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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

64TH MEETING

VOLUME II

Friday, September 17, 1999

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PARTICIPANTS

Blaine F. Hollinger, M.D., Chairperson
Linda A. Smallwood, Ph.D., Executive Secretary

MEMBERS

John M. Boyle, Ph.D.
Corey S. Dubin
Norig Ellison, M.D.
Richard J. Kagan, M.D.
Jeanne V. Linden, m.D.
Gail B. Macik, M.D.
Mark A. Mitchell, M.D.
Kenrad E. Nelson, M.D.
David F. Stroncek, M.D.
Joel I. Verter, Ph.D.

NON-VOTING CONSUMER REPRESENTATIVE

Katherine E. Knowles

NON-VOTING INDUSTRY REPRESENTATIVE

Donald H. Buchholz, M.D.

TEMPORARY VOTING MEMBERS

Mary E. Chamberland, M.D.
Michael G. Fitzpatrick, Ph.D.
Paul R. McCurdy, M.D.
Carmelita J. Tuazon, M.D.

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

2 **Introductory Remarks**

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

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

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

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

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

1 please. For those of you who were not here yesterday, I
2 will just quickly run through the committee and give myself
3 a memory check here.
4 Dr. Gail Macik, Dr. Richard Kagan, Dr. Mary
5 Chamberland, Dr. John Boyle, Dr. Norig Ellison, Dr. Michael
6 Fitzpatrick, Ms. Katherine Knowles, Dr. Donald Buchholz, Dr.
7 Joel Verter, Dr. Mark Mitchell, Dr. Jeanne Linden, Dr. Paul
8 McCurdy. We also have Mr. Corey Dubin. I don't see him
9 here this morning but I assume he will appear.
10 Are there any declarations that would need to be
11 made before we proceed with this meeting concerning any
12 conflict of interest or any perception thereof?
13 Hearing none, then we will follow the agenda as
14 closely as we can. We have a lot today. We will try to
15 meet the time frame that has been established if everyone
16 will cooperate accordingly.
17 At this time, I will turn our meeting over to our
18 Chairperson, Dr. Blaine Hollinger.
19 DR. HOLLINGER: Thank you, Linda. We will stick
20 within our time frame, hopefully, today. This is, I think,
21 an important meeting today as we sit as a medical-device
22 panel for reclassification of HIV drug sensitivity assays.
23 This is, of course, an important issue, also.
24 I think it is going to be an interesting morning.
25 I hope you have all looked at these forms. Mary Chamberland

1 said that she has been in government a long time and she
2 said it took her six hours to fill it out. OMB says one to
3 two hours, but--I told someone that that means that we all
4 get a royalty of about 5 percent on anything that is
5 produced.
6 So, we are going to start this morning with an
7 introduction and background. Andy Dayton is going to start
8 us off today and then we will go to an overview of the
9 device reclassification. Then we will have a presentation
10 of the problems and issues associated with this.

11 **Medical Device Panel Reclassification**
12 **of HIV Drug Sensitivity Assays**

13 DR. DAYTON: Good morning.
14 [Slide.]
15 Today, you are going to be asked for your
16 recommendations as to whether or not HIV drug resistance
17 genotype assays should be reclassified as class II medical
18 devices rather than class III medical devices.
19 This is a timely issue because downclassification
20 would foster rapid and simplified regulation of numerous,
21 currently diverse, HIV genotype assays and this would
22 facilitate antiviral drug studies and, ultimately,
23 accelerate physician access to information useful in the
24 management of individual HIV-infected patients.
25 I am going to give a very short presentation of

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

6 [Slide.]

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

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

24 [Slide.]

25 Currently, there are no FDA-approved or cleared

1 assays for the assays for the determination of HIV drug
2 resistance. Given this, HIV drug genotype drug resistance
3 assays, by default, are class III medical devices requiring
4 premarket approval.
5 An option exists, however, to classify such
6 devices into class II, or 510(k), when general controls and
7 special controls exist to insure the safety and
8 effectiveness of the device. It is FDA's view that adequate
9 special controls can be provided by adherence to a guidance
10 document containing recommendations for study designs,
11 reagent characterization and performance characteristics--
12 for instance, reportable range, sensitivity, precision,
13 specificity, stability, et cetera--and by completion of
14 postmarketing surveillance studies designed to evaluate the
15 correlation between predicted and observed viral phenotypes
16 in a clinical setting.
17 [Slide.]
18 These are the questions that we are going to
19 asking you at the end of the presentation and, of course,
20 you are welcome to alter them as you see fit. Does the
21 committee support the reclassification of HIV drug
22 resistance assays from class III medical devices to class II
23 medical devices? If the answer to No. 1 is yes, what
24 additional special controls or requirements, if any, does
25 the committee recommend?

1 If the answer to No. 1 is no, what additional
2 specific criteria does the committee recommend to allow
3 future reclassification as class II devices?
4 [Slide.]
5 The science involved can be quite complex and,
6 certainly, much desired information is incomplete. However,
7 we urge you to remember that the key issue is not whether or
8 not all the scientific information is complex or whether all
9 the scientific questions have been answered. The key issue
10 is whether or not you believe we can identify special
11 controls which will guarantee reasonable efficacy without
12 requiring the completion of full-blown, traditional clinical
13 trials before marketing.
14 In the next presentation, Len Wilson will focus on
15 this issue from a regulatory perspective.
16 Len?
17 **Overview of Device Regulation**
18 MR. WILSON: My presentation today is to take the
19 committee through the regulatory pathway to classify medical
20 devices. Why do we do this? Because the law says we must
21 classify medical devices. So we go through this exercise
22 periodically as new products come up or we want to change
23 the regulatory classification of existing products.
24 In the past five or so years that I have been
25 engaging in reclassifying devices, this committee has voted

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1 on a number of them, sometimes classifying up from a I to a
2 II, sometimes classifying down from a II to a I, et cetera.
3 So there are no surprises in this process.
4 With that, what I would like to do is have the
5 first slide and essentially start out.
6 [Slide.]
7 What we are trying to reclassify here an HIV
8 mutation test. An essential proposal is that the HIV
9 mutation test can have a reasonable assurance of safety and
10 effectiveness when regulated as a class II medical device.
11 Class II medical devices, as I will discuss later, have some
12 requirements associated with them. One of the requirements
13 is having a special control.
14 The proposal here today is that the FDA would
15 develop a guidance document for the content of the 510(k)
16 filing, the class II medical-device filing, which we would
17 review and we would clear if the manufacturer provided
18 sufficient information to assure the safety and
19 effectiveness of the device.
20 And then there is an additional special control
21 that we are proposing, postmarketing surveillance. This
22 would be used, as Dr. Dayton described, to do some follow
23 up. I want to emphasize that the postmarketing surveillance
24 component of a special control here is not intended to be
25 the basis for the approval of the product, approval or

1 clearance of the product.

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

5 [Slide.]

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

10 [Slide.]

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

16 [Slide.]

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

21 [Slide.]

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

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1 man or animals or--

2 [Slide.]

3 --intended to affect the structure or any function

4 of the body of man or other animals and which does not

5 achieve any of its primary intended purposes through

6 chemical action within or on the body of man or other

7 animals and which is not dependent on being metabolized for

8 the achievement of any of its primary intended purposes.

9 [Slide.]

10 So now we have established that this type of a

11 product would be a medical device. The next question is how

12 would it be regulated by the FDA, either by the Center for

13 Biologics or the Center for Devices, the Center for

14 Biologics Evaluation and Research, the Center for Devices

15 and Radiologic Health.

16 The Center for Devices and Radiologic Health

17 regulates most of the medical devices that are in commercial

18 distribution in the United States. In 1991, there was an

19 intercenter agreement which was issues between the two

20 centers. In general, CBER has the lead for regulating

21 medical devices used or indicated for the collection,

22 processing, storage or administration of blood products,

23 blood components or other analogous products.

24 So, for example, this empowers the Center for

25 Biologics to regulate those test kits which are used to

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1 screen blood donors.

2 [Slide.]

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

9 [Slide.]

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

15 [Slide.]

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

21 [Slide.]

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

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1 device law and regulations. Or if no predicate device
2 exists; in other words, FDA has not cleared a 510(k) for the
3 same device. So a predicate would mean, in this particular
4 situation, has the Food and Drug Administration cleared an
5 HIV mutation test or viral-resistance test before. Is there
6 something that we can compare against?
7 And the answer is no. So, by default, as we move
8 down, it would be in class III in the absence of formal
9 classification. However, there is an option where the FDA
10 can classify products into some other medical-device
11 classification.
12 [Slide.]
13 So the steps, in general, to classify a medical
14 device are found in the regulations, 21 CFR 800 through 899.
15 It can be initiated by FDA or a sponsor. In this particular
16 instance, FDA is bringing it to the committee. A sponsor
17 would mean someone who was petitioning the FDA who would be
18 trying to get a test kit approved or cleared. They can
19 petition the FDA and say, "Gee; I would like to have this
20 regulated as such-and-such as class." And then we would go
21 through this same type of a cycle except it is coming
22 externally.
23 We would obtain a recommendation from an advisory
24 committee, this committee. Based on that recommendation, we
25 would publish, in the Federal Register, for comment, the

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1 outcome of the committee's deliberations and vote and then
2 get some comments, make potentially some changes, and then
3 publish a final rule.
4 Once that final rule is published, into the CFR
5 would appear, once the administrative processes are
6 completed, a section that would be entitled, for example,
7 HIV Mutation Test. It would have a number and then any
8 sponsor who comes to the Food and Drug Administration to get
9 a test approved or cleared, they could cite that as a
10 predicate and they could file, in our proposal, a class II--
11 it would be regulated as a class II and they can file a
12 510(k).
13 [Slide.]
14 In the regulations, the committee should consider,
15 in determining safety and effectiveness--and this is
16 something that you may want to tag on the slides that I gave
17 you--you should consider the persons for whose use the
18 device is intended, its conditions for us, probable benefit
19 to health weighed against risk of us, and the reliability of
20 the device.
21 [Slide.]
22 Which regulatory classification are we attempting
23 to vote on here? Well, all medical devices, as stated
24 earlier, are classified into three classes. Class I,
25 general controls are sufficient to assure the safety and

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

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

15 I will walk through what these controls are.

16 [Slide.]

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

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

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1 their compliance with good manufacturing practices or what
2 we now call QSRs.
3 There was a revision to the good manufacturing
4 practices. Good manufacturing practices are those sets of
5 rules by which manufacturers produce products in a clean
6 environment, have quality control, et cetera, et cetera.
7 Again, these are listed in 21 CFR 800.
8 Recently, within the last two years, the good
9 manufacturing practices section has been revised and
10 upgraded. They are now termed QSR, quality system
11 regulations. The important point here to consider is that
12 they have been strengthened considerably. However, in
13 class I products, design controls, which I will explain in a
14 moment, are not required, in general.
15 Class I general controls also include labeling
16 requirements to make sure that there are adequate
17 instructions for use, et cetera. For a class I, a
18 submission of a premarket notification also known as a
19 510(k) is required. It is also important to note that
20 certain general controls can be exempted, also. That could
21 be done by the Food and Drug Administration as well as by a
22 committee vote.
23 For example, some products we may exempt the need
24 to file a 510(k). This committee voted on such a situation
25 several years ago where we dropped the requirement for a

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1 510(k) for copper sulfate for use in determining hemoglobin
2 in blood donors.
3 [Slide.]
4 Some more general controls; record keeping and
5 requirement for repair, replacement and refund when defects
6 are found.
7 [Slide.]
8 Some examples of class I devices; heat-sealing
9 devices to crimp blood collection tubing; alanine
10 aminotransferase tests. This is a clinical-chemistry test
11 and you can see the it has an asterisk. This, in fact, has
12 been exempted from filing a 510(k). So all the other
13 general controls apply, but they are not required to file a
14 510(k) to get premarket clearance. An ammonia test system;
15 iron-binding-capacity test systems.
16 The 21 CFR 862 is that section which is listed in
17 the regulations and I will show you an example of what you
18 would have in this particular situation for HIV mutation
19 tests as we move towards it.
20 [Slide.]
21 Class II; general controls are insufficient so,
22 therefore, you would need special controls. Now, special
23 controls consist of, for example, a guidance document. And
24 I have bolded that because that is what FDA is proposing. A
25 guidance document would basically have the content of the

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1 510(k) submission spelled out. There would be some clinical
2 data if indicated. There would be contraindications,
3 warnings, adverse effects, et cetera.
4 Now, I want to draw attention to the committee
5 that, in August of 1989, FDA issued what we called then a
6 points-to-consider document. But it is essentially a
7 guideline for manufacturers as to what to submit for a
8 product-license application for a blood screen. This is,
9 conceptually, what we are looking to produce here for this
10 particular product. Dr. Dayton will go into that in more
11 detail.
12 Another special control can be a performance
13 standard. Are there voluntary standards or international
14 standards that can be applied to this type of product. What
15 FDA would do, then, is we would recognize it by rulemaking,
16 notice, comment and rule, and that would be the special
17 control for that particular device if voted on by the
18 committee.
19 [Slide.]
20 There could be special labeling, some
21 restrictions, some additional information that would be
22 imbedded into the labeling that wouldn't normally occur in a
23 medical device because there is some greater concern that
24 has to be mitigated.
25 Patient registries; sometimes, patient registries

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1 are necessary to track particular devices, how they are
2 used, because there could be a problem with them that we
3 would have to get back and notify the patient. Again, I am
4 bolding here postmarking surveillance to answer unanswered
5 questions once the product does get into the marketplace.
6 It is important to note, going back to the GMP
7 part, the QSR, design controls are required for class II
8 medical devices. Now, what are design controls? The short
9 answer is that design controls are part of the manufacturing
10 process where each product has a set of controls placed on
11 top of it where design input, design output, verification
12 and validation of all the manufacturing processes are
13 tightly controlled.
14 This is a new concept because FDA has determined,
15 over the last decade, that failures of medical devices
16 consists basically of two types. They weren't manufactured
17 according to the instructions. The other type is they were
18 manufactured according to the instructions but there was a
19 design flaw and the product didn't work.
20 The objective here of design controls is to insure
21 that the design of the product has been adequately
22 challenged and it insures that the manufacturing process, as
23 well, can be conducted with integrity.
24 [Slide.]
25 Examples of class II devices; an empty container

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

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

13 [Slide.]

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

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

22 [Slide.]

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

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

2 [Slide.]

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

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

20 A difference with the class II is that there is a
21 90-day review cycle. 510(k)s have a 90-day review cycle.
22 PMAs or class IIIs have a 180-day review cycle. The reason
23 for that is that the content of the class III PMA is
24 generally more detailed so FDA is allowed more time to
25 conduct the review.

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1 As I stated earlier, class II products have
2 periodic QSR inspections which are conducted by the field
3 investigators. For a class III device, there is a
4 difference. There is a preapproval inspection and then
5 periodic QSR inspections are conducted. So, with the class
6 III, there is basically a GMP inspection of the plant or QSR
7 inspection of the plant prior to the approval.
8 [Slide.]
9 So, which regulatory classification are we looking
10 at here? Well, in the regulations, Chapter 1, 12 CFR 866,
11 immunology and microbiology devices, subpart D, serological
12 reagents. The proposal would be that, in Section 866, and a
13 number would be assigned, there would appear an HIV mutation
14 test.
15 [Slide.]
16 This is what it would look like, actually, in the
17 regs. Mutation-detection reagents; a, identification, HIV
18 mutation-detection reagents are devices that consist of
19 ligands use to identify mutations in the HIV genome in
20 infected individuals. The identification of mutations aids
21 in the clinical management of HIV-infected individuals.
22 We used the term "ligands" because we wanted to
23 have flexibility whereby this could be done by nucleic-acid
24 testing or, potentially, by other means, serological and the
25 like. So we would have the regulatory designation that we

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

2 [Slide.]

3 The next part of the regulation would basically be

4 which classification is it. It would stated that it is a

5 class II and special controls are required.

6 [Slide.]

7 So the FDA proposal is that an HIV mutation test

8 can have a reasonable assurance of safety and effectiveness

9 when regulated as a class II medical device and the special

10 controls proposed consist of a guidance for the content of a

11 510(k) and postmarketing surveillance.

12 With that, I would ask Dr. Dayton to resume to

13 spell out the concepts associated with the guidance document

14 and the postmarketing surveillance.

15 DR. DAYTON: Do you want to take some questions

16 now because we are going to on to the sort of technical and

17 scientific issues.

18 DR. BUCHHOLZ: I wonder if, for the committee, you

19 could indicate the actual time for the review as opposed to

20 the statutory or guidance times for a 510(k), for a PMA and

21 for a supplement to a PMA, say, an average over the last

22 couple of years, just to give us a feel for how long it

23 takes if, for example, one wanted to make a change in a

24 product that was a PMA product, how long it would take to

25 make that change as opposed to a product that was a 510(k)

1 product.

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

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

14 Now, it is up to the manufacturer how long the
15 manufacturer responds. There is a statutory requirement of
16 30 days an we have the option of actually withdrawing it if
17 they don't respond. I can tell you that many manufacturers
18 have taken a lot more time than 30 days to respond.

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

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1 that.

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

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

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

22 Making changes to a PMA product, more stringent
23 rules are required. So, therefore, a supplement would need
24 to be filed in many instances. The supplement would have a
25 180-day review clock on it.

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1 Did I capture all your concerns?

2 DR. BUCHHOLZ: Thank you.

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

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

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

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1 It was found that, with the data presented to a
2 committee back in the 1980s, that those instruments by
3 centrifugation were found to have sufficient safety and
4 effectiveness regulated at the class II level.
5 Recently, some data has been presented to the
6 committee whereby we have got enough information now. What
7 is enough information? It has been out on the marketplace
8 for a period of time. We have looked at the MDR reports,
9 the medical-device reporting, and found that the problems
10 are not serious and, therefore, we feel that the lower
11 regulatory controls would provide us safety and
12 effectiveness.
13 There are some advantages and disadvantages to
14 which regulatory class a product is in. There are some
15 requirements that manufacturers have to follow--annual
16 reports, for example--with a PMA and the like.
17 Am I helping you here? That would be, for
18 example, where we had safety. Effectiveness, I am stuck
19 here. If I could try to roll the two of them together where
20 the platelet is performing, when separated by filtration, as
21 well as when separated by centrifugation.
22 As you can imagine, there was a lot of detailed
23 analysis to determine platelet function and the like. And
24 it was determined that yes, the platelets were not
25 compromised and the equipment could be felt to be

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1 substantially equivalent.

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

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

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

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

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

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1 You are really allowing your postmarketing
2 surveillance to be your clinical trials. How can you bring
3 it back? How do you get it if we let it out there ahead of
4 time?
5 MR. WILSON: Very good question. First of all,
6 the postmarketing-surveillance order can have a number of
7 different requirements, not necessarily those constituting a
8 clinical trial. Again, the idea here is that the
9 postmarketing surveillance is not intended to be the basis
10 for approval. That would be backwards; we clear the product
11 and then we will find out if it works.
12 No; that is not what we are trying to do here.
13 What we are saying is the product is clearable with what is
14 provided to us. And then there are some logical additional
15 unanswered questions that, from a public-health point of
16 view, probably should be evaluated. So the postmarketing
17 order would be structured on that.
18 Again, Dr. Dayton would be providing you with
19 where we are headed with that.
20 Let's say something goes terribly wrong. We have
21 several regulatory options here. One is an inspection of
22 the facility to determine problems with--complaint handling,
23 to see if there are a number of problems there. We also
24 have some, by law, ways of dealing with products that are
25 not performing; they are either adulterated or misbranded.

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1 So there are compliance mechanisms to control
2 that. I think that, if, over a period of time, it becomes
3 evident that a product has problems that were not foreseen,
4 it could be brought back to the committee and we could
5 present a proposal to upclassify it to the III.
6 Also, as I said earlier, FDA could propose to the
7 committee. Sponsors could also do the same thing. So there
8 are some regulatory remedies. You are not in II forever, if
9 you vote for a II. But we are trying to look at our
10 knowledge base of dealing with guidance documents, dealing
11 with what we already know about these types of tests and the
12 technology and we feel, at least at this point, that a class
13 II would give us reasonable assurance--the law says
14 "reasonable assurance of safety and effectiveness."
15 DR. FITZPATRICK: You mentioned that you don't
16 have to do full-blown clinical trials. So that implies to
17 me that FDA would, then, open the door for the manufacturer
18 to submit data from clinical use that was not part of a
19 clinical trial, which they don't do in some other instances.
20 Is that what you are saying?
21 MR. WILSON: That could be a part of the
22 postmarketing-surveillance order. Again, I think Dr. Dayton
23 would be able to frame out where we are, what we are
24 proposing with that.
25 MS. KNOWLES: I think that I recall that even FDA

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

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

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

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

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

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1 enable us to assure these types of orders and maintain the
2 integrity. For example, for postmarket studies, it would be
3 a postmarketing order, the obligation of the manufacturer to
4 do X, Y and Z.
5 A lot of times, we will have reporting
6 requirements periodically over a period of time. I can tell
7 you first-hand, if we don't get the report, we call them up
8 and say, "Where is the report? You are obligated." We put
9 it in writing. We send it out and, if we don't get it, then
10 we have several other options. Directed inspection; the
11 reviewer can propose, because the manufacturer has not
12 responded to the Office of Compliance, we would like to have
13 a directed inspection to the firm. This can be done on a
14 priority basis depending on the particular product involved
15 or health issue.
16 In many instances, and I have triggered them
17 myself, within a week or two or three or sometimes
18 overnight, we can have inspectors into the plant. They know
19 what the problem or the concern is and the headquarters is
20 often on the phone on a daily basis with the inspectors
21 because they are not the headquarters reviews and they will
22 need a little bit insight. We have got a very good working
23 relationship in that regard.
24 Does the help to answer some of the concerns?
25 MR. DUBIN: Yes.

1 DR. TUAZON: I know that the genotyping and
2 phenotyping assays are being used clinically right now.
3 What regulatory measures do we have on those used at the
4 moment?
5 MR. WILSON: There are no cleared or approved
6 tests by FDA. The products I assume you are talking about
7 are those that would be generically identified as "home
8 brew?"
9 DR. TUAZON: They are really done by the labs do
10 our routine testing for HIV patients.
11 MR. WILSON: Right. But the actual reagents,
12 themselves? They build the test themselves?
13 DR. TUAZON: These labs that we sent through the
14 medical centers are sent through diagnostic labs like LabCor
15 or Quest Diagnostics.
16 MR. WILSON: There is--and this can get a little
17 bit complicated so I am going to try to give a short answer
18 but there is a regulation called the ASR Rule, analyzed
19 specific reagents, which has requirements for some home-brew
20 types of products. I guess I can say that, with the outcome
21 of this vote here, that may have some effect on the
22 regulation of those types of tests.
23 But the objective of that would be to level the
24 playing field. I think it is important to bear in mind
25 that--I think all want good-quality tests of high integrity

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1 that have the reliability, et cetera. Whether it is a home
2 brew or whether it is regulated by FDA as a normally
3 distributed commercial product, it should work well.
4 So we have got two arms for regulation, one for
5 the home brew and the other for traditionally commercially
6 distributed products.
7 DR. HOLLINGER: Thank you, Mr. Wilson.
8 Dr. Tabor?
9 DR. TABOR: Just in further answer to Mr. Dubin's
10 question; provided there is no negative impact on the public
11 safety, the use of the 510(k) mechanism is resource saving
12 for FDA because a lot more FDA human resources have to go
13 into the review of a class III device than a class II
14 device.
15 DR. DAYTON: Let me elaborate on some of the
16 questions that Len just answered and, in particular, let me
17 start with Dr. Hollinger's question about special controls
18 and how you would choose between class II and class III.
19 Let, of course, gave a very accurate answer but the way I
20 wanted to elaborate on it was to portray to you how we feel
21 this decision should be viewed for this particular product
22 today.
23 Imagine--you don't have to imagine. Take a
24 mutation which gives you well-documented resistance to a
25 certain drug. Let's assume that there is a long history in

1 the literature studying that mutation. You see it appear in
2 patients when they are on that drug. If you switch to
3 another drug, it disappears, they do better, et cetera, et
4 cetera, et cetera.
5 This would be the kind of data that we would
6 consider adequate to let this product be regulated under
7 class II. In other words, there is a lot of data in the
8 literature. It is well-done. It is well-known. It is
9 well-characterized. And we don't see a particular need for
10 clinical trials, premarket.
11 Take, by comparison, another mutation. Let's say
12 there is one study which shows that it appears when patients
13 are on a particular drug. We would want to see more data
14 for that second type of mutation.
15 The way we would like to handle this is we would
16 like to--the postmarketing surveillance, essentially, is
17 claim specific. So the way that we would handle this is we
18 would like to let a product under class II regulation go to
19 market for the first type of mutation to back a claim for
20 the first type of mutation.
21 So, in other words, the assay could claim to pick
22 up that particular mutation which is well characterized and
23 that would be of benefit to the patient. If they wanted to
24 have an additional claim for the second type of mutation,
25 the one which isn't so well characterized, they would have

1 to submit additional data in the postmarket period to get
2 that claim.
3 We feel that, by splitting it up like that, we can
4 get these products out there fairly quickly and we can also
5 control them very effectively. The whole issue of claims is
6 very important because that is what the postmarketing
7 surveillance will address. Postmarketing surveillance will,
8 in part, be largely claim-specific. It will address
9 additional claims.
10 In terms of FDA mission, even if there is one
11 mutation out there and it is clinically relevant and an
12 assay can pick it up and can redirect therapy, that is
13 benefit. That is clinical benefit.
14 In the real world, we believe that there are
15 mutations which are fairly well characterized. There are a
16 lot of mutations which are less well characterized. In
17 fact, Dr. Mayers and Jeff Murray will be presenting data to
18 show that, actually, these assays are clinically beneficial.
19 We believe that the reason for that is because the
20 mutations--there are mutations that are correctly
21 characterized.
22 I think that those were the key issues that I
23 wanted to address before I sort of give the introductory
24 talk to the next two speakers.
25 [Slide.]

1 The highly-active antiretroviral therapy has been
2 a tremendously successful approach for treating HIV
3 infections. Unfortunately, it is not perfect and it is
4 still plagued by therapeutic failures. Mostly, therapeutic
5 failure is heralded by falling levels of CD4-positive
6 lymphocytes and rising levels of circulating HIV.
7 However, these two parameters are not always
8 inversely correlated and they are, at best, indirectly
9 measurement of therapeutic failure. Consequently, there is
10 an increasing need for more accurate and more direct
11 measures of therapeutic failure, particularly measures which
12 identify the mechanism of therapeutic failure.
13 [Slide.]
14 HIV drug resistance assays promise to fill this
15 need. One of the most common, but by no means only, causes
16 of treatment failure is the existence or emergence of virus
17 species resistant to the drugs included in the regimen.
18 Various categories of assays exist to measure HIV drug
19 resistance.
20 As general examples, in one approach, virus is
21 isolated from a patient, expanded, titered and tested in
22 replication assays in the presence of antiretroviral drugs.
23 In another approach, the reverse transcriptase and/or
24 protease regions of the infecting virus are isolated and
25 subcloned into well-characterized laboratory strains.

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

7 [Slide.]

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

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

23 [Slide.]

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

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1 the predominant viral species is resistant. This
2 information is used with information about the patient's
3 previous viral regimens and it can be useful in choosing new
4 regimens in patients experiencing therapeutic failure.
5 So it is an important point to realize that these
6 are not stand-alone assays. These are used in the context
7 of the entire clinical picture of the patient. In fact, as
8 you will learn later, these assays often will not detect
9 minor species and there can be minor species of resistant
10 mutants left over from previous antiretroviral therapy.
11 [Slide.]
12 The motivation for FDA's desire to downclassify
13 these genotypes is that we feel it would be an overall
14 benefit to the public health. Downclassification would
15 allow enhanced physician access to these assays by allowing
16 sponsors to go to market with premarket clinical sensitivity
17 and specificity data, allowing postmarket clinical-trial
18 data to further correlate assay prediction with clinical
19 responses.
20 This would significantly facilitate clinical
21 trials for new drugs and therapeutic regimens. As I said,
22 the relevant science can be complex and incomplete but it is
23 FDA's opinion that sufficient information exists to insure a
24 significant level of efficacy of these assays by formulating
25 an appropriate set of special controls.

1 In other words, we feel that, although we are not
2 perfect, there is enough science out there that we can sit
3 down and say, this is what needs to be done. We can
4 identify these studies and they will tell us whether or not
5 these assays are going to be beneficial.
6 It is also FDA's opinion that postmarketing
7 studies can be designed to further improve the efficacy of
8 these assays as increasing scientific knowledge is obtained.
9 [Slide.]
10 We are drafting a guidance document outline
11 requirements anticipated for regulation of HIV drug
12 resistance assays as class II medical devices. Obviously,
13 we won't go very far with that document. If you decide to
14 regulate it a class III, we will just recast it as a class
15 III document and change the ideas.
16 This document,as it stands now, addresses issues
17 pertaining to assay precision, reproducibility and accuracy,
18 quality control of reagents, laboratory testing and pre- and
19 postmarket clinical data requirements. FDA's current
20 thinking about the contents of this guidance document is
21 contained in a September, 1999 concept memo which covers
22 highlights of the guidance document and which has been
23 included with your pre-meeting materials.
24 What we gave you in the pre-meeting materials
25 doesn't cover all of the details in the guidance document

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1 such as the manufacturing controls. We tried to limit it to
2 the critical issues which are relevant to your decision here
3 today.
4 Over the course of the next few minutes, I will
5 review these highlights with you.
6 [Slide.]
7 First, we start with the nonclinical laboratory
8 data and we focus on validation of phenotypes predicted by
9 genotyping. I will start out by saying that in this part of
10 the guidance document, we expect to attract a lot of
11 comment, a lot of discussion. The guidance document will be
12 put out in draft form for public comment after we have
13 cleared it in-house and there will be a lot of scientific
14 input to it at that point.
15 What we are thinking about now, as an example, is
16 that, in general, sponsors will be expected to validate
17 claims that certain genotypes predict certain phenotypes.
18 We expect that validation studies will include in vitro
19 viral-replication assays and determination of the effect of
20 a given genotype on the 50 percent or 90 percent inhibitory
21 concentrations of the drugs in question.
22 We are also entertaining the concept that when
23 non-clinical validation studies demonstrate an eight-fold or
24 greater increase in the IC50 or IC90 associated with a given
25 resistance mutation, validation may or may not also include

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1 certain types of clinical validation studies of individual
2 mutants.
3 We also expect that when nonclinical validation
4 studies demonstrate a less than eight-fold increase in the
5 IC50 or IC90 levels associated with the mutation that
6 validation will require clinical validation studies.
7 [Slide.]
8 We have requirements for analytical sensitivity.
9 We assume that we will ask sponsors to perform sensitivity,
10 precision and reproducibility studies on spiked samples and
11 anticipate that sponsors will submit sensitivity data for
12 all single and multiple mutations for which a claim is
13 sought. Basically, what we are saying here is if it is
14 there in the tube, can you measure it? Can you sequence it?
15 The sensitivity studies should determine and
16 validate both the minimum viral level and the minimum mutant
17 proportions reliably detected by the assay. So we want to
18 know can you pick this up if your viral load is down at
19 1,000 copies per ml, or does it have to be up at
20 10,000 copies per ml.
21 If the resistant mutant is present as 5 percent or
22 10 percent or 25 percent of the infecting population, can
23 you detect it? We assume, but it may not necessarily be
24 true that the assays will demonstrate in these studies
25 sensitivity at viral levels which are clinically relevant.

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1 Certainly, that is our preference.

2 FDA also anticipates requiring accurate titration

3 of sensitivity through and below the minimum detectable

4 levels and proportions. Basically, we want to know how

5 quickly does assay performance deteriorate with decreasing

6 levels or proportions of the analyte.

7 [Slide.]

8 Clinical data. A key issue here is going to be

9 validation of the phenotypes predicted by genotyping because

10 that is the key question. Our current thinking is that

11 validation studies should, optimally, include determinations

12 of the existence or appearance of a given phenotype in

13 patients subject to antiretroviral therapy as well as

14 correlation of the disappearance of a given mutation with

15 changes in antiretroviral therapy.

16 Throughout these studies, FDA will probably want

17 to see data on overall viral burden, as well. We are

18 considering the possibility that viral burden may be an

19 adequate indicator of response to therapy for particular

20 drugs. FDA may variably recommend or require clinical

21 studies to validate the phenotypes of individual mutations

22 according to the changes in IC50 and IC90 determined by in

23 vitro viral replication studies.

24 Basically, what we are saying is, let's see how

25 good your in vitro data is and then we will decide whether

1 or not we will need additional studies. Certainly, we will
2 be interested in seeing data in the literature as well as
3 data done specifically at our request.
4 [Slide.]
5 For clinical sensitivity, one of the things that
6 has been proposed to be done is to do sensitivity and
7 reproducibility studies on a panel of unspiked specimens
8 whose genetic makeup is known. Basically, somebody is going
9 to have to, presumably, sponsor, or industry, is going to
10 have to take a bunch of patients, get specimens on them,
11 determine what the distribution of the viral swarm, or the
12 quasi-species, is and then show that they can always pick up
13 the mutations that they are looking for, or can pick them up
14 with a certain sensitivity. These would be unspiked
15 samples.
16 On this particular issue, of course, and, as on
17 all the others, further discussions will determine whether
18 or not the panel must include representatives of all
19 genotypes to which a claim is sought.
20 [Slide.]
21 The FDA is also considering requiring traditional
22 clinical trials in which assay phenotype predictions based
23 on genotype correlate with changes in viral burden and/or
24 mutant representation in response to antiretroviral therapy.
25 FDA may also allow these studies to be prospective or

1 retrospective on archived specimens.

2 [Slide.]

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

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

17 [Slide.]

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

23 [Slide.]

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

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

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

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

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

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1 accurate. We know a lot more now with these tests that are
2 coming to market, or are coming up, the genotyping tests
3 than we knew in the early days of viral-load testing.
4 There are going to be a lot of questions. I am
5 certainly happy to entertain questions now. You are just
6 about to get two talks that go into the scientific and
7 clinical literature in much more detail than I have
8 described it. So I am certainly willing to answer
9 questions, but if you think it might be answered in the next
10 two talks, you are certainly welcome to wait.
11 DR. HOLLINGER: It doesn't look like the committee
12 thinks they can wait.
13 DR. VERTER: It's a good try, though. In trying
14 to read some of the documents last night and listening to
15 the two presentations this morning, I wonder if you could
16 clarify--I am still having trouble understanding the II/III
17 issue. From what you just described, it seems to me almost
18 like a very fine line. In fact, it almost came down to the
19 statement, "Considering the concept of requiring either the
20 panel-type clinical studies or the traditional clinical
21 trials, but not both," whereas, in a III, do you require
22 both and in the II only one? Can you give me some feel
23 about that?
24 DR. DAYTON: We are kind of skirting the issue a
25 little bit there. And it is confusing. I think one key

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1 point to make is we can make class II regulation as
2 stringent as we want it, if we really want to. So we can
3 make it as stringent as class III, basically.
4 What was the second part of your question?
5 DR. VERTER: I was just trying to clarify in my
6 mind, and maybe in some others, as to where the fine line
7 is. I understood what you just said and I thank you for
8 that comment.
9 DR. DAYTON: The real question is, as I said, does
10 it look like we can identify special controls or studies
11 that are going to make this thing effective, even partially
12 effective. The critical issue is not so much whether we
13 require one pre and one post. That is something that we are
14 thinking of.
15 The real issue is does the science say, "Look; the
16 field is far enough along that some mutations can be fairly
17 well guaranteed to be relevant in measuring them and,
18 therefore, be effective. That is the key issue.
19 Have I answered your question? Have I addressed
20 it?
21 DR. VERTER: You have addressed it.
22 DR. MITCHELL: Can you tell me what do you mean by
23 panel-type clinical studies? Is that presenting panels of
24 known--
25 DR. DAYTON: It would be--basically, as the

1 proposal stands now, we somebody would assemble a panel of
2 50 unspiked patient specimens. Presumably, they would take
3 each one and they would make multiple clones from them by
4 standard microbiological techniques, sequence them in the
5 regions that we are interested in, and come up with a
6 description of the distribution of quasi-species in the
7 viral swarm.

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

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

20 DR. MITCHELL: Yes. Thank you.

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

1 clinical-trial data but it could be done postmarketing?

2 DR. DAYTON: Well, no. In a class II, we actually

3 could require clinical trials premarket if we had to. That

4 is an option. But what we would be doing in a class II

5 situation, in the situation we would like to do, is looking

6 at clinical data in the literature and be able to say,

7 "Look; these mutations here are really quite well

8 established so we are quite confident that they deserve a

9 claim for that."

10 But there are this whole set of other mutations

11 over here that we know a lot less about. So, if you want to

12 claim them, you come back postmarket. You can go to market

13 but you only get a claim for the first set of mutations and

14 you only get the second set of mutations when you come back

15 and prove it.

16 But, again, it could be data in the literature,

17 not necessarily clinical-trial data. We could also specify

18 clinical-trial data in postmarketing, which we may do.

19 Len, did you want to comment on that question?

20 MR. WILSON: Maybe I can help out a little bit. I

21 am going to use an example of something that already exists,

22 CMV assays, class II medical device. The intended-use

23 statement goes on the line of to detect antibody to CMV in

24 the serum of blood donors, or some such. It doesn't say,

25 for the prevention of CMV transmission. It doesn't say

at

1 that.

2 If it said for the prevention of CMV transmission,

3 you would have to run a clinical trial to show that it does

4 that. But since it is limited to for the detection of CMV

5 antibody--all right; what is the content of the 510(k) class

6 II. Many of the concepts that Dr. Dayton has described are

7 just, simply, reproduced in the class II.

8 We have analytical sensitivity data, analytical

9 specificity data. Because it is used for the blood supply,

10 we run a study that is in blood donors to check specificity

11 because you can't check specificity in a blood-donor

12 population any other way than running it. And why would we

13 do that? Because we don't want to have too many units of

14 blood tossed out because of false positives.

15 We do have, and I think along the lines of where

16 Dr. Dayton is going, some known positive samples that we

17 would test--the manufacturers would use the test to

18 determine whether or not, in fact, they truly detect a true

19 positive. But it is not in clinical-trial format in that

20 sense.

21 So, therefore, that enables FDA to clear the

22 product with claims or labeling limited to what the thing

23 has been documented to do. So, in terms of this particular

24 assay, there are a lot more questions and we know that,

25 because of viral resistance and mutations, things are going

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

5 I hope that helps.

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

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

17 Does that answer your question?

18 DR. BOYLE: Yes.

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

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

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1 the moment. We are certainly open minded about how to
2 actually approach this. It should be reasonable for a
3 sponsor to assemble his own panel which might be the
4 quickest way to do it, but it is quite laborious.
5 It would be also possible to have a centralized
6 panel set up. Also a sponsor has the alternative of coming
7 forward with the clinical-trial data while he waits--and
8 doing the panel postmarket. We are trying to make it
9 flexible so that it can go either way.
10 I think Ed wants to comment on this.
11 DR. TABOR: I think the discussion is confusing
12 the issue tremendously.
13 MR. DUBIN: We have done that before.
14 DR. TABOR: I think part of it is that it is
15 focussing on constructing panels and focussing on
16 postmarketing surveillance. The issue is between whether
17 this should be a class III device or a class II device. The
18 discussion should have nothing to do with blood screening
19 because a test that is used for blood screening usually is a
20 licensed product for which a PLA is filed.
21 What we should be focussing on is is the clinical
22 impact of this assay so great and, perhaps, so unknown that
23 you need clinical trials and to file a PMA and have an 180-
24 day review clock which really translates into more than a
25 year of review time with resubmissions or is the clinical

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1 significance of this so clear and is the impact on the
2 patients' health more an issue of management than of life
3 and death such that the manufacturer can file a 510(k), have
4 a 90-day review clock, and have minimal or no clinical data.
5 Postmarketing surveillance is another issue, I
6 think, here. It is not totally divorced from this but you
7 shouldn't be focussing on something that you want clinical
8 data and you are going to wait and get it after marketing.
9 If you want clinical data, it should be a PMA and a
10 class III device.
11 The question here is are the manufacturers going
12 to have to go through a longer review cycle with more
13 clinical data up front or are they going to be able to file
14 a 510(k) with only special controls and any clinical data,
15 really, as icing on the cake.
16 DR. DAYTON: Let me just elaborate on Ed's
17 response. It is absolutely correct. Again, don't feel that
18 you are having to judge a particular product. You are asked
19 to judge, is the science such that we can judge a product,
20 or that a product can be judged.
21 DR. HOLLINGER: I think probably we ought to
22 listen. I think that the next step should probably be to
23 listen and see what the data is out there and see what it
24 means. Let's have one more and then let's go to some of the
25 data.

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1 MR. DUBIN: I was going kind of towards where you
2 were going, Dr. Tabor. Here is how we frame the question.
3 I think, from our perspective, the big plus is if this is
4 going to give clinicians who are actually, at the grass-
5 roots level, treating patients and dealing with resistance
6 problems, then that is going to give the clinicians more
7 freedom and more ability to move.
8 I think, from our perspective, that is clearly a
9 good thing because, certainly, in hemophilia, this is a big
10 problem in the infected hemophilia community. We are having
11 a lot of problems with the resistant strains and a lot of
12 our guys are in trouble.
13 Our only concern, and the way I was trying to
14 frame it, was we have had concerns about how fast-track has
15 gone, things that have happened and have caught our
16 attention and concerned us. But I think, in this instance,
17 the issue is, and I agree with you, if we can do this in a
18 way that provides the freedom to the clinicians and the
19 ability to track it, then it seems like a no-brainer on one
20 level from our perspective.
21 DR. STRONCEK: I have a couple of comments. There
22 are a number of HLA tests where genotyping is used to
23 determine phenotype which are marketed so I presume they are
24 regulated. Are those regulated as class II--class II, I
25 would presume.

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

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

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

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

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

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

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

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1 could try simplifying a little bit this class II and class
2 III.
3 I think, back in 1976 when this device legislation
4 took place, there was an effort to kind of establish risk
5 categories associated with a device. A device, class I, not
6 much risk if something goes wrong; class III, a lot of risk
7 if something goes wrong.
8 I think, in some of the original language, there
9 was the concept of life-sustaining device for a class III
10 device, like an implanted pacemaker. I think the thing that
11 is probably confusing the committee is that there are now
12 some things that are, by fiat, put in class III because
13 there was no predicate device; by that, there was no device
14 like what we have today because the problem didn't exist.
15 So those devices end up being bumped in this
16 class III category until they can get dispersed into,
17 perhaps, a more appropriate category.
18 Does that help a little bit?
19 DR. HOLLINGER: Thank you, Don.
20 Why don't we go ahead, Andy.
21 DR. DAYTON: I guess we are ready for Doug Mayers.
22 **Presentation**
23 DR. MAYERS: I want to thank the FDA for making
24 drug resistance interpretation seem simple.
25 [Slide.]

1 What I would like to do in the next forty minutes
2 or so is go over the background of HIV resistance testing, a
3 little bit about the biology of HIV resistance and then
4 overview the current clinical data both retrospective and
5 prospective. By nature, this is going to be a survey and
6 not exhaustive because there are far too many studies today
7 than the time I have to present them.
8 I just want to make a caveat that I will
9 occasionally use a company slide in this talk because I
10 didn't have a slide to illustrate the point, but those
11 slides are made to illustrate a biological point and not the
12 support any company and, where possible, I have used every
13 company in the area's slides, one of each, so they don't
14 feel like they have been slighted.
15 [Slide.]
16 It is important to recognize of HIV that the
17 replication of the virus is very rapid in a patient such
18 that patients make up to a billion particles each day with a
19 half life of about one day.
20 [Slide.]
21 The reason this is important from an HIV
22 resistance point of view is that the virus, as a replication
23 strategy, makes, on average, one error per each progeny
24 virus. So, if a billion viruses are produced and you have a
25 10,000 base virus making, on average, one error, that means

1 you have 100,000 of every single-base variant and about ten
2 copies of every double-base variant in your patient.
3 So when you have these discussions of do drug-
4 resistant viruses exist at some level, yes, in all of our
5 patients, they exist and they are spontaneously produced
6 every day in the patient. This is the virus' strategy to
7 escape immune pressure and it also uses it to escape drug
8 pressure.
9 [Slide.]
10 In 1989, two years after AZT was introduced into
11 clinical practice, Doug Richmond and Brendan Larder had a
12 paper that came out in Science. What they showed was that
13 viruses were produced in our patients that were 100-fold
14 less susceptible to AZT than when they started therapy.
15 This shows the phenotype assay results from that
16 paper. What you have on the vertical axis of this is the
17 amount of virus replication relative to a no-drug control.
18 On the horizontal axis is drug levels. What you can see in
19 the upper left-hand panel, C, is that for the virus in light
20 blue that the virus is susceptible to AZT and it takes about
21 0.03 micromolar of drug to suppress it.
22 Then, as you watch the viruses over time, you can
23 see that you move out to the yellow virus which is obtained
24 a number of months later and now the virus is 100-fold less
25 susceptible to AZT and it takes about 3 micromolar of drug

1 to suppress it.

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

7 [Slide.]

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

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

21 [Slide.]

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

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

5 [Slide.]

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

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

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

1 you have to have a number of mutations. So it takes the
2 accumulation of three, four or five mutations to get high-
3 level resistance and it takes the virus a period of time in
4 the presence of drug to get to those high levels. But it is
5 fairly easy to describe what resistance is in them because
6 they do get the high levels of resistance.
7 The last group of drugs, ddI, ddC and d4T are
8 really where much of the controversy of interpretation of
9 resistance assays comes from. From these drugs, you never
10 really get very high levels of resistance in the clinic with
11 the drugs. You get four- to five-fold resistance which is
12 almost within the assay variability of a phenotypic assay.
13 So there always a fair amount of debate as to what ddI, ddC
14 or d4T resistance is. This leads to some of the variability
15 in the reports that the clinicians receive from the
16 laboratories.
17 [Slide.]
18 Looking at a crystal structure of the reverse
19 transcriptase, what you can see is that along a loop between
20 about bases 65 and 75, there is a whole string of mutations
21 associated with nucleoside resistance with multiple
22 different agents. And so it wouldn't be surprising that
23 resistance to one drug might be associated with cross-
24 resistance to other drugs in the class.
25 [Slide.]

1 This has clearly been shown. For zidovudine, it
2 produces low levels of resistant to ddI and ddC as you get
3 high levels of zidovudine resistance. But, more
4 importantly, it has been shown that once you have high-level
5 zidovudine resistance, combinations of AZT-ddI and AZT-ddC
6 did not lead to clinical benefit.
7 For 3TC, abacavir, ddI and ddC, these drugs all
8 have overlapping mutations. Clearly, one drug will produce
9 mutations at some level of decreased susceptibility to the
10 other drugs. And d4T hangs out by itself because we really,
11 even in 1999, don't understand d4T resistance very well.
12 [Slide.]
13 An aspect that has been very interesting to
14 virologists but it has complicated things for the clinician
15 is that the virus can take numerous routes to get the high
16 levels of resistance. The good news from a clinical point
17 of view is that the vast majority of isolets do it the way
18 you would expect. They get AZT resistance. They get 3TC
19 resistance. They add the classical mutations together to
20 produce a high-level resistant virus.
21 But, in the last year or two, we have discovered
22 that a small number of patients can go down a different
23 pathway of a 151 mutation and, even more fascinating, the
24 virus can actually add six bases into that loop I showed you
25 and produce high-level resistance by an insertional mutation

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1 which we never expected to see, but it can be easily
2 identified.
3 [Slide.]
4 From a clinical management point of view, though,
5 the vast majority of our patients are failing with 215 and
6 184 with associated other nucleoside mutations. So, from a
7 clinical point of view, the overwhelming majority of
8 patients fail with known mutations and known resistance
9 patterns.
10 [Slide.]
11 Moving to the non-nucleoside drugs, the non-
12 nucleoside drugs have a totally different pocket from the
13 ones of the nucleosides. The picture has actually become
14 relative simple in 1999 because of the use of the non-
15 nucleosides in combination with either AZT or d4T. The vast
16 majority of the non-nucleoside agents right now are failing
17 with a mutation at position 103, a single-point mutation
18 called K103N. This mutation, essentially, inactivates all
19 of the non-nucleoside drugs.
20 [Slide.]
21 This just shows, in a number of clinical isolates,
22 that isolates that only had the 103N mutation with non-
23 nucleoside resistance had developed significant decreases in
24 susceptibility to efavirenz, nelvirapine and delavirdine.
25 [Slide.]

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1 Moving to the protease enzyme, the protease enzyme
2 has sort of a bewildering assay of mutations that you can
3 see but, in all honestly, only about five or six of them are
4 really critically important to high-level resistance. Those
5 are shown in this model by the red balls. They are the
6 mutations that tend to occur in the active site of the
7 enzyme and produce resistance.
8 There are a number of other mutations that are
9 associated, in this figure with the yellow or white balls,
10 and these are compensatory mutations. What you see the
11 virus doing in patients is the virus will develop a
12 critical-site mutation, a red-ball mutation, and get some
13 level of resistance. But then it doesn't grow very well.
14 It doesn't cut proteins as well as a protease so it adds in
15 two or so of the compensatory mutations. Then it adds back
16 in another resistance mutation and it works its way through
17 fitness base.
18 But, for the practicing clinician, what you really
19 need to do is just count how many critical-site mutations
20 were there.
21 [Slide.]
22 This shows the critical-site mutations for the
23 drugs that are currently available. For saquinavir, it is
24 90 and 48. For indinavir, it is 82, 46, 84. Nelfinavir, it
25 has been the D30N, usually L90M, occasionally. And for

1 amprenavir, it appears to be a 50 mutation.

2 [Slide.]

3 An issue that has caused real concern of
4 resistance was initially data from indinavir where they
5 showed that if you had high-level phenotypic resistance to
6 indinavir, there was a loss across the class of resistance.
7 For ritonavir, it is 100 percent. For saquinavir, it is 60
8 percent. Nelfinavir, it is about 75 percent. And, with the
9 newer data for amprenavir, it is probably closer to 55 to
10 60 percent of these isolates would be resistant.

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

16 [Slide.]

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

25 [Slide.]

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

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

9 [Slide.]

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

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

23 [Slide.]

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

1 PI regimens. They looked at ten-fold decreased
2 susceptibility to any of the available agents and showed
3 that about three-quarters of the isolates had decreased
4 susceptibility to all of the agents by the time they got
5 there.
6 [Slide.]
7 Switching over to susceptibility testing, the sort
8 of gold standard for susceptibility testing was an assay
9 developed in 1990 between the ACTC and the Department of
10 Defense in which we took patient isolates, we grew them and
11 expanded them, titered them and assayed them for drug
12 susceptibility on patient-donor lymphocytes.
13 [Slide.]
14 This assay allowed us to look at roughly
15 95 percent of the patients and look at how they were failing
16 on drugs. This just shows the susceptibility pattern. The
17 green and the yellow are pre-therapy isolets--the white and
18 the red are post-therapy isolets--that were obtained from
19 that original study the Doug Richmond did back in 1989.
20 [Slide.]
21 The nice aspect about this assay was we had
22 reasonably good quality control. You could note
23 susceptibility within about three-fold. Sort of a standard
24 of thumb has been that if the decrease in susceptibility is
25 less than three-fold for these types of assays, you are not

1 really sure if it is resistance or just assay variability.
2 The newer assays may be able to get down to the
3 two-fold, two-and-a-half-fold, but I think the two- to
4 three-fold is about as close as you can know a phenotype on
5 a virus.
6 [Slide.]
7 We were able to actually set reasonable cut points
8 for sensitive, partially resistant and resistant that
9 actually had clinically validated meaning. The sensitive of
10 less than 0.2 micromolar was based on patients' isolates who
11 had never seen drug and the range of susceptibilities in
12 wild-type virus. Resistant was associated with loss of
13 clinical activity and clinical disease progression.
14 [Slide.]
15 The problem with this assay is illustrated in this
16 chart. Times 0 on the bottom is the time at which
17 phenotypic resistance emerged in these patients. This was a
18 study done in about 1993. What we showed was that patients
19 who always remain sensitive had good stable CD4 counts. The
20 unfortunate news was that, by the time we saw phenotypic
21 resistance from a co-cultured virus from the cells, the
22 patient was already failing by enough--had had about a
23 50 percent CD4 decline and so the clinicians didn't need our
24 assay to tell them that they were not doing well.
25 [Slide.]

1 About this same time, data began to emerge from
2 3TC and also some of the AZT studies that, if we took the
3 plasma virus and looked at that for mutations or
4 susceptibility that we could actually detect resistance very
5 nicely at the beginning of the rise in the viral load as
6 opposed to the PBMCs where it took a bit longer to show up.
7 So most of the focus on resistance testing has
8 moved from trying to take cells in coculturing virus to
9 looking at the virus that is circulating in the plasma in an
10 individual patient.
11 [Slide.]
12 Currently, all of the assays available, either
13 genotypic of phenotypic, basically PCR a segment of the
14 virus that includes the protease gene and the early 250 to
15 300 bases of the polymerase gene which is where we have
16 identified resistance mutations. So, basically, you lift
17 out from the plasma the protease and part of the RT gene and
18 then, for phenotypic assays, you clip it into a vector and
19 grow it up. For genotypic assays, you sequence it.
20 [Slide.]
21 This just points out that we have to PCR amplify
22 for all the assays we use on that segment of the genome.
23 [Slide.]
24 This just shows what a sequence looks like that we
25 are actually doing. The sequence with the arrow over it

1 shows the detection of the emergence of a subpopulation of
2 virus. So, basically, you either have a peak by itself
3 which can be described as a single amino acid or you have a
4 peak where there is a mixture. Those can be associated with
5 minority populations of virus.
6 For all the assays we use for genotyping right
7 now, they all use population sequencing and we basically can
8 pick up somewhere between 30 and 50 percent minority
9 populations. So these assays clearly do not pick up
10 minority populations well. We are not picking up 5,
11 10 percent virus. We are picking what the predominant
12 circulating virus is in all of these assays.
13 One of the difficulties with doing these assays is
14 also illustrated by the arrow in the second row because the
15 mutation they are pointing out isn't associated with
16 resistance.
17 [Slide.]
18 For the common viruses, we take that same segment
19 of the genome. We PCR amplify it, put it into a deleted
20 vector, grow it up and then test it against drugs. The
21 reason that this has been, I think, very useful in the
22 development of resistance testing is that this allows us to
23 not have the alterations in the virus associated with
24 growing it up for long periods of times in cells. It also
25 speeds up the process so, instead of taking six to eight

1 weeks to get a phenotype back to the clinic, the new RVA
2 assays can turn a result around in about three weeks back to
3 the clinic.
4 So it has been a significant increase in speed and
5 it looks like there has also been an increase in quality
6 control such that their variability appears to be less than
7 the variability we had with the PBMC-based assays.
8 [Slide.]
9 This just shows the types of susceptibility curves
10 that they can get. What you see here is the blue curve on
11 all these figures is a control virus that they put on the
12 plate, and the yellow curve is the clinical isolate. As you
13 can see for 3TC, the virus has essentially no susceptibility
14 to 3TC. As the curves shift toward the right, you are
15 seeing increasing resistance. So these are the types of
16 assays that the companies are doing for phenotypic testing
17 right now.
18 [Slide.]
19 At this point, I would like to switch over to
20 clinical relevance. This has always been a somewhat
21 contentious topic.
22 [Slide.]
23 For clinical significance, zidovudine is the only
24 drug for which we have data for clinical progression and
25 death. I honestly believe that we will probably never have

1 any other single drug for which we will be able to show
2 clinical progression and death because of the use of
3 combinations.
4 But, for AZT, we could clearly show with greater
5 than 1.0 micromolar resistance at baseline if this was the
6 associated progression and death in both the ACTG 116B, 117
7 study and a prospective study in the Department of Defense
8 with about a two-and-a-half to three-fold risk of disease
9 progression. This was independent of the other baseline
10 parameters available to us at that time.
11 [Slide.]
12 For the pediatricians, this is a similar study
13 looking at the 215 mutation in plasma virus. What they did
14 was, the yellow dots are the children who had no disease
15 progression and were doing quite clinically well. The
16 orange dots are the children who were progressing and having
17 disease progression.
18 What you can see is that the children who had no
19 disease progression also had no evidence of the 215 mutation
20 and the children who were progressing developed increasing
21 amounts of the 215 mutation in their plasma virus and it was
22 strongly associated with disease progression in this cohort.
23 [Slide.]
24 The companies have been doing a very good job
25 recently with the new drugs in defining the phenotypes and

at

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

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

13 [Slide.]

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

24 [Slide.]

25 Similarly, for ritonavir and saquinavir, they were

1 able to look at phenotypic and genotypic resistance. What
2 they showed very nicely was that the predictors of failure
3 were the same as we had seen previously for zidovudine, CD4
4 count, disease stage, HIV RNA, but also either phenotypic
5 resistance or genotypic resistance predicted lack of
6 response to saquinavir and ritonavir.
7 [Slide.]
8 Moving into broader-based clinical studies, Andy
9 Zolopa and the group at Stanford looked at patients who
10 received ritonavir and saquinavir who were all PI
11 experienced. They looked at short-term virologic responses,
12 and the clinical predictors were the same as we had seen
13 previously.
14 Of note, drug history, number and prior duration
15 of drugs predicted poor response and simply counting the
16 major protease mutations, the red-ball mutations, I showed
17 you earlier. If you simply counted them, the number of
18 mutations in the virus predicted response to ritonavir and
19 saquinavir. The more you had, the worse you did.
20 [Slide.]
21 Steve Deeks presented data at the same meeting
22 which, I think, gave us a great deal of insight into what
23 you need to get a good response in an experienced patient.
24 They took eighteen patients who had received abacavir,
25 saquinavir, nelfinavir and nelvirapine. These were all four

1 new drugs these patients had never seen. So they took four
2 drugs that the patients were naive to. They looked at a
3 phenotypic assay.
4 [Slide.]
5 What they showed was that seven of the patients
6 had only zero or one active drug in the regimen by
7 susceptibility testing. In those patients, none of them got
8 a response. It was only very transient and none of them
9 went below the limits of detection of the assay.
10 So this was showing the impact of cross-resistance
11 in this population. Eleven patients had two or three active
12 drugs. They all had a sustained response and eight of ten
13 went undetectable. None of them had all four drugs in the
14 combination active. What this basically told us was if you
15 are going to get a good response in a regimen for heavily
16 pre-exposed patients, you are going to need to find two or
17 three active drugs to give that patient.
18 [Slide.]
19 That is the retrospective data. I am now going to
20 move to the two prospective trials that have been done on
21 genotyping. The first trial is the GART trial, GART
22 standing for genotypic antiretroviral resistance testing.
23 It was a trial done by the CPCRA in patients who had had a
24 good response to protease-containing regimen and then lost
25 that response.

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1 The patients had plasma virus, had plasma sent in.
2 The virus was sequenced. It was reviewed by a panel of
3 three virologists; myself, Tom Merigan and John Baxter. We
4 gave the clinicians back a report of susceptibility and we
5 also gave them some recommendations for treatment at that
6 time.
7 You have got to remember this trial started in
8 1996. The community docs really were not comfortable that
9 they could take the sequence data and use it in clinical
10 management at that time. So the test was a test of getting
11 the sequence data with some suggestions versus using your
12 own clinical judgment in the management of these patients.
13 It had a short-term virologic endpoint of 4, 8 and
14 12 weeks of follow up. The reason the data was chopped
15 after 12 weeks was that the patients and their physicians
16 were allowed to switch drug regimens if they hadn't had a
17 good response during that time period. So the test was only
18 relevant during that short period of time.
19 [Slide.]
20 Looking at the randomization, patients had about
21 230 CD4 cells, about 30,000 copies of HIV RNA. The majority
22 of the patients had received nelfinavir for indinavir which
23 was common to the community at that time. About half of
24 them were failing on their first protease-inhibitor-
25 containing regimen and the other half were on their second

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1 or third regimen.

2 [Slide.]

3 Looking at the baseline resistance mutations, as
4 we had shown previously, in this population, about three-
5 quarters of them had both RT and protease mutations. About
6 20 percent had RT mutations alone. And 5 percent had
7 absolutely no mutations in their virus. It is the
8 impression of the clinicians and the virologists in the
9 study that that 5 percent was probably not actually on drug
10 at the time that these susceptibility tests were done.

11 Looking at the mutations, we saw, again, 184 and
12 215 were the overwhelmingly common human-failure mutations
13 with only 1 or 3 percent of patients getting the insertion
14 in the 151 mutation. And we had a variety of protease-
15 inhibitor mutations.

16 [Slide.]

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

22 [Slide.]

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

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1 the 8- and 12-week time period as some patients got a
2 transient response to drug and then resistance reemerged.
3 [Slide.]
4 But it should be noted that, at all time points,
5 about twice as many patients were undetectable using
6 resistance testing as they were if you just used clinical
7 judgment alone. Even at the 12-week time point, about
8 28 percent of our patients were undetectable with genotyping
9 and about 15 percent were undetectable with clinical
10 judgment alone.
11 [Slide.]
12 A point of contention in this study has been that
13 the patients who were getting the genotyping also received,
14 on average, one more drug than the patients who were getting
15 phenotyping based potentially on the fact that their docs
16 could see the resistance data available.
17 [Slide.]
18 But we have actually gone back and reanalyzed the
19 data. If you look for patients who got three drugs, four
20 drugs or five drugs, at every number of drugs, the patients
21 did better if they had genetic data to assist in the
22 management than if they guessed with clinical judgment
23 alone.
24 We think this actually explains the results of
25 this trial. The green curve is the viral-load response that

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

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

13 [Slide.]

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

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

1 Basically, any cell that had more than eight
2 patients in the cell had a significant difference with
3 genotyping.
4 [Slide.]
5 The second prospective study was the VIRADAPT
6 study which was conducted in France. This was a bit
7 different study in that there were basically a number of
8 French clinicians at about three French medical centers who
9 followed a series of patients and did genotpying and then
10 would meet and discuss the results either with genotyping or
11 without genotyping for the manufacturer of individual
12 patients.
13 [Slide.]
14 It is a little bit smaller study. There were
15 43 patients in the control arm and 65 patients in the
16 genotyping arm.
17 [Slide.]
18 The patients in the study were a bit more advanced
19 than the GART patients. They had, on average, a plasma HIV
20 RNA of about 150,000. The CD4 cells were about 200 to 220,
21 and quite a few of them had actually had symptomatic HIV
22 disease.
23 [Slide.]
24 If you look at their prior exposure, they were
25 very heavily exposed. They had seen, on average, one-and-a-

1 half to two PIs when they came into the trial. They had
2 had, on average, about four nucleoside agents and, again,
3 about half of them were first-time failures and the other
4 half were second- and third-line-failure patients.
5 [Slide.]
6 The results in this trial show that they actually
7 got a sustained benefit to six months. The difference
8 between this trial and the GART trial was that if you hadn't
9 gotten a good response at three months, you could retest the
10 patient at three months and go to six months. And so, in
11 GART, you got one test, we followed you. In this trial, you
12 got a test every three months.
13 The data went out to six months in a randomized
14 fashion. As you can see, there is about a half-log
15 difference between the two arms out to six months that
16 persisted. They subsequently extended the analysis out to a
17 year and they have had a stable reduction in RNA out to a
18 year in these patients who could get repeated testing.
19 The trial was no longer randomized after six
20 months because, once the GART results were released, the
21 French unblinded the trial and took everyone over to
22 genotypic testing.
23 [Slide.]
24 Of note, and very similar to the GART results, you
25 can see that roughly 30 percent of patients were

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1 undetectable in the GART arm and about 14, 15 percent of the
2 patients were undetectable in the no-GART arm so, again,
3 about a two-fold difference between genotypic testing versus
4 clinical judgment alone.
5 These results have been remarkably consistent
6 across these two trials that had somewhat different
7 methodologies.
8 Also of interest, both trials used the same
9 algorithm to interpret the data for genotyping. The
10 algorithm is actually contained in table 8 of the Stanford
11 Guide for the Management of HIV-Infected Patients. It is a
12 little pocket guide.
13 [Slide.]
14 So in choosing an effective salvage regimen for
15 patients who are failing on combination therapy, I think we
16 have a number of clinical parameters available; number and
17 duration of prior antiretroviral drugs, knowledge of cross-
18 resistance patterns between the drugs.
19 This data can be supplemented with resistance
20 testing. I think the bottom line is to have an effective
21 salvage therapy in patients who fail combination regimens.
22 You need to be able to find two or three drugs that remain
23 active against the patient's circulating virus.
24 [Slide.]
25 The current dilemma is even with the availability

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1 of repeated genotypic testing, we can only get 30 percent of
2 patients suppressed below 500 copies per ml. This just
3 emphasizes the need for us to continue to get salvage drugs
4 available for these patients.
5 [Slide.]
6 In the last few minutes, I would like to go over
7 the public-health data looking at resistance. This is the
8 percent of patients with AZT resistance by year. Before
9 1987, we never actually saw an AZT-resistant virus in an
10 untreated patient. In 1987, the drug entered clinical
11 practice. It was available to about 20 percent of patients
12 because you had to have late-stage disease to get access to
13 the drug.
14 So, from 1987 to 1990, about 20 percent of our
15 patients had access to AZT and there was about a 1 percent
16 level of transmission of drug-resistant virus. In 1990,
17 because of the 116, 119 results of the ACTG, there was an
18 expansion of the use of AZT to patients with less than 500
19 CD4 cells. Two years after the increased indications for
20 AZT usage, the transmission rate jumped to 7.5 percent and
21 then actually moved to between about 8 and 10 percent for
22 the next five years.
23 [Slide.]
24 So AZT resistance was seen at about an 8 to
25 10 percent level in new seroconverters from 1993 through

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1 about 1996. In 1996, 3TC became available within a year.
2 Because of a single-point mutation, 3TC-resistant
3 transmissions were seen. The most recent data, as we have
4 moved to a very broadened use of combination therapy, is
5 that we are seeing an even increased risk of transmission of
6 drug resistance. This is data from both the military and a
7 cohort led by the group at San Diego.
8 What they showed was that, looking for resistance
9 by phenotype and genotype, they found a level of somewhere
10 between 20 and 30 percent of new infections were infected
11 with drug-resistant virus in 1999. What has become a bit
12 scary to the practicing clinician is an increasing number of
13 these patients actually have multi-drug-resistant virus with
14 both nucleoside- and either protease- or non-nucleoside-
15 associated mutations.
16 [Slide.]
17 So I think we can actually categorize a number of
18 high-risk populations for drug resistance; patients who have
19 lost virologic control on a combination antiretroviral
20 regimen, new HIV seroconverters, HIV-infected infants of
21 HAART-experienced mothers--we don't have very many of them
22 but when they occur, these children are at very high risk
23 for drug resistance--and occupational HIV exposure of
24 healthcare workers. These are four categories of
25 individuals who are at high risk of drug-resistant virus.

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1 [Slide.]

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

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

17 [Slide.]

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

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

7 [Slide.]

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

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

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

23 [Slide.]

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

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

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

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

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

22 I thank you.

23 DR. HOLLINGER: Thank you, Doug.

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

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

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1 DR. HOLLINGER: Let's see if there are some
2 questions here of Dr. Mayers.
3 DR. CHAMBERLAND: In the packet of information
4 that we got, there was a recent Lancet publication on the
5 results of the VIRADAPT study. Has the GART trial been
6 published?
7 DR. MAYERS: The GART trial has been in submission
8 to JAMA for over eleven weeks right now so that if they ever
9 release it, we hope they will publish it.
10 DR. CHAMBERLAND: Because one of these papers, I
11 think, referenced an abstract for the GART study. Could you
12 just clarify, in the GART study, in the methodology, in the
13 GART arm, physicians got results of genotypic testing. In
14 the non-GART arm, what information--I wasn't clear, exactly.
15 It looks like they got the recommendation from--
16 DR. MAYERS: No.
17 DR. CHAMBERLAND: No; they didn't get anything?
18 What did the non-GART get?
19 DR. MAYERS: What the non-GART got was that the
20 team gave them the current recommendations and they gave
21 them regular updates from the ongoing meetings for salvage
22 regimens in that population. So, basically, we sent out to
23 them--after each meeting, we would send out to them an
24 update; "Here is what we are seeing with these drugs in
25 these types of patients."

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1 So we did an educational component, but we did not
2 give them direct recommendations.
3 DR. CHAMBERLAND: So they just got general
4 guidance about current thinking for salvage therapy--okay.
5 But even in the non-GART arm, would you feel that clinicians
6 were probably getting more information than the average
7 treater gets because--
8 DR. MAYERS: I think that is fair. I think the
9 thing that has encouraged us that this was not biased in a
10 significant way is the French study where there was no
11 expert advice given at all and all they got was the genotype
12 given back to them. And the fact that GART and VIRADAPT
13 essentially lie on top of each other at similar time points
14 suggest that there was, probably, not a huge bias in that.
15 DR. CHAMBERLAND: Can you tell us more who the
16 physicians were who participated in the GART and the non-
17 GART arm? Where I am going is that I think there is a
18 spectrum of treaters out there who treat HIV patients. At
19 one end of the spectrum, we have folks like yourself, very
20 knowledgeable, involved in research and, at the other end,
21 are treaters who--and I think they may constitute the
22 majority of treaters--who really are trying very hard to
23 keep up with a moving target.
24 They have these publications from the Public
25 Health Service and from these advisory committees about what

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1 to do, but they are not really well-educated about
2 genotypic, phenotypic, information, et cetera and they get
3 these very complicated reports from these laboratories.
4 They are tough to interpret. I do very limited clinical
5 work and it is tough.
6 DR. MAYERS: I have the same problem, myself,
7 getting some of these reports.
8 DR. CHAMBERLAND: So I kind of wanted to know,
9 because we don't have a publication, unfortunately, who was
10 in the GART trial, where to they fall in this spectrum of
11 treaters because I think this is important to the committee
12 ultimately having to vote on this issue, to have a kind of
13 an understanding of what information is going to be--
14 DR. HOLLINGER: Yes; and how was it determined who
15 was non-GART and GART?
16 DR. CHAMBERLAND: Exactly.
17 DR. MAYERS: Basically, I want to apologize to the
18 committee for giving you the GART study but the rules that
19 the FDA operates under are if I give it to you, I have to
20 put it out on the table out front. Since it is still in
21 submission to JAMA, I could not give it to the committee.
22 The clinicians throughout the CPCRA--these were
23 the community docs in the CPCRA system, so they were at all
24 the sites in the CPCRA, randomly out there. Any doc who
25 sent a sample in could participate from the CPCRA.

1 The randomization was done in such a way that the
2 patient's provider would send a sample into the team, the
3 group of virologists would look at the sample, interpret it
4 and get the report done, submit that report to that stat
5 center not knowing if they were going to randomized or not,
6 and then the stat center would roll the dice and randomize
7 them after they had received the report from the virologist
8 back to the field.
9 So, basically, this was a large group of community
10 physicians throughout the United States and the reports were
11 done the same if you got the report or didn't get the report
12 as far as the virologists were concerned. We didn't know
13 who was going to get a report when it went out.
14 MR. DUBIN: So any one physician who has seen
15 multiple patients, sometimes he is going to get GART and
16 sometimes not?
17 DR. NELSON: Yes; there were some physicians who
18 treated a few patients with the genotyping and a few
19 patients without it. That's correct.
20 DR. HOLLINGER: And decisions for changes by the
21 non-GART was based on CD4s and HIV concentrations that they
22 received back?
23 DR. MAYERS: The clinicians and the virologists in
24 the study knew CD4s, viral loads, and they also knew the
25 treatment history of each individual patient. So you knew

1 how many drugs they got and what drugs they had had toxicity
2 or not had toxicity on. So it was the data that would be
3 conventionally available to a doctor treating an HIV-
4 infected patient.
5 DR. HOLLINGER: And he would make a decision, or
6 she would make a decision, based upon the results that came
7 back to that person.
8 DR. MAYERS: When the patient came back to the
9 clinic for their randomization visit, the doctor would
10 either get a GART report and have to tell us how it impacted
11 his decision making or her decision making, or they would
12 not get a GART report and have to use the data that they had
13 had available to them prior to make a decision as to which
14 drug to switch to.
15 DR. TUAZON: In terms of having--once this test
16 had been approved, where do you see the clinical utility of
17 both assays? I think, for the experienced, PI-experienced
18 patients, you probably would just go ahead with the
19 phenotypic. Accounting for the cost of both of the assays,
20 what are the practical uses of this?
21 DR. MAYERS: I think one of the real surprises
22 that we have seen across both studies has been that the
23 relative benefit has been the same across rounds of therapy.
24 But that is relative benefit in the face of a shrinking
25 response.

1 What I see happening at this point is going to be
2 in newly infected patients who you know are newly infected,
3 not patients who walk in with PCP but newly infected, that
4 they are at fairly high risk and I think there is going to
5 be a move to take this testing to look for newly infecteds
6 fairly soon because the rates are clearly above 10 percent
7 in that population right now.
8 For other patients, I think we will use CD4 and
9 viral load like we currently do. A person who is below
10 50 copies and is doing well without a genotype, I don't need
11 the test. I think, on early rounds of failure, you will
12 probably see genotypic testing used on those patients
13 because it has a fairly quick turnaround time which will
14 probably start to drop to less than a week as market forces
15 develop and it is less expensive.
16 I think that, for people, as they get to the point
17 where the genotype becomes different to interpret and they
18 can't find the drugs they need, you are going to see a shift
19 toward phenotypic testing because it can find holes that you
20 can't find with the genotype testing in these individuals.
21 That current assessment is based on cost and turnaround
22 times.
23 If the phenotypic companies can get their cost
24 down in the same range and the turnaround time in the same
25 range, I really don't see a great deal of difference in

1 early failures between either methodology. They can both
2 show you where there are potential holes to get active drugs
3 and they can both show you were resistance exists.
4 So a lot of it is going to be how fast they turn
5 them around and how much they charge you. I think the
6 interpretations are clearly improving a lot recently. The
7 reports clinicians used to get back a year ago, and even
8 with some companies, as was stated, get now can be difficult
9 to interpret.
10 I know they are difficult to interpret when one of
11 my docs brings it in to me and I look at it and scratch my
12 head and try and figure out what they are saying so that I
13 can tell him what to do. I think that this is an area where
14 there really does need to be some work by industry to
15 develop a standardized reporting format.
16 I can tell you that there are some groups that
17 develop computerized algorithms that give a very nice report
18 that says, sensitive, partially resistant, resistant, just
19 like you would get from your microlab for a bacteria. And
20 you can do it for both phenotype and genotype if the
21 companies want to.
22 DR. NELSON: Again, back to the GART trial. You
23 gave the randomized physicians recommendations for which
24 drugs to use. Did you also measure how the recommendations
25 were followed by the patients and the physicians? Was that

1 done?

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

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

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

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

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

1 So what was the compliance? We now know that
2 probably the greatest challenge is making patients
3 compliant. Those patients who are not compliant with their
4 medications are the ones who different resistance the
5 fastest. So the issue would be is that in the group that
6 was not getting this information, did you measure
7 compliance, other than just asking the patient. Were there
8 any other basic measurements to be sure that these patients
9 were taking their medication as were the ones who were on
10 the GART trial
11 DR. MAYERS: We are currently going back into the
12 trial. This trial, when it was originally done, was done as
13 a pilot study that Tom Merigan and I and John funded off our
14 laboratory internal budgets. So there was a certain limit
15 as to how much testing we could do for free.
16 But what has happened is those restored samples
17 done at every time point on these patients and we are now
18 going back into these samples doing genotyping, phenotyping
19 and drug-level measurements at every time point for every
20 patient with support from a number of the companies. And we
21 will have that data to bring back.
22 We did not have timing so I won't be able to tell
23 you high/low. But I will be able to tell you, yes, they had
24 drug or no, they did not have drug, of a very sensitive
25 assay. The data from the French trial that was recently

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1 completed with de-escalation of therapy suggests that this
2 is adequate data to at least predict were they taking drug
3 at all or not taking drug.
4 And so we are looking at that but it is not
5 available at this time.
6 DR. McCURDY: It appears that even though there
7 are certain mutations where it is pretty well established
8 that either alone, or in combination, they confer
9 resistance. The question that I have is suppose a new
10 mutation or a new group of mutations seems to correlate with
11 resistance, perhaps, to a new drug or something like that.
12 How is the decision made as to how this new work
13 is interpreted? Is this based on limited data and then you
14 follow along?
15 DR. MAYERS: Basically, I can tell you how we do
16 it in the CPCRA where I have a little control. Basically,
17 if the mutation associated with loss of viral activity of a
18 drug or is associated with a clear change in phenotype, we
19 will add it into the algorithm fairly early on and then look
20 for its impact prospectively.
21 I think what is developing over time is a number
22 of groups, the CPCRA, a number of industrial groups, the
23 ACTG, are developing very large databases that include
24 mutation's response to the next round of therapy. So what
25 is going to happen fairly quickly is that as soon as a

1 mutation is detected, or what we think is a polymorphism
2 today is shown to be a true resistance mutation, you are
3 going to be able to have two or three groups very rapidly
4 tell you, yes, we see this to be true or no, this appears to
5 have been an artifact.
6 So I think the ability to actually confirm or rule
7 out these mutations in a very rapid fashion is actually
8 getting much better almost by the day.
9 DR. McCURDY: Dr. Stroncek made the analogy to HLA
10 typing. For a number of years, there were workshops that
11 got together that developed--wet workshops and others that
12 got together to define new types. Is this sort of thing
13 happening? Are the databases getting together or is this an
14 individual entrepreneurial activity?
15 DR. MAYERS: The honest answer is it is not
16 happening as much as it should. One of the problems is that
17 each of the major commercial sponsors have developed a
18 proprietary algorithm which they are trademarking and
19 patenting as quickly as they can so that we don't have sort
20 of your blue-collar framework everyone agrees to at this
21 point for either breakpoints for phenotyping or genotypic
22 interpretation.
23 I think this is an area where we can do better and
24 this is an area where I think there could be some useful
25 work to develop NCCLES type of standards for genotypic and