the way I wanted to elaborate on it was to portray to you how we feel this decision should be viewed for this particular product today.

Imagine--you don't have to imagine. Take a mutation which gives you well-documented resistance to a certain drug. Let's assume that there is a long history in

the literature studying that mutation. You see it appear in patients when they are on that drug. If you switch to another drug, it disappears, they do better, et cetera, et cetera, et cetera.

This would be the kind of data that we would consider adequate to let this product be regulated under class II. In other words, there is a lot of data in the literature. It is well-done. It is well-known. It is well-characterized. And we don't see a particular need for clinical trials, premarket.

Take, by comparison, another mutation. Let's say there is one study which shows that it appears when patients are on a particular drug. We would want to see more data for that second type of mutation.

The way we would like to handle this is we would like to--the postmarketing surveillance, essentially, is claim specific. So the way that we would handle this is we would like to let a product under class II regulation go to market for the first type of mutation to back a claim for the first type of mutation.

So, in other words, the assay could claim to pick up that particular mutation which is well characterized and that would be of benefit to the patient. If they wanted to have an additional claim for the second type of mutation, the one which isn't so well characterized, they would have

to submit additional data in the postmarket period to get that claim.

We feel that, by splitting it up like that, we can get these products out there fairly quickly and we can also control them very effectively. The whole issue of claims is very important because that is what the postmarketing surveillance will address. Postmarketing surveillance will, in part, be largely claim-specific. It will address additional claims.

In terms of FDA mission, even if there is one mutation out there and it is clinically relevant and an assay can pick it up and can redirect therapy, that is benefit. That is clinical benefit.

In the real world, we believe that there are mutations which are fairly well characterized. There are a lot of mutations which are less well characterized. In fact, Dr. Mayers and Jeff Murray will be presenting data to show that, actually, these assays are clinically beneficial. We believe that the reason for that is because the mutations--there are mutations that are correctly characterized.

I think that those were the key issues that I wanted to address before I sort of give the introductory talk to the next two speakers.

[Slide.]

The highly-active antiretroviral therapy has been a tremendously successful approach for treating HIV infections. Unfortunately, it is not perfect and it is still plagued by therapeutic failures. Mostly, therapeutic failure is heralded by falling levels of CD4-positive lymphocytes and rising levels of circulating HIV.

However, these two parameters are not always inversely correlated and they are, at best, indirectly measurement of therapeutic failure. Consequently, there is an increasing need for more accurate and more direct measures of therapeutic failure, particularly measures which identify the mechanism of therapeutic failure.

[Slide.]

HIV drug resistance assays promise to fill this need. One of the most common, but by no means only, causes of treatment failure is the existence or emergence of virus species resistant to the drugs included in the regimen. Various categories of assays exist to measure HIV drug resistance.

As general examples, in one approach, virus is isolated from a patient, expanded, titered and tested in replication assays in the presence of antiretroviral drugs. In another approach, the reverse transcriptase and/or protease regions of the infecting virus are isolated and subcloned into well-characterized laboratory strains.

These derivative viruses are then expanded, titered and tested for drug sensitivity and resistance. Dr. Murray will go into more detail on the types of assays currently available, but these assays are time-consuming, laborious and ill-suited for use in general clinical laboratories.

[Slide.]

HIV genotype assays have been developed as a relatively simple, cost-effective measure for determining the drug resistance sensitivity profile of HIV in infected patients. These assays can either be based on direct sequencing technologies or on hybridization technologies. The information they produce is the nucleic-acid sequence or genotype at critical codons of reverse transcriptase and protease which are known to be critical for determining drug resistance and sensitivity.

In other words, genotype assays determine the viral genotype and use this information to predict viral phenotype which, for our purposes today, is the clinical phenotype which, in this case, is the drug resistance sensitivity profile of the circulating virus or the expected response of circulating virus to clinical intervention.

[Slide.]

The predicted phenotypes are then used to guide treatment choices for patients identifying to which drugs

the predominant viral species is resistant. This information is used with information about the patient's previous viral regimens and it can be useful in choosing new regimens in patients experiencing therapeutic failure.

So it is an important point to realize that these are not stand-alone assays. These are used in the context of the entire clinical picture of the patient. In fact, as you will learn later, these assays often will not detect minor species and there can be minor species of resistant mutants left over from previous antiretroviral therapy.

[Slide.]

The motivation for FDA's desire to downclassify these genotypes is that we feel it would be an overall benefit to the public health. Downclassification would allow enhanced physician access to these assays by allowing sponsors to go to market with premarket clinical sensitivity and specificity data, allowing postmarket clinical-trial data to further correlate assay prediction with clinical responses.

This would significantly facilitate clinical trials for new drugs and therapeutic regimens. As I said, the relevant science can be complex and incomplete but it is FDA's opinion that sufficient information exists to insure a significant level of efficacy of these assays by formulating an appropriate set of special controls.

In other words, we feel that, although we are not perfect, there is enough science out there that we can sit down and say, this is what needs to be done. We can identify these studies and they will tell us whether or not these assays are going to be beneficial.

It is also FDA's opinion that postmarketing studies can be designed to further improve the efficacy of these assays as increasing scientific knowledge is obtained.

[Slide.]

We are drafting a guidance document outline requirements anticipated for regulation of HIV drug resistance assays as class II medical devices. Obviously, we won't go very far with that document. If you decide to regulate it a class III, we will just recast it as a class III document and change the ideas.

This document,as it stands now, addresses issues pertaining to assay precision, reproducibility and accuracy, quality control of reagents, laboratory testing and pre- and postmarket clinical data requirements. FDA's current thinking about the contents of this guidance document is contained in a September, 1999 concept memo which covers highlights of the guidance document and which has been included with your pre-meeting materials.

What we gave you in the pre-meeting materials doesn't cover all of the details in the guidance document

such as the manufacturing controls. We tried to limit it to the critical issues which are relevant to your decision here today.

Over the course of the next few minutes, I will review these highlights with you.

[Slide.]

First, we start with the nonclinical laboratory data and we focus on validation of phenotypes predicted by genotyping. I will start out by saying that in this part of the guidance document, we expect to attract a lot of comment, a lot of discussion. The guidance document will be put out in draft form for public comment after we have cleared it in-house and there will be a lot of scientific input to it at that point.

What we are thinking about now, as an example, is that, in general, sponsors will be expected to validate claims that certain genotypes predict certain phenotypes. We expect that validation studies will include in vitro viral-replication assays and determination of the effect of a given genotype on the 50 percent or 90 percent inhibitory concentrations of the drugs in question.

We are also entertaining the concept that when non-clinical validation studies demonstrate an eight-fold or greater increase in the IC50 or IC90 associated with a given resistance mutation, validation may or may not also include

certain types of clinical validation studies of individual mutants.

We also expect that when nonclinical validation studies demonstrate a less than eight-fold increase in the IC50 or IC90 levels associated with the mutation that validation will require clinical validation studies.

[Slide.]

We have requirements for analytical sensitivity. We assume that we will ask sponsors to perform sensitivity, precision and reproducibility studies on spiked samples and anticipate that sponsors will submit sensitivity data for all single and multiple mutations for which a claim is sought. Basically, what we are saying here is if it is there in the tube, can you measure it? Can you sequence it?

The sensitivity studies should determine and validate both the minimum viral level and the minimum mutant proportions reliably detected by the assay. So we want to know can you pick this up if your viral load is down at 1,000 copies per ml, or does it have to be up at 10,000 copies per ml.

If the resistant mutant is present as 5 percent or 10 percent or 25 percent of the infecting population, can you detect it? We assume, but it may not necessarily be true that the assays will demonstrate in these studies sensitivity at viral levels which are clinically relevant.

Certainly, that is our preference.

FDA also anticipates requiring accurate titration of sensitivity through and below the minimum detectable levels and proportions. Basically, we want to know how quickly does assay performance deteriorate with decreasing levels or proportions of the analyte.

[Slide.]

Clinical data. A key issue here is going to be validation of the phenotypes predicted by genotyping because that is the key question. Our current thinking is that validation studies should, optimally, include determinations of the existence or appearance of a given phenotype in patients subject to antiretroviral therapy as well as correlation of the disappearance of a given mutation with changes in antiretroviral therapy.

Throughout these studies, FDA will probably want to see data on overall viral burden, as well. We are considering the possibility that viral burden may be an adequate indicator of response to therapy for particular drugs. FDA may variably recommend or require clinical studies to validate the phenotypes of individual mutations according to the changes in IC50 and IC90 determined by in vitro viral replication studies.

Basically, what we are saying is, let's see how good your in vitro data is and then we will decide whether

or not we will need additional studies. Certainly, we will be interested in seeing data in the literature as well as data done specifically at our request.

[Slide.]

For clinical sensitivity, one of the things that has been proposed to be done is to do sensitivity and reproducibility studies on a panel of unspiked specimens whose genetic makeup is known. Basically, somebody is going to have to, presumably, sponsor, or industry, is going to have to take a bunch of patients, get specimens on them, determine what the distribution of the viral swarm, or the quasi-species, is and then show that they can always pick up the mutations that they are looking for, or can pick them up with a certain sensitivity. These would be unspiked samples.

On this particular issue, of course, and, as on all the others, further discussions will determine whether or not the panel must include representatives of all genotypes to which a claim is sought.

[Slide.]

The FDA is also considering requiring traditional clinical trials in which assay phenotype predictions based on genotype correlate with changes in viral burden and/or mutant representation in response to antiretroviral therapy. FDA may also allow these studies to be prospective or

retrospective on archived specimens.

[Slide.]

To facilitate these things coming to market, we are giving serious consideration to the concept of requiring either the panel-type clinical studies or the traditional clinical trials but not both to be submitted premarket. Now, certainly, a manufacturer could submit both premarket if they wanted to, but we feel that there is a likelihood that we will be willing to say, "Well, look; if you have got the clinical-trial data, you can do the panel-type data postmarket." Or, "If you have the panel data and you want to go ahead, you can get some of the clinical-trial data postmarket."

In this case, FDA would anticipate requiring the alternative studies to be submitted postmarket, as I have just said.

[Slide.]

As we have discussed here, we are almost surely relying on extensive postmarket studies to further support claims made during the approval or clearance process as well as additional efficacy claims; for instance, new correlations between phenotype and genotype.

[Slide.]

In being asked to classify HIV drug resistance genotype assays as class II medical devices, you are being

technically asked to vote on the classification and on the adequacy of special controls. This presents a little bit of a quandary for you because the special controls are outlined in the guidance document and we have only given you highlights of that guidance document, and it hasn't been finished.

Although the special controls are in a guidance document which is currently in draft format only, we feel that the information presented today will convince you that the clinical and scientific data in the literature are such that our expertise, together with the expertise of all of the scientists, clinicians and members of the general public who choose to contribute to the final document will be sufficient to formulate adequate special controls to insure efficacy and safety.

So, in the upcoming presentations, what you need to look for is does it look like the field is at a point where the field can sit down and identify adequate special controls for at least some mutations which would allow these kits to go to market with such identified special controls.

With that, we have some presentations. Who is up first? Doug? We have going to have Doug Mayers talk. We will entertain questions, but one thing I did want to say in response to Dr. Hollinger's question about class III regulation of viral-load tests. Len was really quite

accurate. We know a lot more now with these tests that are coming to market, or are coming up, the genotyping tests than we knew in the early days of viral-load testing.

There are going to be a lot of questions. I am certainly happy to entertain questions now. You are just about to get two talks that go into the scientific and clinical literature in much more detail than I have described it. So I am certainly willing to answer questions, but if you think it might be answered in the next two talks, you are certainly welcome to wait.

DR. HOLLINGER: It doesn't look like the committee thinks they can wait.

DR. VERTER: It's a good try, though. In trying to read some of the documents last night and listening to the two presentations this morning, I wonder if you could clarify--I am still having trouble understanding the II/III issue. From what you just described, it seems to me almost like a very fine line. In fact, it almost came down to the statement, "Considering the concept of requiring either the panel-type clinical studies or the traditional clinical trials, but not both," whereas, in a III, do you require both and in the II only one? Can you give me some feel about that?

DR. DAYTON: We are kind of skirting the issue a little bit there. And it is confusing. I think one key

point to make is we can make class II regulation as stringent as we want it, if we really want to. So we can make it as stringent as class III, basically.

What was the second part of your question?

DR. VERTER: I was just trying to clarify in my mind, and maybe in some others, as to where the fine line is. I understood what you just said and I thank you for that comment.

DR. DAYTON: The real question is, as I said, does it look like we can identify special controls or studies that are going to make this thing effective, even partially effective. The critical issue is not so much whether we require one pre and one post. That is something that we are thinking of.

The real issue is does the science say, "Look; the field is far enough along that some mutations can be fairly well guaranteed to be relevant in measuring them and, therefore, be effective. That is the key issue.

Have I answered your question? Have I addressed it?

DR. VERTER: You have addressed it.

DR. MITCHELL: Can you tell me what do you mean by panel-type clinical studies? Is that presenting panels of known--

DR. DAYTON: It would be--basically, as the

proposal stands now, we somebody would assemble a panel of 50 unspiked patient specimens. Presumably, they would take each one and they would make multiple clones from them by standard microbiological techniques, sequence them in the regions that we are interested in, and come up with a description of the distribution of quasi-species in the viral swarm.

So, for instance, if there is a particular mutation you are looking for, it might be there 10 percent or 1 percent or 25 percent. Then you would take a panel of these and you would challenge them. You would put them through your assay as opposed to subcloning and sequencing and everything. You would put them through your one-shot assay and you would see how well you pick up the mutations that are there and at what concentration.

In a way, it is like the spiked panel studies except that it is unspiked. It is a more natural environment. And it is a tougher challenge. Does that explain it?

DR. MITCHELL: Yes. Thank you.

DR. BOYLE: I think I am grappling with the same thing everybody else is, but let me see if I understand correctly. In a class III, you would normally require clinical trials before it be approved for use in the marketplace whereas, in a class II, you might require

clinical-trial data but it could be done postmarketing?

DR. DAYTON: Well, no. In a class II, we actually could require clinical trials premarket if we had to. That is an option. But what we would be doing in a class II situation, in the situation we would like to do, is looking at clinical data in the literature and be able to say, "Look; these mutations here are really quite well established so we are quite confident that they deserve a claim for that."

But there are this whole set of other mutations over here that we know a lot less about. So, if you want to claim them, you come back postmarket. You can go to market but you only get a claim for the first set of mutations and you only get the second set of mutations when you come back and prove it.

But, again, it could be data in the literature, not necessarily clinical-trial data. We could also specify clinical-trial data in postmarketing, which we may do.

Len, did you want to comment on that question?

MR. WILSON: Maybe I can help out a little bit. I am going to use an example of something that already exists, CMV assays, class II medical device. The intended-use statement goes on the line of to detect antibody to CMV in the serum of blood donors, or some such. It doesn't say, for the prevention of CMV transmission. It doesn't say

that.

If it said for the prevention of CMV transmission, you would have to run a clinical trial to show that it does that. But since it is limited to for the detection of CMV antibody--all right; what is the content of the 510(k) class II. Many of the concepts that Dr. Dayton has described are just, simply, reproduced in the class II.

We have analytical sensitivity data, analytical specificity data. Because it is used for the blood supply, we run a study that is in blood donors to check specificity because you can't check specificity in a blood-donor population any other way than running it. And why would we do that? Because we don't want to have too many units of blood tossed out because of false positives.

We do have, and I think along the lines of where Dr. Dayton is going, some known positive samples that we would test--the manufacturers would use the test to determine whether or not, in fact, they truly detect a true positive. But it is not in clinical-trial format in that sense.

So, therefore, that enables FDA to clear the product with claims or labeling limited to what the thing has been documented to do. So, in terms of this particular assay, there are a lot more questions and we know that, because of viral resistance and mutations, things are going

to change and the logical issue is that there are going to be new mutations and how does this correlate and the like. That could be done in a postmarketing surveillance type of order.

I hope that helps.

DR. DAYTON: If I can continue on; what I think you will see in the later presentations is that there are quite good laboratory studies for the significance of various mutations. There is data for the appearance and disappearance of these mutations in the literature and there are also studies coming out showing that use of these types of assays has clinical benefit.

So, if you put all of that together, that is really telling you a very strong message; hey, these things work. What we would be saying is, "Okay; these things work but we want to see more in the postmarket."

Does that answer your question?

DR. BOYLE: Yes.

DR. FITZPATRICK: You said the panels have not been developed yet. When we began HIV testing, there were difficulties developing reliable panels in enough source to be provided to all the laboratories doing testing to get similar results. Is your expectation that this is much easier now?

DR. DAYTON: We are leaving that up to sponsors at

the moment. We are certainly open minded about how to actually approach this. It should be reasonable for a sponsor to assemble his own panel which might be the quickest way to do it, but it is quite laborious.

It would be also possible to have a centralized panel set up. Also a sponsor has the alternative of coming forward with the clinical-trial data while he waits--and doing the panel postmarket. We are trying to make it flexible so that it can go either way.

I think Ed wants to comment on this.

DR. TABOR: I think the discussion is confusing the issue tremendously.

MR. DUBIN: We have done that before.

DR. TABOR: I think part of it is that it is focussing on constructing panels and focussing on postmarketing surveillance. The issue is between whether this should be a class III device or a class II device. The discussion should have nothing to do with blood screening because a test that is used for blood screening usually is a licensed product for which a PLA is filed.

What we should be focussing on is is the clinical impact of this assay so great and, perhaps, so unknown that you need clinical trials and to file a PMA and have an 180-day review clock which really translates into more than a year of review time with resubmissions or is the clinical

significance of this so clear and is the impact on the patients' health more an issue of management than of life and death such that the manufacturer can file a 510(k), have a 90-day review clock, and have minimal or no clinical data.

Postmarketing surveillance is another issue, I think, here. It is not totally divorced from this but you shouldn't be focussing on something that you want clinical data and you are going to wait and get it after marketing. If you want clinical data, it should be a PMA and a class III device.

The question here is are the manufacturers going to have to go through a longer review cycle with more clinical data up front or are they going to be able to file a 510(k) with only special controls and any clinical data, really, as icing on the cake.

DR. DAYTON: Let me just elaborate on Ed's response. It is absolutely correct. Again, don't feel that you are having to judge a particular product. You are asked to judge, is the science such that we can judge a product, or that a product can be judged.

DR. HOLLINGER: I think probably we ought to listen. I think that the next step should probably be to listen and see what the data is out there and see what it means. Let's have one more and then let's go to some of the data.

MR. DUBIN: I was going kind of towards where you were going, Dr. Tabor. Here is how we frame the question. I think, from our perspective, the big plus is if this is going to give clinicians who are actually, at the grass-roots level, treating patients and dealing with resistance problems, then that is going to give the clinicians more freedom and more ability to move.

I think, from our perspective, that is clearly a good thing because, certainly, in hemophilia, this is a big problem in the infected hemophilia community. We are having a lot of problems with the resistant strains and a lot of our guys are in trouble.

Our only concern, and the way I was trying to frame it, was we have had concerns about how fast-track has gone, things that have happened and have caught our attention and concerned us. But I think, in this instance, the issue is, and I agree with you, if we can do this in a way that provides the freedom to the clinicians and the ability to track it, then it seems like a no-brainer on one level from our perspective.

DR. STRONCEK: I have a couple of comments. There are a number of HLA tests where genotyping is used to determine phenotype which are marketed so I presume they are regulated. Are those regulated as class II--class II, I would presume.

The other question is are the current NAT tests being done on blood, are they regulated as class III? Ed seemed to suggest that it is something different. Then, if that is true, I am really confused.

DR. TABOR: Let me answer your second question. The NAT test to be done on blood, or for blood screening, they will be required to file a PLA or BLA for licensure the same as for any of the other required or recommended tests for screening blood. There was a very big regulatory issue about two years ago when the manufacturers wanted to just go ahead and do the testing. And we said, "No; there are a number of issues that make this a blood-screening assay."

So those will be PLA tests that are being done under IND now, and they are totally separate from what we are talking about here.

With regard to the HLA test, I think someone from Devices will have to answer that. I am not familiar with that.

DR. DAYTON: I don't know the answer to that.

MR. WILSON: Those HLA tests which are used that are labeled for the detection of the antigens are predominantly class I. There are some which are class II. I am talking about the ones that are non-diagnostic.

DR. BUCHHOLZ: Just having watched this from an industry perspective for a number of years, I wonder if I

could try simplifying a little bit this class II and class III.

I think, back in 1976 when this device legislation took place, there was an effort to kind of establish risk categories associated with a device. A device, class I, not much risk if something goes wrong; class III, a lot of risk if something goes wrong.

I think, in some of the original language, there was the concept of life-sustaining device for a class III device, like an implanted pacemaker. I think the thing that is probably confusing the committee is that there are now some things that are, by fiat, put in class III because there was no predicate device; by that, there was no device like what we have today because the problem didn't exist.

So those devices end up being bumped in this class III category until they can get dispersed into, perhaps, a more appropriate category.

Does that help a little bit?

DR. HOLLINGER: Thank you, Don.

Why don't we go ahead, Andy.

DR. DAYTON: I guess we are ready for Doug Mayers.

Presentation

DR. MAYERS: I want to thank the FDA for making drug resistance interpretation seem simple.

[Slide.]

What I would like to do in the next forty minutes or so is go over the background of HIV resistance testing, a little bit about the biology of HIV resistance and then overview the current clinical data both retrospective and prospective. By nature, this is going to be a survey and not exhaustive because there are far too many studies today than the time I have to present them.

I just want to make a caveat that I will occasionally use a company slide in this talk because I didn't have a slide to illustrate the point, but those slides are made to illustrate a biological point and not the support any company and, where possible, I have used every company in the area's slides, one of each, so they don't feel like they have been slighted.

[Slide.]

It is important to recognize of HIV that the replication of the virus is very rapid in a patient such that patients make up to a billion particles each day with a half life of about one day.

[Slide.]

The reason this is important from an HIV resistance point of view is that the virus, as a replication strategy, makes, on average, one error per each progeny virus. So, if a billion viruses are produced and you have a 10,000 base virus making, on average, one error, that means

you have 100,000 of every single-base variant and about ten copies of every double-base variant in your patient.

So when you have these discussions of do drug-resistant viruses exist at some level, yes, in all of our patients, they exist and they are spontaneously produced every day in the patient. This is the virus' strategy to escape immune pressure and it also uses it to escape drug pressure.

[Slide.]

In 1989, two years after AZT was introduced into clinical practice, Doug Richmond and Brendan Larder had a paper that came out in Science. What they showed was that viruses were produced in our patients that were 100-fold less susceptible to AZT than when they started therapy.

This shows the phenotype assay results from that paper. What you have on the vertical axis of this is the amount of virus replication relative to a no-drug control. On the horizontal axis is drug levels. What you can see in the upper left-hand panel, C, is that for the virus in light blue that the virus is susceptible to AZT and it takes about 0.03 micromolar of drug to suppress it.

Then, as you watch the viruses over time, you can see that you move out to the yellow virus which is obtained a number of months later and now the virus is 100-fold less susceptible to AZT and it takes about 3 micromolar of drug

to suppress it.

We were very lucky with AZT. You have an 100-fold difference between sensitive and resistant virus so it is fairly easy to pick out what resistance was. This is the standard type of phenotypic test that would be reported out to the clinician.

[Slide.]

About six months later, Brendan Larder and Sharon Kemp took paired isolates from that original study. They took studies from before the patients had seen drug and a sample of virus when the patient had highly drug-resistant virus. With six pairs, they were able to show that there were four mutations associated with AZT resistance at positions 67, 70, 215 and 219.

Over the years after that, two more mutations were associated with AZT resistance but most of the story was well explained with six paired isolates. This would be the resistance-associated mutations or a genotypic assay. So you can either grow the virus in the presence of drug or you can look for mutations associated with resistance.

[Slide.]

Once we had these assays available, we were fairly quickly able to show what was associated with the development of resistance; host factors, either advance disease or low CD4-cell counts, virus factors such as very

high levels of HIV RNA in the blood, baseline drug susceptibility and antiviral drug activities, the virologist's paradigm being that if you don't have a drug, you don't have drug resistance.

[Slide.]

Looking at the emergence of resistance, there are three patterns that we see in the clinic. There are some drugs in which you see very rapid emergence of very high-level resistance. These are drugs such as 3TC and the non-nucleoside agents. The reason you see very high-level resistance emerge quickly is that a single-point mutation will produce a hundred- to a thousand-fold resistance to these drugs.

So these viruses preexist in the patient and if you do the calculation, you expect it would take about fifteen days for them to emerge under drug pressure. In monotherapy studies, it took about fifteen days for these drugs to produce high-level resistance. So these are the drugs in which it has very clearly been associated with the loss of activity is associated with single-point mutation.

The next drugs take a moderate amount of time, usually three months or more, to get high levels of resistance. And these would be drugs such as zidovudine, abacavir and the protease inhibitors. The reason these drugs take a bit longer to get high levels of resistance is

you have to have a number of mutations. So it takes the accumulation of three, four or five mutations to get high-level resistance and it takes the virus a period of time in the presence of drug to get to those high levels. But it is fairly easy to describe what resistance is in them because they do get the high levels of resistance.

The last group of drugs, ddI, ddC and d4T are really where much of the controversy of interpretation of resistance assays comes from. From these drugs, you never really get very high levels of resistance in the clinic with the drugs. You get four- to five-fold resistance which is almost within the assay variability of a phenotypic assay. So there always a fair amount of debate as to what ddI, ddC or d4T resistance is. This leads to some of the variability in the reports that the clinicians receive from the laboratories.

[Slide.]

Looking at a crystal structure of the reverse transcriptase, what you can see is that along a loop between about bases 65 and 75, there is a whole string of mutations associated with nucleoside resistance with multiple different agents. And so it wouldn't be surprising that resistance to one drug might be associated with cross-resistance to other drugs in the class.

[Slide.]

This has clearly been shown. For zidovudine, it produces low levels of resistant to ddI and ddC as you get high levels of zidovudine resistance. But, more importantly, it has been shown that once you have high-level zidovudine resistance, combinations of AZT-ddI and AZT-ddC did not lead to clinical benefit.

For 3TC, abacavir, ddI and ddC, these drugs all have overlapping mutations. Clearly, one drug will produce mutations at some level of decreased susceptibility to the other drugs. And d4T hangs out by itself because we really, even in 1999, don't understand d4T resistance very well.

[Slide.]

An aspect that has been very interesting to virologists but it has complicated things for the clinician is that the virus can take numerous routes to get the high levels of resistance. The good news from a clinical point of view is that the vast majority of isolets do it the way you would expect. They get AZT resistance. They get 3TC resistance. They add the classical mutations together to produce a high-level resistant virus.

But, in the last year or two, we have discovered that a small number of patients can go down a different pathway of a 151 mutation and, even more fascinating, the virus can actually add six bases into that loop I showed you and produce high-level resistance by an insertional mutation

which we never expected to see, but it can be easily identified.

[Slide.]

From a clinical management point of view, though, the vast majority of our patients are failing with 215 and 184 with associated other nucleoside mutations. So, from a clinical point of view, the overwhelming majority of patients fail with known mutations and known resistance patterns.

[Slide.]

Moving to the non-nucleoside drugs, the non-nucleoside drugs have a totally different pocket from the ones of the nucleosides. The picture has actually become relative simple in 1999 because of the use of the non-nucleosides in combination with either AZT or d4T. The vast majority of the non-nucleoside agents right now are failing with a mutation at position 103, a single-point mutation called K103N. This mutation, essentially, inactivates all of the non-nucleoside drugs.

[Slide.]

This just shows, in a number of clinical isolates, that isolates that only had the 103N mutation with non-nucleoside resistance had developed significant decreases in susceptibility to efavirenz, nelvirapine and delavirdine.

[Slide.]

Moving to the protease enzyme, the protease enzyme has sort of a bewildering assay of mutations that you can see but, in all honestly, only about five or six of them are really critically important to high-level resistance. Those are shown in this model by the red balls. They are the mutations that tend to occur in the active site of the enzyme and produce resistance.

There are a number of other mutations that are associated, in this figure with the yellow or white balls, and these are compensatory mutations. What you see the virus doing in patients is the virus will develop a critical-site mutation, a red-ball mutation, and get some level of resistance. But then it doesn't grow very well. It doesn't cut proteins as well as a protease so it adds in two or so of the compensatory mutations. Then it adds back in another resistance mutation and it works its way through fitness base.

But, for the practicing clinician, what you really need to do is just count how many critical-site mutations were there.

[Slide.]

This shows the critical-site mutations for the drugs that are currently available. For saquinavir, it is 90 and 48. For indinavir, it is 82, 46, 84. Nelfinavir, it has been the D30N, usually L90M, occasionally. And for

amprenavir, it appears to be a 50 mutation.

[Slide.]

An issue that has caused real concern of resistance was initially data from indinavir where they showed that if you had high-level phenotypic resistance to indinavir, there was a loss across the class of resistance. For ritonavir, it is 100 percent. For saquinavir, it is 60 percent. Nelfinavir, it is about 75 percent. And, with the newer data for amprenavir, it is probably closer to 55 to 60 percent of these isolates would be resistant.

This is one place, as we will see later, where genotyping hasn't been as useful as we might have liked and phenotyping actually has been very useful to help find which of the lucky patients has sensitivity to one of the proteases that remains.

[Slide.]

For nelfinavir, this appeared to be different and amprenavir it appears to be different in that initial resistance to one drug does not produce cross-resistance to the rest of the class. A concern that has come up has been that, even though they don't have primary mutations that are cross resistant, they share a lot of the background polymorphisms and the compensatory mutations and so, are you one mutation short of disaster.

[Slide.]

It appears that may actually be the case for these drugs so that you can get a good response with the next agent but you have to totally suppress the virus or you can rapidly see broad class resistance emerge after that type of protease inhibitor.

This just shows that the addition of a single V82A mutation took a virus from totally ritonavir-susceptible to highly ritonavir-resistant.

[Slide.]

The slide illustrates the point that in the management of patients on protease-containing regimens that a single-point mutation will lead to the initial loss of antiviral activity but if you leave the patient on the protease inhibitor for any extended period of time, you will see the sequential additional of multiple mutations.

The reason this is important is that is important is that, in most instances, there is low-level resistance associated with single-point mutation and not very broad cross resistance. But once you get to five and six mutations in the virus, you have a virus that is highly likely to be both highly resistant and relatively broadly cross-resistant.

[Slide.]

This is just some data that came out of a recent meeting in which they looked at patients who had had several

PI regimens. They looked at ten-fold decreased susceptibility to any of the available agents and showed that about three-quarters of the isolates had decreased susceptibility to all of the agents by the time they got there.

[Slide.]

Switching over to susceptibility testing, the sort of gold standard for susceptibility testing was an assay developed in 1990 between the ACTC and the Department of Defense in which we took patient isolates, we grew them and expanded them, titered them and assayed them for drug susceptibility on patient-donor lymphocytes.

[Slide.]

This assay allowed us to look at roughly 95 percent of the patients and look at how they were failing on drugs. This just shows the susceptibility pattern. The green and the yellow are pre-therapy isolets--the white and the red are post-therapy isolets--that were obtained from that original study the Doug Richmond did back in 1989.

[Slide.]

The nice aspect about this assay was we had reasonably good quality control. You could note susceptibility within about three-fold. Sort of a standard of thumb has been that if the decrease in susceptibility is less than three-fold for these types of assays, you are not

really sure if it is resistance or just assay variability.

The newer assays may be able to get down to the two-fold, two-and-a-half-fold, but I think the two- to three-fold is about as close as you can know a phenotype on a virus.

[Slide.]

We were able to actually set reasonable cut points for sensitive, partially resistant and resistant that actually had clinically validated meaning. The sensitive of less than 0.2 micromolar was based on patients' isolates who had never seen drug and the range of susceptibilities in wild-type virus. Resistant was associated with loss of clinical activity and clinical disease progression.

[Slide.]

The problem with this assay is illustrated in this chart. Times 0 on the bottom is the time at which phenotypic resistance emerged in these patients. This was a study done in about 1993. What we showed was that patients who always remain sensitive had good stable CD4 counts. The unfortunate news was that, by the time we saw phenotypic resistance from a co-cultured virus from the cells, the patient was already failing by enough--had had about a 50 percent CD4 decline and so the clinicians didn't need our assay to tell them that they were not doing well.

[Slide.]

About this same time, data began to emerge from 3TC and also some of the AZT studies that, if we took the plasma virus and looked at that for mutations or susceptibility that we could actually detect resistance very nicely at the beginning of the rise in the viral load as opposed to the PBMCs where it took a bit longer to show up.

So most of the focus on resistance testing has moved from trying to take cells in coculturing virus to looking at the virus that is circulating in the plasma in an individual patient.

[Slide.]

Currently, all of the assays available, either genotypic of phenotypic, basically PCR a segment of the virus that includes the protease gene and the early 250 to 300 bases of the polymerase gene which is where we have identified resistance mutations. So, basically, you lift out from the plasma the protease and part of the RT gene and then, for phenotypic assays, you clip it into a vector and grow it up. For genotypic assays, you sequence it.

[Slide.]

This just points out that we have to PCR amplify for all the assays we use on that segment of the genome.

[Slide.]

This just shows what a sequence looks like that we are actually doing. The sequence with the arrow over it

shows the detection of the emergence of a subpopulation of virus. So, basically, you either have a peak by itself which can be described as a single amino acid or you have a peak where there is a mixture. Those can be associated with minority populations of virus.

For all the assays we use for genotyping right now, they all use population sequencing and we basically can pick up somewhere between 30 and 50 percent minority populations. So these assays clearly do not pick up minority populations well. We are not picking up 5, 10 percent virus. We are picking what the predominant circulating virus is in all of these assays.

One of the difficulties with doing these assays is also illustrated by the arrow in the second row because the mutation they are pointing out isn't associated with resistance.

[Slide.]

For the common viruses, we take that same segment of the genome. We PCR amplify it, put it into a deleted vector, grow it up and then test it against drugs. The reason that this has been, I think, very useful in the development of resistance testing is that this allows us to not have the alterations in the virus associated with growing it up for long periods of times in cells. It also speeds up the process so, instead of taking six to eight

weeks to get a phenotype back to the clinic, the new RVA assays can turn a result around in about three weeks back to the clinic.

So it has been a significant increase in speed and it looks like there has also been an increase in quality control such that their variability appears to be less than the variability we had with the PBMC-based assays.

[Slide.]

This just shows the types of susceptibility curves that they can get. What you see here is the blue curve on all these figures is a control virus that they put on the plate, and the yellow curve is the clinical isolate. As you can see for 3TC, the virus has essentially no susceptibility to 3TC. As the curves shift toward the right, you are seeing increasing resistance. So these are the types of assays that the companies are doing for phenotypic testing right now.

[Slide.]

At this point, I would like to switch over to clinical relevance. This has always been a somewhat contentious topic.

[Slide.]

For clinical significance, zidovudine is the only drug for which we have data for clinical progression and death. I honestly believe that we will probably never have

any other single drug for which we will be able to show clinical progression and death because of the use of combinations.

But, for AZT, we could clearly show with greater than 1.0 micromolar resistance at baseline if this was the associated progression and death in both the ACTG 116B, 117 study and a prospective study in the Department of Defense with about a two-and-a-half to three-fold risk of disease progression. This was independent of the other baseline parameters available to us at that time.

[Slide.]

For the pediatricians, this is a similar study looking at the 215 mutation in plasma virus. What they did was, the yellow dots are the children who had no disease progression and were doing quite clinically well. The orange dots are the children who were progressing and having disease progression.

What you can see is that the children who had no disease progression also had no evidence of the 215 mutation and the children who were progressing developed increasing amounts of the 215 mutation in their plasma virus and it was strongly associated with disease progression in this cohort.

[Slide.]

The companies have been doing a very good job recently with the new drugs in defining the phenotypes and

genotypes associated with loss of activity of their drugs. This is illustrated in this slide from abacavir where the company looked at abacavir in its clinical trials and found out that, if clinical isolates had less than an eight-fold decrease in susceptibility from a wild-type isolate that they could get a good clinical response and if it was more than eight-fold above the wild-type virus that they were not getting good activity.

They also were able to find the genotypes associated with lack of activity of abacavir. As you notice, they are the genotypes that are associated with a multi-drug-resistant, multi-nucleoside-resistant, virus.

[Slide.]

Similarly, for nelfinavir, they were able to, in expanded access, look at the major mutations associated with resistance and were able to show that--they could literally count major mutations and response was related to how many major mutations were present, or they could look at phenotypic susceptibility as broken by four- to ten-fold and show, again, a very nice association with decreased drug susceptibility phenotypically or presence of resistance mutations predicted who would respond or not respond to nelfinavir.

[Slide.]

Similarly, for ritonavir and saquinavir, they were

able to look at phenotypic and genotypic resistance. What they showed very nicely was that the predictors of failure were the same as we had seen previously for zidovudine, CD4 count, disease stage, HIV RNA, but also either phenotypic resistance or genotypic resistance predicted lack of response to saquinavir and ritonavir.

[Slide.]

Moving into broader-based clinical studies, Andy Zolopa and the group at Stanford looked at patients who received ritonavir and saquinavir who were all PI experienced. They looked at short-term virologic responses, and the clinical predictors were the same as we had seen previously.

Of note, drug history, number and prior duration of drugs predicted poor response and simply counting the major protease mutations, the red-ball mutations, I showed you earlier. If you simply counted them, the number of mutations in the virus predicted response to ritonavir and saquinavir. The more you had, the worse you did.

[Slide.]

Steve Deeks presented data at the same meeting which, I think, gave us a great deal of insight into what you need to get a good response in an experienced patient. They took eighteen patients who had received abacavir, saquinavir, nelfinavir and nelvirapine. These were all four

new drugs these patients had never seen. So they took four drugs that the patients were naive to. They looked at a phenotypic assay.

[Slide.]

What they showed was that seven of the patients had only zero or one active drug in the regimen by susceptibility testing. In those patients, none of them got a response. It was only very transient and none of them went below the limits of detection of the assay.

So this was showing the impact of cross-resistance in this population. Eleven patients had two or three active drugs. They all had a sustained response and eight of ten went undetectable. None of them had all four drugs in the combination active. What this basically told us was if you are going to get a good response in a regimen for heavily pre-exposed patients, you are going to need to find two or three active drugs to give that patient.

[Slide.]

That is the retrospective data. I am now going to move to the two prospective trials that have been done on genotyping. The first trial is the GART trial, GART standing for genotypic antiretroviral resistance testing. It was a trial done by the CPCRA in patients who had had a good response to protease-containing regimen and then lost that response.

The patients had plasma virus, had plasma sent in. The virus was sequenced. It was reviewed by a panel of three virologists; myself, Tom Merigan and John Baxter. We gave the clinicians back a report of susceptibility and we also gave them some recommendations for treatment at that time.

You have got to remember this trial started in 1996. The community docs really were not comfortable that they could take the sequence data and use it in clinical management at that time. So the test was a test of getting the sequence data with some suggestions versus using your own clinical judgment in the management of these patients.

It had a short-term virologic endpoint of 4, 8 and 12 weeks of follow up. The reason the data was chopped after 12 weeks was that the patients and their physicians were allowed to switch drug regimens if they hadn't had a good response during that time period. So the test was only relevant during that short period of time.

[Slide.]

Looking at the randomization, patients had about 230 CD4 cells, about 30,000 copies of HIV RNA. The majority of the patients had received nelfinavir for indinavir which was common to the community at that time. About half of them were failing on their first protease-inhibitor-containing regimen and the other half were on their second

or third regimen.

[Slide.]

Looking at the baseline resistance mutations, as we had shown previously, in this population, about three-quarters of them had both RT and protease mutations. About 20 percent had RT mutations alone. And 5 percent had absolutely no mutations in their virus. It is the impression of the clinicians and the virologists in the study that that 5 percent was probably not actually on drug at the time that these susceptibility tests were done.

Looking at the mutations, we saw, again, 184 and 215 were the overwhelmingly common human-failure mutations with only 1 or 3 percent of patients getting the insertion in the 151 mutation. And we had a variety of protease-inhibitor mutations.

[Slide.]

The bottom line was that if you use genotyping to assist in the management of the patient, we could get about a half-log better virologic response at the 4- and 8-week time point than we could by clinical judgment alone. And this was a highly significant p-value.

[Slide.]

This just shows the response over time and shows that, actually, the best response was, unfortunately, at four weeks and there was some paling off of response during

the 8- and 12-week time period as some patients got a transient response to drug and then resistance reemerged.

[Slide.]

But it should be noted that, at all time points, about twice as many patients were undetectable using resistance testing as they were if you just used clinical judgment alone. Even at the 12-week time point, about 28 percent of our patients were undetectable with genotyping and about 15 percent were undetectable with clinical judgment alone.

[Slide.]

A point of contention in this study has been that the patients who were getting the genotyping also received, on average, one more drug than the patients who were getting phenotyping based potentially on the fact that their docs could see the resistance data available.

[Slide.]

But we have actually gone back and reanalyzed the data. If you look for patients who got three drugs, four drugs or five drugs, at every number of drugs, the patients did better if they had genetic data to assist in the management than if they guessed with clinical judgment alone.

We think this actually explains the results of this trial. The green curve is the viral-load response that

you see in these patients. The blue bars show you how many active drugs were present in the no-GART arm and the yellow bars show you how many active drugs were present in the GART arm.

What you can see is that, on average, patients who got the genotypic testing were able to get one more active drug in their regimen than they could get by clinical judgment alone. The response the patients got was clearly associated with the number of active drugs they received. And so it appears that the genotyping allowed us to find, on average, one more active drug to give in a salvage regimen than you could give by clinical judgment alone.

[Slide.]

So the conclusion was that GART, with expert advice in patients failing antiretroviral therapy, was superior to no-GART as measured by short-term viral-load responses. In a greater viral-load response, reduction in GART was attributed to the greater number of active drugs prescribed.

I'm sorry I didn't bring the slides, but one of the truly impressive findings for us in the trial has been the robustness of this finding. This half-a-log difference held up over CD4 ranges, over viral-load ranges, over resistance profiles, over first failure, second failure, third failure.

Basically, any cell that had more than eight patients in the cell had a significant difference with genotyping.

[Slide.]

The second prospective study was the VIRADAPT study which was conducted in France. This was a bit different study in that there were basically a number of French clinicians at about three French medical centers who followed a series of patients and did genotpying and then would meet and discuss the results either with genotyping or without genotyping for the manufacturer of individual patients.

[Slide.]

It is a little bit smaller study. There were 43 patients in the control arm and 65 patients in the genotyping arm.

[Slide.]

The patients in the study were a bit more advanced than the GART patients. They had, on average, a plasma HIV RNA of about 150,000. The CD4 cells were about 200 to 220, and quite a few of them had actually had symptomatic HIV disease.

[Slide.]

If you look at their prior exposure, they were very heavily exposed. They had seen, on average, one-and-a-

half to two PIs when they came into the trial. They had had, on average, about four nucleoside agents and, again, about half of them were first-time failures and the other half were second- and third-line-failure patients.

[Slide.]

The results in this trial show that they actually got a sustained benefit to six months. The difference between this trial and the GART trial was that if you hadn't gotten a good response at three months, you could retest the patient at three months and go to six months. And so, in GART, you got one test, we followed you. In this trial, you got a test every three months.

The data went out to six months in a randomized fashion. As you can see, there is about a half-log difference between the two arms out to six months that persisted. They subsequently extended the analysis out to a year and they have had a stable reduction in RNA out to a year in these patients who could get repeated testing.

The trial was no longer randomized after six months because, once the GART results were released, the French unblinded the trial and took everyone over to genotypic testing.

[Slide.]

Of note, and very similar to the GART results, you can see that roughly 30 percent of patients were

undetectable in the GART arm and about 14, 15 percent of the patients were undetectable in the no-GART arm so, again, about a two-fold difference between genotypic testing versus clinical judgment alone.

These results have been remarkably consistent across these two trials that had somewhat different methodologies.

Also of interest, both trials used the same algorithm to interpret the data for genotyping. The algorithm is actually contained in table 8 of the Stanford Guide for the Management of HIV-Infected Patients. It is a little pocket guide.

[Slide.]

So in choosing an effective salvage regimen for patients who are failing on combination therapy, I think we have a number of clinical parameters available; number and duration of prior antiretroviral drugs, knowledge of cross-resistance patterns between the drugs.

This data can be supplemented with resistance testing. I think the bottom line is to have an effective salvage therapy in patients who fail combination regimens. You need to be able to find two or three drugs that remain active against the patient's circulating virus.

[Slide.]

The current dilemma is even with the availability

of repeated genotypic testing, we can only get 30 percent of patients suppressed below 500 copies per ml. This just emphasizes the need for us to continue to get salvage drugs available for these patients.

[Slide.]

In the last few minutes, I would like to go over the public-health data looking at resistance. This is the percent of patients with AZT resistance by year. Before 1987, we never actually saw an AZT-resistant virus in an untreated patient. In 1987, the drug entered clinical practice. It was available to about 20 percent of patients because you had to have late-stage disease to get access to the drug.

So, from 1987 to 1990, about 20 percent of our patients had access to AZT and there was about a 1 percent level of transmission of drug-resistant virus. In 1990, because of the 116, 119 results of the ACTG, there was an expansion of the use of AZT to patients with less than 500 CD4 cells. Two years after the increased indications for AZT usage, the transmission rate jumped to 7.5 percent and then actually moved to between about 8 and 10 percent for the next five years.

[Slide.]

So AZT resistance was seen at about an 8 to 10 percent level in new seroconverters from 1993 through

about 1996. In 1996, 3TC became available within a year. Because of a single-point mutation, 3TC-resistant transmissions were seen. The most recent data, as we have moved to a very broadened use of combination therapy, is that we are seeing an even increased risk of transmission of drug resistance. This is data from both the military and a cohort led by the group at San Diego.

What they showed was that, looking for resistance by phenotype and genotype, they found a level of somewhere between 20 and 30 percent of new infections were infected with drug-resistant virus in 1999. What has become a bit scary to the practicing clinician is an increasing number of these patients actually have multi-drug-resistant virus with both nucleoside- and either protease- or non-nucleoside-associated mutations.

[Slide.]

So I think we can actually categorize a number of high-risk populations for drug resistance; patients who have lost virologic control on a combination antiretroviral regimen, new HIV seroconverters, HIV-infected infants of HAART-experienced mothers--we don't have very many of them but when they occur, these children are at very high risk for drug resistance--and occupational HIV exposure of healthcare workers. These are four categories of individuals who are at high risk of drug-resistant virus.

[Slide.]

Some unresolved issues. For genotypic testing, I think the companies--I am not aware of any company that has actually brought a technical-validation panel to the FDA. I know the panels are being developed. I think this is probably one of the big issues for the companies is to prove that they have a kit where three different techs and four different labs can get the same result with the same sample

I think that is coming and I think you will see that type of data very soon. Interpretation of complex genotypes is difficult in these patients. The ultimate clinical utility, if you want to go to long-term durability or clinical outcomes, has not been proven but at least at time frames of three months to year, there is a clear benefit of using genotypic testing to get better virologic suppression.

[Slide.]

From our studies, and in the CPCRA, it has become clear that there are a number of instances where phenotyping does have significant utility, potentially more utility than the genotyping assays. One is in patients who are failing with indinavir resistance because we can tell you, from a genotype, that you are likely to be cross-resistant to the other agents but can't tell you which ones you are likely to be sensitive to, whereas the phenotyping can actually

identify the individual drugs to which the virus remains susceptible and then complex genotypes of apparent multi-drug-resistant phenotype where, in a potential of mutational interactions, you can find a drug or two by phenotyping that you won't be able to detect with our knowledge of genotyping.

[Slide.]

For phenotypic resistance testing, I think technical validation remains an issue as well. Of bigger concern are the current susceptibility breakpoints where they are actually set somewhat arbitrarily not related to either clinical progression or to loss of virologic control. I think there is going to be a major effort by the companies to get these breakpoints better established.

A concern is, right now, that it appears that the non-nucleoside susceptibility breakpoints from all the current assays may be set a little bit too low for sensitive virus and they are calling a few false positives for low levels of resistance.

Clinical-utility data is clearly coming from these types of assays but there are no prospective trials available to report at this time.

[Slide.]

So, where are we? I think, for biologic plausibility, this is a slide similar to the slide I

presented in 1996 to this committee for viral-load measurements. I think, for biologic plausibility, we certainly have that for both genotypic and phenotypic resistance. There is good retrospective data for quite a few drugs that both genotypes and phenotypes can predict response to drug and can predict loss of activity to the drug.

For prospective data, the short-term data of three months to twelve months for genotyping from two trials, ongoing trials for phenotypes. There are long-term trials going on for both types of assays at this time.

I point out to the committee that, when it was presented with the decision for viral-load measurements, an approval of viral-load measurements, there were no prospective studies available to the committee when they had to make this decision. At this point, there are two prospective studies for resistance measurements.

Technical validation is ongoing for both types of assays and standardized interpretation in getting the standards out there is also ongoing for both types of assays.

I thank you.

DR. HOLLINGER: Thank you, Doug.

Andy, do you want to go on to Dr Murray?

DR. DAYTON: I will leave it up to you.

DR. HOLLINGER: Let's see if there are some questions here of Dr. Mayers.

DR. CHAMBERLAND: In the packet of information that we got, there was a recent Lancet publication on the results of the VIRADAPT study. Has the GART trial been published?

DR. MAYERS: The GART trial has been in submission to JAMA for over eleven weeks right now so that if they ever release it, we hope they will publish it.

DR. CHAMBERLAND: Because one of these papers, I think, referenced an abstract for the GART study. Could you just clarify, in the GART study, in the methodology, in the GART arm, physicians got results of genotypic testing. In the non-GART arm, what information--I wasn't clear, exactly. It looks like they got the recommendation from--

DR. MAYERS: No.

DR. CHAMBERLAND: No; they didn't get anything? What did the non-GART get?

DR. MAYERS: What the non-GART got was that the team gave them the current recommendations and they gave them regular updates from the ongoing meetings for salvage regimens in that population. So, basically, we sent out to them--after each meeting, we would send out to them an update; "Here is what we are seeing with these drugs in these types of patients."

So we did an educational component, but we did not give them direct recommendations.

DR. CHAMBERLAND: So they just got general guidance about current thinking for salvage therapy--okay. But even in the non-GART arm, would you feel that clinicians were probably getting more information than the average treater gets because--

DR. MAYERS: I think that is fair. I think the thing that has encouraged us that this was not biased in a significant way is the French study where there was no expert advice given at all and all they got was the genotype given back to them. And the fact that GART and VIRADAPT essentially lie on top of each other at similar time points suggest that there was, probably, not a huge bias in that.

DR. CHAMBERLAND: Can you tell us more who the physicians were who participated in the GART and the non-GART arm? Where I am going is that I think there is a spectrum of treaters out there who treat HIV patients. At one end of the spectrum, we have folks like yourself, very knowledgeable, involved in research and, at the other end, are treaters who--and I think they may constitute the majority of treaters--who really are trying very hard to keep up with a moving target.

They have these publications from the Public Health Service and from these advisory committees about what

to do, but they are not really well-educated about genotypic, phenotypic, information, et cetera and they get these very complicated reports from these laboratories. They are tough to interpret. I do very limited clinical work and it is tough.

DR. MAYERS: I have the same problem, myself, getting some of these reports.

DR. CHAMBERLAND: So I kind of wanted to know, because we don't have a publication, unfortunately, who was in the GART trial, where to they fall in this spectrum of treaters because I think this is important to the committee ultimately having to vote on this issue, to have a kind of an understanding of what information is going to be--

DR. HOLLINGER: Yes; and how was it determined who was non-GART and GART?

DR. CHAMBERLAND: Exactly.

DR. MAYERS: Basically, I want to apologize to the committee for giving you the GART study but the rules that the FDA operates under are if I give it to you, I have to put it out on the table out front. Since it is still in submission to JAMA, I could not give it to the committee.

The clinicians throughout the CPCRA--these were the community docs in the CPCRA system, so they were at all the sites in the CPCRA, randomly out there. Any doc who sent a sample in could participate from the CPCRA.

The randomization was done in such a way that the patient's provider would send a sample into the team, the group of virologists would look at the sample, interpret it and get the report done, submit that report to that stat center not knowing if they were going to randomized or not, and then the stat center would roll the dice and randomize them after they had received the report from the virologist back to the field.

So, basically, this was a large group of community physicians throughout the United States and the reports were done the same if you got the report or didn't get the report as far as the virologists were concerned. We didn't know who was going to get a report when it went out.

MR. DUBIN: So any one physician who has seen multiple patients, sometimes he is going to get GART and sometimes not?

DR. NELSON: Yes; there were some physicians who treated a few patients with the genotyping and a few patients without it. That's correct.

DR. HOLLINGER: And decisions for changes by the non-GART was based on CD4s and HIV concentrations that they received back?

DR. MAYERS: The clinicians and the virologists in the study knew CD4s, viral loads, and they also knew the treatment history of each individual patient. So you knew

how many drugs they got and what drugs they had had toxicity or not had toxicity on. So it was the data that would be conventionally available to a doctor treating an HIV-infected patient.

DR. HOLLINGER: And he would make a decision, or she would make a decision, based upon the results that came back to that person.

DR. MAYERS: When the patient came back to the clinic for their randomization visit, the doctor would either get a GART report and have to tell us how it impacted his decision making or her decision making, or they would not get a GART report and have to use the data that they had had available to them prior to make a decision as to which drug to switch to.

DR. TUAZON: In terms of having--once this test had been approved, where do you see the clinical utility of both assays? I think, for the experienced, PI-experienced patients, you probably would just go ahead with the phenotypic. Accounting for the cost of both of the assays, what are the practical uses of this?

DR. MAYERS: I think one of the real surprises that we have seen across both studies has been that the relative benefit has been the same across rounds of therapy. But that is relative benefit in the face of a shrinking response.

What I see happening at this point is going to be in newly infected patients who you know are newly infected, not patients who walk in with PCP but newly infected, that they are at fairly high risk and I think there is going to be a move to take this testing to look for newly infecteds fairly soon because the rates are clearly above 10 percent in that population right now.

For other patients, I think we will use CD4 and viral load like we currently do. A person who is below 50 copies and is doing well without a genotype, I don't need the test. I think, on early rounds of failure, you will probably see genotypic testing used on those patients because it has a fairly quick turnaround time which will probably start to drop to less than a week as market forces develop and it is less expensive.

I think that, for people, as they get to the point where the genotype becomes different to interpret and they can't find the drugs they need, you are going to see a shift toward phenotypic testing because it can find holes that you can't find with the genotype testing in these individuals. That current assessment is based on cost and turnaround times.

If the phenotypic companies can get their cost down in the same range and the turnaround time in the same range, I really don't see a great deal of difference in

early failures between either methodology. They can both show you where there are potential holes to get active drugs and they can both show you were resistance exists.

So a lot of it is going to be how fast they turn them around and how much they charge you. I think the interpretations are clearly improving a lot recently. The reports clinicians used to get back a year ago, and even with some companies, as was stated, get now can be difficult to interpret.

I know they are difficult to interpret when one of my docs brings it in to me and I look at it and scratch my head and try and figure out what they are saying so that I can tell him what to do. I think that this is an area where there really does need to be some work by industry to develop a standardized reporting format.

I can tell you that there are some groups that develop computerized algorithms that give a very nice report that says, sensitive, partially resistant, resistant, just like you would get from your microlab for a bacteria. And you can do it for both phenotype and genotype if the companies want to.

DR. NELSON: Again, back to the GART trial. You gave the randomized physicians recommendations for which drugs to use. Did you also measure how the recommendations were followed by the patients and the physicians? Was that

done?

DR. MAYERS: Yes; we did. Actually, the scariest comment from my first IRB was when the head of the DSME asked me did I actually think the docs were following my recommendations. The honest answer is that some did and some didn't. Some used the data in their own way--

DR. NELSON: It is not only the doc. It is the patient.

DR. MAYERS: Yes; I understand. The bottom line was that for docs who took the advice regularly and consistently, the difference actually increased to almost a log difference between the GART and the non-GART arms. For the docs who didn't use the advice given, it narrowed down considerably. I think that this is one of the things that is going to drive HIV care, especially for the experienced patient, into the special provider and take it out of the primary-care realm.

This is just too complicated to deal with the cross-resistance issues and try and deal with the drug interactions to select an effective non-toxic regimen for these patients.

DR. HOLLINGER: Doug, along those same lines, you obviously have patients who are receiving information that you are imparting to them in the GART test and I presume the same thing was true in the other study.

So what was the compliance? We now know that probably the greatest challenge is making patients compliant. Those patients who are not compliant with their medications are the ones who different resistance the fastest. So the issue would be is that in the group that was not getting this information, did you measure compliance, other than just asking the patient. Were there any other basic measurements to be sure that these patients were taking their medication as were the ones who were on the GART trial

DR. MAYERS: We are currently going back into the trial. This trial, when it was originally done, was done as a pilot study that Tom Merigan and I and John funded off our laboratory internal budgets. So there was a certain limit as to how much testing we could do for free.

But what has happened is those restored samples done at every time point on these patients and we are now going back into these samples doing genotyping, phenotyping and drug-level measurements at every time point for every patient with support from a number of the companies. And we will have that data to bring back.

We did not have timing so I won't be able to tell you high/low. But I will be able to tell you, yes, they had drug or no, they did not have drug, of a very sensitive assay. The data from the French trial that was recently

completed with de-escalation of therapy suggests that this is adequate data to at least predict were they taking drug at all or not taking drug.

And so we are looking at that but it is not available at this time.

DR. McCURDY: It appears that even though there are certain mutations where it is pretty well established that either alone, or in combination, they confer resistance. The question that I have is suppose a new mutation or a new group of mutations seems to correlate with resistance, perhaps, to a new drug or something like that.

How is the decision made as to how this new work is interpreted? Is this based on limited data and then you follow along?

DR. MAYERS: Basically, I can tell you how we do it in the CPCRA where I have a little control. Basically, if the mutation associated with loss of viral activity of a drug or is associated with a clear change in phenotype, we will add it into the algorithm fairly early on and then look for its impact prospectively.

I think what is developing over time is a number of groups, the CPCRA, a number of industrial groups, the ACTG, are developing very large databases that include mutation's response to the next round of therapy. So what is going to happen fairly quickly is that as soon as a

mutation is detected, or what we think is a polymorphism today is shown to be a true resistance mutation, you are going to be able to have two or three groups very rapidly tell you, yes, we see this to be true or no, this appears to have been an artifact.

So I think the ability to actually confirm or rule out these mutations in a very rapid fashion is actually getting much better almost by the day.

DR. McCURDY: Dr. Stroncek made the analogy to HLA typing. For a number of years, there were workshops that got together that developed--wet workshops and others that got together to define new types. Is this sort of thing happening? Are the databases getting together or is this an individual entrepreneurial activity?

DR. MAYERS: The honest answer is it is not happening as much as it should. One of the problems is that each of the major commercial sponsors have developed a proprietary algorithm which they are trademarking and patenting as quickly as they can so that we don't have sort of your blue-collar framework everyone agrees to at this point for either breakpoints for phenotyping or genotypic interpretation.

I think this is an area where we can do better and this is an area where I think there could be some useful work to develop NCCLES type of standards for genotypic and

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

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