

TRANSCRIPT OF PROCEEDINGS

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGIC HEALTH

MICROBIOLOGY DEVICES PANEL

MEDICAL DEVICES ADVISORY COMMITTEE

Volume I

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Pages 1 thru 253

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGIC HEALTH

MICROBIOLOGY DEVICES PANEL
MEDICAL DEVICES ADVISORY COMMITTEE

VOLUME I

9:55 a.m.

Thursday, January 20, 2000

Conference Room
9200 Corporate Boulevard
Rockville, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

PANEL PARTICIPANTS:

Patricia Charache, M.D., Chair

Paul H. Edelstein, M.D.

Frederick C. Nolte, Ph.D.

L. Barth Reller, M.D.

John Rodis, M.D.

Natalie L. Sanders, M.D.

Leonard B. Seeff, M.D.

Steven Specter, M.D.

Lauri D. Thrupp, M.D.

Carmelita Tuazon, M.D.

Melvin P. Weinstein, M.D.

Michael L. Wilson, M.D.

David W. Gates, Ph.D., Industry Representative

Stanley M. Reynolds, Ph.D., Consumer
Representative

Steven Gutman, FDA Representative

Freddie M. Poole, Executive Secretary

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P R O C E E D I N G S

1
2 MS. POOLE: Good morning, and welcome to the
3 Microbiology Devices Committee meeting. We have some
4 administrative information to give you. The first is a
5 conflict of interest statement. The following announcement
6 addresses conflict of interest issues associated with this
7 meeting, and is made part of the record to preclude even the
8 appearance of an impropriety.

9 To determine if any conflict existed, the agency
10 reviewed the submitted agenda for this meeting and all
11 financial interests reported by the committee participants.
12 The conflict of interest statutes prohibit special
13 government employees from participating in matters that
14 could affect their or their employers' financial interest.
15 However, the agency has determined that participation of
16 certain members and consultants, the need for whose services
17 outweighs the potential conflict of interest involved, is in
18 the best interest of the government.

19 Therefore, a waiver has been granted for Dr. Lauri
20 Thrupp for his interest in firms that could potentially be
21 affected by the panel's recommendations. A copy of this
22 waiver may be obtained from the agency's Freedom of
23 Information Office, Room 12A-15 of the Parklawn Building.

24 We would also like to note for the record that the
25 agency took into consideration other matters regarding Drs.

1 Melvin Weinstein, Paul Edelstein, and Barth Reller. Each of
2 these panelists reported interests in firms at issue, but in
3 matters that are not related to today's agenda. The agency
4 has determined, therefore, that they may participate fully
5 in all discussions.

6 In the event that the discussions involve any
7 other products or firms not already on the agenda, for which
8 an FDA participant has a financial interest, the participant
9 should excuse himself or herself from such involvement, and
10 the exclusion will be noted for the record.

11 With respect to all other participants, we ask in
12 the interest of fairness that all persons making statements
13 or presentations disclose any current or previous financial
14 involvement with any firm whose products they may wish to
15 comment upon.

16 For old business from our May--our last panel
17 meeting was held in May 1999. We had two PMAs and a 510(k),
18 Biotrin Parvovirus B19 IgG and IgM was approved by the FDA.
19 The labeling was revised as recommended by the panel. The
20 Gemprobes MPB nucleic acid amplification assay was also
21 approved as modified, and the Digene CMV labeling was also
22 cleared using the suggested terms for signal amplification.

23 Just a reminder. We would ask that if anyone has
24 a cell phone, if you could turn it off, and if you have a
25 pager, if you could put it on the vibrate mode so that it

1 wouldn't disturb the proceedings. Thank you.

2 Dr. Charache?

3 DR. CHARACHE: Good morning. I am Dr. Patricia
4 Charache, Panel Chair of this Microbiology Devices Panel
5 meeting, and we would like to introduce the panel at this
6 time.

7 I am at Johns Hopkins, where I am professor of
8 pathology medicine and oncology, and my current title is
9 Program Director, Quality Assurance and Outcomes Research.

10 DR. WEINSTEIN: I am Mel Weinstein, at Robert Wood
11 Johnson Medical School in New Brunswick, New Jersey,
12 professor of medicine and pathology and Director of the
13 Microbiology Laboratory at the university hospital.

14 DR. SANDERS: I am Natalie Sanders. I'm a general
15 internist, and I am also the medical director for ebiok.com,
16 which is a specialty pharmacy in Santa Clara, California.

17 DR. EDELSTEIN: Paul Edelstein, University of
18 Pennsylvania, Director of the Clinical Microbiology
19 Laboratory.

20 DR. TUAZON: Carmelita Tuazon, professor of
21 medicine at George Washington University Medical Center.

22 DR. RELLER: Barth Reller, Director of Clinical
23 Microbiology, Duke University Medical Center, professor of
24 pathology and medicine.

25 DR. SPECTER: Steven Specter, University of South

1 Florida in Tampa. I am professor of medical microbiology
2 and immunology and Associate Dean for Preclinical Education.

3 DR. GUTMAN: Steve Gutman. I am the Director of
4 the Division of Clinical Laboratory Devices.

5 DR. GATES: David Gates of Bechton Dickinson. I
6 am Director of Quality and Compliance, and I'm the
7 industrial rep.

8 DR. NOLTE: Rick Nolte, Emory University, Atlanta.
9 I'm Director of the Clinical Microbiology Lab and associate
10 professor of pathology and laboratory medicine.

11 DR. STEWART: John Stewart. I'm at the Center for
12 Disease Control in the Division of Viral Diseases, the
13 Herpes Virus Branch.

14 DR. THRUPP: Lauri Thrupp. I am professor in the
15 Infectious Disease Service, University of California-Irvine,
16 Chief of Infection Control and a consultant to the Clinical
17 Microbiology Lab Service at the UCI Medical Center.

18 DR. RODIS: John Rodis. I'm professor of
19 obstetrics and gynecology at the University of Connecticut.

20 DR. WILSON: Mike Wilson, Director of Pathology
21 and Laboratory Services at Denver Health, and associate
22 professor in the Department of Pathology at the University
23 of Colorado.

24 DR. SEEFF: I am Leonard Seeff. I am at NIDDK,
25 where my title is Senior Scientist for Hepatitis Research.

1 And I am also at the VA Medical Center in Washington, D.C.

2 DR. CHARACHE: Dr. Reynolds?

3 DR. REYNOLDS: Stan Reynolds, Pennsylvania

4 Department of Health, Bureau of Laboratories, and I'm the
5 consumer representative.

6 DR. CHARACHE: Thank you. Our new business this
7 morning is to advise on six PMAs from DiaSorin, and we are
8 to advise on the premarket approval applications for in
9 vitro diagnostic qualitative devices to detect hepatitis B
10 serological markers in human serum or plasma. These
11 hepatitis B serological marker assays, when used
12 appropriately in combination, are indicated as an aid in the
13 diagnosis and monitoring of disease and therapy in acute and
14 chronic hepatitis B viral infection, HBV, in both low and
15 high risk adult populations.

16 I will not read the devices that we're going to
17 cover. We will come to them as we go. But it is noted that
18 these devices are not for blood screening, but are
19 diagnostic devices.

20 We would like to--here is Dr. Steven Gutman, who
21 will give us some background information.

22 DR. GUTMAN: Good morning, and in light of the
23 weather I would like to give you a warm welcome. I
24 appreciate your all being here.

25 The FDA's involvement with hepatitis tests

1 preceded the publication of the Safe Medical Device
2 Amendments of 1976. Early regulation was in the context of
3 the Public Health Service Act, was carried out by the
4 organizational precursor of the current Center for
5 Biologics, and was grounded in blood safety. Obviously, in
6 spite of the clear early focus on blood screening claims,
7 almost from the first introduction of hepatitis testing,
8 diagnostic applications have been important corollary uses
9 of this product.

10 Following the introduction of device regulations,
11 the Center for Biologics adopted these to use as a basis for
12 regulation of the diagnostic hepatitis test under its
13 scrutiny. These were treated as Class 3 products.

14 With the introduction of the Bureau of Medical
15 Devices in the late 1970s, a jurisdictional dichotomy was
16 established, with tests with clear potential for use in
17 blood banks and blood product manufacturing facilities--at
18 first these were markers for hepatitis B, and more recently
19 markers for hepatitis C--regulated in Biologics, and non-
20 blood bank applications, hepatitis A, for example, were
21 picked up and regulated in the new Center for Devices.
22 Products were uniformly considered Class 3 devices, whether
23 bloodborne, concomitantly used for screening or not, and
24 were subject to Class 3 oversight in each of the two
25 respective organizational units.

1 Regulation of hepatitis tests for diagnostic and
2 monitoring purposes became an important activity in the
3 Center for Biologics, although the Public Health mission
4 focused first and foremost on blood and blood product
5 claims. Diagnostic data sets were traditionally
6 supplemental to these.

7 Approximately five years ago, fueled by interest
8 from industry, the administrative assignment for diagnostic
9 hepatitis tests, which for almost a decade had been outlined
10 as part of a comprehensive intercenter agreement on device
11 jurisdiction, was revisited. A decision was made to
12 consolidate the diagnostic and monitoring applications of
13 all hepatitis assays in one unit, and that lucky unit was
14 us.

15 Our division has been working collaboratively with
16 industry to determine appropriate thresholds for review of
17 new versions of what are now well established testing
18 product lines, and to determine how to address new potential
19 uses and new technologies; for example, how to assess tests
20 for viral load rather than viral diagnosis.

21 Today and tomorrow FDA will be requesting input
22 from the panel on the first products of both types of key
23 diagnostic hepatitis markers to reach final review in our
24 center; today hepatitis B, and tomorrow hepatitis C. Two
25 important issues should be considered in the background to

1 help frame this discussion.

2 The first is that the biology and pathology of
3 viral hepatitis, although still replete with opportunities
4 for additional learning, have been areas of intense research
5 interest and represent highly explored areas of medical
6 knowledge. To date, MEDLINE, at least since 1966, contains
7 a total of 15,000 entries under the heading of viral
8 hepatitis. Hepatitis testing is also not a particularly
9 arcane topic, and a total of 2,600 entries appear in MEDLINE
10 since 1966.

11 The second is a charge by Congress to FDA via the
12 Modernization Act of 1997, to establish "least burdensome"
13 thresholds for determining the safety and effectiveness of
14 new devices or new versions of old devices. The challenge
15 before us as a review division is to understand how we can
16 work with sponsors to develop user-friendly studies that
17 properly support reasonable claims for devices, and how
18 these studies should be reported in labeling.

19 A theme for both submissions or both days of
20 review is that one possible mechanism for utilizing the rich
21 literature base and maintaining the spirit of "least
22 burdensome" is to entertain general claims about infection
23 without requiring large data sets to provide certainty of
24 performance in particular diagnostic settings.

25 The justification for this approach rests on the

1 ability of practitioners to use knowledge in the literature
2 or from standard practice to extrapolate from existing tests
3 and more general states of disease to specific diagnostic
4 situations. Companies are free to utilize new tests in
5 subsequent studies and, over time, develop more rigorous
6 claims if desired.

7 We will be asking the panel to evaluate a variety
8 of study designs over the next two days, and to help
9 determine whether these studies support safety and
10 effectiveness of use, and what claims and what labeling are
11 appropriate for the studies performed. It is our hope that
12 the discussions for the products at hand will serve as a
13 precedent for guiding a wide variety of important new
14 version of old tests to market.

15 It is important for FDA to reach a balanced
16 approach because it will encourage new technologies. It is
17 also important to allow the agency an opportunity to free up
18 resources for tests which are more cutting edge and which
19 will require heightened attention, tests which in the future
20 will be knocking on the door of this panel, such as assays
21 for new diagnostic markers and/or quantitative tests to
22 monitor therapy.

23 Thank you.

24 DR. CHARACHE: Any questions of Dr. Gutman as we
25 begin?

1 [No response.]

2 DR. CHARACHE: Thank you very much. We'll go on
3 to the manufacturer's presentation. We will, if you have a
4 question about what each speaker is saying, immediately
5 after their talk, for clarification purposes, we can ask a
6 few questions. We'll save our major questions for the
7 manufacturer, from what you hear, when we have heard the
8 entire discussion.

9 Our first speaker for the manufacturer is Judith
10 Smith, who will provide introductions, company background.
11 Ms. Smith?

12 MS. SMITH: Thank you very much. I wanted to
13 welcome you all and thank you for this opportunity, in this
14 beautiful weather we're having today, to present our PMAs to
15 you. We haven't had snow in probably a year, and it's
16 snowing on the day of our advisory panel meeting, so this
17 must be something special.

18 My name is Judith Smith. I'm the Process Owner
19 for Worldwide Regulatory Affairs and Quality Systems at
20 DiaSorin. I will be speaking and presenting most of the
21 clinical trials data. My colleague, Dr. Maurizio Borla, who
22 is the Product Development Manager for Hepatitis of
23 DiaSorin, will be presenting more of the technical issues
24 about the assay.

25 This is just a quick agenda of what we are going

1 to speak about. I have just given the introduction, so we
2 are already done that one. I am going to give you a little
3 bit of background about the company. Dr. Borla will give
4 you a background about the assays themselves, and then I
5 will go into some of the analytical sensitivity data, and
6 then present you with the background for the clinical
7 trials: what we did, how we did it. And that will then
8 lead into Tom Simms' presentation.

9 Just to give you some background on DiaSorin,
10 DiaSorin was formed as a merger of three companies: Sorin
11 Biomedica, which is in Saluggia, Italy; Incstar, which is in
12 Stillwater, Minnesota; and Sienna Biotech, which was a small
13 start-up company in Columbia, Maryland. The merger occurred
14 in July of '97.

15 Sorin Biomedica is the manufacturer of the assays
16 that we are presenting today. They have been licensed by
17 CBER for the manufacture of hepatitis assays since 1986.
18 What we are presenting today are modifications that were
19 made to the originally CBER-licensed and CDRH-approved
20 hepatitis assays, to improve the performance of the assays
21 and to remove the blood bank claim.

22 What is being presented today are six premarket
23 approval applications for these new/modified assays. They
24 are the six markers for hepatitis. The PMAs describe the
25 changes made to our assays and the performance

1 characteristics.

2 Dr. Borla will now give you a description of, so
3 you will understand a little bit about the old licensed
4 assays versus our new modified assays.

5 DR. BORLA: Thank you very much. I am Maurizio
6 Borla. I am the manager of a hepatitis lab in product
7 development, DiaSorin in Italy.

8 DR. CHARACHE: Excuse me, Dr. Borla. Could you
9 pull up the microphone a little bit?

10 DR. BORLA: Yes. Also because I have to apologize
11 for my bad English, and then if anything was not so clear or
12 enough clearer during my speech, please do not hesitate to
13 ask me to repeat or to--

14 DR. CHARACHE: No, it's fine. I just wanted to be
15 sure everyone could hear.

16 DR. BORLA: Thank you. I follow the development
17 of the new line in 1996, and then today I will present in
18 the first part just some common objective of the new
19 DiaSorin hepatitis B line, what we call the PLUS line, the
20 hepatitis B PLUS. Then in the second part we--I will
21 discuss more in detail some major modification in between
22 the current kit already in the market in United States and
23 the new version that is the subject of the new PMAs.

24 Coming from the common objective of the new
25 DiaSorin hepatitis B line, the first goal that we have and

1 we reach in this line was to increase the analytical
2 sensitivity of each kit. After my presentation Judy will
3 give you some more data, more results about this analytical
4 sensitivity for each kit.

5 The second is the increased specificity. We reach
6 this goal with the introduction of an incubation buffer that
7 help us to improve the specificity. All the six assay for
8 the serological marker for HBV have the same procedures, 2
9 hours plus 1 hours at 37 degree and 30 minutes at room
10 temperature for the chromogen/substrate development. This
11 is a great improvement in respect to the current line that
12 has different incubation, different procedure, and then is
13 not for--user-friendly for the customer. The same goal of
14 uniformity was gather also for the sample calibrator and
15 buffer volumes.

16 To make--to keep more user-friendly, we use also a
17 chromogen/substrate ready-to-use instead of the current
18 chromogen/substrate that have to be diluted from the user
19 before adding, before pipetting in the microwell. We are
20 telling about, we are saying about the microplate, one of
21 the advantage of the new line is that we identified each kit
22 with a marker code on a strip, and this is just avoid that
23 the user could mix up different assays and then different
24 microplates or strip of microplates in the same plate.

25 Again, the current version have calibrator and

1 controls in the same kit. The new version, the modified
2 version, we put calibrators and controls in separate vials
3 but in the same kit. The user have all in the same box.

4 The other advantage that the modification we made
5 to make the kit more user-friendly is this incubation buffer
6 that we provide and could be used for the user as a QC step
7 to monitoring the addition of the samples after pipetting.
8 For the environmental point of view, we eliminate all the
9 mercurial preservative and the Sodium Azide, and
10 substituting with the other kind of a preservative.

11 All these modification make this line, this new
12 hepatitis line with the six markers, compatible with
13 automation in the open system, as a procedure, as
14 incubation, as a volume and a vials for this.

15 Coming to the second part of my presentation, we
16 start with the first kit. That is ETI-MAK-2 PLUS. That is
17 intend for use in the qualitative determination for
18 hepatitis B surface antigen, so-called HBsAG. The current
19 version, the ETI-MAK-2, was licensed by CBER in April 1991,
20 and have both the claims, both the intended use, for the
21 blood unit screening and for diagnostic use. The new kit,
22 in the new kit we claim just the diagnostic use.

23 In this case, to increase the sensitivity we
24 improve the ability of the solid phase on the microplate to
25 bind the antigen, the HBsAG antigen, putting two monoclonal

1 antibodies for HBSAG instead of only one that is present in
2 the current version. Again, to increase the sensitivity and
3 also to increase the specificity of the assay, and that is
4 of course one of our goals, now we are using the fragmented
5 immunoglobulin instead of whole IgG conjugated to HRP, the
6 enzyme horseradish-peroxidase.

7 The second assay is the ETI-AB-AUK PLUS. That is
8 intended for use in the qualitative determination of
9 antibodies to hepatitis B surface antigen. Again, the
10 current version was licensed by CBER in April 1991, and have
11 both the intended use for blood unit screening and for
12 diagnostic. The new line have--the new kit, sorry--is just
13 for diagnostic use, just this kind of claim.

14 The main modification we made in this assay is the
15 use of the recombinant HBSAG, both the subtypes ad and ay,
16 instead of the human HBSAG extracted from serum or plasma.
17 This is to improve the lot-to-lot consistency of the
18 material, but also to improve the lot-to-lot reproducibility
19 of the final component, that is, the microplate.

20 In the new kit, the new assay, we introduce also a
21 calibrator with 10 milliunit WHO. That is the recognized
22 concentration as a threshold for the immunity protection
23 against the HBV infection. This kind of calibrator was not
24 present, is not present in the current version.

25 The third, ETI-AB-CORE PLUS, is the kit intended

1 for the qualitative determination of total antibodies to
2 hepatitis B core antigen. Again, the current version is a
3 PLA and was licensed by CBER, with again the two claims,
4 blood unit screening and diagnostic use. The new one have
5 only the diagnostic use claim.

6 In this case, to improve our specificity and our
7 sensitivity, we change the assay scheme of the kit. The
8 current version is a competitive one-step. The new version
9 is (inaudible) by neutralization. This improve the
10 specificity because we introduce a washing step in between
11 the two immunological incubation that could help, with the
12 incubation buffer that we also use in this case, could help
13 to avoid or to prevent some cross-reactivity or some
14 interferences that could bring to false reactivity
15 (inaudible).

16 The other major modification we change, again we
17 made, again to improve the sensitivity and the specificity,
18 is the use of fragmented, in this case the polyclonal, the
19 human polyclonal, in the (inaudible) we use the fragmented
20 immunoglobulin instead of whole IgG, and we conjugate with
21 the enzyme horseradish-peroxidase.

22 The following, please. Thank you. The same
23 modification, the use of fragmented IgG instead of whole
24 IgG, is the only modification, the only important,
25 significant modification we made in the ETI-CORE-IGM PLUS.

1 That is the kit for the qualitative determination of IGM, in
2 this case, antibodies to hepatitis B core antigen. We
3 already have a version on the market, but in this case the
4 diagnostic use is the only claim that we have and that we
5 claim.

6 A special speech is for the ETI-EBK PLUS, because
7 the current available kit is a kit with two different
8 procedures, one for the hepatitis B e antigen determination,
9 qualitative determination. The other procedure is for
10 hepatitis B e antibodies determination. In the same kit we
11 have the two procedure that you could choice if you want
12 determine the presence of antigen or of the antibodies.

13 To have a more user-friendly kit and to have the
14 possibility to automate this kit, in the new version we
15 separated the two processes, and then the classical
16 (inaudible) assay scheme for the antigen, e antigen
17 determination, become ETI-EBK-PLUS, and in this case we
18 improve the sensitivity and the specificity, again adopting
19 two monoclonals against the hepatitis B e antigen instead of
20 one in the solid phase. And so we improve the capacity of
21 the solid phase to bind, to capture the hepatitis B
22 antigen. And the enzymatic tracer again in this case is a
23 monoclonal. Again we use the fragmented immunoglobulin
24 instead of the whole IgG.

25 The same two modification, major modification, we

1 made in the following kit. That is for the determination of
2 antibodies to hepatitis B e antigen, and that is a
3 (inaudible) by neutralization test. Again, we have the same
4 solid phase with two different monoclonal antibodies to
5 hepatitis B e antigen, and again the monoclonal that is in
6 the enzyme, conjugated, is fragmented instead of used as a
7 whole IgG.

8 I have finish, if there is--there are some
9 question. Thank you very much.

10 DR. CHARACHE: Thank you very much, Dr. Borla.

11 Ms. Smith?

12 MS. SMITH: I am just going to spend some quick
13 time describing in a little more detail the analytical
14 sensitivity improvements that we were able to reach with
15 these modifications to the assay that Dr. Borla had alluded
16 to earlier. I'm not going to go through every single one of
17 these numbers, so don't panic.

18 I just want to show you that we tested a number of
19 high titer samples, diluted down. We had a couple of
20 commercial panels. We also used in this case a CBER panel,
21 and we used a Paul Ehrlich Institute quantitated panel, and
22 what we looked at was the last positive dilution. We looked
23 at it against the current assay, the current ETI, what we
24 call the ETI line. We looked at it against the ETI PLUS
25 line, which is the modification we are here for today. We

1 also looked at it compared to Abbott.

2 And in every case we were either as good or
3 better, showed as good or better sensitivity than both our
4 current assay and the Abbott assay. The ones to look at a
5 little bit more closely are the actual quantitated ones.
6 The BBI panels are very highly, well characterized, so they
7 have nanogram per milliliter units to them, and the Paul
8 Ehrlich has the Paul Ehrlich units associated with them.
9 For the Paul Ehrlich we were as sensitive as Abbott, a
10 little bit more sensitive than our current line. For the
11 nanograms per milliliter we were more sensitive than the
12 other two assays.

13 ETI-BAUK, that is how we affectionately call it,
14 is the same situation: high titer samples, BBI panels, a
15 CBER panel, and in this case there was a WHO standard we
16 could use. Once again, the same conclusion: We were as
17 sensitive or more sensitive, in this case more sensitive on
18 the quantitated samples, than both our current assay and the
19 Abbott assay.

20 The AB-CORE, same situation: high titer,
21 different panels, and a Paul Ehrlich. And as you can see,
22 we greatly improved the sensitivity of our assay with these
23 improvements.

24 CORE-IGM, same situation, and you can see from the
25 numbers there--by the way, if I am going too quickly, please

1 tell me to slow down. Okay. As you can see from the
2 numbers there, very quickly, that we reached a better
3 sensitivity or comparable to our old assay. and better
4 sensitivity to Abbott and in some situations our old assay.
5 EBK, that's the HBe antigen assay, and once again
6 we used a sero--in this case we had a seroconversion panel.
7 We were able to look at the first, from the last positive--
8 or the first positive, I'm sorry, the first positive from
9 the first bleed. We also had high titer samples that we
10 diluted down, and the Paul Ehrlich, and we were comparable
11 in every case.

12 The last one is the AB-EBK, and that was the
13 antibody to the e antigen, and you can see that we had
14 comparable sensitivity in the standard prep and better
15 sensitivity on last positive dilution.

16 Now I want to go through and, in preparation for
17 the actual presentation of the data on the clinicals, I want
18 to fill you in, give you some background on what we did for
19 these trials. We conducted the trials at three independent
20 laboratories in geographically diverse areas in the United
21 States. We also did some testing at DiaSorin in Saluggia,
22 Italy. Yes?

23 DR. THRUPP: Can we ask a question about the--what
24 was just presented?

25 DR. CHARACHE: I think probably it would be better

1 to complete this and just make a note of your question.

2 DR. THRUPP: Okay.

3 MS. SMITH: The majority of the samples that we
4 used were frozen repository samples. They were samples from
5 patients with known disease state. That included acute,
6 chronic and convalescent hepatitis B samples, single
7 samples. We also purchased acute and chronic panels, that
8 is, multiple bleeds over a period of time from the same
9 patient to watch the course of the disease.

10 We also had high risk patients that we looked at.
11 Those were hemophiliacs, hemodialysis, and IV drug abusers.
12 We looked at pregnant women. We also looked at healthy
13 first-time blood donors. Healthy first-time blood donors
14 were the fresh--we did--those were not frozen repositories
15 that had been purchased. That came from one of the sites.

16 We tested all six markers as appropriate for the
17 claim, using both the new DiaSorin assay and the currently
18 FDA-approved Abbott assay, so we had 12 results on every
19 single sample.

20 One thing that I did want to note to you was that
21 our HBSAG assay, the ETI-MAK-2, does not include
22 confirmation by neutralization. This is a diagnostic claim,
23 and therefore we felt because this is used in conjunction
24 with other markers, this is more appropriate--this is the
25 acceptable mode for the diagnostic claim. The

1 neutralization is more the--in the blood bank claim.

2 Once again, I'm not going to go through all these
3 numbers for you. I just wanted to have them for you so you
4 could see them. This is a list of all the samples that we
5 did test. We looked at, as you can see, there were
6 chronics, acutes, convalescents, some panels, serial panels,
7 some individual samples, pregnant women, both high and low
8 risk--okay, next slide--patients sent to the lab for HBV
9 testing, hospitalized patients, first time blood donors, and
10 there is our high risks. We also looked at anti-HBs
11 vaccinees, the ones who had received the Smith Kline Beecham
12 or the Merck vaccine, the hepatitis vaccine.

13 One of the things I just wanted to note here for
14 you, for the high risk, that's the hemophiliacs, the IV drug
15 users, and the hemodialysis patients, we only tested HBsAG,
16 anti-HBs, and total anti-core on those, because those are
17 the markers that are usually used in that kind of high risk
18 population to identify whether these people need to be
19 vaccinated or they have already been exposed to the disease
20 and it's too late.

21 The other thing I wanted to note for you was--
22 well, two other things. The vaccinees that were single
23 samples we obviously only measured the anti-HBs in them
24 because the vaccine only stimulates the antibody to surface
25 production.

1 The other thing that I also wanted you to know
2 was, the vaccinees, the serial samples, these represent the
3 pre-vaccination and two doses. The samples were drawn over
4 the course of six months. We have six results, but they
5 only represent two of the three doses. The third dose was
6 not available at the time of our clinical trials. The
7 patients were still undergoing immunization, so we were not
8 able to get the third and final dose. But what we did test
9 was the beginning doses, which is the more interesting area
10 to concentrate on, to see if the patient is starting to
11 generate a response.

12 Now we had an inclusion and exclusion of samples
13 for the analysis. We had a lot of discussions on what to
14 include and what to exclude, because no assay is perfect.
15 So what we tried to do was, we developed an algorithm for
16 inclusion and exclusion. That included all the data that we
17 had on each sample, so it included the results we had from
18 the vendor; the Abbott results that we obtained during the
19 trials; liver biopsy, if we had a liver biopsy result on it;
20 and the known marker patterns as demonstrated by the
21 reference assay results during the trials. We took all of
22 that into consideration when we decided if a sample was in
23 the right population or not, before we started looking at
24 our results compared to that.

25 The other populations, all samples were included.

1 There was no inclusion or exclusion based on patterns. It
2 was purely if you had that characteristic. You know, if you
3 were apparently healthy, a first time blood donor, you were
4 included regardless of what your pattern, your hepatitis
5 marker patterns might look at. High risk, pregnant women,
6 these were all population characteristics and not disease
7 characteristics, so they were all kept in the populations.

8 And here is our inclusion/exclusion criteria.
9 It's a little much but it helped keep--it helped document
10 for us and keep straight for us the decision tree we used.

11 We started out with the first question was, was
12 there a diagnosis by liver biopsy available? If there was,
13 it didn't matter what the clinical trial results were, it
14 was included. And that was the majority of our chronics,
15 chronic patients had liver biopsy results that indicated
16 that they had chronic hepatitis, so they were included.

17 The next question was, did the tests--we ran
18 Abbott and ourselves during clinical trials. The question
19 was, did the vendor test the marker for use as a
20 confirmation of our clinical trial result for the Abbott?
21 If it was yes, and the vendor result agreed with our
22 clinical trial result, then we knew we had a true "true", as
23 close to truth as we could get, description of the sample,
24 and therefore it was included. And we used the two out of
25 two rule: In other words, the Abbott and the DiaSorin

1 result matched, the sample was included, and given that
2 result, positive/positive, it was a positive;
3 negative/negative, it was a negative.

4 Now, if the vendor--if we had a result and the
5 vendor had a result and they did not agree with each other,
6 the question was, did we do any additional testing during
7 the trials? If we did, then we used the two out of three
8 rule: Which two results--I'm sorry. By Abbott, this was
9 always by Abbott. It was not by us. We did not use any
10 inclusion/exclusion based on our results.

11 So if we had--the vendor result was positive for
12 Abbott, the clinical trial result was negative for Abbott,
13 and we did some repeat testing for it and we got another
14 Abbott negative, then the two out of three rule said that it
15 was an Abbott negative and it was included. If we didn't
16 have that and we still had these samples that were
17 discordant, that sample was only included if that marker in
18 the marker pattern--if that was not a critical marker. It
19 could be positive or negative if it didn't matter in the
20 diagnosis of that sample.

21 For instance, in acute, if there was a marker--or
22 chronic, I'm sorry. In the chronic patient, if there was a
23 marker that was not critical, could be positive or negative,
24 it was included. If it had to be positive or negative and
25 we had the two samples, results disagreeing, it was excluded

1 because we didn't know what the sample was.

2 If we did not--here we go--if we did not have
3 vendor results to compare to our clinical trial results,
4 then we went through a whole separate inclusion/exclusion
5 decision tree. And it was included if, in the case, in the
6 specific case of HBsAG, if we could make a diagnosis using
7 the other markers and not looking at the Abbott HBsAG
8 result, then we included the sample and called it acute or
9 chronic or convalescent.

10 I know. It makes a lot more sense when you
11 actually have the data in front of you. Anyway, we went
12 through all these kinds of decision trees.

13 If the marker could be positive or negative, it
14 didn't matter in that particular population, if it didn't
15 affect the diagnosis, it was included. If it affected the
16 diagnosis and the Abbott results didn't match the marker
17 patterns that were recognized marker patterns, and therefore
18 we could not classify them as either acute or chronic or
19 convalescent, we didn't know what bucket to put them in,
20 then they were excluded. So we used this decision tree to
21 ensure that we had each sample identified in the right
22 disease bucket.

23 Okay. I think that's the end of my portion.

24 DR. CHARACHE: I would be glad to open this up now
25 for panel discussion. I would remind the panel that this is

1 our opportunity to ask for clarification or more information
2 not only of what was presented but anything that we have
3 questions about, that the representatives from DiaSorin can
4 assist us in addressing. So if you have any questions that
5 you would like amplified or any further information, it
6 should be addressed at this time.

7 We will start with Dr. Thrupp

8 DR. THRUPP: I was just going to ask, concerning
9 the summary that you presented first of the high titer
10 samples, how were those high titer samples selected? Or are
11 these high titer controls that have been widely used and are
12 stock sera? And what proportion of the populations are
13 going to show similar changes in the sensitivity? Or just
14 how they were selected, is what I was wondering.

15 DR. BORLA: These high titer sera are just the
16 sera out of the panel that was selected, because during
17 previous clinical trials or during previous search of the
18 markers for these kind of serological markers, they have a
19 very high reactivity, and then we dilute these to
20 demonstrate what is the analytical sensitivity, what is the
21 best dilution that the kit could derive specially of.

22 MS. SMITH: They were just individual samples.

23 DR. BORLA: Just individual patients, yes. They
24 are not the pooled, both the sample that we have in our
25 stock in Saluggia or the sample that we purchase from some

1 vendors, but we ask for one samples, not a pool of blood
2 unit or the--of sampled, patient samples. Also because in
3 some cases, for example, the first for ETI-MAK-2 PLUS, we
4 are searching for specific subtypes just to demonstrate that
5 the sensitivity is equal for ad and ay, the main subtypes,
6 and then it is important for us that it was just a single
7 sample. It's not a pool, that we can lose the specific goal
8 that we have to reach.

9 DR. CHARACHE: Other questions at this time?

10 DR. SEEFF: As a matter of interest, do you
11 routinely test in duplicate or use single samples, each time
12 you test?

13 MS. SMITH: Single.

14 DR. BORLA: During clinical--

15 DR. CHARACHE: Excuse me. I wonder if the panel
16 members will please state your names as you speak?

17 DR. SEEFF: Leonard Seeff. The question is
18 whether it's in duplicate or single samples tested each
19 time.

20 DR. BORLA: In single samples.

21 MS. SMITH: And that is the recommendation for the
22 standard use.

23 DR. CHARACHE: And we'll ask you to use the
24 microphone we capture your words.

25 MS. SMITH: It was single samples, and that is the

1 recommended procedure.

2 DR. CHARACHE: Thank you.

3 DR. SANDERS: Natalie Sanders. The patients who
4 had chronic hepatitis B, or those that were in a
5 convalescent state or receiving therapy, monitored for
6 therapy, were they HIV negative?

7 DR. BORLA: For the chronic and the convalescent,
8 yes, because we ask--one of the criteria for the exclusion,
9 we don't have HIV, just do not have any interferences from
10 immune system not for (inaudible), and that was HIV
11 negative.

12 DR. SANDERS: All right. And then I also just
13 had--wondered, Madam Chairman, if I could ask a question
14 about one of the specific--of the six?

15 DR. CHARACHE: Oh, yes. This is our opportunity
16 to share our questions with these representatives.

17 DR. SANDERS: All right. I have a question about
18 the ETI-MAK-2 PLUS and the results in your hemodialysis
19 patients. I was actually very surprised that zero out of 65
20 were hepatitis B surface antigen positive, that they were
21 all hepatitis B surface antigen negative, and I just found
22 that kind of unusual. I would have expected that one or two
23 would have been positive. And so maybe my laboratory
24 medicine and infectious disease colleagues can help me
25 understand that better.

1 MS. SMITH: I don't know. Tom, are you going to
2 be presenting all that data? Okay.

3 Unfortunately I don't have the raw data in front
4 of me that we got.

5 DR. SANDERS: Let me just maybe rephrase it. From
6 an epidemiologic standpoint, patients who are receiving
7 chronic hemodialysis, do my colleagues find it this unusual
8 that none of the 65 were hepatitis B surface antigen
9 positive? And I asked the question because I wondered if it
10 was a select population of dialysis patients.

11 DR. BORLA: Again, we included this population in
12 high risk just for this reason, because they emerge in this.
13 I don't remember how many positive there are, but--

14 DR. SANDERS: There were none.

15 DR. BORLA: None? Okay.

16 DR. CHARACHE: Are there other questions? I'm
17 sorry. Yes?

18 DR. TUAZON: Carmelita Tuazon. Can you just
19 summarize for us how you envision the various kits in terms
20 of the clinical setting? When do you use what?

21 DR. CHARACHE: Perhaps I could amplify on that. I
22 had a similar question.

23 As you have pointed out, some of these tests are
24 used to define past experience with hepatitis; some show
25 viral replication going on at that time. They are used for

1 different purposes. And so I'm hearing the question of,
2 what data do we have that show that each of these tests is
3 effective in specific usage, and how do you plan to guide
4 those who want to use the test? Which one is appropriate
5 for which purpose?

6 MS. SMITH: Yes. What we are recommending is that
7 these are six assays to diagnose--to test the individual
8 markers, and that we are not dictating exactly what markers
9 you are required to use. That would be then dictating the
10 practice of medicine.

11 What we are saying is, we have these available,
12 and whatever the doctor normally uses to identify or
13 diagnose acute, or diagnose--you know, he or she suspects
14 acute, or he or she suspects convalescent or chronic, the
15 results--the markers that you would normally--that you would
16 choose to diagnose that is at the doctor's discretion. But
17 obviously there are certain ones like HBsAG and core that
18 you would use to confirm acute. You might use e or anti-e
19 to confirm what stage of the disease you are looking at.

20 But really we are not dictating exactly which
21 ones, and the data that will be presented in a few minutes
22 will show our assays' performance in those different disease
23 states.

24 DR. SANDERS: So you don't plan to provide the
25 laboratory with guidance as to how to direct--I mean the

1 physicians who order hepatitis tests obviously don't know,
2 in a high percentage of cases. Do you plan to tell them
3 which assays are appropriate to diagnose continuing disease
4 and which assays are appropriate to diagnose past experience
5 with this agent?

6 MS. SMITH: Well, what we were planning to do was
7 to present in the package insert the different marker
8 patterns for the different disease states, so that might
9 help them decide which markers they think are appropriate to
10 test.

11 DR. CHARACHE: Dr. Reller?

12 DR. RELLER: Barth Reller. If one or more of
13 these markers is more sensitive than current assays, why is
14 it for diagnostic purposes only and not for screening of
15 potential blood donors?

16 MS. SMITH: This is--

17 DR. GUTMAN: Actually I can interject. The
18 company decides the claim, and the fact that there might be
19 corollary use for other claims would be interesting but not
20 relevant to our deliberation. If they decided to make a
21 decision to look at screening, it in fact wouldn't come to
22 this panel; it would go to the CBER panel.

23 I don't know if that helps or not, but that is
24 really not an issue. The issue of other uses of the product
25 outside of what is on the table is sort of not actually

1 germane.

2 DR. CHARACHE: Dr. Edelstein?

3 DR. EDELSTEIN: Paul Edelstein. I have a number
4 of questions. First, I don't understand this concept of why
5 you are excluding certain specimens. It's my understanding
6 that you are using as the gold standard the result of the
7 concurrently run Abbott assay. Is that correct?

8 MS. SMITH: To identify, to diagnose the sample,
9 to determine what infection, what disease state it should be
10 put in, yes.

11 DR. EDELSTEIN: So just to give an example, if the
12 Abbott hepatitis B surface antigen test showed that 95 out
13 of 100 specimens were positive, and your assay showed that
14 90 out of those 100 were positive, you would conclude that
15 the sensitivity of your assay was lower than that of the
16 Abbott assay?

17 MS. SMITH: Correct. If we were calculating
18 sensitivity.

19 DR. EDELSTEIN: So it's based exclusively on the
20 results of the comparative assay, and not on the clinical
21 situation or diagnosis. So why then do you exclude any
22 samples? Why don't you just take the Abbott result, run
23 once, as the definitive answer for the sample? Because
24 excluding samples tends to bias the pool. What you are
25 looking for is, you are looking for an enriched population

1 of samples that are guaranteed to be positive, my guess is,
2 high titer positive, which will have the effect of making
3 any assay that you look at look better than it might be if
4 it were being used to screen a less selected population.

5 MS. SMITH: I understand. Again, I can answer
6 that in two ways. First off, the issue of the low titer was
7 addressed with the panels, with the serial panels, the
8 serial draws from patients who developed the disease, so you
9 could watch all the markers go from negative to positive and
10 then back down, depending upon which marker it was. So we
11 did have a population where you were able to look at it go
12 from negative to low positive to high positive to low
13 positive to negative again.

14 The other--the reason we used the Abbott result
15 was, we were defining disease states serologically. We were
16 using serological diagnosis to define specific disease
17 states, and then once we got these samples identified, and
18 clearly this is--this sample is acute, this sample is
19 chronic, or this sample is convalescent, we then looked at
20 our assay's performance in that population to say, in a
21 serologically defined acute state, how did we perform?

22 DR. BORLA: In fact, the excluded sample was not
23 already excluded, because at the end I think that excluded
24 of all of the population was just 12 of them.

25 MS. SMITH: Yes.

1 DR. BORLA: But excluded for a disease state, and
2 maybe included for a different disease state, because the
3 serological pattern of marker indicated that this is better,
4 for example, an acute pattern instead of a chronic pattern.

5 DR. EDELSTEIN: So you are telling me that the
6 excluded samples weren't excluded?

7 DR. BORLA: Weren't excluded for the entire
8 population. Weren't included for this pattern, this disease
9 state, maybe reclassified in the following state, because
10 the marker pattern was more appropriate for this kind of
11 state.

12 MS. SMITH: Unfortunately, I apologize, we seem to
13 have--I am missing one last slide, and that last slide was
14 to show you what we ended up excluding. And we only ended
15 up--there were 11 chronic that we excluded because we had no
16 liver biopsy information on them, and we had no vendor
17 information to support our clinical trial information, and
18 so we felt we didn't have enough information on those
19 samples to identify that they were truly chronic.

20 So those went out, and I believe we had one or two
21 others where it just had no recognized pattern so you
22 couldn't say what disease state it was at all, and that was
23 the only one--thank you. There were two of them, one in the
24 chronic asymptomatic and one in the convalescent, where the
25 pattern by Abbott, no matter what information we had, we

1 just couldn't--we couldn't put them into those disease state
2 categories, so those two were excluded. So of all the
3 samples, we ended up only, with that algorithm, we only
4 excluded 13 of them.

5 DR. EDELSTEIN: So having only seen one of the
6 product inserts for the first time this morning, I don't
7 know what the product inserts actually claim for
8 indications, but does the product insert say hepatitis B
9 surface antigen for the diagnosis of chronic hepatitis, or
10 does it say for the diagnosis of hepatitis B?

11 MS. SMITH: No, it says for--it's used in
12 conjunction with other markers for the diagnosis and
13 monitoring of chronic and acute and convalescent hepatitis
14 B.

15 DR. EDELSTEIN: Oh, okay. I'm sort of missing
16 that, that concept. Now, since you used characterized
17 panels from outside vendors, the majority of which in your
18 line listings have no clinical information at all--they are
19 marked as "N/A"--I would like to know, how reliable is the
20 clinical information that you do have from the vendors? How
21 is that validated?

22 MS. SMITH: For the panels?

23 DR. EDELSTEIN: Yes. Not for the panels, for--I
24 mean, the only, as far as I understand, the only clinical
25 information you have is for the population of patients that

1 are labeled as chronic hepatitis.

2 MS. SMITH: Well, the--

3 DR. EDELSTEIN: And I would like to know the
4 reliability of that.

5 MS. SMITH: Well--

6 DR. EDELSTEIN: How did you independently validate
7 that?

8 MS. SMITH: --for the panels, most of them were
9 received from vendors with accompanying, what I would call
10 package inserts. They are sold by the vendors as a
11 hepatitis B seroconversion panel, so they do have a lot of
12 information in there, and they describe the patient and what
13 kind of treatment they were on and when the disease showed
14 up and where they were located from, so we have that
15 information from the vendor in a formalized insert.

16 The other ones, the chronic, we have the liver
17 biopsy and we have viral load information from the vendor
18 that was provided from the site where they purchased these--
19 where the vendor purchased these samples, and these are very
20 well known vendors, so they were--we accepted their data,
21 their supporting data.

22 DR. EDELSTEIN: Okay. And then I have a final
23 question on your analysis of discordant results, with which
24 I have a lot of problem.

25 MS. SMITH: We didn't use them.

1 DR. EDELSTEIN: Well, you shouldn't have, and--but
2 I was taken by the number of rearrangements of concordance
3 after testing. It struck me as being unusually--being
4 biased towards agreement. And I understand that analysis of
5 discordant specimens always enhances the sensitivity of the
6 assay, but do you have any explanation for that?

7 MS. SMITH: Could you clarify a little bit your
8 phrase "rearrangement of concordance"?

9 DR. EDELSTEIN: Well, not rearrangement but
10 reassignment as to true positive, false positive.

11 MS. SMITH: We used the Abbott results, as I said,
12 to determine this. We never used our results. They were
13 used to serologically diagnose the patients.

14 If we looked at the pattern by Abbott and all the
15 accompanying information and said, "Well, we originally were
16 told it was an acute sample, but now we look at it and it
17 fits more the pattern of chronic asymptomatic," then we
18 moved it over to the chronic asymptomatic group. Rather
19 than totally excluding it from the study because it didn't
20 match an acute result, we looked at the results and said
21 serologically that's a chronic asymptomatic patient, so we
22 moved that over. Rather than lose the sample completely, we
23 moved that over to the asymptomatic.

24 I get the feeling I'm not understanding your
25 question.

1 DR. EDELSTEIN: Yes. I'll have to--I may have to
2 come back once I find some of these data, but in fact you
3 retested both the Abbott as well as your result, and in many
4 cases there--the notations are retesting of the sample, of
5 our result, showed that it truly was concordant with the
6 Abbott. There are a lot of reassignments of those.

7 MS. SMITH: Oh, okay. No, there were not--they
8 were never and will be not used in the calculation of data.
9 We are, from what I understand, we are permitted to discuss
10 resolution of discordance but not recalculate sensitivity or
11 specificity.

12 DR. EDELSTEIN: That's not my concern. My concern
13 is, I'm wondering what the reproducibility of the assays is.

14 DR. REYNOLDS: I think, because I had a similar
15 question, you see these--

16 DR. CHARACHE: Dr. Reynolds, would you--

17 DR. REYNOLDS: Stan Reynolds, Pennsylvania
18 Department of Health, consumer representative.

19 DR. CHARACHE: Thank you.

20 DR. REYNOLDS: When I see these retests done, I'm
21 not really clear what is going on with the retests. In
22 other words, did--on the second test, did your result and
23 the Abbott result agree this time, or did they still
24 disagree and the specimen was reassigned and that changed?

25 MS. SMITH: No, they were never reassigned based

1 on concordance or discordance of us versus Abbott. There
2 were two reasons to do a repeat test. One was if we--we and
3 Abbott have established equivocal zones around the cut-off.
4 If the sample fell into that equivocal zone, it was retested
5 and the new result was used in place of the equivocal
6 result. That is as per the Abbott and our manufacturer's
7 package inserts.

8 The other time was, if it was discordant, we
9 retested it for our own information, to see whether or not--
10 were we always--were we repeatedly wrong? Was Abbott
11 repeatedly wrong? Was there a mixup with the operator?
12 Remember, they were doing 12 tests on each sample. Was
13 there a mixup with the sample?

14 We used the repeats to look at that, but we did
15 not use any of that in the actual calculation of sensitivity
16 and specificity. That was for information purposes only,
17 and to describe it, to give further information in the
18 package insert, but it was not used for calculations. We
19 did not retest or include or exclude samples based on
20 whether we were concordant with Abbott, and I need to
21 reemphasize that. All our inclusion/exclusion never had
22 anything to do with the DiaSorin result.

23 DR. CHARACHE: Perhaps in that same area of
24 reproducibility, in going over the different assays, they
25 did differ in their reproducibility, and the reproducibility

1 of one of them, the core antibody, was--the coefficient of
2 variation was 47 percent for one of them. And I wondered if
3 I am seeing that correctly, or that one appeared to have
4 much more wobble than the surface, for example, and I am
5 wondering if there are factors there that would explain
6 that.

7 MS. SMITH: When it was 47 percent, that was when
8 the OD was very, very low, and that's--

9 DR. CHARACHE: But it was the whole, you know, all
10 of them in that area had very high CVs, and actually that
11 particular analyte had high CVs.

12 DR. BORLA: In this case we have very low
13 absorbance. The kit, the assay is a qualitative, it is not
14 a quantitative, and then the very low absorbance are very
15 far from the cut-off point. In this case it is easy to have
16 a big CV because is when the samples change from, I don't
17 know. .020 to .030, is quite normal that the CV is very
18 high, but is in an area very far from the cut-off, and then
19 without any possibility to reclassification of the cut-off,
20 the samples.

21 The reproducibility status, we put some samples on
22 all of the curve, the possible curve, and then near the cut-
23 off and far the cut-off are more and more. The best CV is
24 in the middle, but this, the bad cut-off--the bad CV are
25 very far from the cut-off, particularly for total core.

1 DR. CHARACHE: Yes. I guess I'm wondering about
2 the data, in other words, where your limits of the assay--
3 where you--what CV would be required before you would say
4 you can't read at that level. And actually that was within
5 run CV was very high. But I'm just wondering how that
6 information was used to determine what you--how you would
7 recommend that the test be applied.

8 DR. BORLA: In fact in all the kit we put a gray
9 zone around the cut-off, just to take account of the
10 possibility variation of the absorbance in that zone, in
11 that area where the cut-off was established. And then for
12 core and all that there is plus or minus 10 percent of the
13 cut-off. When the sample, the user have a sample that is in
14 this area, have to retest to make sure was--

15 DR. CHARACHE: So you have information of how many
16 of the--you know, the percentages of patients of different
17 categories would have that issue with the different test
18 kits?

19 DR. BORLA: In the packages we furnish the data
20 for the reproducibility study that we did, and here the user
21 could see the different area of absorbance and then the
22 different area of positivity or negativity, which is the
23 variation expected for the reproducibility.

24 DR. CHARACHE: Other questions? Dr. Thrupp

25 DR. THRUPP: Just to pursue the same question a

1 little bit further and bring it back closer to our clinical
2 relevance, and to Dr. Sanders' question, too, as an example
3 on the reproducibility and how the data were handled and
4 what is the significance, the question about hemodialysis
5 patients is a good question. And the DiaSorin hep B surface
6 antigen was zero out of 65, whereas the Abbott was 4 out of
7 65.

8 Just as an example, do you have data on what the
9 replicate testing showed with those discrepancies? And,
10 secondly, is there any clinical data to indicate who was
11 correct? I mean, we are calling Abbott the gold, but maybe
12 Abbott wasn't gold. Maybe yours was closer to the clinical
13 situation which is--so I wondered, as an example, if anybody
14 recalls what happened? Because that is 6 percent, and
15 there's an awful lot of hemodialysis patients, so that's a
16 significant discrepancy.

17 MS. SMITH: I can't answer that off the top of my
18 head. We did not have vendor results, hepatitis results on
19 those samples, but we did--I can look up to see if we
20 repeated those samples and to see what the discordant
21 resolution looked like. But it's in my computer and I'd
22 have to--and I need to pull it out, so maybe during the
23 break or at some point I can pull it out and answer the
24 question.

25 DR. CHARACHE: Dr. Rodis?

1 DR. RODIS: John Rodis. My questions pertain to
2 the 324 pregnant women assayed. Were they subjected to the
3 --I guess it's the ETI-MAK-2, just the hepatitis B surface
4 antigen assay, or were they subjected to the entire panel?
5 And then in follow up to that, if they were only subject to
6 the hepatitis B surface antigen panel, how do we know, (a)
7 that they are not false positives, because improved
8 sensitivity could be at the expense of false positives, but
9 then could potentially lead to unnecessary treatment of
10 newborns.

11 MS. SMITH: We just so happen to have a slide
12 here. Did Peter leave? Peter, could you pull up the file
13 called "pregnant"?

14 We brought that data along just in case somebody
15 asked that question. In preparation for that, we tested 199
16 samples of pregnant women--pregnant samples, pregnant women
17 samples were tested at DiaSorin in Italy. They were only
18 tested for HBsAG. There were 125 samples that were tested
19 at the external sites, at the three external sites. That
20 one, we have all six markers for them.

21 So what we did was, we looked at--perfect, thank
22 you--we looked at those samples of the DiaSorin, of the 199
23 DiaSorin HBsAG, only once. A hundred and eighty-one of them
24 were negative. Eighteen of them were Abbott positive. All
25 18 were confirmed by neutralization, Abbott neutralization,

1 so those were true positive HBsAG. Of those 18, 16 were
2 DiaSorin positive and two were equivocal, and due to sample
3 volumes or reagent problems, we were unable to repeat those
4 two equivocals. So in that case it looked like we matched
5 or gave the appropriate or certainly the appropriate
6 response in 16 of them, and in 2 of them we gave enough of a
7 concern in the equivocal zone that would call for drawing
8 another sample a little later to see if the HBsAG had come
9 up.

10 For the external sites, we had 112 Abbott
11 negative, DiaSorin negative. There were 13 where Abbott--we
12 had 12 where Abbott was positive--I'm sorry--12 where we
13 were positive and Abbott was negative, one where Abbott was
14 positive and we were negative. The one where we were
15 negative and Abbott was positive, on repeat testing they
16 both came back as negative. That's that first one.

17 So based on--although we didn't have it--you know,
18 we didn't repeat the Abbott in duplicate, it did repeat as
19 negative. In that population we tend to think of them as
20 negative. We suspect that that might have been an Abbott
21 false positive, but we would not make that claim. We
22 suspect it.

23 The others where we were positive and Abbott was
24 negative, there were nine where all the other markers were
25 negative. Of those nine, when we repeated them, four

1 repeated DiaSorin negative, so those appear to be false
2 positives by our assay.

3 DR. RODIS: Five.

4 MS. SMITH: Oh. Well, one flipped. I wanted to
5 get to that one. There were four where, when we repeated,
6 DiaSorin repeated negative, Abbott repeated negative, we
7 were false positive. There were two where Abbott ended up
8 repeating as positive, so we suspect--we wouldn't conclude,
9 but we suspect--that that was an Abbott false negative
10 initially. There were two where they stayed the same. We
11 were positive, Abbott was negative. Repeat testing, they
12 stayed the same. There was one sample where we flipped,
13 where we ended up repeating as negative an Abbott ended up
14 repeating as positive. I don't know what to make of that
15 one. We had--I'm sorry. Go ahead.

16 DR. REYNOLDS: Stan Reynolds again, Pennsylvania
17 Department of Health. On the one where you flipped, how
18 close was the OD to the cut-off? Do you have that data?

19 MS. SMITH: Yes, in my computer. No, actually we
20 have it in the truck of my car. I brought all the binders
21 with me with all the data so that we could answer these
22 kinds of questions, but it was snowing so badly I left them
23 in the car. I can get that out and get that to you. If I
24 remember correctly, it wasn't like it was real close to the
25 cut-off.

1 DR. REYNOLDS: Okay

2 DR. THRUPP: Lauri Thrupp. Along just the same
3 question with regard to all of the ones that were
4 discrepant, when you reviewed them, did you get any feeling
5 that maybe the cut-off and the equivocal zone should have
6 been a little broader? Were they coming close? And that
7 they might have all been equivocal if the equivocal zone had
8 been broader?

9 MS. SMITH: I believe--I don't think it was an
10 issue of being right at the equivocal zone and so it flipped
11 when it repeated. I think they were samples that went from,
12 you know, what we would call screaming positive to dead
13 negative.

14 DR. CHARACHE: Dr. Seeff?

15 MS. SMITH: But, if I might, Dr. Borla was
16 reminding me, based on this data and looking at this, what
17 we have decided that we will recommend in our passage
18 insert, that is, if you are using our ETI-MAK-2 to screen
19 pregnant women for possible infection, for vaccination of
20 the infant, we will recommend that all positives be repeated
21 in duplicate to ensure that it truly is positive. And if
22 you still have a question about it, perhaps that you would
23 collect another sample in two weeks or four weeks and repeat
24 test.

25 DR. CHARACHE: Dr. Seeff?

1 DR. SEEFF: Just looking at your study populations
2 --sorry, Leonard Seeff--at the study populations, and you
3 have divided them of course into those with disease, either
4 present or past, and then a group that will probably
5 represent controls, I assume, such as hospitalized patients
6 or patients sent to a reference lab for HBV testing, in all
7 of this your diagnoses then are based on using the Abbott
8 data as the gold standard. As a matter of interest, were
9 you able to get your hands on patients who were diagnosed
10 with hepatitis that is non-A, non-B, non-C, non-G, non-
11 everything else, that you might have tested to see whether
12 you could have come up with possibly something that was B
13 positive by your test, that was negative by Abbott's?

14 MS. SMITH: Do you want to answer that?

15 I mean, the answer is no on that. No, we did not
16 test non-A, non-B, non-C, non-D.

17 DR. CHARACHE: Dr. Thrupp?

18 DR. THRUPP: Another general question concerning
19 the data base. Most of the clinical sets were frozen stock
20 panels, and I didn't run across a final answer to the
21 question of frozen versus fresh. Have you answered that
22 problem? Is there no problem with reproducibility from
23 frozen to fresh?

24 MS. SMITH: We had done studies earlier where we
25 did multiple freeze/thaws. We took fresh, froze them and

1 thawed them four times, and tested them all and showed no
2 difference in the performance.

3 DR. CHARACHE: I wonder if I could ask a parallel
4 question about anticoagulants?

5 MS. SMITH: Yes.

6 DR. CHARACHE: Where I looked at the studies of
7 anticoagulants, the heparin, DDTA, the various three that
8 you tested, it indicated that there was no change in the
9 clinical diagnosis, and I wondered, was there a change in
10 titer? And I'm wondering particularly about the frozen and
11 thawed heparin. Did they actually depress the number
12 without changing the diagnosis, and if so, is that possibly
13 because of the titer of the ones you were looking at? How
14 applicable is that across the board?

15 DR. BORLA: Again, for the plasma samples, the
16 different, the DDTA, heparin, we used different samples of
17 different reactivity, near the cut-off or far the cut-off.
18 It is true that in different area maybe the variability is
19 different. The center was not different classification. It
20 means that the sample that we put near the cut-off do not
21 change its classification if they have negative, or if it is
22 positive or not positive. Maybe for the high positive there
23 are some variation, but not so significant to change the
24 classification the same.

25 DR. CHARACHE: But if you had a sample that would

1 be perhaps equivocal or perhaps a positive, did the
2 anticoagulants depress your OD or increase it in any way?
3 Would it--what was the effect of the anticoagulant.

4 MS. SMITH: We didn't do dilutions to look at best
5 positive using the different plasmas. What we did was, we
6 made up a series of samples near the cut-off, some slightly
7 less than--you know, some negative, some positive, and some
8 very near the cut-off, to look at the ODs across the
9 different plasma types for the same sample, and we found no
10 statistically significant differences in the--or in some
11 cases we found some statistically significant differences in
12 the ODs across the different plasma types, but none of them
13 were significant from a clinical viewpoint. They didn't
14 flip a sample from negative to positive. They may have been
15 like flipping between high negative, low equivocal, or very
16 high equivocal, very low positive, but they never showed us
17 a clinically significant depression of the OD where you
18 would go from positive by one sample to negative by the
19 other.

20 DR. BORLA: And any kit have different--different
21 kit will be different.

22 MS. SMITH: But they all showed the same type of
23 performance characteristics. None flipped from a positive
24 to a negative.

25 DR. CHARACHE: And was there a difference between

1 the anticoagulants? So one could go from a positive to
2 equivocal, but not from a positive to a negative?

3 MS. SMITH: Correct. Correct.

4 DR. CHARACHE: Yes?

5 DR. NOLTE: Nolte. I may be simplifying things,
6 but I didn't hear anything about specificity. We heard a
7 lot about increased analytical sensitivity and discordant
8 resolution, but in terms of looking at the individual
9 markers and the false positive rate or specificity as
10 compared to Abbott or whatever marker you are using to find
11 truth. Are we going to talk about that later, or is that--

12 MS. SMITH: Well, we did--we did do some--we did
13 do cross-reactivity studies with other disease states and
14 showed that there was no cross-reactivity from other disease
15 states, such as hep C, hep D, HIV, the other infectious
16 diseases like EVV, toxo, CMV. So--

17 DR. BORLA: Rheumatoid factor.

18 MS. SMITH: Rheumatoid factor. ANA?

19 DR. BORLA: ANA.

20 MS. SMITH: ANA. So we did do those studies. We
21 didn't present them here, but we did do those. They are--
22 no, I don't believe you have them in your handouts.

23 DR. NOLTE: It's a little hard, from my
24 perspective, it's a little hard to buy into the enhanced
25 sensitivity argument without the sort of documenting data

1 that speaks to the specificity aspect of it.

2 MS. SMITH: Well, there are two specificities I
3 tend to think about, the ones where--cross-reactivity with
4 other disease states. The other is, in an apparently
5 healthy adult population, how many positives did we come up
6 with? And I believe--and that population is described in
7 your book there, and I believe we were equivalent to Abbott
8 in that one.

9 We calculated prevalence. That's where you're
10 going to find it. There's a table with prevalence, and we
11 looked at the prevalence of the marker in our assay and the
12 prevalence of the marker by Abbott, and that's where you'll
13 find that.

14 DR. NOLTE: Okay.

15 DR. CHARACHE: Dr. Sanders?

16 DR. SANDERS: Natalie Sanders. Just from a
17 practical standpoint, I just feel I need to comment for the
18 record that these tests are being used in conjunction with
19 clinical diagnosis, physical examination, and the patient's
20 history, so one of the six alone would not be used to make a
21 diagnosis of hepatitis or not a diagnosis of hepatitis. I
22 just felt I needed to say that for the record.

23 MS. SMITH: And I need to say thank you, because
24 that is the point of our presentation.

25 DR. CHARACHE: Dr. Specter?

1 DR. SPECTER: Steven Specter. On follow up on
2 that, that was really my most pertinent question, was that
3 since these are being marketed to be used in conjunction
4 with the other markers, when you look at the discordant
5 results--and there is way too much data for me to be able to
6 summarize it all--but when you look at the discordant
7 results with one marker, how often, when you look across the
8 panel, did you find a result where you couldn't make a
9 clinical decision based on all six markers because of
10 discordance?

11 MS. SMITH: In other words, looking at the panel?
12 Looking at the panel of results for that sample, would we
13 have concluded the same thing with our assay as we did for
14 the other? Gosh. I don't remember if we did that, how we
15 did that. Do you know?

16 Well, what they are reminding me is that the FDA
17 presentation does have a slide describing the hospitalized
18 patients and the patients that were sent for HBV testing,
19 and that we did look at in a recognized pattern, Abbott
20 recognized pattern, did we have a recognized pattern in
21 those populations? So maybe we can look at it and talk
22 about it at that slide.

23 DR. CHARACHE: Yes. I had a similar question,
24 which was the relatedness of the results, not only all six
25 but the correlations that you would expect, such as antibody

1 to hepatitis C and the core and HBc, and antibody to
2 hepatitis s, HBs, or did you find something present that you
3 would not have expected to be present, e where it didn't
4 belong and things like that? Is there data that look at
5 patients?

6 MS. SMITH: Well, I think one of the ways we
7 presented the data, and we struggled with many different
8 ways, was to look at, in an acute population, for example,
9 what did all of our markers look like in that acute? So we
10 looked at--we had HBsAG, anti-HBs core, and what you would
11 expect in that population. So, for instance, with acute you
12 would expect positive HBs, negative anti-HBs. You could
13 have positive core.

14 So what we did was, first we cleaned up the data
15 base by saying, okay, these are truly acute patients, based
16 on the Abbott result. Now, in that truly acute
17 serologically defined population, what were the percent
18 positives and negatives by our assay? And we had 100
19 percent positive with the HBs, 100 percent negative with the
20 anti-HBs. I think, and I wouldn't swear to it, please don't
21 keep me, I think we had very high positive rate in the core,
22 which one would expect except if you have very early
23 incubation, when you only have HBs positive, and we did have
24 one or two samples like that. And then the others were
25 where we had our anti-HBe or HBe positive or negative, so

1 the patterns appear to be appropriate for those disease
2 states.

3 DR. CHARACHE: Thank you. We're going to stop at
4 this time for a break, and it's in part so that those who
5 haven't turned in their lunch vouchers do so right away. We
6 do not want a grumpy panel. Ten minute break.

7 [Recess.]

8 DR. CHARACHE: We are going to continue. Our next
9 presentation was to be Dr. Miriam Alter. When last heard,
10 about an hour or so ago, she was circling over Washington,
11 but her plane apparently ran out of fuel and landed in
12 Richmond. So, lacking a hookup to the Richmond airport at
13 this time, we are going to continue, and we will hope to
14 come back to her presentation subsequently.

15 So the next presentation will be Dr. Kristen
16 Meier, who will discuss the mathematical and biostatistical
17 aspects of these studies.

18 DR. MEIER: Thank you. Actually this talk is
19 going to not be a typical statistical talk, in that I'm
20 actually not going to present any numbers or results.
21 Instead, I'm going to focus on statistical design issues for
22 evaluating diagnostic tests, and then the following
23 presentation by Tom Simms will get into the numbers.

24 What I'm going to talk about today, then, first is
25 I'll review some general design issues for evaluating a

1 diagnostic test. Then I'll discuss some specific aspects of
2 the DiaSorin study design, and finally I'll talk about
3 describing performance.

4 There are five general design issues to consider
5 when evaluating diagnostic tests, and they are summarized
6 here. The first is the representativeness of the study
7 population. Next is the mapping of test results to "truth"
8 data; the completeness of data reporting; the completeness
9 of data recording; and the use of controls. I'm going to
10 focus on the first three bullets, although all five are
11 important, and relate to potential biases that can arise in
12 estimates of a diagnostic test performance.

13 In general, the validity of performance estimates
14 obtained from a study are going to depend on the degree to
15 which potential biases in variability are avoided or
16 minimized. In reality, some of these sources of bias are
17 difficult or in some cases impossible to avoid, due to
18 ethical reasons or due to practical considerations. And the
19 judgment then is which design issues are most critical for
20 providing valid performance estimates.

21 Today we are here to talk about which design
22 issues are most critical for studies for looking at the
23 performance of these hepatitis B assays. The first general
24 design issue is the representativeness of the study
25 population. What are the points to consider?

1 Well, here I use "study population" in a very
2 broad sense, to include both the specimens and the testing
3 conditions. In general, you would like the specimens to
4 cover the entire disease spectrum, or disease severity is
5 another way to put it, and one way to accomplish this is to
6 look at a wide range of different patient subgroups and a
7 wide range of patient enrollment sites. We also want to
8 evaluate all specimen types for which a test is indicated,
9 or demonstrate that there is no difference.

10 For testing conditions, you would like them to
11 cover a full range of conditions, including different
12 testing sites, operators, instruments, materials and
13 reagents.

14 Looking at these points specifically for the
15 DiaSorin study, for the specimens they did look at quite a
16 wide range of patient subgroups, and listed in parentheses
17 there, starting pregnant women, hemophiliacs, first time
18 healthy blood donors, IV drug users, hemodialysis patients,
19 hospital patients, patients sent to the lab for HBV testing.
20 We already had seen some of these before.

21 As I believe was stated, this was not a
22 prospective study. Instead, this was a retrospective study
23 where almost all specimens came from multiple commercial
24 sources, and all those specimens were from frozen repository
25 sera. There were fresh specimens, although they were frozen

1 before testing, and there I wasn't aware that there were
2 plasma specimens tested.

3 They did look at multiple testing sites. They
4 looked at three or did testing at three different U.S.
5 sites, and also at the DiaSorin site in Italy.

6 The second general design issue is the mapping of
7 test results to "truth" data, and there are several points
8 to consider here. First, you need a very precise criteria
9 or algorithm for determining diagnostic "truth" for every
10 test result, and we have seen some of that already this
11 morning. The algorithm should be accepted as "truth" so
12 that we can actually characterize errors, potential errors
13 in the new test, versus potential errors in the "truth"
14 criteria. The same criteria should be used for categorizing
15 all specimens, and the classification should not depend on
16 the new test under investigation.

17 Again, specifically looking at these points for
18 the DiaSorin study, their criteria were based primarily on
19 the referenced licensed HBV assays and sometimes additional
20 criteria from the specimen source. Now, there were
21 different specimen sources, and it was not always clear to
22 us what some of the criteria that were used at these sources
23 for classifying specimens. From at least DiaSorin's
24 original presentation to FDA, FDA has used different
25 criteria for determining "truth" than DiaSorin has.

1 The last general design issue I'll discuss is the
2 completeness of data, data reporting. The points to
3 consider here relate both to the "truth" status results and
4 to the test results. The "truth" results should be
5 determined for all specimens, and include the tough, not so
6 clear-cut cases. There should not be, if you have "truth,"
7 there shouldn't be equivocal, and there should be a final
8 determination. Test results may be equivocal but should be
9 reported and not discarded in performance calculations.

10 Again, looking at these points as they relate to
11 the DiaSorin study, originally there were specimens where
12 the reference assays disagreed with information from the
13 commercial sources and were originally excluded. FDA had
14 asked that these specimens be put back in, and I think some
15 of the presentations will have these in, although there may
16 still be some specimens that we didn't have enough
17 information to classify. In general, though, the question
18 is, do banked specimens include these tough, not so clear-
19 cut cases?

20 The test results, initially equivocal results were
21 retested. However, it is possible that the second result
22 could still be equivocal. And, again, originally the repeat
23 equivocal results were excluded from calculations and we had
24 asked that they be put back in.

25 Based on the study design that was used, our

1 challenge is to determine what is the best way to describe
2 the test performance. Traditionally people have used
3 "sensitivity" and "specificity" to describe performance, but
4 these only make sense under very specific conditions, and
5 those are listed here.

6 First, the study population should be
7 representative of the assay target population. The criteria
8 that you are using for "truth" should be widely accepted as
9 "truth". And, finally, they really require that you have
10 just two complementary diagnostic categories per target
11 population, and that gets a little tricky here, as I will
12 show in the next slide. But, for instance, normally you
13 would like a disease/non-disease category for each target
14 population.

15 What I hope you will think about today, and in
16 fact even tomorrow's presentations, are "sensitivity" and
17 "specificity" appropriate descriptors of performance? That
18 is, are the study specimens representative of the assay
19 target population? Is the "truth" algorithm acceptable?

20 For the stated indications, what are the relevant
21 diagnostic categories? As I said, this is a more
22 complicated case than the simple disease/non-disease. We
23 have acute hepatitis B virus group; we have chronic; we have
24 convalescent; no HBV. There might be additional categories.

25 A separate question is, what are the relevant

1 target populations? That is, which groups actually require
2 separate performance characteristics, versus which are
3 important subgroups to include in a study?

4 I know I found it very confusing with the approach
5 by the sponsor of looking at various populations. There
6 didn't seem to be a distinction between diagnostic
7 categories versus important patient subgroups. For
8 instance, pregnant women, there are specific indications
9 listed for that that you would want separate performance
10 characteristics, but then we have other important patient
11 subgroups that are to be included, and those for example
12 would be symptomatics versus asymptomatics, treatment
13 levels, IV drug users, et cetera.

14 So it's a complicated thing, and we need to think
15 about what again are the diagnostic categories, and then
16 what are the relevant target populations, and determine how
17 to describe performance for those groups.

18 This concludes my presentation of the general
19 design issues. Next, Tom Simms is going to present much
20 more details of this study and results.

21 MR. SIMMS: My presentation is going to take a
22 little while to load on the computer. Perhaps if there may
23 be questions for Dr. Meier?

24 DR. CHARACHE: Any questions for Dr. Meier? Dr.
25 Seeff?

1 DR. SEEFF: Since there is a lag and we're waiting
2 for the show to begin again, I just want to make a comment,
3 and I know that this is meaningless in this particular
4 discussion because it really comes from other data, and
5 that's the classification. The way this is classified here
6 is acute hepatitis B infection; asymptomatic carrier;
7 chronic hepatitis B; chronic hepatitis B patients treated
8 with interferon; and convalescent HBV infections.

9 I must say I personally object to the word
10 "asymptomatic" carrier, because it means symptoms or lack of
11 symptoms, and people with chronic hepatitis B are also
12 asymptomatic in most instances, and I think that that term
13 should ultimately be struck, but we need to rethink this at
14 a later time. But this should really be chronic hepatitis B
15 carrier and chronic hepatitis B, or chronic carrier and
16 chronic--really, I mean, the term "asymptomatic" is probably
17 incorrect. I mean, that's a term that I think may have come
18 from the NIH. I think Jerry Hoofnagle might have used that
19 term originally. I'm going to have to convince him that we
20 need to change that.

21 That's just an aside, really has nothing to do
22 with this, but--

23 DR. CHARACHE: Thank you.

24 DR. GATES: David Gates. I was wondering, on the
25 issue of the sensitivity and specificity, if that could be

1 expanded a little bit? I'm trying to understand whether
2 we're talking about sensitivity and specificity as a
3 function of a disease state, or the presence or absence of
4 an analyte.

5 DR. MEIER: The sensitivity and specificity that I
6 was referring to are more clinical sensitivity/specificity
7 for a disease state. It would be more in support of the
8 diagnostic indication. There are multiple indications, as
9 you see, for the assay, and that was the indication I was
10 focusing on.

11 DR. GATES: Okay.

12 DR. MEIER: Does that answer your question?

13 DR. GATES: Yes. So there's some ambiguity
14 because we may be talking about--

15 DR. MEIER: There are analytical sensitivity,
16 analytical specificity, yes. It's unfortunate that they all
17 have the same name. But, yes, I'm referring to the more
18 diagnostic or clinical sensitivity and specificity.

19 DR. GATES: Oh, okay. Thanks.

20 DR. CHARACHE: In some--some groups will call
21 that, for the first one, analytical validity, and the second
22 one, clinical validity, and you obviously need both to use
23 it.

24 Mr. Simms?

25 MR. SIMMS: Good morning. My name is Tom Simms.

1 I'm lead reviewer for the DiaSorin PMAs. Also Dr. Kristen
2 Meier, who was our statistician, which I was very lucky to
3 have. And I put Dr. Ticehurst's name up also because,
4 although John wasn't directly assigned to the review, he did
5 put up with me and some of my stupid questions, and I
6 appreciate it. Next slide.

7 As you know, we are here today to take into
8 consideration six PMAs that are associated with hepatitis B
9 serology markers. These PMAs were originally submitted as a
10 singular, modular PMA, and some of the questions that were
11 asked previously from the panel about the analytical
12 sensitivity, reproducibility, were covered in the module
13 sections of this PMA. When the final clinical section was
14 submitted to the FDA, it did become a true PMA at that time
15 and was assigned a P number.

16 These have been electronic applications. We have
17 tried to work very closely with DiaSorin, and we believe we
18 have used interactive communication during the review
19 process, utilizing electronic mail, telephone communication,
20 and from a reviewer's perspective this has aided greatly in
21 the review process. Next slide, please.

22 And, as mentioned previously, the assays that were
23 submitted by DiaSorin have been modified from those they had
24 previously licensed or approved, and that multiple products
25 or multiple assays have the same--some of the assays have

1 the same indications for use. Next slide.

2 And hopefully not to upset DiaSorin, but I'm going
3 to use the generic terms for the assays during my
4 discussion, and it helps keep things clearer for me. And as
5 you know, we do have six assays that have been submitted.
6 One is the hepatitis B surface antigen; the anti-hepatitis B
7 surface; the IgM anti-core; the total anti-core; and the
8 hepatitis Be antigen; and the anti-hepatitis Be. Next
9 slide, please.

10 Primary indications for use that are being claimed
11 by DiaSorin, the first three spread across all of the
12 markers, and that is an aid in the diagnosis of acute and
13 chronic hepatitis B virus infection; the monitoring of acute
14 and chronic hepatitis B virus infection; and the monitoring
15 of hepatitis B virus therapy. The hepatitis surface antigen
16 has an indication for use unto itself, where that would be
17 prenatal testing; and the anti-HBs has an indication unto
18 itself for assessing past exposure to hepatitis B, and also
19 to determine immune status in vaccine recipients.

20 And, as has also been previously mentioned, the
21 studies to support DiaSorin's applications were performed on
22 commercially obtained archival material, and the assessment
23 of DiaSorin's assays' performance was based on the DiaSorin
24 results being compared to the serological evidence of
25 hepatitis B infection as determined by a reference method.

1 The manufacturer of the reference method has been mentioned,
2 but during my discussion I will just continue to refer to it
3 as a reference method. We didn't necessarily consider it
4 the gold standard; it's only a reference method.

5 And one of the issues that I need to make clear is
6 that in categorizing patients, we did try to take all the
7 serological markers into consideration. And with some of
8 the data analysis you are going to see, it's going to be a
9 head-on comparison; in other words, all the serological
10 markers essentially had to match for it to be complementary,
11 for DiaSorin to be complementary to the reference method.

12 Now, realize that this perhaps is not the case in
13 how the assays are used in the real world, but to rapidly
14 review a large amount of data and to look at essentially six
15 separate PMAs, this was probably the easiest way for us to
16 go initially, and that probably the best way to go would be
17 to categorize people into disease categories based on
18 serological markers where some of the markers would overlap.
19 But I want to make that perfectly clear up front, that a lot
20 of the data is a head-on comparison to the serological
21 markers. Okay? Next slide, please.

22 And I was hoping that Dr. Alter would be here. I
23 hope she's having a pleasant trip in Richmond. But she was,
24 or perhaps later in the day will be going over the classical
25 presentation of the hepatitis B markers during an acute and

1 a chronic infection, and I just sort of throw this up as a
2 reminder to everyone essentially what it does look like.
3 And, again, we did try to follow the classic textbook
4 presentation of the markers when we could. Next slide.

5 And, again, as already has been mentioned earlier,
6 as a question that was brought up by the panel, that all the
7 DiaSorin assays only test their specimens as singlets. The
8 surface antigen assay does not have a confirmatory step for
9 an initially reactive specimen; that if the result for that
10 specimen is above their equivocal zone, it's considered to
11 be reactive and is to be reported as such. If it's below
12 the equivocal result, it's non-reactive and reported as
13 such.

14 I believe also mentioned earlier that the
15 recommendation for equivocal assay results is that the user
16 reassay the specimen, the same specimen, and report out the
17 result from the reassay. Next slide, please.

18 I'll now get into the presentation of the data.
19 One other thing I should mention up front is, you are not
20 going to get an overview of all of the data that was
21 presented to us. It would take me way beyond the allotted
22 time, and Freddie would be flashing red lights and
23 everything else at me to get off the podium.

24 The way it is, it's probably going to take a
25 little time, and perhaps may be a little confusing. I hope

1 you'll bear with me. If there is any questions, I probably
2 prefer to be interrupted during the presentation and asked.
3 Next slide, please.

4 For the acute hepatitis B infection there were
5 essentially two data sets that were submitted to us. There
6 was nine serial panels of specimens from individuals who had
7 been diagnosed with acute hepatitis B infection, and again
8 earlier today you heard the diagnostic criteria for that,
9 and in reality it's more of a laboratory diagnosis than a
10 clinical diagnosis.

11 There were varying times of collection for each of
12 the specimens within the panel. The times of collection did
13 not match across the nine different panels. And the ages
14 range from--the ages of the individuals range from 28 to 47,
15 and the gender was one female and eight males.

16 The next group that we have was what was
17 classified as a clinically defined group. There were 37
18 individual specimens in this group, and the ages of the
19 individuals range from 21 to 44, with half the specimens
20 coming from Florida and then half from California.

21 DR. CHARACHE: Excuse me. Just one question. Do
22 we know if these patients, particularly the serially
23 monitored ones, were advanced HIV? In other words, would
24 they be expected to have normal antibody responses?

25 MR. SIMMS: One of the exclusion criteria DiaSorin

1 had was that there would be no evidence of HIV infection.

2 DR. CHARACHE: Great. Thank you.

3 MR. SIMMS: So we would conclude that these are
4 all normal individuals, that they could give an
5 immunological response.

6 DR. CHARACHE: Thank you.

7 DR. NOLTE: Are there other immunocompromising
8 states, as well, organ transplantation, chemo involvement or
9 that sort of thing? Is that part of the exclusion criteria,
10 that these are otherwise--

11 MR. SIMMS: No, the only exclusion criteria--I'm
12 sorry--the only exclusion criteria that they did have in the
13 PMA was the fact that the individuals have no evidence of
14 HIV infection, so that wouldn't necessarily exclude a data
15 set from an individual that would have an other
16 immunocompromised disease caused by--or representing
17 immunocompromization.

18 DR. CHARACHE: Those questions were asked by Dr.
19 Charache and Dr. Nolte.

20 DR. NOLTE: Thank you.

21 MR. SIMMS: Okay. For the serial specimens--and I
22 have tried, believe me, I have tried to make data
23 presentation simple, but we'll see how we go along here.

24 What you are seeing here is essentially the
25 comparison of the DiaSorin hepatitis B surface antigen and

1 the HBe antigen to the reference assays. As I stated, the
2 days of draw were not the same for each panel set, so what
3 we are seeing here is an average day per draw per point, and
4 so therefore the end number for each point is going to vary
5 a little bit out of the nine.

6 For example, the specimens right on the end here,
7 there are only two specimens in here, and so therefore the
8 anti--I'm sorry--the HBe antigen spiking by the reference
9 method beyond that last day is surely a fluke or a false
10 positive, I would think a false, personally think a false
11 positive result. But from this, you know, you can see that
12 the DiaSorin results, you know, closely match the results
13 from the reference assay.

14 And here we have the antibody presentation, that
15 again the DiaSorin assay is compared to the reference's
16 total core and the IgM core, and the issue being that they
17 all do rise at equivalent times during the disease state.
18 Next slide, please.

19 And here we have the rest of the antibody
20 presentation, the anti-HBe and the anti-HBs, and again there
21 is--DiaSorin follows the reference assay roughly closely.

22 This is getting into the individual specimens on
23 the HBV acutes. There were 37 specimens within this group,
24 and what we have done here is try to, you know, make that
25 first stab at categorizing the specimens into a disease

1 state. They are all acute, and we decided that perhaps with
2 early acute what we could say about this is that antigen
3 needed to be present, i.e., meaning that hepatitis B surface
4 and HBe are going to be--either/or are going to be there.
5 Then with the acute group we should have the appearance of
6 core, and then with our late acute we would have expected
7 the appearance of anti hepatitis Be.

8 And you can see that for the reference method
9 being in green and DiaSorin being in yellow, that there is
10 fairly close match in the acute. There is one specimen
11 discordant with the early acute, and with the acute phase
12 there is two separate groupings here according to the
13 serological markers that appear on the x axis.

14 And again, the late acute, we did have one
15 specimen that we didn't know how to categorize, and that was
16 a hepatitis B surface antigen positive, a total core
17 positive. It also contained anti-HBe and anti-HBs, and that
18 was by the DiaSorin assays. Next slide, please.

19 This next couple of slides I'm going to try to
20 show you where the discordant results fell for each of our
21 defined disease categories within the acute population; that
22 the one specimen that is missing here from the hepatitis B
23 surface antigen only positive group appears in what we would
24 have determined to be an acute group, where that there is
25 surface antigen positive but DiaSorin showed that that

1 either--that it had total core--total anti-core, or it was
2 an equivocal result for anti-core. Next slide, please.

3 Then with this slide, the two specimens that we
4 are missing from our acute group on the right still stay in
5 the acute group, and the difference being is that they are
6 IgM anti-core positive. Next slide.

7 Then for late acute, we are essentially missing
8 two specimens by DiaSorin. One of these specimens still
9 stays in our late acute group. The difference between it
10 and the other specimens is the fact that DiaSorin found that
11 to either be--was IgM anti-core, either positive or
12 equivocal. And also that one specimen that we couldn't
13 classify came out of the reference method's group here.
14 Next slide, please.

15 Next is the chronic hepatitis B virus infection
16 group. For these we had specimens from 78 individuals. We
17 did not have any laboratory results showing the presence of
18 hepatitis B surface antigen for greater than or equal to six
19 months. We did have histopathological evidence of chronic
20 liver disease on 49, but 29 of the individuals we did not
21 have any liver biopsy results. Next slide, please.

22 And what we tried to show on the graph here is
23 perhaps the difference between the group that we did have
24 histopathological evidence of chronic liver disease, and the
25 next slide will show the group that did not have any biopsy

1 result. We also established a marker pattern that we
2 considered to be equivalent or as a pattern representative
3 of chronic disease, whereas the hepatitis B surface antigen
4 would be positive, the anti-HBs would be negative, the total
5 anti-core should be positive, the IgM anti-core is negative,
6 and that for the hepatitis Be antigen and the anti-HBe, that
7 that could be positive or negative, with the preference on
8 perhaps positive for the HBe antigen. And you can see when
9 there is evidence or histopathological evidence of chronic
10 liver disease, the columns or the DiaSorin matches
11 relatively well with the reference assay. Next slide,
12 please.

13 Now this is our group where we did not have any
14 liver biopsy results. All of them were hepatitis B surface
15 antigen positive. There is perhaps a little more variation
16 in the anti-hepatitis B surface and the total anti-core than
17 in the first group, but where we really see the difference
18 is the presence of anti-HBe. And I apologize that when I
19 re-made this slide, I didn't have my markers correct on the
20 top. Next slide, please.

21 For the monitoring of therapy claims, we had sera
22 panels that were obtained from individuals that were
23 diagnosed with having chronic hepatitis B virus infection.
24 The treatment was listed as interferon, but we have no
25 information on the dosage of interferon given, when it was

1 given, or if there were any other treatments given along
2 with the interferon. And there were multiple draws on the
3 individuals up to approximately one year, and again, not
4 every specimen from each panel was drawn on the same day.
5 Next slide.

6 And again, just to let you know that the criteria
7 that DiaSorin used for exclusion, and this still keeps
8 coming up, is that there be no co-infection. It should read
9 no co-infection with HIV.

10 Their categories for--or their listing for a non-
11 responder was that the hepatitis B antigen and HBV DNA would
12 remain detectable. For a partial responder there would be a
13 decrease in HBV DNA, HBe antigen, and hepatitis B surface--
14 I'm sorry. I should say HBe antigen and HBV surface antigen
15 are transient, but their levels increase when a therapy is
16 stopped. For a sustained responder, the hepatitis Be
17 antigen would disappear for at least six months after the
18 therapy was stopped, and that the anti-HBe and anti-HBs
19 would become detectable. Next slide, please.

20 So with a bar graph, again if I could explain the
21 axes, is that for the days listed here as average day draws,
22 that it's really a range because we tried to group specimens
23 within a particular time group, and so the average would
24 come out to be 28. And rather than trying to do a dot plot
25 showing each individual specimen within that group, we

1 decided to take a percentage of reactivity within the group.

2 And so what we're seeing here is that for the
3 chronic non-responders we had six individuals, serial
4 specimens on six. We can see that the hepatitis B surface
5 antigen for both DiaSorin and the reference do stay reactive
6 across the time of draws. We do get a drop-off in a couple
7 of the markers, and complete--or a rise, sorry, not a drop-
8 off but a rise in a couple of the antibody markers, but they
9 tend to fall back off again.

10 And one of the points I would like to make, again,
11 is that all the DiaSorin assays are qualitative, but the
12 only result that's being reported out is they are reactive
13 or non-reactive. Next slide, please.

14 DR. SPECTER: Tom, before you go on, it wasn't
15 clear from that what the last column shown is in those two
16 temporary responses. On the end for the anti-HBe, it's not
17 clear if it's DiaSorin or the reference that's being shown,
18 actually, since there's only one of them.

19 MR. SIMMS: Oh, here?

20 DR. SPECTER: Yes.

21 MR. SIMMS: That is the DiaSorin assay.

22 DR. SPECTER: Okay. The other one was non-
23 reactive, then?

24 MR. SIMMS: Right. That was non-reactive, does
25 not appear in there. You're right, I should have changed--I

1 apologize, I should have changed my colors on those. Next
2 slide, please.

3 Okay. This is our group of partial responders.
4 We had three individuals within this group, and again up to
5 58 days antigen is present by both DiaSorin and the
6 reference assay. We can see that antigen does start
7 dropping off by both assays. They are not, you know,
8 exactly matched up with one another as far as numbers or
9 percentages, but they do drop off and essentially reappear
10 for 100 percent of the group at the 287-day point. But
11 again, with qualitative results, to me two out of the three
12 would look like probably non-responders. But, anyway, next
13 slide, please.

14 These are our responders. Again, we had three
15 individuals within the group, a fairly close match between
16 DiaSorin and the reference assay as far as the percentage of
17 reactivity goes. We do get full antibody production in
18 these people at, by both DiaSorin and the reference assay,
19 let's call it around day 176 to allow for the drop-off.
20 Next slide, please.

21 For the prenatal screening, we did have a total of
22 326 specimens that were submitted or that were obtained from
23 pregnant women. Seventy-five were from women at the
24 prenatal stage and 50 were from women at perinatal, and for
25 201 they were unclassified. In other words, it was unknown

1 what stage of pregnancy they were at. They were just
2 classified as pregnant. And the ages of the women ranged
3 from 12 to 43. Most of the specimens from the United States
4 were from Southeastern United States. There was also a
5 subset of specimens that were from Uganda.

6 And testing for this group was performed at three
7 U.S. sites and the applicant's site. DiaSorin performed the
8 testing on the specimens from Uganda. Three U.S. sites did
9 the U.S. population. Next slide.

10 So when we look at the whole group of pregnant
11 women specimens, which did number 327, we can see that there
12 was agreement on 16 of the positives by both the reference
13 and DiaSorin. DiaSorin called one of the reference assay
14 positives a false or a negative, and two of the specimens
15 were equivocal. Twelve of the reference negative specimens
16 were called positive by DiaSorin and there was agreement on
17 296. So if we look at positive agreement with this, we have
18 84.2 percent for DiaSorin [positive agreement with the
19 reference method. For negative agreement there is 96.1
20 percent for DiaSorin with the reference method. Next slide,
21 please.

22 DR. CHARACHE: For that slide, what was the
23 positive predictive value? If you got a positive by
24 DiaSorin, what was the likelihood that you had a positive?

25 MR. SIMMS: I didn't calculate that, because to me

1 the positive predictive values actually related to clinical
2 sensitivity.

3 DR. CHARACHE: Well, that's right, but I think if
4 that's your population that you're analyzing--perhaps Dr.
5 Meier?

6 DR. MEIER: Yes. That was the 16 over--

7 MR. SIMMS: Twenty-eight?

8 DR. MEIER: --28.

9 MR. SIMMS: False positive or--

10 DR. MEIER: False positive.

11 MR. SIMMS: Sorry. That was around 67 percent.

12 DR. MEIER: Sixteen over 28.

13 DR. CHARACHE: Yes.

14 DR. THRUPP: Lauri Thrupp. Were those--did those
15 12 happen to be from Uganda?

16 MR. SIMMS: That's what I'll try to show you in
17 the subsequent slides. They're very good.

18 DR. CHARACHE: Can you also tell us the
19 consistency of results between the three U.S. sites?

20 MR. SIMMS: I believe that will be shown in the
21 next slides also.

22 DR. CHARACHE: Thank you.

23 MR. SIMMS: If not, please raise the question
24 again.

25 So what we did was, we did break the populations

1 out to the geographic area of the specimens, where the
2 specimens came from, and for the U.S. population, which
3 numbered 275, we see that--and I will say that they are
4 false positives and false negatives at this time, for lack
5 of a better term--but we see there are 12 false positives,
6 and our one false negative appeared in that prenatal group
7 from the United States. And again, you know, to remind you
8 that all of this testing was done at three U.S. sites, and
9 the specimens appeared to be equally divided amongst the
10 sites.

11 Then for the specimens from Uganda, there were 52.
12 These specimens were assayed at DiaSorin, Italy. There were
13 10 positives which were agreed upon, but two of the
14 positives found by the reference assay, they were called
15 equivocal by DiaSorin, and there was agreement on all 40 of
16 the negatives. Next slide.

17 One of the issues that we were concerned about
18 here was the distribution of results. We wanted to
19 essentially assure that there was equal distribution of
20 results, you know, across the reactive range of the assay,
21 and that's what this plot is trying to represent or show.
22 The green bars are the U.S. specimens. Note that the Y axis
23 does not go up to the maximum value. I cut it short to try
24 to keep the lower bar visible. On our x axis, we calculated
25 a signal over cut-off for DiaSorin--these are only DiaSorin

1 results--but represented a signal over cut-off to try to
2 normalize the results.

3 And, you know, for our large negative population,
4 then our positives, and there is essentially a spread across
5 the active range, but one of the things that did catch our
6 eye was the--essentially what appears to be a skew to the
7 right with the Uganda results. And next slide, please.

8 Okay. It will be the slide after this that I will
9 go into that. That's okay. Stay with this one. For the
10 false positive results, we wanted to see where they did fall
11 just in case there may be a cut-off issue with the assay,
12 and here you can see that our one false negative result by
13 DiaSorin did fall in the range of essentially a good
14 negative; that the false positives were essentially along
15 the reactive range of the assay. And so we decided that
16 our--at least my conclusion was that there was not a cut-off
17 issue here. Next slide, please.

18 As I started mentioning before was the issue of,
19 did the Uganda specimens have higher values associated with
20 them than the U.S. specimens. This graph is a little
21 different than the other because the y axis is in a
22 percentage, and what we tried to do was normalize the two
23 populations to one another for their range of reactivity.

24 So what we're seeing here for the U.S. population
25 that would fall within a range of .3 and .5 signal over cut-

1 off, we are saying that 48 percent of that group--or, I'm
2 sorry, about 38 percent of that group falls within that
3 range. For this range of Uganda specimens, it appears that
4 about 9 percent of them fall in this 0.3 to 0.5 signal over
5 cut-off range. And there does appear to be a skew to the
6 right, higher values for the specimens from Uganda. Next
7 slide, please.

8 For the determination of immune status, DiaSorin
9 submitted to us results from 32 panels of individuals who
10 had been given either the Smith Kline Beecham or the Merck
11 vaccine for hepatitis B, and the patients were drawn six
12 times, once prior to inoculation, then at days 45, 59, 73,
13 87, and 113. Next slide.

14 DiaSorin's cut-off for the anti-HBs is lower than
15 the 10 milli international unit per mL which is the current
16 recommendation of the Immunization Practice Advisory
17 Committee, but DiaSorin does include a 10 milli
18 international unit calibrator in their assay which has been
19 calibrated to the WHO standard.

20 And when we first reviewed the data, it was a
21 little disconcerting that there was a detected response rate
22 of only 12.5 percent, but we did find out, as Ms. Smith
23 mentioned earlier this morning, that these individuals did
24 not receive a full series of vaccination. But for--and
25 again, since we did have a series, our interpretive criteria

1 for response was reactivity being detected on the last day
2 that we had that was above DiaSorin's 10 milli international
3 unit cut-off per their calibrator. We had--78.1 percent of
4 the individuals did not have a response at that time, and
5 there was an equivocal response on 9.4 percent of those
6 patients, individuals. Next slide, please.

7 DR. SEEFF: Can you tell us when these tests were
8 done? Was it after the first injection or second injection?

9 DR. CHARACHE: This is Dr. Seeff.

10 MR. SIMMS: One of the other things we didn't know
11 is that for zero day, we assume that was the date of
12 vaccination. That specimen was drawn prior to vaccination.
13 For the other vaccination points, we don't have the time
14 that they were given. So what I'm saying here is that we're
15 looking at approximately--we're looking at a 113, I believe
16 it was a 113 day end point, without a knowledge of when they
17 received the second or third vaccination.

18 DR. CHARACHE: Yes? Dr. Rodis?

19 DR. RODIS: The lack of that information, the
20 information you don't have, can we draw any conclusions from
21 this? In other words, what would we have expected a percent
22 detection rate to have been, considering the variables of
23 two shots only and the variability of the interval between
24 the last shot and when the tests--

25 MR. SIMMS: Personally, I don't know. I'll have

1 to ask Dr. Ticehurst. Perhaps he has that information off
2 the top of his head.

3 DR. THRUPP: Well, the related question more
4 directly--this is Lauri Thrupp--the related question would
5 be what was the same result using the reference method?

6 MR. SIMMS: Oh, okay. We couldn't use the results
7 from the reference method, because the reference method was
8 done but it was not calibrated to the 10 milli international
9 unit per mL cut-off. The original cut-off, the reference
10 method's original cut-off was used, so we couldn't go back
11 and reevaluate it, because the reference method does sell a
12 calibration kit that apparently needs to be run to obtain
13 the 10 milli international unit cut-off.

14 DR. CHARACHE: Dr. Charache. Are you then
15 suggesting that since these numbers would not parallel those
16 after three doses, and we really don't have any information
17 as to the timing of the samples, that we really can't assess
18 this very readily in terms of its use for post-immunization?

19 MR. SIMMS: I'm really not trying to suggest
20 anything. I'm really just presenting my evaluation of the
21 data set and essentially the numbers that I have drawn from.

22 DR. CHARACHE: Dr. Ticehurst?

23 DR. TICEHURST: I'll try to address Dr. Rodis'
24 question. I don't know the answer to your question. I'll
25 try to find it. I have a chapter here by Blaine Hollinger

1 that might address it.

2 But one of the reasons I haven't attempted to
3 address that question before is that the recommendations of
4 the Advisory Committee on Immunization Practices are that if
5 you are going to assess somebody for a vaccine response, you
6 do it after all three doses, several months afterwards. So
7 in a way it's not really--to me it's not really meaningful
8 to ask whether somebody has responded to one or two doses.
9 I'm not saying your question is not meaningful, but if you
10 are going to assess the value of an assay, the appropriate
11 specimens to look at would be those that are taken at a time
12 point consistent with the ACIP recommendations.

13 DR. CHARACHE: Dr. Reller?

14 DR. RELLER: Because of that, is it that we aren't
15 seeing the data, or that that information is simply not
16 available and we couldn't find it even if we wanted to see
17 it? That is, after the appropriate time after immunization
18 to assess response to HBV immunization in this patient
19 population, are those data available anyplace for this
20 product?

21 MR. SIMMS: The only answer I can make to that is,
22 that information has not been submitted to us for review.

23 DR. CHARACHE: Any other questions? Shall we
24 continue?

25 DR. NOLTE: This is Nolte. I have one more

1 question. I mean, clearly the assay can detect 10 milli
2 international units per mL, I mean in terms of the
3 analytical sensitivity. That's not an issue.

4 MR. SIMMS: That is not an issue. There were
5 analytical studies that were submitted previously to show
6 that, you know, the assay can or appears to be able to
7 detect 10 milli international units per mL.

8 DR. TICEHURST: I found a few data that address
9 your question. I've just been scanning through it. This is
10 from Blaine Hollinger of Baylor's chapter on hepatitis B
11 virus from the second edition of Field's Virology, 1991, and
12 in here he is summarizing data from really the classic
13 efficacy study that was done by Wolf Szmuness and published
14 in the New England Journal of Medicine back in 1990, '91.
15 I'm sorry, '80, '81. Pardon me. This was a trial on
16 homosexual men.

17 "Anti-HBs response was observed"--I'm quoting
18 here--"was observed in 31.4 percent of the subjects within
19 one month of the first injection. By two months, 77 percent
20 of the vaccinees had developed antibody, and this rate
21 increased to 87 percent by the third month. Fully 96 to 98
22 percent of the vaccinees had developed an anti-HBs response
23 by nine months, three months after the third injection."

24 One thing to keep in mind in that population is
25 that these people were at extremely high risk of becoming

1 infected, and so that that's a compounding factor, that some
2 of that antibody may have been the result of natural
3 exposure.

4 MR. SIMMS: Next slide, please.

5 DiaSorin did submit to us a group of specimens--
6 information on a group of specimens from what were
7 categorized as hospitalized patients. As you can see, these
8 were patients that had numerous diseases or conditions
9 associated with them. We are assuming that none of these
10 patients had hepatitis. Well, I'm sorry, I shouldn't say
11 that. We are assuming that the physician had no reason to
12 suspect that any of these patients had hepatitis. Next
13 slide, please.

14 And then for this group, and this is one of the
15 groups that again I would like to make it clear that we used
16 the serological markers, but there was a head-on comparison
17 between the marker set that was being presented with
18 DiaSorin. If the markers didn't match essentially exactly,
19 that was a miss by DiaSorin. We did take equivocals into
20 consideration, that if there was an equivocal result by
21 DiaSorin and it was reactive by the reference method, we
22 considered the equivocal to be reactive and categorized it
23 as such.

24 With that said, we had a negative--DiaSorin had a
25 negative agreement with the reference assay of 93.8 percent,

1 and there was also some positives within this group, and
2 there was positive agreement with the reference assay for
3 64.3 percent. Next slide, please.

4 And what I tried to do with this slide was perhaps
5 show some of the differences between DiaSorin and the
6 reference assay as far as marker patterns would go. This is
7 where the reference assays were nonreactive, all assays
8 nonreactive, and DiaSorin had a reactive result. We can see
9 that in six of these DiaSorin found or said that there was
10 the presence of anti-hepatitis B surface; that for eight of
11 the specimens there was total anti-core present; and again
12 there were a couple of equivocal in here, but we did count
13 them as positive; and that for five specimens there was
14 anti--I'm sorry--there was hepatitis B surface antigen
15 present when the reference assay said it was nonreactive.
16 Next slide, please.

17 Now, this is where the reference assay is reactive
18 for one marker or the other, but DiaSorin is saying that all
19 markers are absent. So the reference assay said there was
20 anti-hepatitis B surface in two specimens that DiaSorin said
21 were nonreactive; there was total anti-core in three; HBe
22 antigen in six; and surface antigen in one. Next slide,
23 please.

24 Then we had a group of patients that were also--or
25 specimens of individuals that were also hospitalized, but

1 where the physician had requested HBV testing be performed.
2 In other words, we would have to assume that the physician
3 had a suspicion of hepatitis in these individuals. And so
4 therefore there was 100 samples, there were approximately 54
5 females, 40 males, and the age range was from 5 to 88 years,
6 and came from Florida, Georgia, Pennsylvania, California,
7 and Utah.

8 And again, the same criteria was used by us in
9 evaluation as was used in the last data set. With this
10 group there was a negative percentage agreement by DiaSorin
11 with the reference of 44.9 percent; a positive agreement
12 with the reference of 86.4 percent. And this again is head-
13 on-head to the marker patterns. Next slide.

14 Then again, to try to show some of the differences
15 between the marker patterns, this is where the reference
16 assays have reported nonreactive but there is a reactive
17 specimen or analyte in here from the DiaSorin assays. In
18 six of the reference nonreactives, DiaSorin found the
19 presence of hepatitis B surface antigen. Two were surface
20 antigen and total anti-core. And we can continue going down
21 the line with the numbers that are present. Next slide,
22 please.

23 We did have--and then I decided since we did have
24 such a small group here of only really three discordants, to
25 look at those and see how discordant they really were.

1 Again, the small data set for the discordants allowed us
2 that luxury. We can see for this first group here that the
3 discordant issue is DiaSorin saying that there is anti-
4 hepatitis B or anti-HBs present, where the reference assay
5 says there is surface antigen present. Both are telling us
6 that there is core present. I believe this does give you a
7 different picture on the patient, whichever way--whose assay
8 you look at.

9 For the next group, our only difference, both are
10 telling us that hepatitis B surface antigen is present.
11 DiaSorin is saying that the e antigen is present where the
12 reference says it's absent, so that's our discordant. But
13 would that make a difference in the laboratory diagnosis of
14 that patient? I personally don't think so.

15 Then we do have one specimen where the only
16 discordant issue is for the IgM core. DiaSorin said that
17 there was IgM core present and the reference assay said
18 there was not, but the other markers are the same. And it
19 would perhaps give us the same picture by using either
20 assay's method--or results, I'm sorry.

21 That concludes my presentation. If there is any
22 further questions, I would be happy to try to answer them
23 for you.

24 DR. CHARACHE: Dr. Reller?

25 DR. RELLER: Barth Reller. Could we go back two

1 slides?

2 MR. SIMMS: Do you have--

3 DR. RELLER: Forty-seven. Forty-seven. When I
4 look at this slide, these were among the 100 patients whose
5 physician sent a specimen to a laboratory for hepatitis B
6 virus testing.

7 MR. SIMMS: That's correct. That's the
8 information that was in the application.

9 DR. RELLER: For some reason, presumably suspicion
10 of infection or assessing whether or not the patients were
11 immune, or for some plausible reason. Is that correct?

12 MR. SIMMS: Correct.

13 DR. RELLER: And a cleared product, currently in
14 use, was nonreactive.

15 MR. SIMMS: That's correct.

16 DR. RELLER: For all of these markers.

17 MR. SIMMS: That's correct.

18 DR. RELLER: So that if I had sent that specimen,
19 I would conclude that the patient was not--had no evidence
20 of chronic carriage or had no evidence of acute infection or
21 had no evidence of immunity. I mean, they were negative.

22 So far, so good?

23 MR. SIMMS: I trust you completely.

24 DR. RELLER: And if this product were being used,
25 that in 13 instances, I don't know how many of the 13 were

1 equivocal or positive, but if I had immunized my patient,
2 some proportion of that 13 I might have reasonably
3 concluded, if they had got the full immunization series and
4 it was somewhere between six to nine months after the
5 initiation of the series, that those patients were immune to
6 hepatitis B.

7 DR. SPECTER: No, five.

8 DR. RELLER: The bottom one only. Well, what
9 about the one just above it?

10 MR. SIMMS: That--

11 DR. RELLER: Well, okay, let's skip the
12 immunization. They either had evidence of immunity or that
13 they had responded to immunization.

14 MR. SIMMS: That would be the five. I would
15 believe that would be the 5 and the 13.

16 DR. RELLER: I mean, I may have the history--

17 DR. SPECTER: Right.

18 DR. RELLER: But basically somewhere between 5 to
19 18 patients were not susceptible to this virus.

20 MR. SIMMS: And in accordance to the DiaSorin
21 assay markers, that's correct. I wouldn't--

22 DR. RELLER: No, I'm just saying that--I mean,
23 we've got 100 patients, and if I were using this test to
24 make some judgment, because I mean there's a panoply of
25 testing there and, you know, it's my judgment as to whether

1 I assess my patient, but if I were to do that, in somewhere
2 between 5 to 18 of them I would have made, based on whether
3 I know what the immunization history was, the bottom line
4 conclusion is that I would say that those patients were not
5 susceptible to infection with hepatitis B. I mean, that--or
6 that would be a plausible conclusion. And these were
7 patients who presumably the physician that sent it, since
8 presumably only physicians can order these tests, would have
9 been asking a question, and I would have on a substantial
10 proportion of them come to a conclusion that was different
11 from the reference method.

12 MR. SIMMS: Right.

13 DR. CHARACHE: Going on with the same approach, we
14 would have thought that at least eight patients were
15 infectious because they had hepatitis B surface antigen
16 present, whereas--

17 MR. SIMMS: I believe the number is six. If we're
18 still on this slide, it would be six.

19 DR. CHARACHE: Six? It would be eight.

20 MR. SIMMS: Oh, I'm sorry. I'm sorry. You're
21 correct.

22 DR. CHARACHE: So it would be 8 percent of these
23 patients were infectious, whereas the reference method would
24 have said that none of them were.

25 MR. SIMMS: According to the data that was given

1 to us for review, yes.

2 DR. CHARACHE: Dr. Seeff?

3 DR. SEEFF: There are six patients here who are
4 surface antigen positive and anti-core negative, and I don't
5 know, perhaps John or you could tell us, or perhaps Miriam
6 can tell us how often you have surface antigen positivity in
7 the absence of anti-core, unless you are very early on in
8 the early incubation period before they develop it. And of
9 course much of this could be answered if we had follow up
10 samples to see what has happened to these people
11 subsequently, or it would give us a lot more information
12 about the validity of this thing. But I wonder what
13 proportion of people who are surface antigen positive, are
14 anti-core negative?

15 MR. SIMMS: Personally I think that's the luck of
16 the draw, that you would probably have someone that's
17 asymptomatic or without symptoms to begin with, and it would
18 be the luck of the draw.

19 Do you want to comment, John?

20 DR. TICEHURST: Yes. Once again I don't know the
21 answer to a panel member's question, but I think in making
22 educated guesses, Dr. Seeff, I think you sort of answered
23 your own question. Given a sample set of this size, to find
24 sort of true results, specimens with an HBSAG-only
25 reactivity that was an indication of a very early infection,

1 nonreactive, truly nonreactive for HBeAG and the anti-core
2 antibodies, you would expect that to be a very low
3 proportion, and I think six out of whatever the end value--
4 the end is not 43, it's some number larger than that.

5 MR. SIMMS: It's 100.

6 DR. TICEHURST: Okay. That's still, I think, a
7 very high proportion. And again, if you consider the
8 selection criteria here, presumably some portion of these,
9 as Dr. Reller went through, there were probably a number of
10 different reasons the physician was asking for hepatitis B
11 virus testing, but most of those where it would be related
12 to a diagnosis of an infectious state would have been based
13 on, I would have thought, based on symptoms or physical
14 findings.

15 DR. CHARACHE: If we can just take a moment, I
16 understand that Dr. Alter has completed her tour of Richmond
17 and perhaps could address this particular question.

18 DR. ALTER: Thank you, and I apologize for being
19 late, or Delta does, anyway.

20 In addressing this issue, Dr. Seeff is correct in
21 that early in the incubation period HBsAG appears, and
22 without other evidence, other serologic markers, and we
23 often see this happen when we screen chronic hemodialysis
24 patients on a monthly basis to monitor transmission within
25 the hemodialysis unit. But it's about the only setting in

1 which we are able to detect the early incubation period,
2 because of the frequency with which we screen.

3 In other studies that we have done of both high
4 and low risk individuals, we I would say virtually never
5 detect HBSAG alone that is indicative of true infection, and
6 that in the instance--although we often do have HBSAG
7 positivity in the absence of other markers, when we
8 neutralize the HBSAG or--you know, we find that it doesn't
9 neutralize and therefore is presumably a false positive, and
10 on follow up testing of these individuals they do not
11 seroconvert.

12 DR. CHARACHE: Thank you. We will come back to
13 this after lunch when Dr. Alter speaks.

14 Let me ask if there is any public comment at this
15 time.

16 [No response.]

17 DR. CHARACHE: Okay. I think at this time we will
18 break for lunch. We will reconvene, let's say at 1:45.

19 [Whereupon, at 1:00 p.m., the panel adjourned, to
20 reconvene at 1:45 p.m. the same day.]

AFTERNOON SESSION

[1:55 p.m.]

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2
3 DR. CHARACHE: We are going to reconvene at this
4 time. We are going to continue with hearing Dr. Miriam
5 Alter's discussion and presentation, and will follow that
6 without a break for the open committee discussion of the FDA
7 questions.

8 Dr. Alter?

9 DR. ALTER: Thank you again. I was asked to
10 review today or give a brief review today of the serologic
11 testing for HBV infection from the CDC perspective, so what
12 I've chosen to do is review how we use the different
13 serologic tests that are available, and under what
14 circumstances. I thought it would be useful to give a very
15 brief review of the features of HBV infection, both
16 clinically as well as epidemiologically, so that we all
17 understand where these tests are most likely to be used and
18 how they might be affected by the individual they are being
19 used in.

20 The incubation period for acute HBV infection
21 averages about 8 to 12 weeks, with a range of 6 weeks to
22 close to 6 months. Clinical expression of acute illness is
23 indirectly related to age. Children under five years of age
24 are unlikely to have clinical expression of illness, whereas
25 older children and adults may express symptoms about 30 to