

1 50 percent of the time.

2 Fortunately, the case fatality rate is relatively
3 low, about .5 to 1 percent. Chronic infection, however,
4 develops in 30 to 90 percent of young children, and in fact
5 in infants born to infected women, chronic infection
6 develops in--transmission occurs 90 percent of the time and
7 chronic infection develops in 90 percent of those infants.
8 And chronic infection develops in 2 to 10 percent of older
9 children and adults.

10 Among individuals chronically infected, about a
11 third may be what we call healthy carriers, in that they
12 have no evidence of liver disease, and about two-thirds have
13 chronic hepatitis. Premature mortality from chronic liver
14 disease due to HBV infection can occur at as high as 25
15 percent of the time.

16 In the United States the burden of HBV infection
17 is actually considerable. During the last half of the '80s,
18 we estimate there were over 400,000 new infections per year.
19 Fortunately, this has declined dramatically to about 180,000
20 in the last year for which data are available. About 5
21 percent of the population in the United States has been
22 infected at some point in their life, and about 1.25 million
23 are chronically infected. HBV accounts for 10 to 15 percent
24 of chronic liver disease in the U.S., and is related to
25 5,000 deaths per year from chronic liver disease.

1 HBV is transmitted by--basically by sex and drugs,
2 by direct percutaneous exposure to blood, or as well as
3 through mucosal exposure to blood and body fluids that might
4 contain blood. High risk sexual activity accounts for most
5 cases of hepatitis, of acute hepatitis B currently in the
6 United States, with 45 percent due to high risk activity
7 between men and women and 15 percent among men who have sex
8 with men. An additional 21 percent are injecting drug
9 users.

10 Other groups at risk, who represent a small
11 proportion of cases, are household contact with individuals
12 who are chronically infected; health care workers with
13 occupational exposure to blood; and dialysis patients. Next
14 slide.

15 So why do we test? We test primarily to make a
16 clinical diagnosis in an individual with either acute or
17 chronic disease, and we test to screen, to detect
18 individuals with asymptomatic infection, to determine
19 whether or not an individual is susceptible to infection,
20 and to determine response to vaccination.

21 Serologic tests for HBV infection, you are all
22 aware of what they are so I will just so on to the next
23 slide. For diagnosis, as you know there are three antigen
24 antibody systems, and serologic tests are available for
25 actually all but one, and that is hepatitis B core antigen,

1 because it is not expressed in sera. But HBsAG develops
2 about 30 to 60 days after exposure, as shown in this slide.
3 In an individual who recovers from HB infection, HBsAG will
4 disappear, usually over a two to three-month period.

5 Anti-core develops in all HBV infections, and
6 indicates previous or ongoing infection with HBV, and with
7 recovery obviously will eventually represent previous
8 infection. Anti-core appears at the onset of symptoms or
9 liver test abnormalities, when they exist, in acute HBV
10 infection, rapidly rises to high levels and persists for
11 life.

12 Acute or recently acquired infection can be
13 distinguished by the presence of IgM anti-core, a very
14 critical marker in the series of markers for HBV infection
15 because it does allow a one-time test to distinguish an
16 HBsAG positive individual as to whether or not they have
17 been recently infected or they are chronically infected.

18 And it's also important that IgM anti-core have a
19 definite life, in other words, a limited life, so to speak,
20 of detection. And currently IgM anti-core, in addition to
21 being detected at the onset of acute disease, persists for
22 about six months, and being able to count on that reliably
23 occurring is very important both for clinical purposes as
24 well as research purposes. Although I will say there are
25 exceptions to every rule, and there are people with chronic

1 hepatitis B in whom IgM anti-core is detectable, because
2 nothing is 100 percent.

3 In persons who recover from HBV infection, HBsAG
4 is eliminated from the blood, usually in two to three
5 months, and anti-HBs develops during convalescence. And
6 there is usually a window period, which you can see on this
7 slide but I can't point to, between the hot pink line and
8 the light pink line, where the only marker--markers--
9 actually detectable are total anti-core and IgM anti-core.

10 Now, in individuals who progress to chronic HBV
11 infection, HBsAG remains detectable, as does total anti-
12 core. Obviously, IgM becomes undetectable by six months,
13 and anti-HBs is usually not detectable as well.

14 Now, let me tell you that every combination
15 possible can occur in individuals who are tested. And
16 having been the recipient of these phone calls for 20 years,
17 I can tell you that every--no matter how good the test is,
18 you would be surprised at the constellation of markers that
19 are detected in individuals, and most of the time you can
20 interpret it but you have to--something has got to be a
21 false positive, I mean. So it's important to be able to
22 distinguish these individual markers. Next slide.

23 Now, these markers can occur biologically, I would
24 say, either alone or in combination. HBsAG occurs alone
25 only in the early incubation period of hepatitis B, and we

1 rarely--and this is rarely observed because by the time most
2 individuals have onset of acute illness, they have anti-core
3 detectable as well. Acute infection is characterized, as I
4 mentioned, by HBsAG and anti-core, with IgM anti-core being
5 the predominant class of antibody.

6 Resolving infection with HBV, an individual will
7 have anti-core alone but will be IgM positive, indicating
8 hopefully that the individual's HBsAG is declining and anti-
9 HBs has not yet had a chance to develop. An individual who
10 has recovered and is immune to hepatitis B will have both
11 total anti-core, will be IgM negative, and have anti-HBs.

12 An individual with chronic infection will have
13 HBsAG and total anti-core but be IgM anti-core negative.
14 And occasionally you will see someone with a little bit of
15 anti-HBs at least detectable on the test, and we usually
16 assume that that's just, you know, that's just a false
17 positive.

18 Remote infection, occasionally it can also be
19 characterized by anti-core alone, with the IgM class being
20 negative, and this is a tough one. I mean this has been a
21 difficult marker to interpret in a variety of populations.
22 When it isn't a false positive, we assume that it means that
23 anti-HBs levels have waned below detection, or HBsAG is
24 circulating at very low levels not detectable by current
25 commercial assays.

1 And given how sensitive the assays are, this
2 virtually makes the patient non-infectious except when a
3 large dose is involved, such as a blood transfusion.
4 However, it's very--there is no real way to determine in
5 most circumstances what the infection status is of a
6 particular individual, and in many instances or in some
7 studies they have vaccinated these individuals, and many of
8 them have had a primary response to the vaccine, indicating
9 that in fact they did not have a previous infection.

10 And, finally, anti-HBs alone is usually a marker
11 of successful immunization with vaccination, but it also can
12 occur or it also appears to occur naturally.

13 When one of these markers appears alone, there is
14 also the chance of it being a false positive. When you're
15 doing the entire panel and you have a variety of markers, in
16 a way one confirms another. If you have HBSAG and anti-
17 core, it's unlikely you're going to get both of them. Both
18 of them are going to be false positives. But in many
19 settings one will occur all by itself, or they only use one
20 test, and that brings us to the screening setting, where
21 very often screening is performed using only one serologic
22 marker.

23 Now, the objectives of screening are to identify
24 chronically infected individuals in order to prevent
25 transmission to others, so we screen all pregnant women in

1 order to identify those for whom their infants require
2 prophylaxis immediately following birth, and I will tell you
3 that over 90 percent of the pregnant women in the United
4 States are screened prenatally.

5 And we also screen to identify these chronically
6 infected persons for medical management, so that we can
7 evaluate them for the development of more severe disease or
8 for possible therapy. We screen people either pre- or post-
9 vaccination. We screen health care workers to evaluate them
10 after an exposure, and of course we use these markers to do
11 epidemiologic studies. Next slide, please.

12 Now, the test performance, no matter how good the
13 test, will vary depending on the setting, and we usually
14 refer to, or one of the most important markers of this is
15 the positive predictive value. The probability that a
16 person with a positive test is a true positive varies
17 depending on the prevalence of infection in the population
18 being screened. This doesn't--this is true no matter what
19 test you are looking at. False positives occur even with
20 the best tests because nothing is perfect. Next slide,
21 please.

22 So I want to give you an example of how this
23 works, and if we assume that the currently available HBsAG
24 tests have a sensitivity of 99.9 percent and a specificity
25 of more than 99 percent--and we have never really been able

1 to determine exactly what that is, I haven't, so that's why
2 I don't know specifically, but it's close enough--and if we
3 have a population in whom the rate of chronic infection is
4 relatively high, and let's assume for the purposes of this
5 example we're talking about pregnant women.

6 So in a population of pregnant women who are of
7 Asian background and have emigrated to the United States,
8 the prevalence of chronic HBV infection is going to be about
9 10 percent, which means that out of every 1,000, 100 are
10 actually infected with HBV. And so we want to know, of all
11 the positives that the test identifies, how many of those
12 are true positives, and you can see the test performs
13 beautifully. It identifies, with that high a sensitivity,
14 every single one of the true positives, but it also--and it
15 identifies one false positive, and so the predictive value
16 of the test is 99 percent. It's wonderful.

17 But when we go to a population of, let's say,
18 Caucasian women who are being screened, we find the
19 prevalence there, the true prevalence is only about .5
20 percent, so out of every 1,000 pregnant women, only 5 are
21 really chronically infected with HBV. The test again
22 performs quite well, in that it identifies every single one
23 of those positives, and it only identifies one false
24 positive. But because the prevalence is so low, the
25 predictive--positive predictive value of the test is only 83

1 percent. That means about 20 percent of the HBsAG positives
2 identified in this low prevalence population are false
3 positives. Go ahead, next slide.

4 The same occurs with anti-core. Oh, let me just--
5 I'm sorry, let me back up a minute. When we're talking
6 about HBsAG, one of the ways that we can deal with this
7 false positivity is by neutralizing HBsAG, so that when you
8 perform the assay and it does come out and it is repeatedly
9 reactive or positive, you then neutralize it in order to
10 determine whether or not it represents a true positive, and
11 that's how we are able to use this test in screening
12 settings. Sorry.

13 Going on to anti-core, we have a little more
14 problem because it's an antibody and we can't neutralize it,
15 and so it's very difficult to determine whether or not it's
16 a true positive. And again, if you look at two different
17 populations of prevalence, one being about 20 percent--let's
18 say men who have sex with men have a--young men who have sex
19 with men have a prevalence of 20 percent. So out of every
20 1,000 men who have sex with men, 200 would have evidence of
21 infection, and the test identifies 198 of them, which is
22 very good, but it also identifies 8 who are not infected or
23 8 false positives, but still the positive predictive value
24 is 96 percent.

25 Now, in the general population where the

1 prevalence is about 5 percent, out of every 1,000 we would
2 have 50 individuals who are truly infected, and again the
3 test performs quite well. It identifies 49 of those 50, but
4 it also identifies 10 false positives, and so again the
5 positive predictive value is at 83 percent. And so 20
6 percent of those in a low prevalence population of anti-core
7 alone are potentially false positives. This is a problem,
8 particularly when using only a single test for screening,
9 which is what we recommend in many circumstances because
10 it's the most cost-effective.

11 And finally we come to anti-HBs, which has its own
12 issues. It also actually has low level false positivity.
13 When it's found in combination with anti-core, we rarely
14 question it, and it indicates recovery from past infection
15 with immunity. But when it's found alone, it can represent
16 an immune response to vaccine; possibly transferred antibody
17 from HB Ig, although we don't usually test for that; or
18 something that has been described as a natural immunization-
19 line effect.

20 And in studies of individuals pre- and post-
21 vaccination, it was determined that in fact, based on the
22 test being used to measure anti-HBs, a standard was set of
23 10 milli international units per mL that indicated
24 protective immunity following vaccination, even though the
25 signal to cut-off ratio was actually lower for positivity.

1 And because the sensitivities of these test kits changed
2 over time, in 1993 the CBER of FDA and CDC recommended that
3 a 10 milli international unit per mL standard reagent
4 referenced to the WHO anti-HBs standard be included in all
5 anti-HBs test kits so that protective immunity could be
6 established.

7 And I think you have to remember that most--the
8 lab does not know who is being tested. They don't know what
9 individual they are performing the test on. Therefore, the
10 test has to perform regardless of the individual in whom the
11 test is being--the sample has been collected from.

12 And, just very briefly, e antigen and anti-HBe are
13 markers of viral replication or lack thereof, but we
14 consider all HBsAG positive persons infectious regardless of
15 their e antigen or anti-HBe status, mainly because they can
16 transmit under certain circumstances. These two markers are
17 most useful for management of patients receiving antiviral
18 therapy, and we do not consider them necessary for routine
19 diagnosis or screening.

20 In conclusion, the variety of serologic tests for
21 HBV infection can be used for infection can be used alone or
22 in combination with each other. When used in combination,
23 it's usually easier to interpret them. When used alone,
24 there are a lot of difficulties.

25 There are many different purposes for which these

1 tests are used, and the performance of these tests varies
2 with the population being tested. It's important from our
3 perspective that the configuration of the test kits ensure
4 accurate results under all circumstances and when testing
5 all populations.

6 Thank you.

7 DR. CHARACHE: Questions for Dr. Alter?

8 DR. SPECTER: Steven Specter. Do you believe,
9 since--well, my experience is that there are few serologic
10 markers as confusing to physicians as the panel of hepatitis
11 B markers.

12 Do you believe that, if there are reagents out
13 there, that there should be recommendations for use? You
14 clearly have distinctive opinions, from what you showed us,
15 so do you feel that such markers should be just put out
16 there and anybody use any way they want, or should there be
17 recommendations to go along with how the markers should be
18 used in the test kits?

19 DR. ALTER: You mean as to which tests you should
20 use for particular circumstances?

21 DR. SPECTER: Exactly.

22 DR. ALTER: Well, I think that in the clinical
23 setting where you are managing patients with disease, I
24 think it's very difficult to make such recommendations,
25 because physicians want to be able to order, you know,

1 their--the tests that they think are appropriate.

2 We do make recommendations in terms--in the
3 screening settings for which tests are most appropriate and
4 how they should be used, so in those instances we have done
5 that. But I think for--in the clinical setting that's much
6 more difficult.

7 What's important is that the physicians know how
8 to interpret what they get. And usually what happens is
9 that the laboratories decide on a panel. They decide what
10 constellation of tests they're going to offer. And so the
11 physician checks off "hepatitis panel" and they get a
12 variety of tests, some of which they don't need.

13 Well, to make--to do whatever it is that--now, I'm
14 not saying there's anything wrong with that, but what
15 happens is sort like the more variables you put into your
16 data, the more likely you're going to get something that's
17 significant. And what happens is, the more--I have found
18 the more tests you do, then you get some you cannot
19 interpret. And I don't really know, but I don't think--it's
20 difficult. I don't know that there is an effective way to
21 get that message out in a clinical setting.

22 One of the clear requirements is that you provide
23 the information required to interpret the test. So if the
24 laboratory result format, if this so-called post-analytical
25 component of the test CDC requires would say that if you

1 have a certain test positive, it may suggest chronic active
2 disease or whatever, should--to follow up on the previous
3 question--should the kit therefore provide guidance to the
4 laboratory so that they know what these tests mean? Because
5 not all laboratory directors are experts in hepatitis.

6 DR. ALTER: Well, I think the labeling should be
7 clear as to what--you know, if there are issues with respect
8 to the test, I think the labeling needs to be clear. I
9 don't really know what the responsibility of the
10 manufacturer is for providing that information to the
11 laboratory.

12 And I think that you can--I think that that--if
13 that were a recommendation, then that information should be
14 standardized. It shouldn't be--it shouldn't differ between
15 manufacturers based on the interpretation. I'm not
16 necessarily saying that a manufacturer would make the
17 information inaccurate. It's just that everyone interprets
18 these differently. Not everyone, but there are different
19 interpretations, and how they are expressed may differ, and
20 so I think if we were going to do something like that, it
21 should be standardized.

22 DR. CHARACHE: Dr. Thrupp

23 DR. THRUPP: Lauri Thrupp. There is a subset I
24 would like to ask your opinion about, Dr. Alter. I
25 thoroughly agree with your suggestion about e antigen

1 testing, that it's not necessary for routine diagnostic
2 testing. But the question on infectiousness in a subset of
3 exposed needle stick--exposed employees, health care
4 workers, if the donor serum is e antigen positive as opposed
5 to e antigen negative, do you know if the CDC's data sets
6 would suggest there is in fact less risk for transmission?

7 DR. ALTER: Oh, definitely the risk for
8 transmission differs based on e antigen status, and there is
9 about a fivefold difference in infectivity

10 DR. THRUPP: So that would be one set, one subset
11 where the test would be worthwhile.

12 DR. ALTER: But what you would do about it would
13 make no difference. In other words, first of all, all
14 health care workers at risk are supposed to be vaccinated.
15 But--but--if you have a needle stick, you are going to--and
16 the individual is surface antigen positive, you are going to
17 do the same thing. Their e antigen status isn't going to
18 make any difference.

19 And the same is true for mothers who give birth.
20 For mothers--for the e antigen status, excuse me, of
21 pregnant women, we don't make a distinction in terms of
22 prophylaxis for those infants, even though the risk of
23 transmission is lower, but the risk isn't absent and that is
24 really the issue.

25 DR. CHARACHE: Dr. Reynolds?

1 DR. REYNOLDS: Stan Reynolds, Pennsylvania
2 Department of Health. A couple of people have already asked
3 whether the manufacturer should give guidance to the lab and
4 to the physician as to how to interpret the data. And one
5 of the things that you just pointed out with the positive
6 predictive value, it varied greatly according to the
7 population, and most of the time the folks in the laboratory
8 have no idea what populations they are testing.

9 Should there be something in the report or in the
10 package insert that really addresses this issue, tells the
11 doctor, "You know who your patient is. If they are in a low
12 risk population and you have a positive, you have to
13 consider that differently. Maybe you need to do additional
14 testing."

15 DR. ALTER: It's a great idea, you know, and this
16 is going to come up tomorrow when we discuss one of the
17 other viruses, but I think the test needs to--I think the
18 test, the algorithm for testing and providing the result
19 needs to be the same regardless of who you're testing.

20 First of all, physicians don't always understand
21 what makes a person at high risk or low risk. Now, in some,
22 for some diseases it's very clear, but for others it isn't.
23 There could be controversy surrounding it, or there just
24 could be misinformation. Physicians are very busy.
25 Particularly with rapidly changing fields, they can't always

1 keep up with every little tidbit that, you know, is put out
2 there.

3 So I don't think that the laboratory testing
4 should be based on, or the algorithm or interpretation
5 should be based on whether or not the individual is low risk
6 or high risk. I think that when you report out the result,
7 the result should have, if there is a way to do this, the
8 result should have the same accuracy no matter who you are
9 testing, if there is a way to do that.

10 DR. CHARACHE: Dr. Seeff?

11 DR. SEEFF: As you know, because of the cost of
12 tests and reimbursement issues, a lot of laboratories now
13 are turning to develop their own panels and are asking that
14 you submit an acute panel or a chronic panel for both
15 hepatitis B and C. And whether this is correct or not, I'm
16 not sure, but this is certainly what is happening.

17 And I think the American Association of Clinical
18 Chemistry, Dr. Defore--and I think you were on this, and I
19 think, Miriam, you had a chance to look at that--have put
20 something together which they will be publishing in Clinical
21 Chemistry very shortly, and this has got the approval of the
22 American Association for the Study of Liver Disease, which
23 will be describing what tests are available and perhaps what
24 panels might be useful, and I guess this will be published
25 shortly, very shortly.

1 DR. CHARACHE: Dr. Thrupp?

2 DR. THRUPP: One other question, Dr. Alter. When
3 HIV testing was developed, the guidelines were in the
4 recommendations for utilization, required a repeat to
5 confirm a positive, and then if the repeat is positive, a
6 Western blot to confirm the validity of the positive. Would
7 you be more comfortable, in a broad sense, if an HBsAG
8 positive were required by the package insert or whatever,
9 the guidelines, to be repeated, and then if positive, to be
10 subject to a neutralization test?

11 DR. ALTER: Yes. Yes. And in fact, I mean, I
12 think that given that this is antigen, not antibody, that
13 there should be a confirmation test required.

14 DR. CHARACHE: Any other questions at this time?

15 [No response.]

16 DR. CHARACHE: Thank you very much.

17 DR. ALTER: Thank you.

18 DR. CHARACHE: We will go on now to the discussion
19 of the questions of the FDA, open committee discussion. Mr.
20 Simms?

21 Perhaps we should, while you're loading that, we
22 will look at the questions and read them so that the entire
23 perspective can be put into order. It's on page 25 of the
24 FDA section, and I'll read them while we wait for the
25 loading.

1 Question 1: For the claim of diagnosing chronic
2 HBV infection: Are the criteria of HBV serologic markers
3 alone, in the absence of information that HBs antigen has
4 been present for more than six months, adequate to establish
5 the assay's performance characteristics? If not, what
6 additional data and/or change in this indication would be
7 appropriate?

8 Question 2: In the prenatal screening study, 12
9 of 16 or 67 percent of DiaSorin's positive results were
10 nonreactive by the reference assay. DiaSorin does no
11 recommend an HBs antigen confirmatory step. Should this
12 issue be dealt with in labeling by changes in the intended
13 use, by changes in recommendations for confirmatory testing,
14 and/or by some other manner?

15 Question 3: The acute HBV infection group
16 included many samples with an absence of IgM anti-HBc
17 reactivity with the "reference" and the DiaSorin IgM-HBc
18 assays. This may have been due to the analyte being labile.
19 Does this impact sufficiency of the data to establish the
20 DiaSorin's IgM anti-HBc assay's performance? If so, what
21 additional studies or labeling changes might be used to
22 address this issue?

23 Question 4: The studies submitted are based on
24 archival specimens, characterized primarily by using
25 algorithms based on laboratory testing. Are the numbers and

1 types of specimens adequate to demonstrate the effectiveness
2 for the indications stated in these applications? If not,
3 what additional data or changes in indications would be
4 appropriate?

5 Question 4, continued: Indications for use: An
6 aid in the diagnosis of acute and chronic hepatitis B viral
7 infection; monitoring acute and chronic hepatitis B viral
8 infection; Monitoring of HBV therapy; HBs antigen testing
9 during pregnancy; anti-HBs, to assess past exposure to
10 hepatitis B in potential hepatitis B vaccine recipients and
11 to determine the presence of an immune response in vaccine
12 recipients.

13 Question 5: The DiaSorin anti-HBs assay detected
14 responses to HBV vaccines in 12.5 percent of the study
15 specimen sets. Is this sufficient to demonstrate
16 effectiveness for the anti-HBs indication for determining
17 immune status? If not, what additional data or change in
18 indications would be appropriate?

19 Question 6: Currently CDRH-approved devices that
20 are not cleared or licensed by CBER for blood and blood
21 product screening contain the warning: "This assay has not
22 been FDA cleared or approved for the screening of blood or
23 plasma donors." Since a number of these assays under
24 consideration today are also used to protect the U.S. blood
25 supply, i.e. HBs antigen, total anti-HBc, and anti-HBs, is

1 this current warning sufficient or should there be stronger
2 or different labeling to ensure the assays are only used for
3 in vitro diagnostic use or monitoring indications?

4 As we discuss these, I will also ask that the
5 primary reviewers of these specific tests that are being
6 reviewed address these questions and others they want to
7 call to our attention as it applies to the information you
8 derived and the questions that the FDA would like to see
9 addressed. Some of these questions will clearly apply to
10 all of the analytes, and some to specific ones.

11 Let's address the first question first. This
12 pertains to the diagnosing of chronic HBV infection.

13 MR. SIMMS: Right, and it's utilizing all of the
14 HBV serologic markers that have been submitted to us. One
15 of the issues here is the fact that, for this population
16 that we looked at, we did not have information that the
17 hepatitis B surface antigen was present in these individuals
18 for greater than or equal to six months. And does the panel
19 believe this is adequate data to establish the assay's
20 performance characteristics? If not, what additional data
21 and/or changes in this indication would be appropriate?

22 DR. CHARACHE: So you're asking about the absence
23 of the definition of chronic, which is based on greater than
24 six months antigen?

25 MR. SIMMS: Correct, and the fact that we just had

1 serological marker evidence that these were chronic,
2 chronically infected individuals.

3 DR. CHARACHE: Dr. Seeff?

4 DR. SEEFF: I thought they had liver biopsy
5 information as well.

6 MR. SIMMS: There was liver biopsy on a group of
7 the individuals that noted they had chronic liver disease,
8 correct.

9 DR. CHARACHE: Oh, chronic liver disease, but not
10 necessarily what the cause of the chronic liver disease was?

11 MR. SIMMS: Right. Yes, the biopsy report, or
12 what was reported to us in the application, that the biopsy
13 report said "chronic liver disease."

14 DR. SEEFF: As far as I am aware, we have been
15 struggling with this issue about how we define chronic
16 hepatitis. By definition, most people have suggested that
17 chronic infection requires that there be hepatitis B surface
18 antigen present for at least six months. This may not be
19 correct. It may be that three months, you could do that,
20 but I think that for the moment that's what most people
21 believe.

22 Chronic hepatitis requires that there be abnormal
23 enzymes and hopefully histology which would be defined
24 histopathologically, and there are specific histopathologic
25 findings that should define the existence of chronic

1 hepatitis. You cannot tell, as far as I can tell, between
2 chronic hepatitis C and chronic hepatitis B histologically.
3 I would hope that that were the case, other than the fact
4 that you may through special stains find the presence of
5 hepatitis B surface antigen positive cells by using various
6 criteria, but otherwise, unless that is there, the
7 histopathology doesn't distinguish between the two. But at
8 least it describes or defines the presence of chronic liver
9 --chronic hepatitis.

10 So I guess if what you are saying is that the
11 samples that were selected were based on what the company
12 was told was chronic hepatitis, but I understand that they
13 were all biopsied and all of them showed--

14 DR. CHARACHE: No, about half of them.

15 MR. SIMMS: If I remember correctly, the numbers
16 were around 49 that we had histopathological evidence that
17 there was chronic liver disease, and I believe it was around
18 29 that we did not have liver biopsy results on.

19 DR. SEEFF: I mean inferences can be drawn, I
20 guess, by looking at the whole panel of hepatitis B
21 serologic markers. If a patient has hepatitis B surface
22 antigen and is IgM anti-core negative but he is total anti-
23 core positive, and for example is e antibody positive, you
24 could infer that that surely comes from someone with chronic
25 hepatitis, but I think histology is what you would need more

1 to be absolutely certain.

2 If you are going to be studying the effectiveness
3 of a test, I think you would need to have the best possible
4 criteria for making a diagnosis of chronic hepatitis, I
5 believe, and that would be the presence at the present time
6 of--talking about chronic hepatitis, not the healthy carrier
7 state. That was the word I was thinking of.

8 DR. CHARACHE: Chronic hepatitis.

9 DR. SEEFF: I didn't like "asymptomatic carriers."
10 That really needs to be dropped. It's "healthy carriers,"
11 that's actually what ought to be used, not "asymptomatic
12 carriers." But for chronic hepatitis B, you need the
13 presence of hepatitis B plus the other markers that go with
14 it, the presence of abnormal enzymes, and at least the
15 current criteria are that they should exist for--they should
16 be there for six months, and that the histology should in
17 fact confirm that this is chronic hepatitis, if we're
18 actually doing a specific test. I think in a clinical
19 setting you may approach it in a different way, but if we
20 want to be absolutely certain about the validity of a test,
21 I think we should use the best possible criteria.

22 DR. CHARACHE: Dr. Thrupp

23 DR. THRUPP: Lauri Thrupp. Would you--I agree
24 with what you said. It sounds very logical. But would you
25 back off a little bit if the term is "chronic HBV

1 infection"? Because that doesn't, that term "infection"
2 doesn't really imply that you know the histology.

3 DR. SEEFF: Yes, but I said that's--

4 DR. THRUPP: And is that adequate for what they
5 are trying--

6 DR. SEEFF: --for distinguishing chronic hepatitis
7 B from chronic HBV infection. I think chronic hepatitis B
8 requires that there be evidence of chronic hepatitis, and
9 that derives from--

10 DR. THRUPP: Right.

11 DR. SEEFF: --abnormal enzymes, and in the setting
12 of what we are trying to do now-

13 DR. THRUPP: I agree that that would be ideal, but
14 what we are being asked is the term "chronic HBV infection."

15 DR. SEEFF: I see. I'm sorry, I'm not--

16 DR. THRUPP: Well, I mean, your point is very well
17 taken, but that's what we are being asked, and for just
18 establishing infection you wouldn't necessarily expect to
19 have the histology.

20 DR. SEEFF: Right, right

21 DR. THRUPP: Therefore, one question I was going
22 to raise again, and I may have missed it in the packages and
23 it may have been in the presentation, was in the panels that
24 were provided to the sponsors for the testing that were
25 labeled "chronic HBV infection," do those vendors that have

1 those panels provide you assurance that the HBsAG had been
2 in fact documented to be present for more than six months?

3 MS. SMITH: What they had documented to us was
4 that the patient--sorry. What the vendor had provided to us
5 was that the patient had chronic hepatitis B infection for
6 greater than six months. That's the way it was phrased to
7 us. They also had varying times between the time the
8 diagnosis was made and the time the sample was drawn. Some,
9 very few were drawn at diagnosis. Others were, most of them
10 were at least three to six months or so, or years after the
11 diagnosis.

12 DR. THRUPP: And what was the size of that sample
13 that they assured you--

14 DR. CHARACHE: Excuse me, Dr. Thrupp. We're not
15 allowed to do this. We'll let her answer this, but--won't
16 you answer, because the question has been asked? But then
17 we won't direct questions this way.

18 MS. SMITH: Could you repeat the question? I'm
19 sorry.

20 DR. THRUPP: What was the size of that sample that
21 they assured you was over six months?

22 MS. SMITH: I believe it was--Tom, do you
23 remember?--it was the 29 that were the serological, that
24 didn't have the liver biopsy.

25 MR. SIMMS: It was around that.

1 MS. SMITH: It was the ones that didn't have the
2 liver biopsy, I believe.

3 DR. CHARACHE: Dr. Specter?

4 DR. SPECTER: Steve Specter. Tom, if you could
5 help me out a little in terms of addressing this, my
6 impression was that there wasn't a difference in the
7 performance of the test in the populations that we knew were
8 indeed chronic infection versus not. And so my concern
9 would be, if the test performed differently in a population
10 that was chronically infected, then there would be concern
11 about whether this is effective for this use or not. But if
12 it's performing like it is in all other circumstances, I
13 would feel that it should be adequate if all the other uses
14 are adequate, and I'm not saying they are or they're not at
15 this point. But is it different?

16 MR. SIMMS: Let me do one sidebar.

17 DR. SPECTER: While you're sidebarring, can I
18 bring up another point?

19 DR. CHARACHE: Yes, please.

20 DR. SPECTER: Because it really impacts on all of
21 this, and it's really a question for Dr. Meier. And that
22 is, in a number of these tests, I noticed it more so with
23 the antibody test, there are very wide ranges of CVs for
24 run-to-run comparison, lot-to-lot, and even in-run
25 comparisons. And I have no way, because I am not expert in

1 that, to know if these are valid when you have such a wide
2 range of CVs or not. And that was a question that was of
3 great concern to me, is are these good tests or is there a
4 problem if the CVs are that varied?

5 DR. MEIER: They are varied, and I guess, what
6 does that mean? That means you can get very different
7 answers on repeat testing, is what that means, and it's not
8 really a statistical question. I mean, the statistical
9 method is to quantify what that variability is. It's large.
10 Does that sometimes have implications in the call you will
11 make being positive or negative? Well, possibly, depending
12 on where you are. It depends.

13 If you test a lot of specimens that have very high
14 values, then it's not going to matter as much; if you have
15 very low, it's not going to matter. It's going to matter if
16 you have ones in the mid-range, and that's why it becomes
17 critical that the specimens you are looking at are
18 representative of what you are going to get out there. If
19 you are going to get a lot of these not so clear-cut cases,
20 then yes, that CV becomes extra critical.

21 So my answer is, I guess it becomes important
22 depending on where people typically fall, but I can't--it's
23 not really a statistical determination that it is too high,
24 too low, other than just understanding how it impacts.

25 MR. SIMMS: If I could perhaps expound on that a

1 little bit, I believe that's why most of your diagnostic
2 assays actually have an equivocal zone. The issue of
3 prevalence going into--if you have a disease population that
4 has a high prevalence, there's a very good possibility that
5 you're going to catch people early in disease that have very
6 low values of the analytes, you know, But then we've also
7 got to look at the issue of the assay's reproducibility
8 around the cut-off. How is that going to affect the final
9 result?

10 So therefore for me, at least in my review
11 process, is I try to look at the equivocal zone and take
12 those issues into consideration. Is the equivocal--does the
13 equivocal zone cover the variance around the cut-off. If
14 you pay attention to the equivocal, are you going to lose a
15 true positive? So I believe that's an important safeguard
16 in in vitro diagnostic tests. Now, the DiaSorin assays do
17 have an equivocal zone.

18 Did that help with that issue?

19 DR. SPECTER: Yes. In reality, some of the larger
20 CVs were at the extremes rather than in the middle.

21 MR. SIMMS: Right.

22 DR. SPECTER: So maybe it's not as big--

23 MR. SIMMS: Right.

24 DR. CHARACHE: Dr. Sanders?

25 DR. SANDERS: Natalie Sanders. And where those

1 CVs were most variable, they were with antibodies. And if
2 you are, say, monitoring interferon response, you're really
3 measuring not just an antibody, so where you might really
4 want to do something like that serially, it's not really a
5 big issue.

6 MR. SIMMS: I believe we got the low carrier field
7 from your initial question about the chronics, and please
8 refresh me. What is your question?

9 DR. SPECTER: The issue was whether the test
10 seemed to perform differently in that population that you
11 could say truly were chronics, as opposed to those that were
12 claimed to be chronic or other circumstances, so that you
13 would have a concern as raised in the question here: Is the
14 test going to perform adequately for diagnosing chronic HBV
15 infection?

16 MR. SIMMS: The intent of the question was to
17 bring up the point that we did not have what we consider to
18 be one of the prime categories to actually say the
19 individual is chronic, and that is the presence of the
20 hepatitis B surface antigen for six months or greater. That
21 information wasn't present.

22 So even with the biopsy results that we had, if I
23 am remembering correctly--and you'll have to forgive me,
24 I've looked at a lot of data in the last couple of weeks--is
25 that we didn't have the dates of the biopsy. We took the

1 biopsy on face value. If it said "chronic liver disease,"
2 we said, "Okay, this chronic disease, does the marker
3 patterns match?"

4 A little long-winded, but the issue here is to go
5 back to what I believe Dr. Seeff brought up, was that do we
6 need the evidence that surface antigen is present for
7 greater than six months in an individual to categorize them
8 as being chronically infected? And if we don't, then what
9 other data would the panel find appropriate, or should there
10 be a change in the indication for use in the various
11 products?

12 DR. CHARACHE: Dr. Gates?

13 DR. GATES: To make sure I get an understanding,
14 the question isn't so much how the test is performing but
15 whether or not the samples that were put in the chronic pool
16 are in fact chronic or not. And that's something I guess
17 that can be debated, but in terms of how the test is
18 performing, to Steve's question, if there is a reference
19 test that is being done in parallel and they are both
20 matching up, it seems like there wouldn't be any difference
21 anyway.

22 DR. CHARACHE: Perhaps later, when the DiaSorin
23 group can answer, they can tell us whether that large
24 discrepancy group was skewed towards any particular patient
25 population that we saw.

1 Have we answered your question, or would you like
2 us to go around--

3 MR. SIMMS: May I make a comment further?

4 MS. POOLE: Okay, go ahead.

5 DR. CHARACHE: Please.

6 MR. SIMMS: One of the other questions that's
7 going to follow this is on an issue of what we consider to
8 be the lack of IgM reactivity in a certain group of
9 specimens, and that's also really the case perhaps with the
10 chronics also.

11 We made an assumption, because of the--for the
12 lack of the IgM reactivity being due to perhaps specimen
13 storage conditions, because these were all archived
14 specimens that had been frozen previously. We have no idea
15 how the specimen storage was treated, you know, if they were
16 frozen and maintained in a proper manner.

17 So I believe that's also an underlying issue here,
18 is from some of our other data sets, the lack of them
19 showing IgM reactivity perhaps when they should have, is
20 that an issue?

21 DR. CHARACHE: Could we have some comments on
22 that, please? Dr. Thrupp?

23 DR. THRUPP: On the storage issue, we brought that
24 up earlier. I would have assumed that the data submitted on
25 the storage issue would have included all classes, including

1 the IgM assay. The implication that Tom is asking is
2 whether the IgM was more labile. That should have shown up
3 in the frozen/thawed controls, if that were the case, I
4 would have hoped.

5 DR. CHARACHE: Dr. Nolte?

6 DR. NOLTE: I guess I'm getting a little confused
7 here. We are bringing forth a hypothesis that the
8 difference in storage or perhaps the improper storage
9 condition affected one assay relative to the other? Weren't
10 the reference assay and the assay in question here done
11 concurrently on the same aliquot? So you're suggesting that
12 perhaps, somehow or another, the way the specimens were
13 handled affected the DiaSorin assay but not the other assay?
14 Is that what you're suggesting?

15 DR. CHARACHE: No, I think neither was positive,
16 and IgM does not store as well as IgG. So the question is
17 what data there is to show the storage of the IgM.

18 DR. NOLTE: So the action is in both the reference
19 and the DiaSorin assay? Okay.

20 MR. SIMMS: I'm sorry. I lost track of the
21 question. I'll ask Dr. Ticehurst to respond to that,
22 please.

23 DR. TICEHURST: I think there is a thread of
24 evidence that is being put forward, and maybe being put to
25 the panel to address this question. As you may have seen in

1 the data that Tom presented this morning, and I think a
2 later question for us is this: The vast majority of the
3 specimens that came with a label on them as representing
4 acute infection were in fact IgM anti-core nonreactive with
5 the reference assay, and most of them also with DiaSorin's
6 assay.

7 That raised to us, as we reviewed the data, the
8 question as to whether any specimen in the portion that were
9 studied, if the results of an IgM anti-core assay could be
10 relied upon, if, as was stated earlier, I think Dr. Seeff
11 made the point that, as many of you know, if in fact when
12 you have a number of reactivities, the key reactivity to
13 distinguish between acute and chronic infection is the lack
14 of IgM anti-core, it raises--it puts a little more weight on
15 this question here, in my opinion.

16 DR. SEEFF: I think the point to be made about
17 what you are discussing at the moment is, it's extremely
18 difficult to distinguish between acute and chronic
19 hepatitis. We know that you can have chronic hepatitis B
20 and have a flare-up, and if you didn't know that this person
21 in fact was chronic hepatitis B, you may see the flare-up
22 for the first time and call it acute hepatitis.

23 So we are dependent, unfortunately, on the
24 serology helping us to distinguish between acute and chronic
25 hepatitis, not on clinical findings, unless you have

1 obviously end-stage liver disease and you have all the
2 features of portal hypertension and splenomegaly and
3 thrombocytopenia, in which case it's obviously chronic. But
4 basing it simply on serum enzymes may not be enough to
5 distinguish between acute and chronic, so we're stuck with
6 having to distinguish between acute and chronic looking at
7 the serology, and that seems to have been worked out fairly
8 well.

9 And the question is, if that's the case, then
10 what--the question, it seems to me, that's being asked here
11 is can we be comfortable that the selection of cases that
12 were called either acute or chronic were really acute or
13 chronic? And the only way, I think, at the present time to
14 accept it is to base it on serology and on the current gold
15 standard. And the question, is that sufficient, and can you
16 compare what we're looking at to this gold standard?

17 But I would think that we--that the combination of
18 tests, looking at surface antigen, IgM anti-core, total
19 anti-core, e antigen, e antibody, anti-HBs, gives us a great
20 clue as to whether we are dealing with acute or chronic
21 liver disease. I still think that for the purpose--I think
22 there is going to be a difference between the way this is
23 used out in clinical practice, because we may use it
24 somewhat differently from what we are trying to establish
25 now.

1 What we are trying to establish now, as accurately
2 as possible, is how effective are these tests, given that I
3 think we do have to stick with the criteria that we have all
4 accepted, that the chronic disease is chronically abnormal
5 enzymes for six months, the chronic infection is chronic--is
6 the HBsAG present for at least six months, and I think those
7 are the minimal criteria that we will be using for the
8 purposes of this discussion.

9 Ultimately, as I say, when we get out into
10 practice, people may deal with it differently and six months
11 may be too long, because we are certainly beginning to say
12 that with hepatitis C, that six months may be too long. We
13 can think of other ways of dealing with that.

14 So I think that the six months for chronic disease
15 is important and we need to have that known. And when the
16 liver biopsy says "chronic liver disease," that could be
17 chronic alcoholic liver disease, that could be chronic
18 autoimmune hepatitis, that could be chronic cholestatic
19 liver disease. We don't know.

20 So I think we need to know more about what that
21 histology showed. Did it show chronic hepatitis as we
22 define--chronic viral hepatitis, as best as we can define
23 it? I guess that much we do need to know.

24 DR. CHARACHE: All right, so we have heard Dr.
25 Seeff make the point that the gold standard for chronic

1 hepatitis is positive antigen for six months. The question
2 then is whether the material submitted responds to that.
3 Dr. Thrupp raised the question of whether the appropriate
4 pattern of serologic tests would be definitive, and we have
5 heard a question raised about the crucial test, the IgM,
6 whether this was--had perhaps changed on storage for both,
7 because of the absence of IgM in patients diagnosed as acute
8 hepatitis.

9 Do we have other thoughts, comments that people
10 would like to add? Does someone want to speak to one of
11 these points or another, to provide further guidance? Dr.
12 Reller?

13 DR. RELLER: It seems to me when one looks at the
14 natural history of the serology in hepatitis B infection,
15 that there is a period of time in the six months after
16 infection where the other markers may or may not be
17 positive, and there are questions about how accurate these
18 markers are in terms of reproducibility, et cetera.

19 So if we have tests that may or may not be
20 positive, that a given test may or may not match the
21 performance of some other test, and the standard is six
22 months, it seems to me unless one--you know, whether or not
23 the patients under review here actually were positive for
24 six months with hepatitis B surface antigen or not, if we
25 don't have the data that demonstrates that, we don't have a

1 basis for saying anything about the claim of diagnosing
2 chronic hepatitis B infection.

3 DR. CHARACHE: Yes? Do you want to make one brief
4 comment?

5 DR. ALTER: Yes, very brief, actually, and I
6 apologize--

7 DR. CHARACHE: Could you go to the microphone,
8 please?

9 DR. ALTER: Since I wasn't here this morning, I
10 may be making a comment that is not relevant, but it seems
11 to me that what we really need to know is whether the
12 combination of markers that are usually used to distinguish
13 chronic infection from acute or convalescent infection, are
14 these--are the data that have been presented for this
15 manufacturer, do they distinguish between--do they accurately
16 diagnose an individual who is infected with HBV, and do they
17 distinguish chronic infection from acute or convalescent?

18 It seems to me that--and I still haven't seen the
19 data, so I obviously don't know, but it seems to me that's
20 what we really need to know. I mean, is it reliable when
21 IgM anti-core is absent? Are there data that show that IgM
22 anti-core lasts for only, you know, let's say six months, so
23 that when you do follow an individual over time and they
24 become chronically infected, they will have HBSAG and anti-
25 core, and it will be predominantly IgG? I mean, that to me

1 is the question.

2 DR. CHARACHE: Dr. Weinstein?

3 DR. WEINSTEIN: Yes. Mel Weinstein. I am swayed
4 also by the need to meet what the current standard is, and
5 while the standard may change in some period of time, there
6 is a fairly well accepted definition of chronic hepatitis B.
7 And I think, given that that's what we know at this point in
8 time, that's the criterion we need to use for making a
9 recommendation.

10 DR. CHARACHE: Dr. Sanders?

11 DR. SANDERS: Natalie Sanders. I don't disagree
12 with what has been said about the criteria for determining
13 whether chronic hepatitis B infection exists, but we also
14 have data here from DiaSorin compared with what we would all
15 agree is a reference laboratory methodology that we feel
16 very comfortable with. So I think we have kind of got two
17 things here. We have got the issue of the source material
18 for their study, but we also have a reference methodology
19 that is already out there and being used, that we all feel
20 very comfortable with.

21 DR. CHARACHE: Dr. Gates?

22 DR. GATES: Yes, I would have to agree. I guess,
23 like I said before, there is two issues, it seems like. One
24 is, is the algorithm correct, and did they put the right
25 samples in the right bucket, basically, in terms of chronic

1 or acute. And then the second one is, compared to the
2 reference method, are they both giving the same results
3 regardless of whether or not it is in the right bucket or
4 not?

5 And I guess partly to that point and just because
6 I don't know, I realize the gold standard for chronic, as
7 was said, was antigen for six months, but the fact that
8 there is a liver biopsy and the presence of antigen,
9 regardless of what amount of time, seems to me pretty
10 suggestive of a chronic infection too. And I--is that true?

11 DR. SEEFF: I disagree. I think the operative
12 word there is "suggestive". I mean, all I'm saying is that
13 out in clinical practice, I think when we do a liver biopsy
14 on a patient and we have one hepatitis B surface antigen
15 that's positive, and you see chronic hepatitis that most
16 pathologists can agree is chronic viral hepatitis, and the
17 patient is anti-core positive but not IgM anti-core
18 positive, you call that chronic hepatitis.

19 I was just saying that in this particular
20 circumstance where we are trying to judge the effectiveness
21 of a test, ideally I think that if we're going to call it
22 chronic hepatitis, we should have six months worth of
23 chronic enzyme for the hepatitis and chronic surface antigen
24 for the virus, and ideally I guess IgM anti-core for the
25 acute disease. Now, that does not mean that you can't have

1 acute hepatitis C that's not IgM anti-core positive. That
2 may occur. But the question is, under the present
3 circumstances of what we are trying to determine, can we
4 feel comfortable?

5 Now, the very fact that the reference test shows
6 the same thing doesn't mean to say that the reference test
7 is any better. It still would require six months of the
8 reference test to be positive to make it chronic, I would
9 guess, or this presence of certain things that we are
10 looking at now. That would be my view.

11 It would be lovely if we could all make just one
12 test and say, "Ah, ha," it's acute or it's chronic, but
13 hepatitis B is a very complicated disease that, as you know,
14 it has flares, it has--you're going to have states where you
15 have replication and it becomes nonreplicative, and then you
16 can get replication again. This could happen in various
17 ways, be stimulated by, for example, steroids, and you
18 withdraw steroids and they have in fact an acute flare, and
19 you didn't know that this person was a carrier before this.
20 Or they get delta hepatitis, for example, and they have an
21 acute flare, and it turns out that this is really chronic
22 liver disease but you identified it as acute. And the best
23 we can do at the moment is to have either a solid diagnostic
24 set of criteria, or we have to make do. That would be my
25 read.

1 DR. CHARACHE: Yes? Dr. Reller?

2 DR. RELLER: Just to bring to completion the point
3 Dr. Seeff made, may I ask one of our colleagues on the panel
4 a question?

5 DR. CHARACHE: Yes.

6 DR. RELLER: Dr. Seeff, is it reasonable or fair
7 to expect of this or any test on a single testing, given
8 what you said, to accurately make a claim for diagnosing
9 chronic hepatitis B virus infection? I mean, if the
10 definition is persistence--or part of the definition,
11 regardless of whether or not there is histologic activity,
12 is persistence of hepatitis B surface antigen for six months
13 or more, subject to change in the future, how can one with
14 certainty make that assessment on a single testing?

15 DR. SEEFF: I don't think you can. I mean, if you
16 have--all you have is hepatitis B surface antigen, all that
17 you have is hepatitis B surface antigen. You don't know
18 whether that's acute or chronic. By looking at the other
19 tests, at the whole panel, you come up with I'll say some
20 inference--if it's IgM, if you also have IgM anti-core, then
21 that with hepatitis B surface antigen presumably represents
22 acute disease. If you have IgG anti-core and anti-HBe, then
23 that presumably represents chronic disease.

24 So with that (inaudible) you can infer that, by
25 the definition that you generally expect clinically, the

1 view that we have taken, and I do believe it's going to
2 change, but the view that we have taken up until the present
3 time is that we need a duration, and that six months
4 actually (inaudible) goes back to the early studies that
5 were done by Mayo Clinic when they were looking at
6 autoimmune hepatitis, and they found a distinction between
7 acute and chronic hepatitis. And when they looked at all
8 their cases, they said virtually everybody with acute
9 hepatitis recovered at the end of six months. Therefore--

10 DR. CHARACHE: Could you speak into the
11 microphone, sir?

12 DR. SEEFF: I was trying to look around.
13 Therefore, the presence of abnormal enzymes or surface
14 antigen for six months is what they said would define
15 chronic hepatitis, and that's what we have stuck with. And
16 we may have to redefine it as we go along, and in fact there
17 is an effort to do that, but for the moment that's what we
18 are accepting.

19 So I think a single test, a single surface
20 antigen, doesn't tell you if it's acute or chronic. Even if
21 it's in the presence of transaminators, for example, of
22 1,000, the inference would be that this is probably acute,
23 but as I say, you can have a flare-up and have tremendously
24 high transaminators, hepatitis B surface antigen, and if
25 that's the only test you have, you can guess but you

1 wouldn't know for certain, so these other tests would help.

2 DR. RELLER: So it seems that even if it were
3 possible to have a combination of markers, the standard
4 against which that combination would be assessed for
5 accuracy would be an unequivocal population group that had
6 demonstrated persistence by current criteria of hepatitis B
7 surface antigen for six months or more?

8 DR. SEEFF: As I say, I think that if we were out
9 in clinical practice taking care of patients as a
10 hepatologist, we may infer, based on a shorter period of six
11 months, that this is chronic liver disease, and may even
12 start treatment. But that would be probably based on what
13 you see histologically before you do that. I think that in
14 general as clinicians we tend to say chronic liver disease,
15 or chronic infection, requires the persistence of the test,
16 whether it be the serum anti-immunotransferases or hepatitis
17 B surface antigen, for six months.

18 And I say, in the situation in which we are
19 discussing this now, should that be the absolute criteria?
20 My--you know, I'm no seer. I mean, I don't know. Other
21 people may have disagreements, and I don't know if other
22 people would like to say something. I see Miriam is putting
23 her hand up.

24 DR. CHARACHE: I think we had better go on to the
25 second question. Some of these same points will come

1 forward.

2 Question 2: In the prenatal screening study, 12
3 of 19 or 67 percent of DiaSorin positive results were
4 nonreactive by the reference assay. DiaSorin does not
5 recommend an HBs antigen confirmatory step. Should this
6 issue be dealt within labeling, by changes in the intended
7 use, by changes in recommendations for confirmatory testing,
8 and/or some other manner?

9 Dr. Rodis?

10 DR. RODIS: My concern regarding this question and
11 also is going to come back in Question No. 5, I believe, is
12 both the false positive related to Question 2 and the false
13 negatives perhaps related to Question 5, as I recall the
14 data, there were twice as many, if you will, positive
15 results in the pregnant patients with the DiaSorin assay
16 versus the reference assay, leading potentially to twice as
17 many pregnant women being falsely assigned a diagnosis of--
18 or we have a diagnosis, but putting at risk perinatal
19 transmission, warranting further testing.

20 My concern is--and the manufacturer I think have
21 already suggested that they will change the label in this
22 regard, different from the label that we have. My concern,
23 is that enough? Will the label insert change each
24 individual laboratory's reporting of the results to the
25 obstetricians? In other words, will the results say

1 "hepatitis B surface antigen positive," or will they really
2 say, "However, this kit we use, if it's positive, you really
3 should have a confirmatory test."

4 How good--and again, I'm really asking the
5 question to those of you who run labs--how good are you all
6 of getting that little piece of information into the actual
7 laboratory result the physician might see? Or is the
8 physician going to just treat this like all other patients
9 with hep B surface antigen? Which means the neonates will
10 get hepatitis B immune globulin perhaps that they didn't
11 need. So I guess that's my question relating to the false
12 positives.

13 DR. CHARACHE: Dr. Edelstein?

14 DR. EDELSTEIN: Edelstein. I have a couple of
15 comments. First, we don't know their performance of a
16 confirmatory test for this assay because no data has been
17 presented on that. Second, we don't know how repeated
18 testing would perform in this situation because we don't
19 have the data on that, either.

20 And as far as the question goes as to what a
21 clinical laboratory would do, if the product insert
22 specifically said that all positive assay results must be
23 confirmed by x procedure before reporting, then most
24 laboratories would do that. But the manufacturer has to
25 show us that that process is valid, and since we don't have

1 the data here, we really can't make any judgment on it.

2 And, finally, I think since we are all skirting
3 around Question 4, the major problem with this data set and
4 several of the other data sets is that we really don't have
5 clinical information on the patients. We have serum taken
6 from panels submitted to chemistry laboratories or whatever.
7 We don't have follow up information. We may not have
8 multiple marker information. So it's very difficult to
9 interpret a lot of the results of this evaluation.

10 DR. CHARACHE: I think we have to remind ourselves
11 that in this case particularly we are not talking about
12 correlation with disease state; we are talking about
13 correlation with a reference method. So here what we're
14 saying is that 60 percent of the time the DiaSorin test will
15 call it positive whereas the reference method would call it
16 negative, and that's the data we have to work with.

17 DR. EDELSTEIN: But the possibility is that these
18 are true positives and the test is more sensitive than the
19 reference test, but in order to know that we need clinical
20 information, follow up information on these patients which
21 we don't have, so we can't make that judgment.

22 DR. CHARACHE: But you will remember this isn't
23 just sensitivity because the numbers were high. It wasn't
24 at the cut point. It was different.

25 DR. EDELSTEIN: I'm talking clinical sensitivity.

1 DR. CHARACHE: Right.

2 DR. SPECTER: I think that's the critical thing,
3 and I agree completely with Paul that without knowing what a
4 test result means because you don't have a pedigree for the
5 patient, it's really hard to make a decision as to whether
6 this is a worst test or a better test in terms of how it can
7 be used. And, you know, maybe it is more sensitive and it's
8 doing a much better job. We have no way to know that, and I
9 don't see how one can make a decision as to whether the test
10 is performing correctly when you're using a reference test
11 which clearly, it has been established, is not a gold
12 standard but is a reference test. And without a gold
13 standard, we're clueless as to what the results mean when
14 there's discrepancy.

15 DR. CHARACHE: Dr. Thrupp

16 DR. THRUPP: Question 2 starts out referring to
17 the prenatal screening study, which is a good illustration
18 of the high percentage of false positives, depending on the
19 population that you're studying.

20 But the concluding part of the question asking for
21 would we--should it be recommended that confirmatory testing
22 be done, which presumably would be preceded by a repeat of
23 the same test and then confirmatory testing, is what we just
24 asked Dr. Alter a few minutes ago. And her response was
25 yes, and I would certainly agree with that as a principle,

1 given the importance of this test clinically in terms of
2 what is done with subsequent testing and what is done
3 clinically with these patients.

4 But there is a major issue that I think we need a
5 little comment from Dr. Gutman or somebody from the FDA
6 standpoint, and from the issue of a level playing field, if
7 we were to recommend that this test requires a repeat and a
8 confirmatory test, shouldn't that also be required of the
9 reference test that's already out there, and is there any
10 mechanism for addressing that?

11 DR. CHARACHE: It is required.

12 Dr. Gutman, do you want to comment? I'm sorry.

13 DR. GUTMAN: Yes. I mean, the issue here you are
14 addressing, and so I'm trying to be non-leading, frankly, is
15 that this isn't a pristine data set, and what the agency is
16 asking for is taking this non-pristine data set and using
17 this sort of serologic diagnosis, where we can go and how
18 far we can go, and I'm very happy to hear this discussion.
19 We're trying to establish a least burdensome threshold;
20 we're not trying to sell the product down the river. But--I
21 guess that's all I'll say.

22 DR. CHARACHE: Tom?

23 MR. SIMMS: For Dr. Thrupp, the reference assay
24 that was used is an assay that's licensed by CBER, so
25 therefore it does require a repeat and a confirmatory assay.

1 Okay?

2 I would also like to offer a clarification on the
3 data here. The 12 non--or the 12 positive DiaSorin results
4 which were negative by the reference assay, these specimens
5 also had other markers done on them with the reference
6 assay, and there was no evidence with these other markers
7 that this was an acute infection

8 DR. THRUPP: I'm just a little confused, then,
9 because I thought we heard this morning and I thought I read
10 somewhere in here that for purposes of these analyses, the
11 first test of the reference method was compared with the
12 first test of the DiaSorin test, so it was not confirmed.

13 MR. SIMMS: It was our expectation and our
14 understanding, the way the data was initially evaluated by
15 DiaSorin, was that the DiaSorin tests, the first test result
16 was the one that was evaluated. But let's say with the
17 hepatitis B surface antigen, they had to follow the licensed
18 procedure for that assay, so if the assay result was
19 initially reactive, it had to be repeated; duplicative
20 reactive, it had to be confirmed.

21 DR. REYNOLDS: That data is not presented; is that
22 correct?

23 MR. SIMMS: I'm sorry?

24 DR. REYNOLDS: That data was not presented.

25 MR. SIMMS: It should be in your--in the books

1 that were sent to you.

2 DR. CHARACHE: I would like to ask one other
3 question as to reference. We have the 12 apparent false
4 positives in that pregnancy area. If we have apparent false
5 positives with no other confirmatory evidence of hepatitis
6 or acute hepatitis in that population, should we ask
7 questions about that assay in general that goes beyond the
8 pregnancy questions? Because we've heard that there were
9 six positive hepatitis antigens with no positive core in a
10 second population, so I think we should wonder if this goes
11 beyond the pregnancy question into the question of the
12 hepatitis surface antigen test itself. Any thoughts? Yes

13 DR. THRUPP: Just a reminder. We--Dr. Sanders
14 brought it up this morning, but the hemodialysis is exactly
15 the reverse. There appear to be "false negatives" instead
16 of false positives.

17 DR. CHARACHE: Any other comments on this second
18 question? Dr. Nolte?

19 DR. NOLTE: Again I have to apologize for either
20 my stupidity or naivete, but these false positives we are
21 talking about, there is data in the packet that documents
22 what the repeat DiaSorin results were and what--and DiaSorin
23 has a confirmatory assay, I presume. Okay, so we at least
24 have repeat reactivity information on those 12 "false
25 positives," and how did that turn out?

1 DR. CHARACHE: Well, that, I think that's an
2 additional question because they weren't broken down into
3 the two populations, the American group versus the group
4 from Africa that read differently.

5 Dr. Seeff?

6 DR. SEEFF: When we're talking about repeat, are
7 we saying the same specimen was tested a second time, or a
8 second specimen was obtained?

9 DR. CHARACHE: No, the same test--specimen was
10 tested, but we don't have the data on how that fits these
11 particular samples.

12 Can we go to the third question, please?

13 This question has already been raised. It has to
14 do with the fact that the hepatitis B infection group
15 included many samples with an absence of IgM antibody--with
16 absence of IgM HbC reactivity with the reference and
17 DiaSorin IGM-HbC assays. This may have been due to the
18 analyte being labile. Does this impact sufficiency of the
19 data to establish DiaSorin's IgM anti-HbC assay's
20 performance? If so, what additional studies or labeling
21 changes might be used to address this issue?

22 Dr. Rodis?

23 DR. RODIS: I think both this question and the
24 last question potentially pertain to a false positive
25 hepatitis B surface antigen assay. Both could be explained

1 by that.

2 DR. CHARACHE: I think we may actually have
3 answered this before when we noticed--when we asked whether
4 there was an unusual dissociation between the diagnosis of
5 acute hepatitis and the presence or absence of the anti-IgM
6 core compared to other reference studies.

7 Shall we try Question 4? Oh, one other question
8 on Question 3. We didn't really address the last two
9 questions of it, I am reminded. One is, does this impact
10 sufficiency of the data to establish the IgM anti-hepatitis
11 B core assay performance, this finding that we have just
12 been asked about? And, if so, should there be additional
13 studies or labeling changes?

14 Can we address that question, please? Dr.
15 Edelstein?

16 DR. EDELSTEIN: Yes, and yes.

17 DR. CHARACHE: Dr. Reller?

18 DR. RELLER: Like Dr. Edelstein's discussion of
19 Question 2, I mean, how much of an effect and what labeling
20 changes would be made? Do we have the data to tell us what
21 they should be? I mean, unless one has samples that are
22 shown to--the effect of how the samples--I mean, if handling
23 the samples, freezing, at what temperature and so on, makes
24 a difference, then that has to be shown right now.

25 Most people are relying on IgM anti-HBc as an

1 important indicator of acuteness of infection on a single
2 sample testing. And if the performance of the test is
3 altered by how the specimen is handled, to make
4 recommendations on how to handle the specimen seems to me
5 require data on how they should be handled and what happens
6 if they're not handled that way, and we don't have that
7 information.

8 DR. EDELSTEIN: And, in addition, we don't have
9 adequate information on the true performance of the test. I
10 think that's my concern, is it may be fine, it may not be,
11 but I don't know, based on the data presented, and I'm very
12 worried about that.

13 DR. CHARACHE: Dr. Thrupp

14 DR. THRUPP: There is a concern that has been
15 mentioned, but it goes over to Question 4 from Question 3.

16 DR. CHARACHE: All right. Let's look at
17 Question 4.

18 DR. THRUPP: But it may relate to IgM perhaps even
19 more than some of the other assays, namely that clinically
20 the testing--these tests are going to be used very
21 frequently and as diagnostic tests in a variety of patient
22 populations, and those are going to be very important tests
23 in STD clinics; in the HIV positive populations; in immune-
24 suppressed, transplant patients, oncology patients. These
25 are all patients that we want to screen for HBsAG and hep B,

1 C antibody--hepatitis C antibody.

2 It seems to me that if the product is going to be
3 able to be out there and used clinically appropriately,
4 there should be additional clinical subsets that are studied
5 to make sure that maybe there's not funny IgM results in
6 some of these other populations. And we have heard that
7 there were some other sets that they did test, but I'm not
8 sure whether there is enough that was presented to really
9 assure that there was no cross-reactivity. And if the other
10 subsets for cross-reactivity were adequate, then the
11 labeling should allow the lab to guide the clinician and
12 say, "Yes, you can use it as a diagnostic test in all of
13 these populations."

14 DR. CHARACHE: Dr. Seeff?

15 DR. SEEFF: The only way that I am aware of to
16 make a diagnosis of acute hepatitis B, as is true for most
17 other virologic conditions, is to have IgM, the IgM
18 positive, other than a liver biopsy where you see acute
19 hepatitis without--but nobody biopsies people with acute
20 hepatitis, so we can't use that. So we are stuck with the
21 fact that the only way to make a diagnosis of acute disease
22 is to have IgM activity. And I guess in this particular
23 instance what--the comparison between the reference IgM
24 anti-c and the DiaSorin Igm anti-c was pretty good. Isn't
25 that right?

1 DR. CHARACHE: Yes.

2 DR. SEEFF: So, you know, we really should not be
3 using the cases as evidence of acute hepatitis in which IgM
4 anti-HBc was negative, because you don't know for sure that
5 those are cases of acute hepatitis. But within the category
6 of reference IgM anti-core positivity, DiaSorin seemed to
7 work pretty adequately. It was very comparable.

8 DR. CHARACHE: Although there were many more
9 positives, about a third more positives with the DiaSorin
10 than with the reference method in the study that compared
11 them. Yes?

12 DR. WILSON: Mike Wilson. I think that the issue
13 with Question No. 4 does trail back to Question No. 3, and
14 that is, if you are using archival specimens, there are
15 always concerns about whether or not the specimen is labile,
16 particularly for IgM.

17 But I think a second issue that is just equally
18 important is the issue of cross-reactivity with other
19 interfering substances. If one is to rely on panel archival
20 sera, those should be extremely well characterized as to
21 exactly what is in there and what is not in there. A good
22 example is, rheumatoid factor is notorious for interfering
23 with some of these immunoassays, and they mentioned there
24 was some data on that.

25 But I think that is one of the key issues, is when

1 you are dealing with archival sera, you really need to know
2 exactly from whom those specimens came, what diseases they
3 had, and what was the state of those specimens before they
4 went into the freezer. Otherwise, one will never know what
5 is coming out of the freezer some time later.

6 DR. CHARACHE: Can we now address specifically the
7 questions raised in 4, noting that as--and continuing the
8 discussion--that these are archival specimens, and the
9 question is, are the numbers and types of specimens adequate
10 to demonstrate effectiveness for the indications stated in
11 these applications? And this is what you were addressing.
12 Could you clarify your answer in terms of that question?

13 DR. WILSON: I would just reiterate what Dr.
14 Edelstein and Dr. Reller said earlier. We don't know. I
15 mean, these were sera that came from sources labeled as a
16 disease state, but we really have no clinical data, we have
17 no histopathological, and we have no follow up data.

18 So I don't really know what it means when they say
19 a specimen came from a patient with "chronic hepatitis." I
20 don't really know what that means. And I have concerns
21 about even the patients who were labeled as acute hepatitis,
22 because clearly some of those sera were not reliable when
23 they were tested.

24 So I would say that the answer is no. And in
25 terms of what additional data or changes, I would want to

1 have a very well characterized panel of sera.

2 DR. CHARACHE: Other questions or comments? Dr.
3 Specter?

4 DR. SPECTER: Steve Specter. Two questions.
5 Rather than a flat "no" I would say there wasn't a real
6 problem with numbers in terms of theoretical numbers, even
7 though they weren't particularly good. So I think they had
8 the proper numbers, had they been well pedigreed, is the
9 term I'll use.

10 The other thing, though, that I think is important
11 is the last point on there which actually ties in with
12 Question 5, and that is in terms of vaccination. And I
13 think it's very clear that with the response rate they had
14 for looking for anti-HBs in vaccinated patients, the results
15 were rather alarming.

16 And I don't think it's difficult at all to find
17 vaccinated individuals in the United States to get
18 sufficient numbers to do this, and they should be people who
19 are known to have had the full series of vaccinations, to
20 know in fact that you are getting rates that are either
21 historically correct or you're checking against another
22 panel. That you should be able to do very easily, and I
23 think that is a must. You know, 100 such specimens should
24 be easy to come by, and should be quite sufficient to give
25 you a definitive answer there.

1 DR. CHARACHE: Mr. Simms?

2 MR. SIMMS: I need to comment on this, as DiaSorin
3 did submit a data set, single samples from vaccinees, but
4 the measured value on these specimens was like around 80,000
5 international units or greater for each specimen. We
6 believed that was too high to adequately assess their
7 assays, so that's why we only paid attention to the vaccine
8 recipients who we initially thought had received the full
9 regimen of vaccinations.

10 But to your comment that it's easy to come by, you
11 know, yes, it is. But then again you're looking at people
12 that have very high levels of antibody after the full
13 vaccination series. Thank you.

14 DR. WEINSTEIN: Can I ask a question?

15 DR. CHARACHE: Yes.

16 DR. WEINSTEIN: Can you just clarify that last
17 comment? Some of the paperwork that was sent, I think you
18 were questioning the validity of the very high titers. Are
19 you saying now that you believe them, but because it was too
20 close to vaccination, that you wanted to throw them out?

21 MR. SIMMS: I didn't mean to imply that I
22 disbelieved the results that were submitted to us. My
23 comment was intended that one of the things that we should
24 be looking at is the accuracy around the cut-off. The cut-
25 off is set for an immune status at 10 milli international

1 units, so in my estimation one of the good ways to measure
2 that is from a vaccination series. So that was the gist of
3 my comment, not the fact that I disbelieved any of the
4 documentation that was submitted to us.

5 DR. CHARACHE: Dr. Edelstein?

6 DR. EDELSTEIN: Edelstein. I would like to remind
7 everybody that this is one case where the reference test
8 wasn't used, because we need to know whether the cut-off
9 point was close to the 10 milli international units. And we
10 don't have that data for the reference set, so it makes it--
11 and that's what we are interested in. We're not interested
12 in people with very high titers. We're interested in those
13 who have something close to the break point.

14 DR. CHARACHE: All right. I think we are--yes,
15 Dr. Seeff?

16 DR. SEEFF: In that regard we have to remember,
17 too, that in time, even after third injection, you begin to
18 lose antibodies, so that by the time you're 10 years out you
19 may find that you're down to this particular figure. So I
20 think if we're going to be wanting to find out if this is
21 effective to screen for a response to vaccine, it should
22 probably be done after the third injection and probably,
23 hopefully within the first year, because at that point I
24 guess we would expect the peak percentage to be positive.

25 DR. CHARACHE: Any other comments on 4? Dr.

1 Sanders?

2 DR. SANDERS: Dr. Sanders. I don't mean to
3 belabor the issue of testing during pregnancy, but I'm still
4 really not clear if a neutralization test was done to
5 confirm the hepatitis B surface antigen positivity of the 12
6 false positives.

7 DR. CHARACHE: It's--please correct me if I'm
8 incorrect, but I believe that the reference method had the
9 confirmatory test performed, according to the standards of
10 that method; but not the DiaSorin, is that correct?

11 DR. SANDERS: So the reference test with
12 neutralization was negative, and the DiaSorin 12 positives
13 were positive but they were false positive?

14 MR. SIMMS: I'm getting a shaking of the head from
15 Ms. Poole.

16 DR. THRUPP: Wasn't it half of them? Six of the
17 12 were false? Wasn't--

18 DR. SANDERS: I just need clarification on that,
19 and maybe DiaSorin can, when they have a moment.

20 DR. CHARACHE: And shall we go on to Question 5?
21 This question refers to the one we actually had discussed a
22 little bit, which is, the assay detected responses to
23 hepatitis B vaccine in 12.5 percent of studied specimen
24 sets. Is this sufficient to demonstrate effectiveness for
25 the anti-HBs indications for determining immune status?

1 I think this has been discussed, but let's go on
2 and say, if not, what additional data or changes in
3 indications would be appropriate?

4 A recommendation has been made that they be new
5 vaccinees. Are there other recommendations that can help
6 the FDA or the manufacturer? Dr. Edelstein?

7 DR. EDELSTEIN: Yes. That they use a parallel
8 test that's properly calibrated. That seems obvious, but--

9 DR. CHARACHE: Dr. Rodis?

10 DR. RODIS: The numbers raise an issue of concern
11 again regarding false negativity. From all the comments,
12 the last three or four comments referred, one would have
13 imagined that after two assays that hadn't been done years
14 later, but clearly weeks later from two injections, we
15 should have expected, I think, a higher rate than 12.5
16 percent. This in conjunction with the fact that in the
17 dialysis group we identified none of those patients as
18 hepatitis surface positive, whereas the reference lab I
19 think had six of them. Again, both of those together give
20 me concern that there is a high false negative rate
21 regarding this assay.

22 DR. TUAZON: Maybe they can use this--Tuazon--
23 maybe they can use all this assay on already specimens
24 banked on clinical trials that have used the efficacy of
25 this vaccine.

1 DR. CHARACHE: Yes, there may be other sources
2 that would be available.

3 DR. TUAZON: Right, like those that is--that has
4 shown very high antibody responses.

5 DR. CHARACHE: Shall we go to the last question,
6 Question 6?

7 DR. GUTMAN: Can we backtrack to the previous
8 question?

9 DR. CHARACHE: Yes.

10 DR. GUTMAN: Because the sponsor did have
11 information that would be relevant, I think, to clarifying
12 the previous point about the testing and the reference
13 method versus their method.

14 DR. CHARACHE: Excellent. Please, Ms. Smith.

15 MS. SMITH: To answer Dr. Sanders' question, to
16 clarify things, there were the external site testing and the
17 internal. The internal, all the positives were confirmed.
18 Confirmatory testing was performed on the Abbott on all
19 those samples. DiaSorin was just the one because we don't
20 have a confirmatory step.

21 On the external, the 12, they were repeated by our
22 assay and by the Abbott assay but were not--confirmatory
23 testing was not performed on either one of those.

24 DR. CHARACHE: Thank you very much.

25 Dr. Reller?

1 DR. RELLER: On the Abbott confirmatory testing,
2 how was that done, and was neutralization part of it?

3 MS. SMITH: Yes, with all of the Abbott packages.

4 DR. CHARACHE: Questions? Yes, Dr. Specter?

5 DR. SPECTER: The data set here, I mean, there was
6 a comparison done, and you have 192 specimens that were
7 tested. These are in vaccinees, now. Okay? One hundred
8 and sixty were negative by Abbott, and 154 were negative by
9 the DiaSorin.

10 DR. TUAZON: Steve, what page is that?

11 DR. SPECTER: It's on page 47 of the second
12 section of the book on anti-HBs. So in essence you have
13 seven discrepant samples, that is, positives. You had 28
14 positives by the Abbott test, and 35 of those--or 35
15 positives by the DiaSorin, so you had 7 more positives by
16 the DiaSorin test. So they were compared, actually.

17 DR. EDELSTEIN: But not using a calibrator. The
18 Abbott test didn't use a calibrator.

19 DR. SPECTER: It does not appear to show that. I
20 don't know what the "NC" stands for.

21 DR. EDELSTEIN: Not calibrated.

22 DR. SPECTER: Not calibrated? Well, no. No, but
23 it gives--it's "NC plus .05". Negative control?

24 MS. SMITH: In the data set that you have it was
25 positive by Abbott, positive by us. It was based on cut-

1 off, comparison to cut-off. What Tom is presenting and what
2 the 12 percent is, is not compared to the cut-off but
3 compared to the 10 milli international unit calibrator which
4 Abbott did not have as part of their standard kit.

5 So the data you're looking at is positive to
6 positive. The data that Tom was looking at was positive
7 that was greater than 10, rather than positive that was
8 between a negative and 10. So, yes, there was more
9 reactivity going on than just the 12 percent, but Tom's
10 point was that it didn't make it above the 10 for many of
11 these samples.

12 DR. SPECTER: Right, but in this particular case
13 the numbers aren't that far off, and the terms of the
14 percentage is even positive, so it's a good reflection and--

15 MS. SMITH: Correct. It's a good reflection that
16 perhaps these people really didn't boost up very well at
17 that point.

18 DR. SPECTER: Right, but the important point is,
19 the comparison to the other test here is quite favorable.

20 MS. SMITH: Yes. Thank you.

21 DR. SPECTER: That was what we needed to know.

22 DR. CHARACHE: Yes, that's helpful. Could we look
23 at Question 6, please?

24 Currently CDRH approved devices that are not
25 cleared or licensed by CBER for blood and blood product

1 screening contain the warning: "This assay has not been FDA
2 cleared or approved for the screening of blood or plasma
3 donors."

4 Since a number of these assays under consideration
5 are also used to protect the U.S. blood supply, i.e.
6 hepatitis surface antigen, total anti-HBc, and anti-HBs, is
7 this current warning sufficient or should there be stronger
8 or different labeling to ensure that the assays are only
9 used for in vitro diagnostic use or monitoring indications?

10 So the question is, will the wording, "This assay
11 has not been FDA cleared or approved for the screening of
12 blood or plasma donors," be sufficient to ensure that it is
13 not used for that purpose? Any thoughts? Dr. Nolte?

14 DR. NOLTE: I mean, as a laboratory director, that
15 would be sufficient for me. I mean, under penalty of death?

16 DR. WILSON: I wouldn't have a particular concern
17 that the Red Cross or AABD blood banks are going to be
18 confused and think that they can use this.

19 DR. EDELSTEIN: My comment would be, why not say
20 it has not been FDA cleared or approved for the screening of
21 blood or plasma donors and should not be used for such?
22 Just include that "should not be"?

23 DR. CHARACHE: Perhaps that would help slow people
24 down as they read it, because there is a lot of things that
25 have that other warning, but that might help, just those

1 three words.

2 Dr. Rodis?

3 DR. RODIS: I'm not sure of the science behind
4 adding that. In other words, do we have data--that suggests
5 to me that there is data that says it would be bad to use
6 it, as opposed to it's not approved for that indication,
7 that we have data that says it's not a good thing to use as
8 screening. The "should" part, there's just a judgment there
9 that sounds like there's some evidence that we have that
10 it's bad? Is there? Why do we need to change that, if
11 we've already heard from lab directors that they wouldn't
12 use this, or the Red Cross wouldn't?

13 DR. EDELSTEIN: Because we don't have the data on
14 their performance in that population, so it could perhaps be
15 dangerous.

16 DR. CHARACHE: Ms. Poole?

17 MS. POOLE: And that data would also have to be
18 submitted to the Center for Biologics and the Center for
19 Devices and Radiological Health, which we only look at
20 indications for diagnostic use and not for screening blood
21 or blood products.

22 DR. GUTMAN: Yes, let me comment on this, This,
23 as I told you this morning, has been a product line that has
24 been transferred, and the people at CBER take a very broad
25 view of the mechanisms that are involved in public health.

1 It would be unlikely Red Cross would do something
2 iconoclastic, but it's possible that a smaller lab in the
3 middle of the night might do something iconoclastic, and so
4 we would like to make our labeling as good as it could be.
5 You know, we would interact with CBER and try and be
6 comfortable, and I personally like the inclusion of the
7 extra language, in that it makes it a little bit more
8 forceful.

9 We have the Modernization Act which suggests we're
10 really not supposed to go outside of the four corners of the
11 wall, of the labeling, but this has been an area that's
12 sensitive to them, and any language that might help them
13 feel more comfortable probably would be good.

14 DR. CHARACHE: It probably would be helpful for
15 DiaSorin as well, to emphasize how they want their product
16 employed. Yes, Dr. Thrupp?

17 DR. THRUPP: Lauri Thrupp. Parenthetically, it
18 might be observed that the development of the new generation
19 DiaSorin products may have the--possibly are more sensitive,
20 at least in certain populations, and it's conceivable that
21 it might even be a better product for blood bank screening,
22 too, but the data has not been presented and so we can't
23 take that into account in our deliberations here, but in the
24 future that might be a development.

25 DR. CHARACHE: But we won't see it if it is.

1 Okay. I want to thank everybody for these
2 questions.

3 The next item on the agenda would be to welcome
4 the sponsor's response to provide comments, respond to any
5 issues that were raised during this discussion, and we would
6 appreciate your thoughts.

7 MS. SMITH: Thank you all very much for the day.
8 It has been very interesting. There were several comments
9 made that I would like to either correct or clarify in your
10 mind.

11 During lunch we went back and looked at the
12 hemodialysis samples. There were five Abbott positive--
13 reference assay positive, DiaSorin negative samples in that
14 population. Now, we don't have multiple retesting by Abbott
15 as per the package insert. We did retest them once. We
16 retested four out of the five samples once. They all came
17 up negative, so that gives us a suspicion that the initial
18 was a false positive.

19 Now, to address why were there so few positives in
20 the hemodialysis group, there are a number of possibilities.
21 One that we have looked--one that is kind of an interesting
22 concept is, according to the CDC, hemodialysis patients are
23 no longer listed as a major risk. And that could be because
24 there is a lot of vaccination going on, they are catching
25 them early, and they are also segregating the hepatitis

1 positive dialysis patients from the hepatitis negative
2 dialysis patients, keeping the machines separate so that
3 there is no possibility to accidentally transfer from one to
4 the other. So I think that could be the reason why.

5 The pregnant women, once again I wanted to
6 emphasize that the 18 positives that were tested at
7 DiaSorin, confirmed positive, DiaSorin results--confirmed
8 positive by Abbott, DiaSorin results, 16 were positive on
9 initial testing, 2 were equivocal.

10 Of the 12 that were done at the external sites
11 that did not have confirmatory, we did have some initial
12 repeat testing. Four of them, the DiaSorin became negative.
13 Four of them, the Abbott became positive. So when you look
14 at that, we end up--it ends up being 4 out of the 324
15 samples that were false positive by us turns out to be about
16 1.5 percent, which is about the same as what Abbott got in
17 that population also, so you need to look at it in those
18 terms, too.

19 The issue with the ABAUK, the anti-HBs and the
20 vaccinees, what we would offer is that the panel with all
21 the vaccinations are now available from the vendor, and we
22 would offer to purchase them and do the testing on them to
23 show that.

24 In addition, we do have the single samples. They
25 do have very high titers. That was because these particular

1 patients apparently were kept--their titers were enhanced on
2 purpose to keep--they are then used to draw, to donate for
3 immunoglobulin, HBV immunoglobulin vaccines, so their titers
4 are kept high. That's why they were 80,000. Anyway, that
5 kind of clarifies that question. So we will purchase those
6 panels with the final draw.

7 Oh, the other question that was with that was
8 where we didn't know--there was no information about when
9 the draws were. Day zero represented the first vaccination.
10 That was pre-vaccination and the first dose. So they drew
11 the blood, then they gave them their first dose. The next
12 sample was drawn at day 45, I believe. That was, they drew
13 the blood and then gave another dose, so day 45 was the
14 second dose. And then the subsequent doses were days 83,
15 and I forget. They ended at day 108, so all the subsequents
16 to day 45 were simply additional draws against the second
17 dose. The third dose came at 180 days. Okay? So hopefully
18 that clarifies some of that for you.

19 The issue about the IgM and whether it was--the
20 fact that the acutes were not--did not seem to have them, I
21 emphasize again and I remind you again, we did also have
22 panels, acute panels. We had nine of them, where we show
23 these nine individuals who had acute infection, we show the
24 M going up and the M coming down, and I think that's a much
25 more interesting thing to look at because it points out Dr.

1 Seeff's earlier comment that we should really be following
2 this patient to see what happened to him. One snapshot
3 doesn't give the answer. So we do have several chronic and
4 several acute panels where you do see the M go up and down.

5 And I think that was--that covered all the issues.
6 So I thank you all very much, and have a good afternoon.

7 DR. CHARACHE: Thank you.

8 MS. SMITH: Should I stay up for questions?

9 MS. POOLE: No.

10 DR. CHARACHE: She said it, I didn't.

11 Okay. I think now the panel will be voting on
12 each of these in turn. Freddie Poole, our Exec Sec, will
13 read the regulations as they apply to the vote and indicate
14 for us who is authorized to vote in this particular panel.

15 MS. POOLE: I will now read the panel
16 recommendations or options you have, according to the
17 premarket approval applications. The Medical Device
18 Amendments to the Federal Food, Drug and Cosmetic Act, as
19 amended by the Safe Medical Devices Act of 1990, allow the
20 Food and Drug Administration to obtain a recommendation from
21 an expert advisory panel on designated medical device
22 premarket approval applications that are filed with the
23 agency. The PMA must stand on its own merits, and your
24 recommendation must be supported by safety and effectiveness
25 data in the application or by applicable publicly available

1 information.

2 Safety is defined in the Act as "reasonable
3 assurance, based on valid scientific evidence, that the
4 probable benefits to health, under conditions on intended
5 use, outweigh any probable risk." Effectiveness is defined
6 as "reasonable assurance that in a significant portion of
7 the population, the use of the device for its intended uses
8 and conditions of use, when labeled, will provide clinically
9 significant results."

10 Your recommendation options for the vote are as
11 follows:

12 Approval, if there are no conditions attached.

13 Approvable with conditions. The panel may
14 recommend that the PMA be found approvable subject to
15 specified conditions, such as physician or patient
16 education, labeling changes, or a further analysis of
17 existing data. Prior to voting, all of the conditions
18 should be disclosed by the panel.

19 Or the third choice, not approvable. The panel
20 may recommend that the PMA is not approvable if the data do
21 not provide a reasonable assurance that the device is safe,
22 or if a reasonable assurance has not been given that the
23 device is effective under the conditions of use prescribed,
24 recommended or suggested in the proposed labeling.

25 Following the voting, the Chair will ask each

1 panel member to present a brief statement outlining the
2 reasons for their vote. Our voting members today are
3 Natalie Sanders, Carmelita Tuazon, Melvin Weinstein, and
4 Michael Wilson. In addition, to meet a quorum we have
5 permission and authority to appoint temporary voting
6 members.

7 "Pursuant to the authority granted under the
8 Medical Devices Advisory Committee charter dated October 27,
9 1990, and as amended August 18, 1999, I appoint L. Barth
10 Reller, Leonard Seeff, Steven Specter, and Lauri Thrupp as
11 voting members of the Microbiology Devices Panel for this
12 meeting on January 20th and 21st. For the record, they are
13 special government employees and consultants to this panel
14 or other panels under the Medical Devices Advisory
15 Committee. They have undergone the customary conflict of
16 interest review and have reviewed the material to be
17 considered at this meeting."

18 And it is signed David W. Feigel, Jr., M.D. MPH,
19 Director, Center for Devices and Radiological Health.

20 Dr. Charache?

21 DR. CHARACHE: One moment.

22 The first PMA that we are going to vote on is
23 hepatitis B surface antigen, and the indications for use in
24 the material which we received, it says that the test is an
25 in vitro enzyme immunoassay, EIA, intended for use in the

1 qualitative determination of hepatitis B surface antigen,
2 HBsAG, in human serum or plasma. This assay is indicated
3 for use as an aid in the diagnosis and monitoring of acute
4 and chronic hepatitis B virus, HBV, infection in both low
5 and high risk adult populations. This kit may also be used
6 for hepatitis surface antigen testing during pregnancy, and
7 for monitoring of HBV therapy. This test is not for blood
8 donor screening. This test should be used in conjunction
9 with other hepatitis B serologic assays to ensure proper
10 assessment of the patient.

11 May we have a motion from a voting member for
12 approval, approval with conditions, or not approval?

13 DR. SANDERS: Sanders. I move that we approve the
14 hepatitis B surface antigen test by DiaSorin, also known as
15 the ETI-MAK-2 PLUS, without conditions.

16 DR. CHARACHE: We have a recommendation that the
17 hepatitis B surface antigen be approved without any
18 recommendations or conditions. Do we have a second?

19 DR. SPECTER: I second.

20 DR. CHARACHE: We have a second. Moved and
21 seconded. Discussion? Does a member have any concerns
22 about approving the hepatitis B as we read its usage,
23 without any recommendations for modification or change? Dr.
24 Weinstein?

25 DR. WEINSTEIN: Yes. I guess I still have

1 concerns over not having enough data, and I'm trying to
2 think in my own mind whether it only applies to the hep B
3 surface antigen or whether it applies to all that we have
4 heard and discussed today. So at the moment that's my
5 concern. I would like to hear what other people have to
6 say.

7 DR. CHARACHE: Dr. Tuazon?

8 DR. TUAZON: Tuazon. I thought we had some
9 discussions about the need for some data in terms of this
10 test being used during pregnancy. I thought that's one of
11 the discussions that we had, that we are asking for more
12 data.

13 DR. SANDERS: Sanders. That was mentioned.
14 However, I was perfectly satisfied with the last explanation
15 that Ms. Smith gave, and that is why I asked for approval
16 without conditions.

17 DR. CHARACHE: Oh, you were satisfied that when
18 they took the 12 positives and retested them, although there
19 were no other--we heard from Mr.--oh, I'm sorry. I'm sorry.
20 I am instructed we have to vote on the motion. This is for
21 approval. We are out of order to discuss this one. If we
22 vote to approve it with no changes or recommendations of any
23 kind, then we vote at this time. We only discuss it if
24 there's recommendations for change. So we will vote at this
25 time. Dr. Seeff? We'll go around.

1 DR. SEEFF: I would not support that.
2 DR. CHARACHE: One against.
3 DR. WILSON: Against.
4 DR. CHARACHE: Against
5 DR. THRUPP: Against.
6 DR. CHARACHE: Against. Sorry. Voting members.
7 Sorry. Doctor?
8 DR. SPECTER: For.
9 DR. RELLER: Against.
10 DR. TUAZON: I am against.
11 DR. SANDERS: For.
12 DR. WEINSTEIN: Against.
13 DR. CHARACHE: So that motion does not--it was two
14 for and the remainder against. Could we have a show of
15 hands, please, on that, just to be sure we have it correct?
16 How many people were in favor of that motion?
17 [A show of hands.]
18 DR. CHARACHE: There were two. How many were
19 opposed to that motion?
20 [A show of hands.]
21 DR. CHARACHE: Okay. Do we go around to explain
22 votes or not? Okay. I'm sorry. I'm not following my
23 table, my crib sheet.
24 Now we ask then for a new main motion, which now
25 may be either approve with conditions or not approvable.

1 May we have another motion, please?

2 DR. SANDERS: Sanders. Since no one else has
3 taken the lead on that, I will ask for approval with
4 conditions, with one of the conditions being, I'm going to
5 make an assumption for my colleagues, that there be more
6 data submitted about the use of this test in pregnant women,
7 and that there be some type of post-market study.

8 DR. CHARACHE: Okay. We are going to first take
9 the motion. Do we have a second to the motion, approvable
10 with conditions?

11 DR. SPECTER: Second.

12 DR. CHARACHE: We have a recommendation and a
13 second. Now at this time we do have discussion. I'm going
14 to suggest that each person jot down the areas they would
15 like to discuss, and then we will discuss them, these
16 issues, as they come up, one at a time, but you won't forget
17 the points that you would like to see addressed during the
18 course of the discussion.

19 So the first discussion item which has been put--
20 Dr. Reller?

21 DR. RELLER: Excuse me. It would help if we could
22 have the indications that you read out the list at the
23 outset.

24 DR. CHARACHE: Yes. Do we have a copy of those?
25 Okay, indications for use. An aid in the diagnosis of acute

1 and chronic hepatitis B viral infection, monitoring acute
2 and chronic hepatitis B viral infection, monitoring of HBV
3 therapy, HBV antigen testing during pregnancy, anti-
4 hepatitis surface to assess past exposure to hepatitis B.

5 Here we go. Thank you. Oh, I'm sorry, that's for
6 a different one, that's not for this. All right, let's take
7 up the--

8 DR. RELLER: So it's for the first four on that
9 list, in accord with the ETI-MAK-2 PLUS intended use
10 statement.

11 DR. CHARACHE: Yes.

12 DR. RELLER: I'm ready.

13 DR. CHARACHE: All right. Let's take up first the
14 discussion point raised by Dr. Sanders. Would you like to
15 restate the point you would like discussed, Dr. Sanders?

16 DR. SANDERS: I would recommend that there be some
17 type of post-marketing data collected on the use of the MAK-
18 2 PLUS in pregnant women. And I would also, with regard to
19 that, recommend that that include the DiaSorin assay, the
20 development of and data subsequently submitted to this panel
21 of confirmatory neutralization antibody type of testing on
22 the positive--

23 DR. CHARACHE: No, we're going to take one at a
24 time. So the first question has to do with the pregnancy.
25 We'll come back to any other issues that people want. The

1 use in pregnancy, and I think the suggestion has been raised
2 that there be additional data. The group can recommend what
3 type of data you would like to see, if there are specific
4 data; whether you feel it should be pre- or post-market
5 information that is obtained.

6 Can we address the question that has been raised
7 about the use of this test during pregnancy, its
8 recommendation of intended use? What further information
9 would you wish? Dr. Weinstein?

10 DR. WEINSTEIN: Well, I'm still uncertain as to
11 whether the DiaSorin HBsAG assay is more sensitive or less
12 specific than the Abbott assay or the reference, the
13 reference assay. So I think we need more data to assess
14 that particular problem.

15 DR. CHARACHE: I believe also that we heard from
16 Mr. Simms that they did do all the other tests on those
17 samples, the 12 that were positive that the Abbott gave an
18 initial negative on, and no other markers were positive
19 other than the antigen. Are we correct on that? Is Tom
20 here?

21 MR. SIMMS: [Nods affirmatively.]

22 DR. CHARACHE: Okay, he is shaking his head that
23 this is correct, so that that was the only marker that was
24 positive, was the antigen alone. Now does that help at all
25 in other information that you would like to see? Dr. Reller?

1 DR. RELLER: Not only were there 12 of 19 that--
2 differences, although there has been some additional
3 explanation. What I would like to know from the agency's
4 standpoint, are there guidelines to industry for the number
5 of validated positives that are required, against which a
6 new diagnostic product needs to be measured?

7 For example, we already, I think it's clear that
8 for antigen detection that one wants to have a confirmatory
9 test and a neutralization, with neutralization. But is the
10 number of positives delineated anywhere, and could we have
11 some statistical--either define that it is, or some comment
12 about the statistics? Looking at these numbers, I'm very
13 uncomfortable, no matter what the performance is, to make a
14 statement for diagnostic use in pregnant women.

15 DR. GUTMAN: Yes. There in fact are not
16 guidelines or not standards in place. And that would drive
17 the statistics, so Kristen is not going to be able to help
18 us, since we can't tell her reasonable targets. I think
19 that's one of the reasons we are actually having the panel
20 meeting, is to establish reasonable targets, and part of
21 that deal is to decide what claims you can or can't support
22 off of this data set and what data you need pre- or post-
23 market. But I don't have an answer. Hopefully you'll give
24 me the answer, collectively.

25 DR. RELLER: Well, there are some very serious and

1 expensive implications for accuracy in this testing, and I
2 would like to hear what Dr. Rodis has to say about this.
3 But it seems to me, as many pregnant women as there are in
4 this country and the number of HIV--I mean, excuse me,
5 hepatitis B positives, that I mean we don't--we shouldn't
6 have to make--no one should be in the position of having to
7 make decisions about a widely used test based on 19 positive
8 samples. Now, what the number should be is open to
9 discussion, but this just seems totally inadequate to me for
10 an indication.

11 DR. CHARACHE: Dr. Specter?

12 DR. SPECTER: I would like a clarification,
13 because the data set I have shows no other markers. So was
14 there or was there not other markers done on these? I mean,
15 they--

16 DR. CHARACHE: Could you speak in the microphone,
17 please, to be very clear on this?

18 MR. SIMMS: The initial data set that we received
19 and that you have copies of does not have that information
20 in it. The later data set, if you remember, early on in my
21 talk I mentioned that we were under essentially active
22 review with DiaSorin and exchanging electronic files, and
23 one of the files that we did receive contained this
24 information on those 12 specimens, so the FDA does have it.
25 You don't have a copy of it.

1 DR. CHARACHE: Ms. Smith?

2 MS. SMITH: Two points that I just want to
3 clarify, too. There weren't 19 positive samples. There
4 were 37 positive samples.

5 The other issue was, we--the external sites, due
6 to just the testing, it was easier to tell them to test all
7 12, you know, do all six markers on Abbott reference and us
8 while you're doing the testing, than to say to them, "Okay,
9 only do this. Don't do those for these couple of samples."
10 So for the external sites, they just went ahead and did all
11 the markers.

12 We initially only submitted the HBSAG because
13 that's the only one we were claiming that you use for
14 testing on pregnant women. Subsequent review by Mr. Simms,
15 he asked, "Gee, it would be nice to know what the other
16 markers were, to know if these were true positives or not."
17 We then provided that data from the external sites. The
18 internal testing only did the HBSAG.

19 DR. CHARACHE: Thank you. Dr Thrupp

20 DR. THRUPP: I'm not sure I heard what Dr.
21 Reller's vote was tending to be, whether your comment was
22 meant to say you would not support even approvable with
23 conditions of more data or something. Were you tending to
24 not want to approve it, period, based on the numbers?

25 DR. RELLER: Approvable with conditions of

1 requiring more numbers and not approvable is--I mean, it
2 seems to me a semantic issue. Based on the data currently
3 available, you know, my notion if it came to that and my
4 vote would be to not approve it as it stands, period

5 DR. THRUPP: Well, I was trying to think of a way
6 to phrase it that would try to move things along a little
7 bit because, one, we have said this before and it has come
8 out in the discussion, not only in pregnant women but as a
9 diagnostic aid in patients that are being referred in the
10 hospital practice or in office practice where there is some
11 disease going on, whether it be rheumatologic, or there's a
12 lot of other manifestations of hepatitis, the entry point
13 for these are the two tests. The screening for all of these
14 people is the surface antigen test and the B antibody.

15 Then the algorithm should be built in, and I would
16 think that at some point in this deliberation we could
17 consider a recommendation that the package insert emphasize
18 this point, so that testing with all of the markers need not
19 be done on the ones that are negative for HBSAG. But that
20 might take a separate motion. To respond to the present
21 question, I would raise the issue that it would be
22 approvable but that a condition would be, data would be
23 submitted along the lines that a repeat test and a
24 confirmatory neutralization test be required for the surface
25 antigen test, just as it is for the CBER-approved reference

1 test.

2 DR. CHARACHE: Okay. I am pretty sure, and I will
3 check on this, that we can't make that recommendation
4 because the company has not submitted any confirmatory test
5 or any--

6 DR. THRUPP: Well, no. I meant that they could do
7 so.

8 DR. CHARACHE: Okay. Let's at this time vote on
9 this issue of the use in pregnancy, and let's do it in two
10 ways. First let's vote whether we think there should be
11 more data made available, and then we'll vote on whether
12 that data should be pre-market or post-market. So we'll
13 vote on whether we need more data to understand whether this
14 should be used in its current form as a test during
15 pregnancy, yes or no, whether we need more data. And then
16 we'll determine whether that increased data should be pre-
17 or post-market. Dr. Seeff?

18 DR. SEEFF: I think we need more data.

19 DR. WILSON: More data.

20 DR. CHARACHE: Dr. Thrupp

21 DR. THRUPP: More data, whether or not pre or
22 post.

23 DR. CHARACHE: Dr. Specter?

24 DR. SPECTER: More data.

25 DR. RELLER: More.

1 DR. TUAZON: More data.

2 DR. SANDERS: More data. However, I would like
3 for the record to restate that Ms. Smith did say that the
4 false positive rate was 1.5 percent in the overall picture
5 of the pregnant samples, and that was comparable to the
6 current reference test. I just need to state that.

7 DR. WEINSTEIN: More data.

8 DR. CHARACHE: Okay, so it was unanimous that we
9 need more data. Now let's determine whether that should be
10 post-market follow up information or whether it should be
11 pre-market. So we'll just ask you to say pre-market or
12 post-market.

13 DR. SEEFF: Why don't you start at that end for a
14 change?

15 DR. CHARACHE: I'll start at that end on the next
16 one.

17 DR. SEEFF: Unfortunately, I feel we need more
18 data for all of these, not only for this, and I am sort of
19 confused about what the difference is between approving it
20 with conditions and not approving it, because those
21 conditions have to be met, in my view, in order to approve
22 it.

23 DR. CHARACHE: Well, we will, after discussion,
24 we'll vote on the whole question.

25 DR. SEEFF: I think I would like it pre-market.

1 DR. WILSON: Pre-market
2 DR. THRUPP: Pre.
3 DR. SPECTER: Post.
4 DR. RELLER: Pre.
5 DR. TUAZON: Pre-market.
6 DR. SANDERS: Post-market.
7 DR. WEINSTEIN: Pre-market.
8 DR. CHARACHE: Okay. There were two pre-market
9 and six post-market.
10 We'll go in the other direction on the next issue.
11 Now what is the next issue that someone would like to see
12 modified?
13 DR. TUAZON: Its indication in terms of high risk
14 adult population, especially the HIV positive population.
15 DR. CHARACHE: Could you clarify that? You want
16 to know whether--
17 DR. TUAZON: No, because in terms of what is
18 written, intended use, it includes both low and high risk
19 adult populations.
20 DR. CHARACHE: So you would like to see more--
21 DR. TUAZON: We don't have any data on HIV
22 population.
23 DR. CHARACHE: So you would like to see data on
24 HIV populations before they say low or high risk
25 populations?

1 DR. TUAZON: Exactly.

2 DR. CHARACHE: Okay. Any discussion of that? Any
3 other discussion of that issue

4 DR. THRUPP: HIV and immune suppressed and STD.

5 DR. CHARACHE: Okay, so this just addresses the
6 question of whether the claim should be high risk without
7 more data. Okay.

8 DR. THRUPP: Well, there is need for more data,
9 but those populations should be available readily.

10 DR. CHARACHE: Okay. Dr. Reller?

11 DR. RELLER: Well, the intended use statement for
12 the surface antigen assay, I mean, says for use in high and
13 low risk, and we haven't been presented data on high and low
14 risk performance.

15 And then it says in the diagnosis and monitoring
16 of acute and chronic hepatitis B virus infection. For the
17 diagnosis and monitoring of acute and chronic, and we had a
18 prolonged discussion earlier about the ambiguities in the
19 data base having to do with true chronic or not, based on
20 the lack of the chronicity being adequately established with
21 the comparison.

22 And an aid in monitoring, I mean, I just--I have
23 not seen the data in terms of how that would be employed,
24 and I had thought that the use of the--the purpose of the
25 package insert was to, you know, inform the user as to how

1 the product should be appropriately used and the data base
2 on which its safety and efficacy for that purpose was
3 established.

4 And this may be a fantastic diagnostic product
5 that can do all of those things, but I just have not seen
6 the data base to support the claim in the intended use
7 statement, any of those claims. To me, there are not
8 sufficient data to support any of the claims in the intended
9 use section.

10 DR. CHARACHE: Dr. Thrupp

11 DR. THRUPP: I would suggest, however, that I get
12 the impression from the discussion from the sponsor that, at
13 least for the establishment of the chronicity, that they
14 should be able to, if we wanted to say pre-marketing, the
15 data should be accessible, such that they could establish or
16 document to our satisfaction that the chronicity, the
17 greater than six months was indeed established. They were
18 told that it was, but they don't have the data. But I think
19 it sounds as though that data should be readily accessible,
20 such that the collection of 100-some-odd--there was 50 and
21 73 and what others, maybe 150 patients that would probably
22 be documentable as to chronic infection, so that they may be
23 able to come up with. It's the other groups for diagnosis
24 that I'm more concerned about.

25 DR. CHARACHE: Any other comments?

1 DR. SEEFF: I can't agree with Dr. Thrupp. I'm
2 struggling with this because I'm not sure exactly what
3 should be done. I'm still convinced that if we're going to
4 make a recommendation, that we need to have pristine cases
5 of acute and pristine cases of chronic hepatitis against
6 which we can in fact--and the data presented to us that we
7 can understand that.

8 Now, it is probable that those data are available,
9 and I think if it was possible to tease that out and present
10 it in such a way that we could truly understand it, I would
11 be much more comfortable and be able to cast a vote to
12 support its use. I am concerned about a couple of things.
13 I'm still concerned about the high rate of surface antigen
14 positivity in the absence of anti-core, so that even in the
15 screening I'm not sure exactly how to deal with that, and I
16 need to--I would love to know more about that.

17 But, more than that, I do wish that we were able
18 to be clearer that we know that these studies were done
19 using cases that nobody would argue about. Looking at
20 where they were, I don't know who they were, and I suspect I
21 know who the groups were because I know the people in
22 California and I know the people in Florida, and I'm sure
23 they are correct. But I don't have those data that present
24 it to me in such a way that I can make sense of this. I
25 suspect this is a good test and is a useful test, but I

1 can't cast a vote until I know what I'm voting for, and I'm
2 not sure what I have.

3 DR. CHARACHE: Yes. I think this is very
4 important. We work from our best understanding.

5 DR. SANDERS: Sanders. I don't disagree with the
6 need for pristine data. However, I just want to remind the
7 panel that we have been asked to advise, and the FDA has
8 tried to implement a program that is least burdensome. To
9 request pristine data is not least burdensome and it is
10 definitely not minimal cost.

11 DR. SEEFF: I disagree. I mean, you have to come
12 up with a test that has meaning, and if you don't know what
13 it is that you have tested, how can you possibly come up
14 with a recommendation simply because you want to simplify
15 things? I think you can only simplify if you know what
16 you're dealing with, and frankly I'm certain--I think the
17 data are here.

18 And, as Dr. Thrupp says, they are there and can
19 probably be pulled out, and I would like to see those data
20 pulled out in such a way that I would be comfortable, pre-
21 marketing, because how could I in fact approve something to
22 be marketed when I don't know exactly what the test was
23 being used for or how to interpret the data? That's my
24 sense at this present time.

25 DR. CHARACHE: I think at this point we should

1 vote on the issue whether more data is required, and may we
2 change that to define acute or chronic, or would you like to
3 vote on the acute alone?

4 DR. GUTMAN: Can I just interject a couple
5 comments to make sure people understand some of the
6 semantics floating around here?

7 DR. CHARACHE: Please.

8 DR. GUTMAN: All right. I recognize there is a
9 certain ambiguity between not approving and approving with
10 conditions, although I suspect that is more than semantic to
11 the sponsor. If you approve with conditions, it does mean--
12 and you have asked that those conditions be met pre-market,
13 it does mean that that data set holds that submission
14 hostage until the conditions have been met. And if they are
15 not met, even if you say it's approvable, but those
16 conditions aren't met, then it never does become approvable.

17 So the post- to pre-market does change things, and
18 also the condition with approval versus unapprovable or not
19 approvable also changes things. And I don't know that the
20 division has a very long track record with either--with a
21 lot of pre-market conditions. In general, we have had some
22 pre-market studies, and it may be a matter of extent.

23 The issue of pristine data is on the table.
24 Actually that was my term, but it's a really important issue
25 to us as you are thinking about this because we are, as I

1 said before, looking for least burdensome without a sellout.
2 So we are--your comments on how much or how pristine the
3 data is, is really essential to the life of this submission
4 and submissions to follow it. And I alluded to, and it may
5 become more obvious in future panel deliberations, that in
6 searching for least burdensome we've been trying to figure
7 out ways where you might generalize the claim without
8 perhaps having the same sets of data and be more liberal.

9 Dr. Reller hit the nail on the head when he said,
10 "Yes, but you won't be able to label it in the way that
11 we've always labeled things." We have not labeled things
12 with general claims. We have tended across the division,
13 certainly in the Microbiology Branch, to covet more
14 information about a particular subset of patients.

15 And so it's really--your recommendations here are
16 really quite profound for this submission and for future
17 submissions in terms of, one, whether you want pristine
18 data, or how pristine is pristine; two, are you willing to
19 take this data set or other data sets and general claims off
20 of more general data. And frankly, you know, this is kind
21 of the cutting edge in terms of premarket requirements for
22 conditional approval.

23 DR. CHARACHE: Dr. Reller?

24 DR. RELLER: For efficiency, and this may not be a
25 question that Dr. Gutman can answer, to make the process

1 less burdensome, is it better to--recognizing that the
2 advisory committee is only that, that the decision rests
3 with the agency--is it better to have approvable with lots
4 of pre-market conditions, or to simply say, as it stands,
5 it's not approvable, and these are the kinds of data that we
6 think, in an advisory capacity, would be advantageous in the
7 public's interest to have presented to the agency, either
8 teased out, reformulated, or gathered prospectively to move
9 the process along; so to have something, you know, clean and
10 neat as a recommendation at this meeting, or to have
11 something that has so many strings attached to it that it--
12 what's the better way to go? What's the advice to the
13 advisory committee? I think we know what we want to do.
14 It's just how do you want us to package it?

15 DR. GUTMAN: The deal here is that you're on such
16 new ground for us, it's just--I just don't know that I can
17 answer. I can't answer. We have no--you're hitting me in
18 an area where I have no experience.

19 DR. CHARACHE: I think we just have to move ahead
20 as an advisory board and decide ourselves whether we have
21 enough information to be very specific about what kind of
22 data we would like to see, whether it has to be generated or
23 just simply reanalyzed, or whether we as a board want to
24 vote against this particular recommendation and go with the
25 third, which is disapproval, along with recommendations.

1 And I think that in either event, to be least burdensome, we
2 have to be very specific for DiaSorin so that they know
3 exactly what the issues are and where to go.

4 So I think at this point we perhaps should vote,
5 and let's just vote on the issue that was raised, which is
6 whether we have seen enough data, either by inference or by
7 fact, which would permit us to say that we need more
8 information about acute--about patient populations to go
9 forward with this, and then we can decide whether it should
10 be pre- or post-market, on the high risk patient population.
11 So we'll go with the high risk patient population question.
12 Have we seen enough to feel that the data is complete, or do
13 we need more data either pre- or post-market.

14 This time we'll start on this side.

15 DR. SANDERS: Madam Chair, I do have to ask,
16 DiaSorin defined high risk as their hemophiliacs, IV drug
17 uses, and hemodialysis patients, so if we're going to vote
18 on that, let's specify what we consider high risk.

19 DR. CHARACHE: Dr. Sanders, we can't do that
20 because their recommendation used the word "high risk," and
21 as someone would read that, they would include patients at
22 high risk of getting hepatitis, which would be the full high
23 risk population. So we have to use their term, which is
24 high risk population.

25 Let's start with Dr. Weinstein and we'll go around

1 the other way.

2 DR. WEINSTEIN: I think we need more data.

3 DR. CHARACHE: Dr. Sanders?

4 DR. SANDERS: I'm satisfied with the data.

5 DR. TUAZON: More data.

6 DR. RELLER: More, pre.

7 DR. SPECTER: More data, post.

8 DR. CHARACHE: Dr. Thrupp

9 DR. THRUPP: I hate to try to split a vote, but I
10 was hoping that the question would be more focused. I think
11 that there--

12 DR. CHARACHE: This is focused on high risk
13 population.

14 DR. THRUPP: The additional groups of high risk
15 populations could be obtained post-marketing.

16 DR. WILSON: More data.

17 DR. SEEFF: Yes, I would like to see more data.

18 DR. CHARACHE: All right. May we have a show of
19 hands of how many believe we have more data of--with one
20 person feeling that the data is acceptable? Let's have a
21 show of hands of those who feel that the additional data can
22 be post-marketing, and then we'll vote on premarketing. How
23 many would recommend that the more data be post-marketing?

24 [A show of hands.]

25 DR. CHARACHE: Two. How many feel that it should

1 be pre-marketing?

2 [A show of hands.]

3 DR. CHARACHE: Five. Okay. So we have addressed
4 two aspects of this, which is that it's felt there should be
5 more data, pre-marketing, on the use of the hepatitis B
6 surface in the pregnant women and in the high risk patient.

7 Is there any other issue that people would like to
8 address? Dr. Weinstein?

9 DR. WEINSTEIN: Again, I wonder if this relates
10 solely to the hepatitis B surface antigen assay, but I think
11 there was a consensus--I think there was a consensus--that
12 we needed more data or at least a better defined patient
13 population with chronic hepatitis B, having to do with
14 meeting the current standard for that diagnosis, namely at
15 least six months with a positive hep B surface antigen.

16 DR. CHARACHE: All right. We have discussed that
17 fairly extensively. Is there anyone who would like to add
18 anything prior to voting on that recommendation?

19 [No response.]

20 DR. CHARACHE: All right. We'll do it the same
21 way. We'll get an understanding of who would like to see
22 more data or a more precise definition of chronic hepatitis,
23 and then we'll say whether this should be pre- or post-
24 market. Dr. Weinstein?

25 DR. WEINSTEIN: I make the motion, more data.

1 DR. SANDERS: I'm satisfied with the data.

2 DR. TUAZON: More data.

3 DR. RELLER: More.

4 DR. SPECTER: More data.

5 DR. CHARACHE: Dr. Thrupp

6 DR. THRUPP: I thought we already covered this,
7 but I think they have the data.

8 DR. CHARACHE: Yes, but the question is, do you
9 want to see more?

10 DR. THRUPP: See it? Yes.

11 DR. WILSON: More data.

12 DR. SEEFF: More data.

13 DR. CHARACHE: All right. And now I'll ask again
14 for a show of hands of how many would like to see more data
15 post-market.

16 [A show of hands.]

17 DR. CHARACHE: And pre-market?

18 [A show of hands.]

19 DR. CHARACHE: So it's one post-market and six
20 pre-market.

21 All right, so we have addressed the question of
22 chronic hepatitis, and the use in pregnancy, and the use in
23 susceptible populations. Let's look again at this and see
24 if there's anything else that we would like to see, or
25 whether you would like to make any other recommendations on

1 this.

2 DR. THRUPP: A point of clarification.

3 DR. CHARACHE: Yes.

4 DR. THRUPP: Did we vote on the seeing more data
5 on repeat test and confirmatory test for SAG?

6 DR. CHARACHE: No, we did not. Would you like
7 to--

8 DR. THRUPP: I thought that's what the first
9 motion was.

10 DR. CHARACHE: No, that was to use it in its
11 current form in pregnancy. So you would like to see a
12 confirmatory test for positive antigen, or a repeat test

13 DR. THRUPP: Repeat and confirmatory, just as the
14 CBER-approved reference method does.

15 DR. CHARACHE: All right. Now, that would be an
16 extension. That would be asking that they change their
17 product.

18 DR. THRUPP: That doesn't change the product. It
19 asks for repeat tests and then a confirmatory test. I guess
20 that would have to be added to the product. I guess you
21 would have to call it a change.

22 DR. CHARACHE: Dr. Reller?

23 DR. RELLER: Reller. There was the implication
24 earlier in the discussion that a change in the way things
25 were done for the testing might be appropriate. And to me

1 the issue as to whether this or any other test had to have
2 confirmatory testing or neutralization testing depends on
3 the performance of the product, so that if there were a
4 standard against which it was being compared that clearly
5 requires it for appropriate use currently, that a new
6 product would be required to either match that performance
7 straight out and show that you don't need to have
8 confirmatory testing and neutralization, or that if you did
9 do confirmatory testing, that it would perform adequately
10 with those additional steps.

11 And in this case we have none of the latter. That
12 is, we have a test that was done once, and whether or not
13 doing something additionally would match the performance to
14 our comfort with adequate number of patients is an unknown.
15 I mean, it may or may not. I just don't know. So to attach
16 specific studies that need to be done is whatever it takes
17 to perform adequately, and I can't prejudge that and we have
18 seen no data to assess it.

19 DR. CHARACHE: So you would favor not making that
20 recommendation but rather looking at the product after the
21 additional data is obtained, to see whether additional steps
22 might be required?

23 DR. RELLER: Well, I think the discussion is very
24 helpful, because clearly if in an organization's assessment
25 of their own data, or if there be any questions up front, I

1 mean the time to get that additional information is while
2 you're doing the comparisons and the studies, because that
3 would be the standard that people would be looking for in
4 terms of performance.

5 And I would like to just--maybe it's an
6 appropriate time to interject, because we're talking about
7 screening issues, and I wonder if it might not be helpful in
8 whatever, in this and subsequent products where this issue
9 about whether or not a test goes for diagnosis without
10 screening or if screening--now, I'm talking about blood
11 products or blood donor screening--that as long as that use
12 is in the province of CBER, that if there was a new product
13 that was not cleared for that and was cleared only for
14 diagnostic use, that the warning label say something.

15 One, it be more clearly delineated, like a warning
16 box, but that it actually go ahead and say, which would help
17 educate all potential users within the country, something
18 along the lines, if there be such a product, that this
19 product has not been cleared by CBER for screening blood
20 products and therefore should not be used for that purpose,
21 or should be used only for diagnostic purposes.

22 But it would delineate that the okay or not okay
23 for use in blood donors is in the province of CBER, and
24 unless a product is cleared for that use, it should not be
25 used, so you don't get into some of the other discussions