1 bacteria, but we don't know what part of it is.

2 The data seems to be fairly straightforward to
3 get, especially in terms of what else we are doing for blood
4 and the other things we see at scientific meetings. Blood
5 is safe now, but things change. The incidence of disease
6 changes. The way we process blood changes, and so on.

7 There are a number activation steps coming down
8 the line that might take care of the bacteria, if we don't
9 need it. So I think it is kind of imprudent right now
10 without more data to not vote yes for this.

11 DR. HOLLINGER: David, you made some statements.
12 I don't know how you can say that something is not
13 transmitted by blood when you are testing for it. Let's
14 just take NAT testing of HCV right now. If it were the one
15 test that would being used, you might say that patients with
16 HCV don't transmit HCV to people because you have eliminated
17 that.

18 I am not saying it is transmitted, but it doesn't
19 seem like we have the data to make that statement. So the
20 fact that we may not have seen any transfusion-transmitted
21 cases may be because it is not transmitted. It may be
22 because the test is eliminating those but you would ask,
23 well, what about the ones in the window period. Why don't
24 we even see some of those coming through.

25 But we have missed a lot of positives. Even all

1 those HCV cases which we are now detecting, those sort of
2 don't come to the forefront in the clinical arena anyway
3 about why haven't we seen all these cases anyway. They are
4 probably there. We are just not detecting them. So I am
5 not sure that that is--
6 DR. STRONCEK: I agree with you. I meant to say
7 we are not seeing transmission.
8 DR. HOLLINGER: Sorry about that.
9 DR. SIMON: I thought the data that were presented
10 indicated that a fair number of people have the spirochete
11 in their circulation who test negative, that our test is not
12 specific. So we know, in fact, that we are not picking them
13 up and they are being transfused, and yet we are not having
14 cases. Isn't that correct, based on the data?
15 DR. STRONCEK: Yes; but there is other data that
16 suggests that none of the donors are--it is all old
17 infections. So I think that the data is still unclear on
18 what is going on.
19 DR. HOLLINGER: I am going to call for the
20 question, then, that we have up there so we can vote on it.
21 We will be voting on the first question of, do committee
22 members agree that current scientific data are insufficient
23 to warrant discontinuation of donor testing for antibodies
24 to syphilis. Again, a yes vote here would mean that you
25 believe that currently the testing should continue because

1 of lack of the scientific data at the present time.

2 So all those that are voting yes, in favor of this

3 question, raise your hand.

4 [Show of hands.]

5 DR. HOLLINGER: All those opposed?

6 [Show of hands.]

7 DR. HOLLINGER: Abstain?

8 [No response.]

9 DR. HOLLINGER: Toby? Industry?

10 DR. SIMON: Opposed.

11 DR. HOLLINGER: Kathy I think left you something.

12 Ms. Knowles.

13 DR. SMALLWOOD: Ms. Knowles would agree with those

14 that voted "yes."

15 DR. HOLLINGER: Please read the results.

16 DR. SMALLWOOD: The results of voting on Question

17 1a), there were 13 "yes" votes, 2 "no" votes, no

18 abstentions. The industry representative agreed with the

19 "no" vote and the consumer rep left a note that she would

20 agree with the "yes" vote.

21 DR. HOLLINGER: Carmelita, do you want to comment

22 about anything? The reason I am asking you is that you have

23 a great deal of experience with this but, also, it goes into

24 the second part of the question in 1b). So if you wouldn't

25 mind, could you share with us--

1 DR. TUAZON: I think we have data for thirty years
2 that there are no cases of transfusion-transmitted disease.
3 And we know historically that, in terms of the clinical
4 presentation, if a transfusion-transmitted disease is to
5 occur, it will present systemically, that you can diagnose
6 and it is easily treatable.
7 In contrast to the implications in terms of
8 transfusion-transmitted HCV and HIV, syphilis is very
9 treatable and curable compared to those other diseases. So
10 those are, really, the major reasons that I think that the
11 testing could be eliminated, plus the fact that, as
12 mentioned earlier, there may be cases that are not
13 serologically positive with blood that has been donated and
14 has been transfused, and yet we have not documented
15 transfusion-transmitted syphilis or over 30 years.
16 DR. HOLLINGER: Thank you.
17 Paul, do you have any comments?
18 DR. SCHMIDT: I agree and I think I said my
19 feelings before.
20 DR. HOLLINGER: Okay. I think what we will do,
21 because we will come back to this 1b) if we have some time
22 here. There has been a lot of discussion anyway on part
23 1b), so I want to go to 2 for a minute so we can get the
24 questions out of the way. The second question, basically,
25 is saying--it really is a moot point, I suppose, basically,

1 now that I look at it again. It is kind of a moot point.

2 DR. SIMON: It is moot, or does the FDA want to

3 know this when those data come in?

4 DR. HOLLINGER: Do you want to know the answer to

5 this anyway--I mean the vote anyway?

6 DR. RUTA: Sure.

7 DR. HOLLINGER: The question is, do committee

8 members believe that donor testing for antibodies to

9 syphilis should be retained as a surrogate marker of

10 deferrable risk behavior even if it is proven that such

11 testing no longer is useful for prevention of transfusion-

12 transmission of syphilis.

13 As I say, it is kind of a difficult question to

14 deal with because we have already said the answer above.

15 DR. EPSTEIN: I think we would like the question

16 voted because, after all, this is advisory and we are not

17 sure where the agency will come out and, perhaps, in a year

18 we may all feel comfortable dropping it for prevention of

19 syphilis transmission and question 2 will still be hanging

20 in the air.

21 DR. HOLLINGER: Are you saying you may not pay

22 attention to what we do here anyway?

23 DR. EPSTEIN: Oh; we listen very closely, Blaine,

24 particularly to you.

25 DR. HOLLINGER: Let's act is if we, then, answered

1 that question the other way and then answer the question
2 about whether you think it should be retained as a surrogate
3 marker for deferrable high-risk behavior. That is basically
4 the question.

5 Ken? Please.

6 DR. NELSON: The way the question is stated, I am
7 not sure, and given the reality of the situation, I am not
8 sure how I would vote. But if, in fact, the specificity of
9 the test were--if we could eliminate the false-positives
10 that are the major problem for the blood banks right now--if
11 that issue could be dealt with in some way, then I would
12 vote yes.

13 The reality is that we are going to retain the
14 test anyway. But I think it does have value as a surrogate
15 marker. The problem is that there are so many--with the
16 current blood-donor population, there are so many false-
17 positives that significantly impact the blood bank. But I
18 think it is of value as a surrogate if, in fact, the
19 specificity were higher.

20 It has been shown in all of the HIV studies. That
21 was in the original CDC case-control cohort of KS, that was
22 the KS patients before AIDS was actually defined, that was
23 the strongest association. There have been odds ratios of
24 10. So, even though it turns out in the blood-donor
25 population that it isn't such an important surrogate--and

1 the reason is that is it is nonspecific, mostly.

2 DR. HOLLINGER: So we will go ahead and vote on

3 this. The question, then, really is just a "yes" vote here

4 would be that you believe that the testing for antibodies to

5 syphilis should be retained as a surrogate marker of

6 deferrable high-risk behavior. That is what a "yes" vote

7 would be .

8 All those who would vote "yes" on this question,

9 raise your hand. In other words, should it be retained as a

10 surrogate marker of deferrable high-risk behavior assuming

11 that we had voted not to--all those that believe that.

12 [Show of hands.]

13 DR. HOLLINGER: All those "no?"

14 [Show of hands.]

15 DR. HOLLINGER: Abstaining?

16 [One hand raised.]

17 DR. HOLLINGER: Dr. Simon?

18 DR. SIMON: I agree with the "no"s.

19 DR. HOLLINGER: Could you read those please?

20 DR. SMALLWOOD: The results of voting on question

21 no. 2, there were 5 "yes" votes, 9 "no" votes, one

22 abstention. The industry representative agreed with the

23 "no" votes. The consumer representative would have agreed

24 with the "yes" votes.

25 DR. HOLLINGER: Dr. Chamberland?

1 DR. CHAMBERLAND: I guess I just wanted to say
2 that the reason I voted to abstain is that I think probably
3 I would have been able to vote "no," but I feel like this is
4 kind of an add-on to a discussion that was largely focussed
5 to address the first question.

6 Alan Williams did a very nice job with his
7 presentation, but I think there are other data that may not
8 even contradict his final findings, but there are other
9 data. I think Ken Nelson alluded to that. So I think my
10 sense is that it just didn't get adequate time for
11 presentation and full discussion, the lateness of the hour,
12 et cetera.

13 So that was why I sort of came down on the
14 "abstain" side of things. It may very well merit another
15 go-around.

16 DR. HOLLINGER: Thank you. We have got just a few
17 minutes because the more important thing is the cafeteria is
18 going to close before too long. But have we responded, with
19 all this done today and the discussions in regards to the
20 adequacy of additional studies as proposed, to resolve the
21 value of testing?

22 I think the feeling was that some of these studies
23 should be done and they could be done internationally. I
24 think there was some discussion of that and there should be
25 some review of individuals--I mean, some of the laboratory

1 studies for blood products, if it is done properly.

2 DR. RUTA: I think we heard some valuable advice.

3 DR. EPSTEIN: I would encourage members of the

4 committee that have further comment on potential studies

5 simply to communicate with the agency over the next couple

6 of weeks.

7 DR. NELSON: One additional study that I could

8 think of to answer the question about PCR measure of

9 infectivity is you could take patients with active syphilis

10 who are being treated and repeatedly study the decay, if you

11 will, of the PCR positivity in their blood as treatment

12 progresses, or after treatment.

13 My prediction is that PCR would disappear rapidly.

14 But I don't know that there are data on that.

15 DR. HOLLINGER: Very good.

16 It is now around 1:30. We are going to break

17 until 2:15. I would like you to meet back in here so we can

18 then deal with the medical-devices issue for HLA and then

19 into the site visit. Thank you.

20 [Whereupon, at 1:30 p.m., the proceedings were

21 recessed to be resumed at 2:15 p.m.]

A F T E R N O O N P R O C E E D I N G S

[2:20 p.m.]

DR. HOLLINGER: This committee often sits as a medical devices committee for medical devices. This is a session today on the classification of HLA devices.

If you have read the stuff that they sent you, this should be, I think, a relatively straightforward issue here. But I think we need to have someone talk to us a little bit about these class I, class II, class III devices.

Sheryl Kochman?

**IV. Classification of HLA Devices**

**FDA Presentation of the Issue**

MS. KOCHMAN: My charge today is go over some of the issues pertaining of the classification of HLA devices.

[Slide.]

First, I would like to provide you with an introduction and background to issues. My objectives are to provide an overview of the current regulatory status of HLA devices, to provide a background regarding medical-device classification. We will ultimately also provide an overview of the third-party review program.

[Slide.]

For the purposes of today's discussion, we are defining HLA devices as in vitro diagnostic reagents and kits for use in determining the HLA phenotype of genotype of

1 an individual or for detecting and identifying antibodies to
2 HLA antigens.
3 [Slide.]
4 These HLA devices include characterized polyclonal
5 or monoclonal antibodies for determination of phenotype and,
6 for those of you who are blood bankers, you can view these
7 as being analogous to blood-grouping reagents. They also
8 consist of DNA-based assays for determination of HLA
9 genotype. They also include characterized leukocytes for
10 detection and identification of antibodies.
11 Again, for those who are blood bankers, this would
12 be analogous to reagent red-blood cells. Those products are
13 currently CBER-licensed IVDs, just to give you a sort of a
14 sense of where there might be some parallels.
15 We are not, during this discussion, including
16 those in vitro diagnostic reagents or kits that are used to
17 predict disease; for example, anti-HLA-B27 can be used to
18 detect the HLA B27 antigen as a marker for ankylosing
19 spondylitis. Those specific products are regulated by the
20 Center for Devices and Radiological Health, so we are not
21 covering them today.
22 [Slide.]
23 I will provide you with some regulatory history.
24 A lot of this was in the packet that was distributed ahead
25 of time. The first product license for leukocyte-typing

1 serum, which is what they were called at the time, was
2 issued in December of 1974. In December of 1977, FDA
3 guidelines for the production, testing and lot release of
4 leukocyte-typing sera were issued.
5 In August of 1980, FDA issued a proposed rule
6 recommending that the additional standards for leukocyte-
7 typing serum be revoked. Finally, the final rule was issued
8 on August 10 of 1982 revoking the additional standards for
9 leukocyte-typing serum and revoking the licenses that went
10 along with those.
11 [Slide.]
12 The effect of those proposed and final rules was
13 that they utilized the expanded-control authority under the
14 Medical Device Amendments to the FD&C Act. This means that,
15 in addition or instead of the standards that were being
16 applied at the time, there were provisions against
17 adulteration, misbranding, registration.
18 There was a need for classification requirements
19 regarding banned devices, notification and other remedies,
20 records and reports, in some cases, restrictions on sale,
21 distribution or use and good manufacturer practice.
22 [Slide.]
23 Furthermore, all manufacturers that had been
24 previously licensed and also new unlicensed manufacturers
25 were notified that they were to register and list under

1 21 CFR 807. New manufacturers additionally were required to
2 submit premarket notification submissions, commonly known as
3 a 510(k) submission, Part 21, CFR 807. It added the
4 requirement that labeling conform to 21 CFR 809.10 which is
5 labeling for in vitro diagnostic substances, also the
6 requirement that manufacturing be conducted so it conforms
7 with 21 CFR 820.
8 At that time, they were known as the current GMPs
9 and this is currently known as the Quality System
10 Regulation. The proposed and finals rules also indicated
11 that device classification would follow.
12 [Slide.]
13 In the meantime, CBER received, reviewed and
14 cleared a number of 510(k) submissions. According to my
15 records, there were approximately 65 submissions that were
16 processed. Letters variably refer to the devices as class I
17 and class II despite the fact that there was never a formal
18 classification rule issued.
19 So, when that was discovered, it was determined
20 that the current letter should list the devices as being
21 unclassified, which is what current letters go out as.
22 [Slide.]
23 The basis for this confusion appears to be that
24 the proposed rule clearly states that a request for
25 classification has been made and will be published upon

1 receipt. But that proposed rule also stated that if the
2 proposal were to be published in final form, the device
3 would be subject to the General Controls Provisions. This
4 will come a little clearer later on when I talk about the
5 difference in classification.
6 There was also a statement that agency believes
7 that these and other general controls applicable to medical
8 devices are sufficient and also that the appropriate
9 regulatory status of the product will be considered in the
10 course of classification.
11 [Slide.]
12 Because of the lack of classification, we have had
13 a number of problems the first of which is confusion in
14 industry about which standards should be applied to the
15 manufacture and distribution of those devices. In addition,
16 there has been confusion within CBER about what review
17 criteria should be applied to the review of the 510(k)
18 submissions.
19 There also appears to have been an erroneous
20 belief within the industry that registration, listing and
21 510(k) submissions are not needed. We have a number of
22 anecdotal reports that there are manufacturers out there
23 manufacturing and distributing these kits without having had
24 them registered or 510(k)-cleared.
25 There is also confusion in ORA about whether or

1 not to inspect these devices and what standards to apply
2 during an inspection. This is based on the fact that,
3 because of limited resources, the field has had to make some
4 cuts as to what will and will not be inspected. They have
5 gone to a risk-based approach in their inspection process
6 and, as a result, class I devices, which are generally
7 considered to be low-risk, are usually not inspected. Class
8 II devices are inspected basically on an as-needed basis and
9 class III devices tend to be inspected more regularly.
10 The other problem that is associated with the lack
11 of classification here is that we have been unable to
12 proceed with some of the initiatives pertaining to FDAMA,
13 the Food and Drug Administration Modernization Act.
14 Specifically, we would like to proceed with making these
15 devices eligible for third-party review.
16 [Slide.]
17 I want to briefly go over device classification.
18 First, we will talk about preamendments devices.
19 Preamendments devices are those which were on the market
20 prior to the enactment of the Medical Device Amendments of
21 1976. There are three classes into which those devices are
22 placed; class I, class II and class III.
23 [Slide.]
24 Class I devices are those in which general
25 controls alone are sufficient to provide reasonable

1 assurance of safety and effectiveness or it is unclear if
2 general controls alone are sufficient to provide reasonable
3 assurance of safety and effectiveness but the device is not
4 life-supporting, life-sustaining or of substantial
5 importance in preventing impairment of human health.
6 [Slide.]
7 General controls, which is the thrust of putting a
8 device in class I, include establishment registration,
9 product listing, conformance to the QSR and, as I mentioned
10 before, this was previously the GMP, conformance to device
11 labeling requirements, submission of a 510(k), if
12 applicable. Some class I devices do not require submission
13 of a 510(k) any longer. Others do.
14 And there are also other controls within the Act
15 that are applied to devices in class I.
16 [Slide.]
17 Most class I devices are now exempt from the
18 requirement to submit a 510(k). Those that are not exempt
19 are designated as reserve devices. Most class I devices are
20 not subject to the design-control provisions of the QSR.
21 For those of you not familiar with the medical device
22 portion of the CFR, design controls are relatively new and
23 have been put in place to assure that a device is designed
24 to meet its intended specifications.
25 But, in the case of most class I devices, they

1 don't have to adhere to those. Furthermore, some class I
2 devices are even exempt from the requirements of the CSR.
3 It is important to note that class I is the least stringent
4 regulatory category.
5 An example would be a blood grouping view box, the
6 old-fashioned slide agglutination viewer.
7 [Slide.]
8 For a class II device, general controls alone are
9 insufficient to provide reasonable assurance of safety and
10 effectiveness and there is sufficient information to
11 establish special controls.
12 [Slide.]
13 Special controls include performance standards,
14 special labeling requirements in addition to those required
15 for class I devices, use of guidance documents, use of
16 recommendations during the review process, possibility of
17 including patient registries, postmarket surveillance and
18 "other actions deemed appropriate by the Commissioner."
19 It is important to note that, for a class II
20 device, special controls are used in addition to the general
21 controls, so it is a higher level of control.
22 [Slide.]
23 Class II devices are generally considered to be
24 moderate-risk devices. They may be life-supporting or life-
25 sustaining. Some have been exempted from the requirement to

1 submit a 510(k). And the most common example in the blood-
2 bank area of a class II device would be an automated blood-
3 grouping and antibody-test system.
4 [Slide.]
5 For a class III device, there is insufficient
6 information that general or specific controls, as I just
7 previously described, will provide reasonable assurance of
8 safety and effectiveness and the device is life-supporting,
9 life-sustaining or of substantial importance in preventing
10 impairment of human health or it presents a potential
11 unreasonable risk of illness or injury.
12 [Slide.]
13 Premarket approval is required for class III
14 devices. The manufacturer must submit these during the
15 process of a premarket review. Scientific and regulatory
16 review is done to insure the safety and effectiveness of the
17 device.
18 [Slide.]
19 Again, class III devices are high-risk devices.
20 This is the most stringent regulatory category. General
21 controls also apply here. A current example of class III
22 device used on blood banks would be the electromagnetic
23 blood and plasma warming device.
24 [Slide.]
25 There is also a device classification of post-

1 Amendments devices. Post-Amendments devices are those which
2 are introduced to the market after enactment of the Medical
3 Device Amendments of 1976. Now, if you will remember, I
4 stated that the first license for HLA devices was issued in
5 1974. So, clearly, HLA devices were on the market prior to
6 the enactment of the Medical Device Amendments.
7 The classification process that I just described
8 would apply but, just to provide full background
9 information, when the device comes to market after 1976,
10 there are two routes of classification. They can either be
11 the same regulatory class as the device to which it is
12 deemed substantially equivalent or it can be a class III if
13 not substantially equivalent to a device already legally on
14 the market.
15 The big question there is what is substantial
16 equivalence. Substantial equivalence means the device has
17 the same intended use as the predicate device and it has the
18 same technological characteristics as its predicate device
19 or it has different technological characteristics but does
20 not raise new concerns of safety and effectiveness.
21 Are there any questions on the classification
22 process?
23 DR. HOLLINGER: Just a question about substantial
24 equivalence. It always seems a little unfair to me--I am
25 sure there is a reason for it, obviously, but you have

1 somebody comes in, the initial group, and they do all this
2 work to get their device on the market, and then someone
3 else comes along afterwards that has a comparable device and
4 they don't have to do all this work.
5 Is that I understand substantial equivalence to
6 mean?
7 MS. KOCHMAN: It doesn't really mean that they
8 don't have to do as much. The first device sort of sets the
9 standard. So the subsequent submitters would have to make
10 sure that their device has been through the same level of
11 rigor and testing, the same level of GMP and manufacturing.
12 So the following people have to do everything as well as or
13 better than the initial submitter.
14 But some of the mystery is taken out of the
15 process of how to get it through the FDA, especially if they
16 choose--once a device has been cleared, the packet is
17 available under freedom of information for other device
18 manufacturers to find out, well, how did these people get
19 their device to market.
20 So the first people do sometimes have the
21 difficulty of treading a new path. But, as far as the
22 amount of work that is done, the followers on actually do
23 the same level of work. They just have a little bit better
24 map of how to get there.
25 DR. HOLLINGER: The financial costs are about the

1 same?

2 MS. KOCHMAN: Yes; I would think so.

3 DR. HOLLINGER: Any other questions?

4 Thank you.

5 Eric Rechen will talk about the third-party review

6 program.

7 **Third Party Review Program**

8 MR. RECHEN: Thank you very much.

9 [Slide.]

10 I am Eric Rechen. I am with FDA's Center for

11 Devices and Radiological Health and I helped to coordinate

12 the third-party review program in that center. It is a

13 pleasure to address the panel today, hopefully very briefly

14 for your sake, about this program. The reason I am talking

15 about this program is because, depending on how HLA devices

16 are classified, this program could be used to facilitate

17 rapid marketing clearance of those products, of new models

18 of those products. And that is the essence of the 510(k)

19 program which is what the third-party review program applies

20 to.

21 [Slide.]

22 The basic purpose of the third-party review

23 program is twofold. It is to provide an alternative to

24 FDA's process that can yield more rapid marketing clearance

25 decisions than FDA's traditional review. It also, then, by

1 doing so, by offloading reviews to third-party reviewers, it
2 frees up FDA resources to focus on higher-risk products.
3 [Slide.]
4 The origin of the program was about four years
5 ago. At that time, our center had experienced some
6 significant 510(k) review backlog and so, as a reinventing
7 government initiative, we started what we then thought would
8 be a two-year pilot program to see whether third-party
9 reviews improved the efficiency of our 510(k) process.
10 Before that two-year pilot ran its course, in 1997
11 Congress enacted the FDA Modernization Act and they
12 basically codified this pilot program into the Food, Drug
13 and Cosmetic Act. So it is now a statutory program.
14 The law gave us a year to convert our pilot into
15 the accredited persons program, and we did that. And so we
16 formally implemented the accredited persons program late in
17 1998. On this slide, I have noted a website. We have a
18 third-party web page on our center's web site, and this has
19 all the relevant documents for this program, some of which I
20 will refer to in a few minutes.
21 [Slide.]
22 In a nutshell, here are the main features of the
23 program. First, FDA acts as the accreditor for outside
24 review organizations under this program. The law required
25 that we issue a Federal Register notice that laid out what

1 our accreditation criteria would be. Essentially, we
2 consider whether an organization is technically competent,
3 whether it has adequate personnel to do reviews of the
4 devices they seek to review, and we also look to see that
5 the organization and its personnel are not conflicted to do
6 these reviews.
7 We have, at this point in time, accredited twelve
8 organizations to do various types of device 510(k) reviews.
9 It is a voluntary program from the manufacturer's
10 standpoint. What I mean by that is a manufacturer can elect
11 to use this program or they can elect to still submit to
12 FDA. It is the manufacturer's choice.
13 If the manufacturer chooses to submit to an
14 accredited person, the process is essentially this. The
15 manufacturer contacts one or more organizations that are
16 accredited to review the types of device that the
17 manufacturer makes or is intending to make.
18 The manufacturer negotiates for a review and pays
19 a fee for service, which is determined through that
20 negotiation between the third party and the manufacturer.
21 They then send the 510(k) to the organization they have
22 contracted with. The accredited person reviews the 510(k)
23 using the same criteria as FDA and documents its review and
24 submits it recommendation and documented review and the
25 original 510(k) to FDA.

1 FDA still has authority to issue the final
2 decision. Under the law, FDA is required to issue a
3 decision within 30 days of receiving a third-party
4 recommendation.
5 [Slide.]
6 This next slide just shows you the twelve
7 organizations that are currently accredited to do reviews
8 for various devices. The only thing I would point is there
9 is a diversity of organizations here. Most of them are
10 U.S.-based test or certification houses that are also
11 European notified bodies and test houses.
12 There is an organization from Taiwan. There is
13 even one state government. The California Department of
14 Health is an accredited person. At this point in time, of
15 course, none of these organizations are accredited
16 specifically to review HLA devices, but it is an open
17 accreditation process and so, at any time, these
18 organizations or other organizations could apply to become
19 accredited of HLA products are included in the program.
20 [Slide.]
21 A key point is what products are eligible for
22 accredited-person review. The statute actually doesn't say
23 what is eligible. It says what is not eligible. This
24 slides summarizes what accredited persons may not review.
25 They may not review the highest-risk products, essentially.

1 That is, they can't review class III products that are
2 subject to premarket approval or that will be made subject
3 to premarket approval but are currently being reviewed under
4 the 510(k) process.

5 And they also may not review certain types of
6 class I devices, and that is--the first category would not
7 apply to HLA products, but the permanently implantable
8 devices. They also may not review life-supporting or life-
9 sustaining devices and they may not review 510(k)s that
10 require clinical data for determination of substantial
11 equivalence.

12 That is a little, perhaps, more difficult
13 criterion to understand but, basically, to equate HLA
14 products to the in vitro devices that we review in our
15 center, we have many IVDs that are included in the program
16 even though they typically require comparative testing of
17 human samples of using an established test and the product
18 that is the subject of a 510(k).

19 That normal comparative test, just involving human
20 samples, has not been defined for purposes of this program
21 as being excluded. So many IVDs are included in the
22 program. However, if an IVD requires a full-blown clinical
23 study where patients are tracked and the results of those,
24 and the patient outcomes and the test results are being
25 matched, then that is something that typically would be

1 excluded under this program.

2 [Slide.]

3 Based on the statutory criteria, the agency has
4 put out a list of device types that are eligible for
5 accredited-person review. At this time, the list includes
6 211 types of medical devices, all class I devices that are
7 not exempt from 510(k) plus 57 selected class II device
8 types.

9 In Fiscal Year 1999, we received more than 1600
10 510(k)s for eligible device types. We very recently, I
11 think in June, proposed a very broad expansion of the
12 program that would essentially include all remaining
13 products that meet the statutory criteria for accredited-
14 person review. That is about 460 additional class II device
15 types.

16 When I say "all," I mean all that are regulated by
17 our center.

18 [Slide.]

19 At this time, devices that are reviewed by CBER or
20 CDER are not included in the program but, of course, they
21 could be. Very rapidly, what our program experience has
22 been was industry participation up to this point is still
23 low. We only have about 3 percent utilization of the
24 program for eligible products.

25 But the utilization is growing. This year, we are

1 receiving about 40 to 50 510(k)s that were reviewed by an
2 accredited person. The reviews that we are getting have
3 essentially been very good quality reviews. In Fiscal Year
4 1999, we accepted 100 percent of accredited-person
5 recommendations without changing the recommendation and, in
6 90 percent of the cases, we were able to accept that
7 recommendation without requesting any substantive additional
8 information.

9 Essentially, we accepted it on our first FDA
10 review cycle. The reviews so far, the accredited-person
11 reviews, have yielded, on average, more rapid marketing
12 clearance.

13 In Fiscal Year 1999, there were 29 510(k)s cleared
14 through that process with a third-party review and, in those
15 cases, the average total elapsed time from the day that an
16 accredited person initially received a 510(k) to the day we
17 issued a final clearance was 57 days. That was about
18 46 percent faster than traditional in-house reviews
19 conducted by FDA.

20 So that is all I have prepared to say. I hope
21 this gives you some information that might be useful to you
22 in determining how to provide an efficient clearance process
23 for HLA products if they are classified such that they are
24 eligible for this program.

25 DR. HOLLINGER: Questions? Paul?

1 DR. SCHMIDT: It was my understanding that the
2 reason that we are special government employees while we are
3 on this committee and cannot accept any foreign emoluments
4 or anything else is that the FDA could only accept advice
5 from federal employees, and not from outside bodies.
6 I am sure that is a different mechanism, but how
7 do you see that in relation to the program you are
8 discussing in which the work is being farmed out?
9 MR. RECHEN: This is a program provided under
10 different statutory authority and so, essentially, Congress
11 has made the cut that here is another mechanism by which the
12 agency can obtain recommendations about marketing clearance.
13 So these bodies, again, are subject to a lot of the same
14 conflict-of-interest controls that you are accredited
15 through a specific process provided by law.
16 Does that answer your question?
17 DR. SCHMIDT: Could that be applied to the
18 clearance of blood products in the same way in the future?
19 MR. RECHEN: Certainly, products that meet the
20 statutory criteria, meaning class I or class II, that meet
21 the other criteria could be made eligible should the agency
22 elect to make them eligible.
23 DR. SCHMIDT: Thank you.
24 DR. HOLLINGER: Does that also mean that an
25 accredited person could not be an SGE?

1 MR. RECHEN: An accredited person cannot be a
2 federal government employee. I assume that would also apply
3 to special government employees.
4 DR. HOLLINGER: Yes? Gail?
5 DR. MACIK: Of the various ones that have gone
6 through this process of the various 510(k)s, how many of
7 those were class I and how many were class II?
8 MR. RECHEN: I don't have an exact cut for you
9 right here. I certainly could provide one. But in Fiscal
10 Year 1999, the vast majority of those 29 that we cleared
11 were class II products. So most of them are on the higher-
12 risk spectrum of the low to moderate-risk ones that are
13 eligible for review.
14 DR. MACIK: But they had no clinical data? So
15 these were really just looking at GMP-type aspects,
16 sensitivity, specificity of the device, or whatever?
17 MR. RECHEN: We are looking at--and I tend to
18 speak in more broad device terms; under the 510(k)
19 substantial equivalence process, we are essentially looking
20 at the technology of the product--that is, its design,
21 materials, and such, and also its intended use, does it have
22 the same patient population and indications for use as its
23 accredited product.
24 DR. MACIK: But that also includes whether or not
25 it performs as it is said to perform; right?

1 MR. RECHEN: Correct. Particularly the way the
2 substantial-equivalence criteria are spelled out in the
3 Food, Drug and Cosmetic Act, if there are differences
4 between a newly proposed product in its technology from a
5 previous one, then the 510(k) needs to show that this
6 product is as safe and effective as the previous product.
7 That often involves performance data, bench-type
8 testing or animal testing, in the case of other types of
9 devices.
10 DR. MACIK: Those still could be done by this
11 outside group as long as there was no tracking of clinical
12 data?
13 MR. RECHEN: The manufacturer is responsible for
14 providing all the data. So they are not the ones
15 responsible for testing--I mean the accredited person is not
16 the one responsible for testing the product.
17 DR. MACIK: But you need someone how can review
18 what the manufacturer gives them and see that, yes, all
19 those tests were done, all the comparisons were done and
20 understand what they are looking for with that. So that is
21 all done by this outside group.
22 MR. RECHEN: That's right. They essentially act
23 as FDA's primary reviewer and then we act as a quasi-
24 supervisor of that review.
25 DR. HOLLINGER: It looked like everything you

1 showed up there was an organization, not a person, as you
2 looked at it. Do you accredit an organization or do you
3 accredit persons within the organization, or persons, also?
4 MR. RECHEN: The term "person" is used in the law
5 in its legal sense. Essentially, what we are looking at is
6 organizations. I guess, theoretically, it could be a person
7 that we accredit, but, typically, what we are looking at is
8 an organization.
9 DR. HOLLINGER: Mary?
10 DR. CHAMBERLAND: In your slide in which you
11 detailed the list of eligible devices, your last bullet said
12 that devices that are reviewed by CBER and CDER were not
13 included. Is that because both of these centers chose not
14 to utilize, or at least initially utilize, this option.
15 And, with this HLA device that we are going to be looking at
16 today, which comes under CBER's purview, would this, then,
17 be the first CBER device to be utilizing the accredited-
18 person review?
19 MR. RECHEN: I answer to your second question
20 first, yes; this would be the first one that would be made
21 eligible under this program. Of course, other ones could be
22 made eligible. The reason they are not included; there is a
23 little history there. This program, as I said, was
24 initiated as a center initiative by the Devices Center. So
25 it kind of just started out as a center pilot.

1 It was then codified into the law which would have
2 allowed, certainly, other center's devices to be enrolled.
3 Correct me if I am wrong, I believe that CBER has elected,
4 to this point, not to include its products because the
5 number of such reviews that they typically do at this point
6 are so low that it wasn't cost-effective for them to train
7 their staff and get involved in the program.
8 But I think, at this point, they are looking to
9 rethink that.
10 DR. HOLLINGER: How do you get away from a
11 conflict of interest here? It seems to me you have got an
12 organization out there who has something and they want to
13 get it reviewed. They can choose the accredited person and
14 then they can work out a contract of how much to pay that
15 person. The person could charge them $10,000 an hour if he
16 wanted to, or the organization could.
17 That looks just like a conflict of interest to me.
18 It is almost as if I were on an advisory board, or
19 scientific advisory board for a company, that was coming
20 before this committee for a review of something and I would
21 have to recuse myself because of that.
22 So I am not sure I understand how you get away
23 with from that kind of conflict.
24 MR. RECHEN: It is a good question and one that I
25 think a lot of people have grappled with, although I guess I

1 would point out that this program is certainly not unique.
2 There are car-inspection programs and other things where
3 that same kind of model applies. But, basically, yes; there
4 is a fee for service and, on its surface, that has the
5 appearance of a conflict. Someone is getting money to
6 provide a service.

7 What we do, though, is when we accredit the third
8 party, we look at their policies and procedures to insure
9 that they don't have a financial or other conflict, meaning
10 that they don't have personnel who are involved in medical-
11 device work, that design devices, that manufacture or sell
12 devices.

13 There are a whole set of criteria that we look
14 for. There are, also, under our law, criminal authorities
15 where we can take criminal action if a third party takes a
16 bribe or anything to that effect. These organizations, to
17 point to some of the ones that were on that list, are like
18 underwriters' laboratories or others who have a long history
19 of being involved in accepting money from outside parties to
20 test or to certify their products and have fairly well-
21 established procedures to insure that they have a reputation
22 that is not tarnished by the fact that they are taking
23 money.

24 That is a fairly vague answer, but I think if you
25 looked at our accreditation criteria, we certainly could

1 make the a little bit more specific.

2 DR. SIMON: Just briefly, I would speak to that

3 because we have had recent experience becoming ISO

4 certified. It is the same situation. In fact, British

5 Standards Institute, which was the first organization on

6 that list, is a common ISO-certifying organization. It is

7 the one we use.

8 I guess you are speaking more for the conventional

9 FDA paradigm which, obviously, does not have this

10 involvement. But, also, this has now gotten into clinical

11 research. I would guess the majority of clinical research

12 is done by IRBs that are paid, also, for the review of

13 protocols.

14 So it is obviously something that has gotten into

15 our society, for better or for worse.

16 DR. HOLLINGER: Mr. Rice?

17 MR. RICE: I just have a question. You say that

18 there is low utilization of the program currently. Is that

19 simply because of its infancy, or is this additional cost,

20 perhaps, to getting their products on the market where they

21 are not paying the FDA if they choose to use FDA's approval

22 process?

23 Just as a question of interest, are these costs

24 maybe prohibitive to hire out the third-party analysis as

25 opposed to waiting for the FDA? Maybe that explains the low

1 utilization, or is there still a lack of trust of industries
2 to be able to take comfort in this new paradigm?
3 MR. RECHEN: Again, a very good question. I think
4 you hit on a lot of the reasons. It is a new paradigm and
5 it takes some getting used to. People in the device
6 industry have been using the 510(k) process and submitting
7 to FDA for over twenty years now.
8 So it takes some reeducation to learn to do
9 something different. There is some uncertainty involved,
10 but I think our experience, to this point is trying to
11 dispel some of that uncertainty.
12 The fee is an issue. For device reviews, we do
13 not have user fees. So, for an FDA review, there is no fee
14 other than the time it takes to submit to FDA. For third
15 parties, there is a fee. A major factor, though, is since
16 this program was initiated, our own internal review times
17 have improved significantly and we are not running backlogs
18 right now in our center.
19 So that negates some of the incentive to look
20 elsewhere.
21 MR. RICE: The only thing I can see, perhaps, just
22 a question in my mind, is if the industry has the choice of
23 either going the accredited-persons route or the FDA route,
24 would there, or might there be, a tendency maybe for an
25 industry to choose the accredited-person route because maybe

1 they don't feel the FDA's review would be as sympathetic, or
2 kind, since you are leaving it up to the industry's choice
3 to go either route? It is just a question.
4 MR. RECHEN: I will address it, and I will try to
5 be brief. Accredited persons know that FDA has to buy off
6 on their review and so they are going to be out of business
7 real quickly if they do something that they know we are not
8 going to approve of. So they are in the business of trying
9 to make us happy as well as the manufacturer.

10 **Open Public Hearing**

11 DR. HOLLINGER: There is one industry presentation
12 here by Pel-Freez. I don't have the name of the individual.
13 I'm sorry. Is there someone here from Pel-Freez that wishes
14 to comment?
15 Then I think we move into the charge to the
16 committee.

17 **Charge to the Committee**

18 DR. SMALLWOOD: I will be very brief. The charter
19 of the Blood Products Advisory Committee permits this
20 committee to sit as a medical-device panel when it is
21 necessary to review or discuss issues related to the seeking
22 of advice, recommendations for approval or, in this case,
23 classification of medical devices which are regulated by the
24 Center for Biologics Evaluation and Research.
25 For this particular session, we have Dr. Khanal

1 Matal of NIH who formerly was the Chief of the HLA lab here
2 at FDA. And we also have Dr. Carmelita Tuazon who is a
3 member of the CDRH Microbiology Panel.
4 When this committee is sitting as a medical-device
5 panel, there are specific voting procedures when approval is
6 sought or, again, in this case, a specific recommendation is
7 desired. Accordingly, this panel, then, will be
8 specifically requested to do one of three options, the first
9 being to vote in agreement with the recommendation. The
10 second is to vote in agreement with the recommendation with
11 conditions which must be specifically defined. Thirdly, to
12 not agree with the recommendation.
13 You will hear, after my presentation, the specific
14 question or questions that have been prepared by the CBER
15 FDA Review Committee regarding this classification. After
16 you have had your discussion, then you will vote as I have
17 indicated. What happens next after your recommendation is
18 that the FDA will make a decision on the appropriate class.
19 There will then be published a notice of the panel
20 recommendation to classify these devices.
21 Following that, there will be a review of comments
22 from the public and then there will be a final published
23 Federal Register notice classifying these devices.
24 Are there any questions? Thank you.
25 **Questions for the Committee**

1 MS. KOCHMAN:

2 [Slide.]

3 Before I get to the questions, I thought it might
4 be helpful if I reviewed some of the provisions that we just
5 went over.

6 [Slide.]

7 This is to kind of give you a status, remind you
8 of where we are, where do HLA devices fit in the scheme of
9 things that were presented today.

10 [Slide.]

11 Current CBER review incorporates special controls;
12 that is, we have performance standards. As an example,
13 there must be at least 80 percent concordance between a new
14 device and a device currently legally on the market. We
15 currently employ special labeling requirements and we
16 currently have recommendations that are issues during the
17 510(k) review.

18 So we are clearly, at this point in time, applying
19 special controls. As you will recall, special controls are
20 what is used when a device is class II.

21 Also, CBER does not view the device as being high-
22 risk. We view it as being moderate-risk since it is not
23 life-supporting, life-sustaining or of substantial
24 importance in preventing impairment of human health and does
25 not present a potential of unreasonable risk of illness or

1 injury.

2 [Slide.]

3 How would CBER propose to regulate the HLA devices
4 in the future. We would propose that we continue to require
5 submission of a 510(k), that we would continue to require
6 special labeling, we would continue to review against our
7 performance standards, we would continue to apply
8 recommendations, that we would prepare and implement a
9 guidance document to assist both the industry and FDA
10 reviewers in knowing what criteria to apply to these
11 devices, and, once that guidance document was available, we
12 would make HLA devices eligible for third-party review.

13 That would also require that we identify and
14 accredit third-party reviewers. So, right now, CBER's
15 recommendation is that HLA devices, as defined earlier in
16 the presentation, should be placed in class II.

17 The question, therefore, to the panel is, does the
18 committee agree that HLA devices for use in detecting
19 antibodies to HLA antigens or determining HLA phenotype or
20 genotype should be classified as class II devices. Further,
21 from that, since class II devices can either be exempt or
22 nonexempt reserved, should these devices be exempt from the
23 requirement to submit a 510(k)?

24 DR. HOLLINGER: Thank you.

25 **Committee Discussion and Recommendations**

1 Are there questions on the issue about HLA
2 devices, anyone that has any thoughts? Just to refresh my
3 memory, all the HLA testing, a lot of HLA testing, is used
4 for things such as organ transplants?
5 MS. KOCHMAN: Yes.
6 DR. HOLLINGER: Then, I guess if I were looking at
7 that, then I would come back over where it says devices of
8 moderate risk; it says, it is not life-supporting, not life-
9 sustaining. But then it says, "or of substantial importance
10 in preventing impairment of human health and does not
11 present a potential unreasonable risk of injury or illness.
12 I would then say, well, if the results that were obtained
13 from a device that it would alter what would happen with the
14 transplant, that would create a problem for me.
15 MS. KOCHMAN: That is one of the reasons we have
16 Dr. Matal here. I feel he is uniquely qualified to answer
17 those kinds of questions.
18 DR. MATAL: Mr. Chairman, before we get into that,
19 really what would be very interesting to hear is what
20 Devices is doing in handling the B27 device that they have
21 already been marketing for some time and has gone through
22 Devices. Would you comment on that? That is not being
23 reviewed by third-party review.
24 MR. RECHEN: Unfortunately, I can't answer that
25 question specifically, but I certainly could get an answer

1 to that.

2 DR. MATAL: It seems to me that the two devices

3 would be very similar. HLA B27 reagents are very similar to

4 what we are talking about.

5 DR. HOLLINGER: Gail?

6 DR. MACIK: I totally disagree with that. You are

7 using the one device to diagnose a disease or a disorder.

8 You are using the other device to determine compatibility

9 for a transplant in which, if you are incompatible, you have

10 a major reaction and/or, in the case of bone-marrow

11 transplant or liver transplant, could lose the organ.

12 So I think these are very different devices.

13 DR. MATAL: Let me separate the two issues here.

14 One is these reagents are really diagnostic reagents who

15 type for our genetic profile, the genes and antigens that we

16 have. That is a genetic marker, like blood typing. Now,

17 what happens in transplantation is the second step where how

18 you match a donor and recipient, whether it is a bone-marrow

19 or a kidney transplant.

20 If matching is done properly, then the transplant

21 succeeds. If it is done poorly, it will not succeed. The

22 fact that these reagents are all devices to type our genetic

23 markers, that is pretty much the same for B27 or for any

24 other reagent. Applicability is a second-step issue, is the

25 way I see it.

1 I mean, in terms of quality control of these
2 reagents, we could have pretty much the same quality control
3 because, basically, you are typing basic genetic markers.
4 DR. MACIK: But, in classifying these, you have
5 already tied it to a level of risk associated with a device
6 to decide what classification. The level of risk is
7 significantly different between something used as a
8 diagnostic for a disorder and something used as a
9 compatibility--
10 DR. MATAL: I totally agree. The only part that I
11 am mentioning is that accuracy of typing is the issue in
12 trying to classify this product. False-positives, false
13 negatives. I think premarket notification would be very
14 useful which lists the incidence of false-negative and
15 false-positive typings.
16 But in terms of applicability of this profile, is
17 the next step. I think the two could be separated. For me
18 to think that the HLA typing, done correctly, could make a
19 difference between the success or failure of a transplant,
20 would not happen. It is not actually typing that determines
21 the success or failure of a transplant. It is the matching
22 of the donor recipient that makes the success or failure of
23 a transplant.
24 MS. KOCHMAN: I would like to point out also that-
25 -I understand your point about the risks associated with

1 transplant, but keep in mind that there also risks
2 associated in transfusion. The automated blood-grouping
3 instruments that determine a donor's type and presence or
4 absence of antibodies are currently class II.
5 Certainly, if you give an incompatible blood
6 transfusion, you can have a fatality. So if you put it in
7 that perspective, there is very much a parallel between the
8 automatic blood-grouping systems and the HLA typing
9 reagents.
10 DR. MACIK: I would agree with that. But I would
11 also agree that transfusing a blood component would also be
12 associated with a serious life-threatening consequence if it
13 were not done appropriately. I think both of them, for that
14 one statement as Dr. Hollinger pointed out, if you are
15 inaccurate in your typing, whether it is HLA or AB/O typing,
16 you can cause a serious and, perhaps, fatal event with that
17 mismatch.
18 MS. KOCHMAN: Right. But we know enough about
19 both blood grouping and about HLA phenotyping to know what
20 is important to have the kit be able to do. We can
21 prescribe the standards that a device must meet in order to
22 assure safety and effectiveness.
23 In order for it to go to the level of class III,
24 there has to be an assessment that we don't really know what
25 is necessary to insure safety and effectiveness. I would

1 say that, for blood-grouping instruments and for HLA test
2 kits, we know what is necessary.
3 We can develop performance standards that say the
4 device must detect this, this, this and this. The device
5 must be specific. The device must not have cross-
6 reactivities, et cetera, et cetera. So it is a subtle
7 difference between--and I am not discounting that injury is
8 possible. But my definition of class I devices also
9 included that injury could be possible.
10 But is there a substantial risk of injury? I
11 would say if the device conforms to the performance
12 standards we use, then there is not a substantial risk.
13 There is an implied risk, but not a substantial risk. It is
14 a risk we can mitigate by having performance standards.
15 DR. HOLLINGER: Dr. McCurdy?
16 DR. McCURDY: I think, when one is talking about
17 organ transplants, solid-organ transplants, what I
18 understand about the situation is exactly as you say. When,
19 on the other hand, you are talking about stem-cell
20 transplants, marrow, peripheral blood, cord blood, I think
21 it is a moving target. I think that now DNA-based
22 technology is here for both class I and class II HLA
23 categories, but the degree of resolution varies and I don't
24 think we know exactly what standards should be applied to
25 the matching of stem-cell transplants where you have got a

1 two-way street; that is, you can reject the transplant or
2 the transplant can reject the host with GVH.
3 I don't think I am really suggesting that this
4 should be class III, but I think the standards necessary for
5 stem-cell matching versus solid-organ matching versus B27
6 classification--I think the risks are considerably
7 different.
8 DR. MATAL: I very much agree with this and I
9 would say that this is why you really don't want to have it
10 in class III. But in class II, you have very good, solid
11 special controls, is what you need, in addition to general
12 controls.
13 DR. HOLLINGER: Dr. Simon?
14 DR. SIMON: I would agree with the class II. I do
15 agree with the discussion that this is not trivial and
16 should not be class I. I think of class III as something
17 like if a respirator stops, boom; the individual is gone.
18 So I would speak for the class II.
19 Where I am having more trouble is the second
20 question on the requirement to submit a 510(k). I wonder if
21 one of our two experts could speak to that.
22 DR. HOLLINGER: To what additionally this asks
23 for? The additional things?
24 DR. SIMON: Yes; whether they should or should not
25 be exempt for a requirement to submit a 510(k). I wouldn't

1 know how to vote on that.

2 DR. MATAL: I am very much in favor of their

3 submitting the 510(k).

4 MS. KOCHMAN: Yes; as I mentioned, we would

5 propose, in the future, to still require a 510(k)

6 DR. SIMON: So you would propose that we answer no

7 to that second question.

8 MS. KOCHMAN: Correct.

9 DR. SIMON: Yes to the first question and no to

10 the second.

11 MS. KOCHMAN: Correct.

12 DR. HOLLINGER: And the 510(k) is just what?

13 MS. KOCHMAN: It is a submission of all of the

14 data that the manufacturer has collected to show that his

15 device is substantially similar. I will use substantially

16 similar. I think that is a little bit easier for people to

17 understand--substantially similar to a device that has

18 already been cleared to go on the market.

19 So, right now, we have FDA scientists reviewing

20 that data package. Once we get a classification, we can,

21 then, target our program to having third-party reviewers

22 also be eligible to review that data package.

23 DR. HOLLINGER: Yes, David?

24 DR. STRONCEK: My impression is the best labs that

25 do the highest, the best, typing for stem-cell transplants

1 are using in-house-generated tests. After we vote to
2 clarify the regulation of HLA, will that have implications
3 for these in-house tests? Will the universities and
4 cutting-edge labs that use those tests not be able to get
5 reimbursed if they are not licensed?

6 DR. MATAL: I think any time you are using a cell
7 that came out of a human being, you always can get an HLA
8 profile of that donor by using the regular sample. And that
9 is what they do. They have the HLA profile of that donor
10 from whom they extracted the cell that led to your
11 collection of the stem cell.

12 So whatever other special tests they do, they are
13 probably for identification of whatever. I am not quite
14 clear as to what your point is, about inside tests of
15 institutions.

16 DR. STRONCEK: I think most transplant centers
17 probably don't buy a commercial kit. These are probably
18 low-resolution kits used by labs that don't regularly test.
19 If we pass this regulation, is that going to have
20 implications for these cutting-edge laboratories that do the
21 best testing, that they won't be able to charge insurance
22 companies?

23 Right now, bone-marrow-transplant patients, when
24 they finally go to transplant, the testing is extremely
25 thorough but very expensive. Those are not done with Pel-

1 Freez kits. I can tell you that. Will this mean that if
2 the transplant center wants to charge $2,000 for this typing
3 that they are going to have to go through and get their in-
4 house kits licensed?
5 DR. MATAL: No, no. I didn't quite understand
6 your question before. Any HLA laboratory in the country has
7 the freedom to use any reagents, all the reagents they can
8 find, from anywhere. And then they try to come up with the
9 best phenotype of a given person.
10 No two laboratories in this country, in this
11 world, use the same reagents for typing. Actually, even in
12 the same lab, over time reagents change. So, no. What
13 every laboratory is trying to do is to come up with the
14 best, most accurate, phenotype with the reagents available
15 to them.
16 Different laboratories buy different kits from
17 different companies and they use what they consider works
18 best in their hands or what they can afford, and so forth.
19 DR. HOLLINGER: Dr. Kagan, did you have something?
20 DR. KAGAN: Given the fact that we are going to be
21 looking at a bit of a moving target, as Dr. McCurdy had
22 suggested, does the agency possess the authority to modify
23 the special controls over a period of time once this has
24 been classified, perhaps, as a class II device?
25 MS. KOCHMAN: Yes.

1 DR. MATAL: As a matter of fact, the very first
2 controls that you approve to be applied ought to be
3 scrutinized pretty well because that is where--this is a
4 complex technology, as we all know. So the first set of
5 standard special rules that are chosen to be applied for
6 accreditation or whatever, they ought to be thought through
7 well.
8 MR. RICE: I think, for me, the key point is the
9 substantially equivalent classification. The FDA is going
10 to decide whether or not the submission, the new device
11 submission, is substantially equivalent to some established
12 or existing predecessor before the company gets to decide
13 whether or not they are going to pursue a class II outside
14 of the agency, go through the accredited person?
15 MS. KOCHMAN: I'm sorry; I didn't understand the
16 question.
17 DR. MATAL: If I may address this one. If, let us
18 say, there is one of those companies--although I did not see
19 any of them which had known expertise in the field of HLA,
20 but let us say there is an institution that has been
21 accredited to evaluate a kit submitted to FDA.
22 One of the most practical ways to do that is that
23 this institution that is doing the accrediting has a way to
24 phenotype human beings. They may have a type panel--
25 actually, they should have a type panel of donors. This new

1 kit comes in and they test it against known donors and
2 against known reagents that they have already on board.
3 So it is a question of comparison. And they have
4 to satisfy themselves that here is an unknown donor and you
5 are doing HLA typing of this unknown donor. Is the
6 phenotype reasonably accurate and complete or not? It does
7 not matter what reagents they use. The key thing is did
8 they come up with the correct phenotype?
9 The phenotype of a human being is verifiable. Our
10 HLA phenotype is our biological identity card. You can get
11 a person's type anywhere. So known typing panels is one way
12 to establish accuracy of comparisons.
13 DR. HOLLINGER: I think we will go ahead and call
14 for the--Gail, do you have something?
15 DR. MACIK: Just a couple of quick things. One is
16 that I agree that many places do their own typing because
17 they are not that comfortable with kits and what is
18 available or sending it out to special labs because this is
19 not a testing system that is well controlled.
20 You already brought up the fact that many of these
21 systems out there are not even classified yet and what are
22 we going to do. It has just been hanging out there. So I
23 think it is a good idea. But the one question that actually
24 comes back a little bit more to the special persons for
25 accrediting, when we were talking about conflict of interest

1 with these outside agencies, one of the things that you had
2 mentioned was that no agency that had any particular
3 interest in the field would be reviewing it and then, on the
4 other hand, it says, well, there has to be a company that
5 has special HLA expertise that you would send it to.

6 Those seem to be a little contradictory.

7 DR. MATAL: See, the way you deal with conflict of
8 interest, first of all, let's say, honorable people are
9 doing the review. That is one thing. The second this is,
10 as long as they do not have a direct financial involvement
11 with the manufacturer or any of their relatives or family.
12 You check for that and then you leave it to honorability of
13 the parties doing it because, after all, as you said before,
14 if they are passing everything going through just for the
15 money, they will not be in business very long.

16 DR. HOLLINGER: I think we will call for the
17 question. I will read it and then we will vote on it. The
18 first question is, does the committee agree that HLA devices
19 for use in detecting antibodies to HLA antigens or
20 determining HLA phenotype or genotype should be classified
21 as class II devices.

22 All those that agree with that recommendation,
23 raise your hand.

24 [Show of hands.]

25 DR. HOLLINGER: All those that disagree?

1 [No response.]

2 DR. HOLLINGER: Abstain?

3 [No response.]

4 DR. HOLLINGER: Dr. Simon?

5 DR. SIMON: Agree.

6 DR. SMALLWOOD: The results of voting on the first
7 question, there were 13 "yes" votes, there were no "no"
8 votes, no abstentions. The industry representative agreed
9 with the "yes" vote and the consumer representative left a
10 note that she agreed with the "yes" vote.

11 DR. HOLLINGER: There is a second part to this and
12 I presume this would be under the second part that you
13 mentioned, Linda, about whether there is agreement with the
14 recommendations with conditions. One of the conditions that
15 is put up there is should they be exempt from the
16 requirement to submit a 510(k)? Should they be exempt from
17 the requirement to submit a 510(k)?

18 All those that agree that they should be exempt
19 from the requirement to submit a 510(k), raise your hand.

20 [No response.]

21 DR. HOLLINGER: All those opposed?

22 [Show of hands.]

23 DR. HOLLINGER: Abstaining?

24 [No response.]

25 DR. SIMON: Opposed.

1 DR. SMALLWOOD: The result of voting on the second
2 question, there were zero "yes" votes, 13 "no" votes, no
3 abstentions. The industry representative agreed with the
4 "no" votes. I do not have a report from the consumer
5 representative in her absence.
6 DR. HOLLINGER: Thank you.

7 **V. Report of Intramural Site Visit**
8 **Laboratory or Molecular Virology**
9 **Division of Emerging and Transfusions Transmitted Diseases**

10 DR. HOLLINGER: The final session is on the report
11 of the intramural site visit, Laboratory of Molecular
12 Virology, Division of Emerging and Transfusion Transmitted
13 Diseases. Two of our committee members were part of that
14 site-visit committee, Dr. Nelson and Dr. Stuver. So they
15 will be here to help us also as we look through this.
16 You all have received this, anyway. We have some
17 introductions and overviews of the programs here. We will
18 start with Dr. Nakhasi who is the Director, Division of
19 Emerging and Transfusion Transmitted Diseases.
20 Dr. Nakhasi?

21 **Introduction and Overview**

22 DR. NAKHASI: Thank you, Mr. Chairman and thank
23 you, committee members. This is my first committee meeting
24 here because I was appointed as the Division Director only a
25 few months back, so I think it is a new experience with this

1 committee. Even though I have been in the FDA for the last
2 sixteen years in the Office of Vaccine and other advisory
3 committee meetings.
4 [Slide.]
5 I know it is getting late and I think the
6 important thing is the people whose labs were site-visited,
7 they need to spend some time. So I will just go quickly
8 through the organization and what the performance is and the
9 activities are in the Division of Emerging and Transfusion
10 Transmitted Diseases.
11 The Division of Emerging and Transfusion
12 Transmitted Diseases is abbreviated DETTD. This is the
13 Office of the Director where myself and other people are
14 helping me out. The organization is in the form of three
15 laboratories, research laboratories, and one testing lab.
16 The three laboratories are the Laboratory of
17 Bacterial Parasitic and Unconventional Agents--Dr. Asher is
18 the chief of that--the Laboratory of Molecular Virology--
19 Indira Hewlett, whose lab was site visited and you will hear
20 from her the representation--and also, then, we have a
21 Laboratory of Hepatitis and Related Emerging Agents. Dr.
22 Robin Biswas is Acting for the time being. And we have the
23 Lot Release Testing for all these, HIV-1, HIV-2 and the
24 hepatitis test kits which is under the leadership of Dr.
25 Roberts.

1 [Slide.]

2 The Laboratory of Molecular Virology, whose site
3 visit was held in June, is organized in five sections. There
4 is a Regulatory Section, and then there are four research
5 sections. The Molecular Virology Section, which is Dr.
6 Indira Hewlett's lab, she will be presenting today and Dr.
7 Subhash Dhawan whose section also was reviewed, he will be
8 presenting their scientific review.

9 [Slide.]

10 The mission of the division is to plan and conduct
11 research on pathogenesis, evaluate and standardization of
12 retrovirus hepatitis, parasitic bacterial and transmissible
13 spongiform encephalopathy related to blood screening and
14 diagnostic tests.

15 With the laboratory personnel reviewed, evaluate
16 and recommend appropriate actions on investigational new-
17 drug applications, biological applications, PMAs, 510(k)s--
18 you just heard what the 510(k) is--I am trying to learn,
19 myself, that--related to viral, parasitic and bacterial
20 tests for blood screening and diagnostics, and also help to
21 disseminate policies, procedures and guidelines and we seek
22 your help whenever we have to change the policies, as you
23 know very well.

24 [Slide.]

25 It performs the inspection of the manufacturing

1 facilities where these products are being made and performs
2 laboratory tests and reviews manufacturing of lot-release
3 protocols by the licensed test kits. In addition to that,
4 it provides scientific expertise and technical advise to
5 other components of FDA, PH agencies, advisory committees.
6 And we, the people in the laboratory, also are involved on
7 national collaborations with other academic institutions
8 related to the safety and efficacy of blood screening and
9 diagnostic kits for these infectious diseases.
10 [Slide.]
11 Last year, we had some 247 INDs, PLAs, IDEs, PMAs,
12 all these things reviewed in one year.
13 [Slide.]
14 The research activities which are going on in the
15 laboratory are HIV pathogenesis, diagnostic testing of blood
16 safety. Those are the things which you will hear from
17 Indira's laboratory and also Dr. Subhash Dhawan's
18 laboratory. We also have some activity of HTLV-I and II, a
19 detection assay for blood donors. But it is a minor
20 activity. The majority of tests are related to HIV.
21 Then we have the activities going on, research
22 activities going on, and the detection for the PSE, tissue
23 spongiform encephalopathy in individual culture, in vitro
24 and in vivo models.
25 [Slide.]

1 In my laboratory, we are working on these
2 parasitic diseases. We have chosen Leishmania because that
3 is what I have been working on for the last ten years. In
4 addition to that, we are now working also on the malaria and
5 chagas diseases because these are all bloodborne pathogens.
6 [Slide.]
7 In addition to that, there is a laboratory working
8 on bacterial contamination of blood and blood products and
9 which you heard in the morning, syphilis. Even though we
10 don't work with syphilis, we are developing tests for other
11 bacterial contaminations.
12 There is a laboratory which is involved in studies
13 the pathogenesis of hepatitis B and C and the development of
14 DNA-based diagnostic kits.
15 [Slide.]
16 The total number of people in the division are
17 around 38 and out of which there are six tenured senior
18 investigators and a regulatory staff of 13. The rest of
19 them, except the administrative staff, are mostly research
20 fellows which are helping these tenured investigators with
21 an annual measly amount of $600,000.
22 [Slide.]
23 We published last year 22 articles in peer-
24 reviewed journals and the members of the division have been
25 invited to national and international meetings and also have

1 established quite a bit of collaboration with international
2 and national institutions.
3 [Slide.]
4 The purpose of the site visit was to review Dr.
5 Hewlett's research program. That was one thing. The second
6 was to review Dr. Dhawan's program and make recommendations
7 for the future recommendation to GS15. The other activity
8 which was just for information's sake was Dr. Cowan's
9 regulatory activity on HTLV. But that is not part of
10 today's discussion. These are the two things which are
11 related to the research activity.
12 At this point, I will turn the mike over to Dr.
13 Indira Hewlett. She will talk about her research program
14 and give a little detail about her laboratory. Then Dr.
15 Dhawan will talk about his program.
16 Thank you.
17 DR. HEWLETT: Good afternoon.
18 [Slide.]
19 I will try to be as brief as possible. I know it
20 is getting very late in the day and I am sure you are trying
21 to run out of here and catch your flight out of wherever you
22 are flying out of. My name is Indira Hewlett. I am Chief
23 of the Laboratory of Molecular Virology. What I am going to
24 try to do is give you a very brief overview of the this
25 programs and then talk a little bit about some of the

1 projects that were presented at the site visit that was held
2 in June of this year.
3 [Slide.]
4 LMV was first created during the reorganization--
5 this is the CBER reorganization of 1993. It was reorganized
6 further in 1999 to include the HTLV section.
7 [Slide.]
8 The regulatory mission of the laboratory is to
9 review and license product applications for in vitro tests
10 to detect HIV and HTLV in blood, plasma and other body
11 fluids. We develop guidelines, review criteria and
12 standards for validation of tests and policies related to
13 their use, and some of this activity involves making
14 presentations to the Blood Products Advisory Committee, as
15 you probably know.
16 In 1991, FDA--that is, the Centers for Devices and
17 our center, CBER, agreed in the Intercenter Agreement, to
18 move all of the HIV or the human retroviral test kits under
19 the purview of CBER. They were actually always under the
20 purview of CBER, but there was some question as to whether
21 to split up the jurisdiction of diagnostic versus the blood-
22 screening kits between the two centers.
23 However, as a result of this agreement, all of the
24 kits are now reviewed by our center and, specifically, in
25 our laboratory. These tests include those for donor

1 screening, conventional and rapid test for diagnosis, tests
2 for patient monitoring, drug-resistance tests as well as
3 home-use tests.
4 [Slide.]
5 To support the regulatory mission of the
6 laboratory, we have some research programs that are focused
7 primarily on basic and applied aspects. So there is basic
8 and applied research on HIV-1, HIV-2, and HTLV disease. We
9 conduct laboratory investigations on disease transmission
10 and pathogenesis and we develop and evaluate methods to
11 insure blood safety from HIV and HTLV transmission including
12 testing for viral markers.
13 Finally, we have been engaged, over the past
14 couple of years, in developing laboratory standards and
15 panels for HIV and HTLV tests, and we have participated in a
16 number of international collaborative efforts to evaluate
17 and standardize nucleic-acid-based tests for HIV.
18 [Slide.]
19 This just shows the organization of the
20 laboratory. You have already seen from Dr. Nakhasi's slide
21 how the division is organized but the laboratory consists
22 of, as he said, five groups. This group, which is actually
23 manned by regulatory scientists, we, at the present time,
24 have about three regulatory scientists that spend
25 100 percent of their time on new activities.

1 We have four research sections, the Molecular
2 Virology Section which I head and I am going to very briefly
3 discuss some of the work going on in this group. The
4 Immunopathogenesis Section is run by Dr. Dhawan and he is
5 going to talk about his work after my presentation.
6 The Gene Regulation Section is headed by Dr.
7 Andrew Dayton. This group is looking at the molecular
8 biology of HIV infection focussing on tat and rev. Finally,
9 we have the HTLV Section that is looking at HTLV
10 pathogenesis and is looking at developing diagnostic tests
11 for HTLV as well.
12 [Slide.]
13 So now, switching to the Molecular Virology
14 Section specifically, my group has been engaged in projects
15 on pathogenesis and diagnosis. These are just a couple of
16 the projects that have been ongoing in the past four years.
17 We have been looking at the virologic and genetic
18 characteristics of two groups of two specific types of
19 infections; that is, isolates from rapid and long-term
20 nonprogessors. These are clade-B-virus infected
21 individuals.
22 And then we have another area of research looking
23 at isolates from patients with unusual variants,
24 specifically the HIV group-O viruses. We are also looking
25 at genetic diversity of HIV-2. We are looking at inhibitors

1 such as the T20 which is an inhibitor of virus entry, using
2 this to look at mechanisms of virus entry, specifically the
3 clade-B virus and its interaction with t-cells.
4 We also have some projects in diagnostics, and I
5 will discuss this later. Finally, we have developed some
6 reference reagents and are continuing to engage in
7 developing reference reagents for the subtypes of HIV.
8 [Slide.]
9 So, in the next couple of slides, I am going to
10 just briefly discuss some work in HIV group O.
11 [Slide.]
12 The reason we got interested and involved in
13 looking at variants and, actually, for the past three or
14 four years, we have been moving towards looking at genetic
15 diversity, specifically with an eye toward looking at
16 evolution of viruses and, obviously, their impact on
17 diagnostic tests because those are the products we regulate
18 at CBER within my branch.
19 But it was this report and a couple of other
20 reports which I think some of you on this committee may be
21 familiar with and aware of that were discussed, actually, at
22 the BPAC in 1994, 1995, where it was observed that some
23 specimens from patients with HIV group O were not detected
24 by FDA-licensed assays, specifically assays that contained
25 synthetic peptides or recombinant antigens.

1 Obviously, this observation caused much concern in
2 the area of blood safety and the issue of whether currently
3 licensed tests were safe and were we protecting our blood
4 supply from new variants of HIV.
5 [Slide.]
6 We obtained some isolates from collaborators in
7 Germany and Spain. We did some virologic studies. This is
8 infection of the PBMCs with three different isolates. What
9 we observed was these viruses were able to replicate in
10 PBMCs.
11 [Slide.]
12 They were able to infect monocyte-derived
13 macrophages. This is p24 antigen production. This is
14 actually--I guess it is reversed--it is reverse-
15 transcriptase activity on the Y axis.
16 [Slide.]
17 We looked at coreceptor usage and, as observed by
18 other investigators, the subtype was not the determinant of
19 coreceptor usage. Rather, it was the phenotype of the
20 virus. So NSI viruses--that is, isolates that were typed as
21 NSI viruses--used CCR5. The ones that were of SI phenotype
22 used the CXCR4 coreceptor.
23 [Slide.]
24 We did sequence analysis to make sure that these
25 were group O viruses. This is just a phylogenetic tree

1 analysis placing the isolates--they are in red here--in the
2 group O cluster of viruses.
3 [Slide.]
4 So our conclusion, and that was just a snapshot--
5 we obviously did a number of other experiments as well, but
6 those were just the key observations. Our conclusion was
7 that both the target cells that are used by HIV viruses,
8 namely the PBMCs and the MBMs, monocytes, are susceptible to
9 infection by group O, similar to clade-B HIV-1.
10 We found that the coreceptor use was related to
11 phenotype, not genotype. We also looked at the chemokine
12 and cytokine production and found no differences in
13 chemokine production between the group-O viruses and the
14 clade-B viruses.
15 Sequence analysis of these isolates indicated that
16 there was variability in the V3 region to the extent that is
17 seen in clade-B strains and there was also a high degree of
18 conservation in the core region. We looked at the protease
19 genes, again, similar to what was seen with clade-B viruses.
20 So our overall conclusion was that virologic
21 characteristics were similar to group-M viruses. In fact, I
22 didn't show you any of the clade-B data in the interest of
23 time.
24 [Slide.]
25 In the second part, I will discuss some of the

1 work we are doing on diagnostics.

2 [Slide.]

3 As I mentioned earlier, there was concern about
4 peptide-based assays and their ability to detect variants,
5 not just group O but variants in general. But we focused on
6 the HIV group-O issue. What we did here was to make a
7 number of peptides from the envelope region. This just
8 shows the sequences of the peptides.

9 [Slide.]

10 We screened them using a couple of group-O sera
11 that were made available to us and we found that there was
12 differential reactivity depending on the combination of
13 peptides.

14 What we did was to make combinations and screen
15 them this way. This particular sample turned out to be also
16 negative on Western Blot, so it is possible there wasn't
17 enough antibody here and we may need to--it either lost its
18 antibody on storage or it may not be an adequate sample for
19 testing.

20 [Slide.]

21 We tested a couple of additional specimens that we
22 obtained from Genetic Systems using one of these
23 combinations. And we find you get very good reactivity even
24 at a very high dilution. This is a 1 to 1000 dilution.

25 [Slide.]

1 We have developed some primers for detection of
2 group M and group O. These are just the regions from which
3 the primers were derived. There is pol and envelope-based
4 primer sequences.
5 [Slide.]
6 We have analyzed a limited number of isolates.
7 But, since the time this slide was made, we have actually
8 checked a couple of additional isolates and what we think we
9 have is a couple of--one set of primers that is cross-
10 reactive for the different subtypes. We have got a couple
11 that are specific for each of the groups--that is, group O
12 and group M. We are looking, specifically, at clades A
13 through F in this particular slide but there are, obviously,
14 other additional clades that have been identified.
15 At the time that we developed these reagents,
16 group N had just been discovered. It is very difficult to
17 get samples of group N subtype to test. However, we have
18 also developed group-N-based assay.
19 [Slide.]
20 So, using these tools, we have just initiated a
21 study with the Cameroon Ministry of Health looking at blood
22 banks. In the future, we will be looking at STD clinics.
23 These studies involve using rapid tests to screen samples
24 and to look at interesting samples--that is, those that are
25 weakly reactive or have unusual patterns. We will be doing

1 virus isolation, further testing using in-house assays.

2 We will also do nucleotide-sequence analysis
3 looking for recombination and mutation, the goal being to
4 look at new variants and to identify or to study their
5 virologic and diagnostic characteristics.

6 [Slide.]

7 Finally, another aspect of our research is
8 development of reference reagents. We have developed two
9 panels for HIV, one which is based on a plasma specimen.
10 The second is a cultured virus spiked into negative plasma.
11 These panels have been evaluated in multicenter
12 collaborative studies that are of an international nature
13 under the auspices of the WHO.

14 The first panel, panel A, has actually been
15 adopted as the WHO international standard at this point, so
16 it is a lypohylized preparation that is available for
17 standardization of HIV RNA tests.

18 [Slide.]

19 We are continuing this work by pursuing clade
20 panel development in collaboration with a number of
21 organizations including the CDC, Walter Reed, the Navy and
22 NIH and NIBSC.

23 [Slide.]

24 So to summarize the research activities in LMV, we
25 are looking at viral and host factors in disease

1 progression. We have got projects in diagnostics looking
2 at--where we are developing in-house PCR and immunoassays
3 for the different HIV groups. We have applied this assays
4 on occasion to investigation of products, and if we have
5 time to talk about that today, and to clinical disease.
6 We are also engaged in laboratory studies to
7 define optimal strategies for detection of different
8 variants. You saw some of that research. We are also
9 continuing to be engaged in the development of reference
10 agents for quantitation and lot release of HIV RNA assays.
11 [Slide.]
12 This is the final slide, just to acknowledge the
13 people who were involved in the research that I just
14 discussed. These are the people in my group. We obtained
15 group O samples from Enzo Soriano, from Lutz Gertler in
16 Germany and some from Leopold Zekeng. The standardization
17 work was done with the NIBSC.
18 Thank you.
19 DR. HOLLINGER: Thank you, Indira.
20 Any questions of Indira? The next person who is
21 going to talk is Dr. Dhawan in the Laboratory of Molecular
22 Virology, also.
23 DR. DHAWAN: Good afternoon, Mr. Chairman and
24 committee members. My name is Subhash Dhawan and I will be
25 talking about part of the work that I presented in the site

1 visit. But, in the interest of time, I will discuss only
2 the work that I either published or is in press only in the
3 past one year.

4 [Slide.]

5 I will begin my talk with this slide showing the
6 structural organization, very briefly. I head the
7 Immunopathogenesis Section in Dr. Hewlett's lab and, without
8 going into all the details, I have currently one ORISE post-
9 doctoral fellow and one staffer that needs to be filled.

10 My responsibility at LMV is 50/50, research and
11 the regulatory process. As a regulatory, I review products
12 related to HIV diagnostics. I occasionally respond to
13 correspondence from blood-bank organizations and also have
14 performed inspections in the past.

15 My research interests would constitute 50 percent
16 of my time, more or less. My interests are in the viral
17 immunology of HIV infection.

18 [Slide.]

19 This is the HIV pathogenesis and study the role of
20 virus and host factors that promote HIV pathogenesis. I
21 will limit my talk to ten or fifteen minutes. I realize
22 that this has been a very busy meeting, but, being the last
23 speaker, I do have certain advantages. I can go for another
24 five minutes. Right, Mr. Chairman?

25 [Slide.]

1 Very briefly, I would just to highlight my
2 accomplishments in the past four years since the last site
3 visit. I submitted twenty research articles and was asked
4 to write three book chapters, most of them published. I
5 filed three patents with the U.S. and abroad, international,
6 and I am happy to say that these patents are now being
7 considered for licensing by a leading manufacturer.
8 In 1996, I received CBER's Director's Targeted
9 Scientific Achievement Award for Research. In 1999, last
10 year, I received at Director's Targeted Award for $120,000 a
11 year for two years to support my research.
12 [Slide.]
13 In addition to research, I also am involved in the
14 regulatory process, as you can see. Since the last site
15 visit, I chaired sixteen PLAs, which are major and minor
16 supplements. They could be from two volumes to thirty
17 volumes. And two PMAs, original. And one PMA supplement
18 where it was not approved.
19 As a reviewer, I participated in two PLA
20 committees, three INDs originally, one IDE which now--this
21 is an old slide--which I have received and I am currently
22 reviewing it. I responded with correspondence with blood-
23 bank organizations. But, of course, as a regulatory
24 responsibility, I attend several pre-IND and IND meetings.
25 In the past, I have inspected two facilities.

1 [Slide.]

2 In the next ten minutes or so, fifteen minutes,
3 maybe, I will be talking about the studies on the tat
4 protein, which is the progress report from 1996 to the
5 present and which I am updating right now. It will
6 approximately from July 1999 until last month. I will be
7 discussing only very briefly.

8 My interest has been studies on HIV tat protein.
9 Here I am talking about tat protein in Dr. Gallo's meetings
10 on human virology, the entire session they are discussing on
11 tat right now. So my interest in tat protein is because of
12 its important role in the disease progression.

13 [Slide.]

14 My interest was first in its role in the
15 pathogenesis and as a diagnostic tool for HIV and the
16 factors that contribute to promote viral pathogenesis and,
17 also, because it is important in the disease progression, my
18 interest was to use this protein or the antibody of this
19 protein as a little bit as a diagnostic tool for HIV
20 infection and also, third, because of this involvement in
21 AIDS pathogenesis, to use this as a potential AIDS vaccine
22 which Dr. Gallo had proposed.

23 The very recent summary from his institute, which
24 came out last month, he is proposing a clinical trial in the
25 United States and Europe in 2002 and it is expected to be on

1 the market in 2003.

2 [Slide.]

3 HIV tat is produced by HIV-infected cells in the
4 acute phase of infection. It is known to produce HIV
5 pathogenesis and causes apoptosis and immunosuppression of
6 normal cells even in the absence of HIV infection.

7 [Slide.]

8 This is an old slide taken from a book chapter by
9 Bill Hazeltine which he published in 1984 demonstrating the
10 role of tat, how tat can be pathogenic, how it works,
11 basically. Very briefly, again, tat is released by HIV-
12 infected cells and it can be taken up by the cell that it
13 has produced. It can also be taken up by the adjacent
14 cells.

15 When the tat is taken up by the cell that it has
16 produced, it promotes HIV replication, activates IV LTR and
17 promotes viral pathogenesis and HIV replication. The way it
18 acts on adjacent cells, it activates those cells and makes
19 them more susceptible to HIV infection which is the role of
20 extracellular tat.

21 [Slide.]

22 I wish I had more time to talk about this, but
23 with the time limitation--this is the model that I proposed
24 nearly five years ago. I am happy to say whatever is in the
25 slide, it is all published. This constituted, basically,

1 the two-thirds of my work that I presented at the site visit
2 I will not have time to go into details.
3 But, very briefly, HIV-infected cells release tat
4 protein and it binds to leukocytes, promotes the binding to
5 endothelial cells, and then the cell that is activated, it
6 migrates and responds to the tat which is left by infected
7 cells in tissue and released as protease as oxygen radicals
8 and resulting in tissue damage.
9 This work that I described in two sentences took
10 me five years to do. And it is all published.
11 [Slide.]
12 Just to show you how tat works and what does tat
13 do; as you can see over here, the tat enhances the HIV
14 replication of monocytes. This is the control, HIV-infected
15 cells, and the cells that were treated with HIV tat protein.
16 You can see that the virus replication, as a measure of p24,
17 was twofold to threefold and, in some cases, even more.
18 The panels on the bottom show the HIV-associated
19 cytopathic effect which we determine as a measure of
20 multinucleated giant cells. You can also see this tat-
21 enhanced cytopathic effect dramatically in monocytes.
22 [Slide.]
23 This is the very recent work we have published in
24 the Cutting Edge Section of the Journal of Immunology last
25 year. We wanted to find out--we all know, between this

1 slide and the previous slide, there are a number of steps,
2 which I don't have time to go through, but we know that tat,
3 and everybody knows, that the tat mediates cell
4 pathogenesis.
5 But the question was the tat is about 86 amino-
6 acids long and what portion, what domains of these tat
7 proteins that consist of core domain basic and RGD domains,
8 what domains are responsible for the pathogenesis.
9 So what we did was we mapped the entire sequence
10 and made several synthetic peptides, not only from Group M
11 but also consists of B, and also with other subtypes, and
12 examined their ability to promote viral pathogenesis which
13 is shown in the next slide.
14 [Slide.]
15 This shows the cells that were treated with
16 recombinant tat as well as different synthetic peptides.
17 And we measured p24 as an index of virus replication. As
18 you can see here, controlled cells not treated with
19 anything, just only infected with the monocyte strain of
20 HIV, the p24 level was 471. When these cells were treated
21 with recombinant tat, the p24 level was dramatically,
22 fourfold, higher as compared to the control ones.
23 I would like to draw your attention to this
24 peptide, tat 21 to 40, which had activated similar to what
25 we saw in recombinant tat. And we found this peptide

1 represents one of the active domains of the tat protein.

2 Very briefly, again, as you can see, this peptide

3 is a very difficult peptide and, yet, very important. It

4 has seven cysteines, six cysteines, seven cysteines, in it.

5 These two cysteines at 22 and 27 are very extremely

6 important for the activity because when we treated these

7 cysteine residues from this peptide, we lost almost half the

8 activity of the peptide.

9 Another peptide is 53 to 68 derived from the basic

10 domain also enhanced the virus replication by greater than

11 twofold. To figure out these two domains are very important

12 to promote viral pathogenesis. The other peptides taken as

13 a control had apparently no effect on them.

14 [Slide.]

15 This slide shows the HIV-associated cytopathic

16 effect. As we can see, previous to what we saw in the

17 previous table, the recombinant tat enhanced the

18 pathogenesis measured, or scored as the formation of

19 multinuclear giant cells, was much higher compared to

20 infected cells not treated with tat.

21 When we treated the cells with these two peptides,

22 especially with 21 to 40, the cytopathic effects were at

23 least fourfold to fivefold higher. This is just the control

24 peptide, had no effect and the morphology of these cells was

25 similar to what we saw in the control cells. This panel

1 represents the morphology of uninfected monocytes.

2 Just to summarize, these two peptides were

3 extremely important.

4 [Slide.]

5 This is--very briefly, again, we tested the

6 ability of these peptides to promote angiogenesis formation.

7 As we know, tat is involved in the Kaposi's sarcoma, with

8 the angiogenic-related diseases, at least in the HIV-

9 infected individuals. So we wanted to know if tat can

10 promote the formation of new blood vessels.

11 This experiment was done by using fertilized eggs,

12 the cam assay, basically. We tested this peptide, placed it

13 on a cover slip, and put it on cam of the fertilized eggs,

14 and examined the blood-vessel formation. As you can see,

15 this represents the control with no peptide. That is the

16 vehicle. That is the recombinant tat. This is the peptide

17 21 to 40, 51 to 68. And this is the control peptide.

18 As you can see, it is very clear that these

19 peptides, just like the recombinant tat protein, promoted

20 the formation of new blood vessels as seen over here by the

21 spoke-wheel pattern. This is just to summarize the data,

22 but the bottom line is that these peptides turn out to be

23 having more activity that is promoting HIV replication.

24 [Slide.]

25 Again, this data was published last year in the

1 Cutting Edge Section of the Journal of Immunology. This
2 work--a major contributor in this study was Bob Boykins and
3 myself and the rest, the others, helped a lot, too.
4 [Slide.]
5 Actually, I switched the slide here. Now it is
6 IV-tat and anti-tat antibody potential progressive
7 prognostic marker for HIV disease progression. I had
8 mentioned earlier, the tat is related to disease progression
9 and in the seropositive, non-progressive, they are reported
10 to have a high level of anti-tat antibody.
11 Currently, the prognostic markers for inhibition
12 of clinical symptoms are CD4, interferon count, interferon
13 alpha and viral load, and so forth. But, to identify
14 accurately the disease state of an individual, it may take
15 several months or even years. So there is a need for a
16 rapid diagnostic test.
17 So I took advantage of the information that the
18 seropositive, non-progressive, they have high-level of
19 antibody compared to rapid progressors, and designed,
20 attempting--actually, we are attempting to design a test
21 using the synthetic peptide we talked about previously.
22 [Slide.]
23 The next slide is very preliminary data, but this
24 study, again, was done in a blinded fashion on the sample
25 that was provided by Cindy Clayberger at Johns Hopkins. We

1 tested the reactivity of the cocktail on the peptide we
2 talked about in the previous slides and showed that the--our
3 interpretation was, and let me point it out here--it is
4 based on the level of anti-tat antibodies.

5 These are clinical diagnoses. These were the
6 identity of individuals that were provided to me by Cindy
7 Clayberger, undecoded samples. As you can see over here,
8 within reasonable agreement, we were able to accurately
9 interpret the clinical stage of the disease although we
10 realize there are some cross-reactivities with the normal
11 specimens and also some false positives.

12 But this study was done only on thirteen samples
13 so we need to do more study on that, and so we are currently
14 working on it.

15 [Slide.]

16 Now, the HIV-tat multiple peptide, the peptide
17 missing here, peptide conjugate--now, we have designed a
18 novel synthetic immunogen to develop a potential AIDS
19 vaccine.

20 [Slide.]

21 In the earlier few slides we saw 21 to 40 and 53
22 to 68, these two peptides, they were involved in
23 pathogenesis. We later on identified tat 9 to 20 sequences
24 from group O. We also enhanced virus replication in
25 monocytes by threefold to fourfold.

1 [Slide.]

2 We used these synthetic peptides and designed a
3 synthetic construct and successfully attached these three
4 peptides on a single core, and produced a very homogeneous
5 molecule that was 12 kiloDalton molecular weight as shown in
6 the SDS electrophoresis to the right panel. It was very
7 pure and the first time we were able to prepare this
8 molecule in the past.

9 [Slide.]

10 This, again, just to show the physical
11 characteristics of the peptide, this MPC, we did a mass spec
12 analysis and found that the theoretical mass and observed
13 molecular mass, they were in very close agreement. No one
14 has been able to show this correlation so far because of the
15 complexity of this molecule.

16 [Slide.]

17 This again is to show this MPC. This is a Western
18 Blot analysis of the MPC molecule over here, and you can see
19 it ranges from 0.5 to 5.0 micrograms. I would like to draw
20 your attention here, I used recombinant tat protein as a
21 control.

22 Now recombinant tat protein is being considered as
23 a potential candidate for the AIDS vaccine. Can we approve
24 this molecule for a vaccine? We can see there are multiple
25 bands here and we don't know which of the bands are

1 responsible for the activity.

2 On the other hand, our construct is a homogeneous

3 species, close to about 12 to 13 kiloDalton, and, in spite

4 of heavy loading, up to 5 microgram per ml as opposed to 1

5 or 2.5 micrograms of recombinant tat protein, we didn't see

6 anything over here. It showed a good reactivity with

7 polyclonal anti-tat antibody.

8 [Slide.]

9 We tested the ability of this peptide conjugant to

10 examine immune response. What we did was we immunized

11 BALB/c mice at different concentrations of doses of this MPC

12 molecule. As you can see, this induced a very high immune

13 response at all three different doses that the mice were

14 immunized with. The antibody level was high enough to be

15 detectable up to 243,000 dilutions.

16 The bottom panel shows the effect of these

17 antibodies--by the way, this was done only in mice, so far.

18 We are working on the other animals, especially, right now--

19 but we tested the ability of this anti-tat MPC antibody to

20 see if it can inhibit HIV replication.

21 As you can see over here, the anti-MPC antibodies,

22 when added in vitro, to in vitro culture, substantially

23 inhibited HIV replication in monocytes.

24 [Slide.]

25 This is again a pictorial demonstration of the

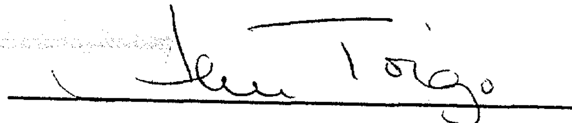
1 cytopathic effect of the ability of anti-tat antibody on HIV
2 pathogenesis. This is an HIV-infected cell culture in the
3 absence of tat; tat, as you can see, enhanced the cytopathic
4 effect. Inclusion of this anti-tat antibody to either of
5 these cultures significantly reduced the cytopathic effect.
6 [Slide.]
7 I wish I had more time to talk about this. That
8 was using the laboratory strain, the BALB strain, of HIV.
9 The next question was how effective this could be when we
10 take the clinical isolates.
11 So what we did was we isolated viruses from cells
12 isolated from rapid progressive, late progressive and long-
13 term non-progressors and did the same experiments that we
14 did with the laboratory strain and found, very briefly, that
15 it was able to inhibit HIV replication in monocytes by these
16 clinical isolates up to 58--67 percent, actually.
17 Of course, there is some variation, but that
18 depends on the viral isolate and also the susceptibility of
19 cells to these viral isolates. But the results were very
20 impressive.
21 [Slide.]
22 This is to show the diagrammatic representation of
23 the mechanism that I propose, how this MPC could inhibit HIV
24 pathogenesis. HIV-infected monocytes, HIV-infected cells,
25 are shown over here. HIV-infected cells that produce tat,

1 as I mentioned earlier, it can be taken up by the cell,
2 itself, or it can act on the adjacent cells and can produce
3 and result in cell fusion and cause multinucleated giant-
4 cell formation and, hence, increase viral production.
5 We believe that the addition of anti-tat MPC
6 antibody blocked this step. It inhibited the cell fusion
7 and, hence, reduced the viral production by infected cells.
8 This work I actually presented in July at the meeting and I
9 got good response on that from one of the audience from my
10 talk. He called me when I came back and he showed his
11 interest in collaborating with me. And he is from one of
12 the primary centers in San Antonio, Texas He has proposed a
13 collaboration to test in the primate model.
14 [Slide.]
15 In summary, basically, our study defined a role
16 for HIV tat in the regulation of immune function which I did
17 not talk about today, and in the pathogenesis of HIV
18 infection. We have identified a functional domain of the
19 HIV tat protein that is sufficient to transactivate, induce
20 HIV replication and trigger angiogenesis.
21 Our findings provide a new approach to developing
22 potentially effective and safe subunits of HIV tat vaccine.
23 This is important to know because this is a totally
24 synthetic construct and does not have any viral components
25 and it poses to threat to the recipient, and it can be

1 produced in bulk, in a large quantity, and also in a bigger
2 lot size for the consistency.
3 Our preliminary results of the serum specimen
4 performed in a blinded fashion, as I indicated, the
5 correlation of anti-tat antibody with the actual disease
6 stage of the patient and we are currently screening more
7 patient samples to substantiate our findings.
8 [Slide.]
9 I believe this is the last one. I would like to
10 thank you all.
11 DR. HOLLINGER: Thank you, Dr. Dhawan. Any
12 questions for Dr. Dhawan? If not, I think, this ends the
13 open public meeting. We will need to clear the room except
14 for people from the FDA and committee.
15 DR. SMALLWOOD: This does close out our open
16 session. We are going into closed session.
17 Thank you.
18 [Whereupon, at 4:21 p.m., the meeting was
19 adjourned.]

# *CERTIFICATE*

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



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