

1 -and, as you just heard Miriam Alter saying, and I think
2 also Dr. Dienstag, the predominant use of such assays will
3 be for initially identifying such individuals.

4 [Slide.]

5 One reason to go in this direction is that we have
6 heard over and over from manufacturers that it is extremely
7 difficult to come up with well-characterized specimens that
8 represent specific states of HCV infection, particularly
9 acute infection.

10 Furthermore, we felt that without such
11 characterization, the studies to determine the performance
12 would be predominantly based on comparative assays--or,
13 using the terminology from yesterday, reference assay
14 testing for anti-HCV. By that specifically, we mean two-
15 step testing like that that was described by the folks from
16 Abbott--detection with a licensed anti-HCV EIA followed by
17 reactivity in a recombinant immunoblot assay--but without
18 necessarily having information about the state of infection
19 or disease.

20 However, for the same reasons that we just
21 mentioned, most such uncharacterized specimens, if they are
22 collected in recent years, are also going to represent
23 chronically infected individuals.

24 [Slide.]

25 Therefore, specimens can be studied to determine

1 the safety and effectiveness with regard to a major
2 indication for anti-HCV testing--again, the additional
3 identification of individuals who are presumed to be
4 chronically infected--even without extensive
5 characterization of individuals from whom study specimens
6 were collected.

7 Now, the limitation in all that--which this panel
8 might want to consider--is the lack of demonstrated
9 performance with regard to precise states of infection,
10 particularly with regard to acute infection because--again,
11 as previous speakers have stated--different assays perform
12 differently with regard to how early they will detect
13 evidence of seroconversion, and there is also the biological
14 factor that we as infected individuals take a while to crank
15 up an antibody response.

16 The indication for use that Abbott has proposed is
17 very similar to this in conjunction with this, with our
18 support.

19 [Slide.]

20 There is a second concept, and that is testing
21 algorithms. There are a couple of thoughts behind that that
22 we considered for comment in the draft guidance document.
23 One was that a manufacturer should establish at least one
24 equivocal or gray zone--this is typical of virtually any
25 qualitative assay that detects antibodies to microorganisms,

1 at least--and that there is a possibility that different
2 equivocal zones or different cutoffs might be appropriate
3 for different indications for use.

4 And I'll point out again very briefly, as has been
5 stated in somewhat different ways earlier today, that
6 traditional EIAs for anti-HCV, those that are already on the
7 market, those that are licensed, essentially designate all
8 values greater than the cutoff as equivocal in that
9 specimens that are tested initially as a single aliquot are
10 not given a conclusive interpretation until they are
11 retested in duplicate and before results are interpreted and
12 recorded.

13 So that these in essence represent a presumptive
14 result usually, and consistent with the algorithm that Dr.
15 Alter was just talking about, that a reactive or positive
16 result from such an EIA would usually be regarded, unless
17 the clinician had additional information, as presumptive
18 evidence of infection with HCV that would need supplemental
19 testing.

20 We did say that we would consider stand-alone
21 assays--that is, an anti-HCV assay that in and of itself
22 would provide conclusive evidence that the patient was HCV-
23 infected. Now, it should be obvious that this is in direct
24 conflict with the algorithm that Dr. Alter was just
25 presenting. And again, I won't mention that we discussed

1 this with a number of people around the country, including
2 indirectly with Dr. Alter, and the consensus was that these
3 concepts made sense.

4 [Slide.]

5 And I'd just like to point out with regard to the
6 AxSYM HCV assay that Abbott established, primarily through
7 the reproducibility data, the use of an equivocal zone
8 between a sample-to-cutoff ratio of 0.8 and 1.2, so that
9 when specimens gave that result from testing of an initial
10 aliquot, it would then be rested in duplicate.

11 However, if the sample-to-cutoff ratio were
12 greater than 1.2, it would then be conclusively interpreted
13 as reactive from that single aliquot. As has also been
14 discussed to some degree this morning, with regard to
15 supplemental testing, in the proposed package insert, the
16 Intended Use statement does not directly comment on
17 supplemental testing; however, the Interpretation of Results
18 section does recommend supplemental testing.

19 Tom, if you would please advance to Slide Number
20 9.

21 [Slide.]

22 What I'd like to do briefly is discuss some of the
23 criteria that were used in interpreting the clinical data
24 that Abbott presented to give you an idea of some of the
25 limitations and the assumptions, at least, that we had

1 identified in terms of defining these people more or less
2 pristinely, to go back to a word that was used yesterday.

3 First of all, with regard to the anti-c100
4 criterion that was used in the first group of specimens that
5 were to have represented acute HCV infection, again, these
6 represented specimens from a university study; they had
7 symptoms and signs of acute hepatitis, very high ALT and AST
8 levels and, among a number of other pieces of information,
9 no serologic evidence for acute HAV or HBV infection.

10 The criterion that was selected was the lack of
11 reactivity to c100 antigen as detected by the recombinant
12 immunoblot assay and, as I think Dr. Dienstag pointed out
13 nicely in the graph he showed this morning, antibody to that
14 antigen, which was the antigen in the first-generation
15 assays, develops later. So it seemed reasonable that if you
16 had other antibodies but not that one, that maybe a
17 seroconversion would develop.

18 The limitation is that these were based on single
19 serum specimens, and in terms of the data that we have on
20 hand, it was not possible to demonstrate a seroconversion of
21 that antigen. So the assumption is that coupled with the
22 other criteria, the lack of that antibody in a single
23 specimen is highly predictive of acute hepatitis C virus
24 infection.

25 [Slide.]

1 Next, we will discuss some of the assumptions and
2 limitations about the criteria that were used in the
3 patients who had a physician diagnosis of chronic infection.
4 I will point out that we did not know the data on which that
5 diagnosis of chronic infection was made, nor did we know the
6 specific criteria on which it was made.

7 I'd like to first discuss the Interferon
8 criterion. The principle was that having a history of
9 Interferon therapy indicated active disease that is likely
10 to be HCV-associated and supported the physician's diagnosis
11 of chronic hepatitis C because to my mind, at any rate, it
12 is highly unlikely that a physician would give Interferon
13 unless he or she was quite certain that the patient had
14 chronic hepatitis C.

15 We did not have any information on when that
16 Interferon therapy was given, so that that is the
17 limitation. So the assumption that were made and that we
18 identified with regard to that was that Interferon was used
19 to treat chronic HCV and not chronic HBV. In general, we
20 had no information--I'm sorry--in most patients, we had no
21 information about other possible causes of chronic hepatitis
22 in these people.

23 The other assumption is that we assumed that the
24 Interferon therapy had not been given prior to the question
25 of the study specimen and cleared the HCV infection, so that

1 at the time the specimen was collected, there was no longer
2 an active chronic infection. That was an assumption.

3 [Slide.]

4 Now, with regard to the RNA criterion, something
5 that is not stated--well, it is sort of stated on here, but
6 I just want to back up for a minute--we were presented with
7 data representing several different HCV RNA assays, all of
8 which I think provided quantitative data but we used them in
9 a qualitative forum. There were only two of them that
10 impacted on the interpretation of the specimen. So for
11 example, the data that accompanied the seroconversion panel
12 specimens that you saw earlier today did not impact on the
13 criteria for acute infection, so we didn't really consider
14 the validity of those assays or whether they should be used
15 or not.

16 Coming back to the point here that we are in a bit
17 of a bind here, as is everybody, that we've got something
18 that is on the one hand a standard of medical practice now,
19 detecting HCV RNA, as the only virologic evidence that the
20 virus is replicating, and on the other hand that none of
21 these assays has received the stamp of FDA approval.

22 However, the principle that was used here with one
23 of the two assays that was applied to the patients who were
24 identified as chronically infected--and I'm sorry--I will
25 mention that two assays were used; one was a home brew

1 assay, and there were no data provided to validate that
2 assay, so we discounted those data; and the other assay, and
3 I'll come back to that in a second. So the principle was
4 that the detection of HCV RNA on the same date or subsequent
5 to the collection of study specimen indicates an active HCV
6 infection.

7 The assumption that we made, at least for the
8 purpose of today's discussion, is that the commercial assay
9 that was used on those patients was valid. The other
10 assumption that was made was that the patient had not
11 cleared infection prior to the study specimen being
12 collected and then been reinfected at a later time, so that
13 in fact, that HCV RNA represented a subsequent infection.
14 It seemed like a reasonable assumption.

15 [Slide.]

16 Finally, in those patients for whom we did not
17 have evidence of a six-month period of anti-HCV reactivity
18 prior to the study specimen being collected--this was
19 analogous to the HCSAG criterion that was discussed
20 yesterday--using histopathologic changes as a criterion for
21 HCV activity--I'm sorry, I'm ahead of myself--forget what I
22 just said.

23 This is in those patients where we did have
24 evidence of greater than six months of anti-HCV reactivity,
25 so they did meet a criterion that they had been infected

1 with HCV for at least six months prior to collection of the
2 study specimen, but because anti-HCV could represent a
3 resolved infection or a cleared infection, we don't know if
4 the infection was active at the time it was collected.

5 So the principle that was used here was that these
6 histopathologic changes at any time--and in reviewing the
7 data, they met the criterion that there was evidence of
8 chronic infection or evidence of fibrosis or cirrhosis--that
9 these were likely to be HCV-associated histopathologic
10 changes in these patients.

11 Again, the limitation was that we generally had no
12 data to exclude other possible causes of chronic hepatitis
13 and cirrhosis. So the assumptions were that these
14 histopathologic changes were caused by HCV and that if the
15 biopsy had been collected prior to the study specimen, that
16 the infection had not cleared afterwards. These seemed like
17 reasonable assumptions.

18 [Slide.]

19 Now, in those people where there was not evidence
20 of a chronic HCV infection--this is the group of patients
21 that Dr. Hojvat described as individuals who were HCV-
22 infected, state not determined, with chronic hepatitis--we
23 used the histopathologic changes as a criterion for chronic
24 hepatitis, the principle being that histopathologic changes
25 that occurred any time before the study specimen was

1 collected or within six months after it was collected or
2 within five years after it was collected, if there was
3 fibrosis or cirrhosis identified, was likely to indicate
4 chronic disease at the time the study specimen was collected
5 that may have been HCV-associated.

6 Again, the limitation was that in most of the
7 patients, there were not data to exclude other possible
8 causes of these histopathologic changes, so in those
9 settings, we in the company did not assume that these
10 histopathologic changes were caused by HCV and therefore
11 could not conclude that the study specimen was collected at
12 a time that represented a chronic HCV infection.

13 I believe that that concludes my remarks.

14 Thank you.

15 DR. CHARACHE: Thank you. We'll come back with
16 questions for Dr. Ticehurst after we have heard from Dr.
17 Dubois.

18 DR. DUBOIS: I guess I'd like to mention that the
19 lead reviewer for this PMA was Dr. Phil MacArthy. He was
20 unable to give this presentation today because of a family
21 emergency, so I'll go ahead and provide the information.

22 [Slide.]

23 The review team for the Abbott AxSYM HCV PMA
24 consisted of four scientists: Dr. Phil MacArthy, whom I
25 just mentioned, the lead reviewer; Dr. John Ticehurst; Dr.

1 Chang Lao; and Ms. Freddie Poole.

2 Abbott has provided a detailed overview of their
3 study. To summarize, the sponsor studied a total of
4 approximately 5,600 clinical specimens at seven sites; they
5 defined different populations representing different states
6 of HCV infection in groups with different risks of HCV
7 infection. They proposed to use this information collective
8 to support a general claim for the ability of the assay to
9 detect serological evidence of infection without specifying
10 a particular state of HCV infection.

11 [Slide.]

12 Now, this Intended Use was read a couple times
13 this morning, and what I'd like to do here is just mention
14 that this general claim does not allow for specific
15 predictions of performance in unique clinical settings, but
16 as Dr. Gutman suggested today and yesterday, and as Dr.
17 Ticehurst just described, this claim may be appropriate in
18 light of what is known about antibodies to HCV.

19 [Slide.]

20 Most clinical laboratory assays have a single
21 indication for use. The experience at FDA has been that
22 PMAs for such assays usually contain results from studies at
23 three or more sites for determining clinical performance.
24 As just discussed, Abbott has claimed one general indication
25 for use, and does not claim that their assay is indicated

1 for a diagnosis of any particular state of HCV infection or
2 disease. For this PMA, studies were performed, as I
3 indicated previously, at seven sites, but each specimen
4 category other than first-time blood donors was studied at
5 one or two sites. Single-site studies were performed for
6 the two categories--the hospital patient with physician
7 orders for hepatitis testing, and individuals at increased
8 risk of HCV infection, from which specificity was determined
9 for the claim general indication for use. This data will be
10 discussed shortly.

11 In addition, single-site studies were performed
12 for each of three HCV-infected categories--asymptomatic,
13 acute and chronic--that pertained to potential indications
14 for use. While there is no claim for diagnosis of any
15 particular state of HCV infection or disease, the company
16 proposes to present in the package insert the data sets
17 obtained from each HCV-infected specimen category.

18 [Slide.]

19 This data was discussed this morning briefly and
20 presented by Abbott. Here again, single-site studies were
21 performed in distinct population. In hospital patients with
22 physician orders for hepatitis testing, 99 clinical
23 specimens were tested with a specificity of 99 percent. For
24 individuals at increased risk of HCV infection, 150 clinical
25 specimens were tested with a specificity of 89 percent.

1 Now, because these specificity estimates differ in
2 the two populations, positive predictive values could be
3 expected to vary depending on the population. The sponsor
4 does not recommend supplemental testing in the Intended Use
5 Statement. However, in the Interpretation of Results
6 section of the package insert, the sponsor does recommend
7 that reactive specimen be investigated by an additional,
8 more specific test.

9 [Slide.]

10 The review team would like to pose the following
11 questions. Here again, this is the Intended Use Statement.

12 Does the data support this general indication for
13 use? If not, a) what additional data are needed; or b) what
14 changes in the indication for use would be appropriate?

15 [Slide.]

16 Question 2: Single-site studies were performed
17 for each of three HCV-infected categories that pertain to a
18 potential indication for use. The company does not claim
19 that their assay is indicated for a diagnosis of any
20 particular state of HCV infection or disease, but proposes
21 to present in the package insert the data sets obtained from
22 each population category. Is this appropriate? If not,
23 what additional data or studies are needed to enable such
24 presentation, or b) what presentation do you recommend?

25 [Slide.]

1 Question 3: Are the criteria described by Abbott
2 appropriate for categorizing individuals as being acutely
3 infected with HCV? If not, what changes should be made in
4 these criteria?

5 Question 4: Are the criteria here again described
6 by Abbott appropriate for categorizing 30 individuals as
7 being chronically infected with HCV? If not, what changes
8 should be made in these criteria?

9 Thank you.

10 DR. CHARACHE: I will ask if the panel has
11 questions of any of the three FDA speakers. I'll call first
12 on Mr. Reynolds, who had a question of the first speaker.

13 MR. REYNOLDS: I can't remember what my question
14 was now.

15 DR. CHARACHE: We'll call on someone else while he
16 finds his question. Are there any other questions for the
17 FDA speakers?

18 [No response.]

19 DR. CHARACHE: I have one question of Dr. Dubois.
20 Of the single site that were used for testing of the high-
21 risk patients and the patients for whom physicians requested
22 hepatitis testing, am I correct in my interpretation of an
23 earlier comment that the single site was at Abbott as
24 opposed to a hospital laboratory, or was that tested at a
25 hospital laboratory? I have a lot of confidence in the

1 skill of Abbott.

2 DR. DUBOIS: I'm not involved in the actual review
3 of the submission, so I'll defer that question to Dr.
4 Ticehurst.

5 DR. CHARACHE: Thank you.

6 DR. TICEHURST: And I'm going to have to ask for a
7 little help from Abbott to answer your question.

8 DR. CHARACHE: Surely.

9 [Pause.]

10 DR. ALTER: While you're doing that, I was going
11 to clarify the blood donor data that Dr. Seeff had asked
12 about earlier.

13 DR. CHARACHE: Yes. Thank you--Mr. Reynolds, do
14 you have your question?

15 MR. REYNOLDS: Actually, I had two comments. One
16 did have to do with the blood donor data. For those of you
17 who haven't noticed, I do have my Red Cross pin on. I'm a
18 donor for the Red Cross, and I help to set up bloodmobiles.
19 So I see this information, first-time volunteer whole blood
20 donors, and I don't know how many of you folks give blood on
21 a routine basis, but normally what happens at bloodmobiles,
22 you don't have individuals coming in--you have groups.
23 People normally give as groups. There are groups from work,
24 groups from school, groups from a club. So you have large
25 groups coming in who normally have things in common.

1 And all I want to indicate is if you had a couple
2 of large groups that for some reason had risk factors beyond
3 what we would think of, it could easily skew this data and
4 push it up. In the City of Philadelphia, we just had a
5 situation where 5,000 firemen were tested for hepatitis C,
6 and their incidence is 4 percent.

7 So if you have a couple of large groups like this
8 come in, and all of a sudden, you can really skew your data.

9 DR. CHARACHE: Thank you.

10 Do you have the answer?

11 DR. TICEHURST: To answer your earlier question,
12 the first group, hospital patients with physicians' orders
13 for hepatitis testing, were tested at Stanford University
14 Laboratory, and the second group, populations at increased
15 risk for HCV infection, were tested at Serologicals, which
16 is a reference laboratory.

17 DR. CHARACHE: Thank you very much.

18 Dr. Alter?

19 DR. ALTER: I also wanted to clarify the issue
20 about the blood donors. First of all, most of the
21 prevalence data that are given for blood donors or have been
22 given in the past are based on a mixture of first and repeat
23 donors, and the majority of donors are made by repeat donors
24 who have the lowest rates. So when you combine the
25 populations, the very low-prevalence estimates that we

1 normally see, which are on the order of 0.1 to 0.2 percent
2 now, really represent repeat donors who have been screened
3 many times, and essentially, we have screened out most of
4 the HCV-positives. First-time donors will have higher
5 rates, although that is a bit high even for first-time
6 donors.

7 In terms of the geographic distribution, although
8 in NHANES, there is no significant difference between
9 regions, I understand that in blood donation, the South has
10 the highest rates of anti-HCV positivity among first-time
11 donors, so that could have skewed the results.

12 Also keep in mind that when someone is giving a
13 prevalence in a, quote, general population or donor
14 population like fire fighters, that 1.8 percent in NHANES is
15 a broad age range, and if you were to focus in on the
16 individuals, let's say, between 30 and 50, the rates would
17 be more like 4 to 6 percent or 3 to 6 percent. So that,
18 depending on the age group and the racial/ethnic make-up of
19 the individuals you are comparing, they may not be any
20 higher than the general population. But it does make one
21 wonder about whether they are answering the questions on the
22 screening interview accurately.

23 DR. SEEFF: Actually, when they come in a big
24 group such as you are talking about, at least it's my
25 understanding that before they donate, they have to answer

1 many questions for potential risk factors--is that correct--

2 MR. REYNOLDS: I'll tell you what the problem is
3 there. You're sitting there with your buddies, and the
4 nurse is asking you the questions--

5 DR. SEEFF: They don't have forms to fill out--
6 this is a questionnaire--

7 MR. REYNOLDS: No, no, no, no. And then what
8 happens is at the end, what you're supposed to do is you go
9 into a little booth, and you have a sticker that says "Use
10 my blood" or a sticker that says "Do not use my blood." So
11 if you know that you lied when you were sitting there at the
12 interview booth, you're supposed to put the sticker on that
13 says "Do not use my blood," and nobody is supposed to see
14 which sticker you put on, because it's bar-coded, and they
15 know that they are not supposed to use that blood. But the
16 reality is that you are doing that questionnaire sitting
17 right there with the nurse with all your buddies there with
18 you, so if you've been doing something that you don't want
19 everybody else to know about--let's say you had male sex
20 partners--who, me? Of course not--you know.

21 DR. SEEFF: If they're female, it's okay, I guess.

22 [Laughter.]

23 DR. CHARACHE: I think with that comment, I'll ask
24 if there are any other questions of the FDA discussants.

25 Yes, Dr. Gates.

1 DR. GATES: I just wanted to get clear on one of
2 the more general questions in terms of the indications for
3 use for diagnostic versus nondiagnostic. The question is
4 that the indications for use wouldn't be for diagnosing a
5 disease state but basically for a particular analyte. I
6 guess first of all, is that true; and then, second, based on
7 our discussions yesterday, it was a long day, but one of the
8 issues as I remember it was that there wasn't enough
9 evidence for that particular submission in terms of
10 characterizing the disease state. Is there some
11 reconciliation for those two things, or are they just
12 different intended uses?

13 DR. TICEHURST: There is some semantic discussion
14 here that will hopefully help answer your question, Dr.
15 Gates. At least the way I think about some of this
16 information, within a package insert, there is an Intended
17 Use Statement, and I generally think--and I think it's based
18 on some teaching I've gotten here, although I'm not sure
19 you'll see it in writing--that the first part of the
20 Intended Use refers specifically to what does this assay
21 detect, what's the analyte. And the second part of it,
22 which has always been, at least to the best of my knowledge,
23 an important consideration for this Center, is, okay, now
24 what are you going to use it for--in this case, what does
25 the company propose to use it for--and if it is approved,

1 and there is evidence that it is safe and effective for
2 those uses, those, we refer to as "indications for use."

3 The semantic point of using the term
4 "nondiagnostic" on those slides isn't to imply that these
5 aren't used in a diagnostic process. It is that this
6 general indication for use that has been proposed is that
7 the evidence of infection would not necessarily be linked to
8 a particular diagnostic state, a particular state of HCV
9 infection, a particular state of disease, whether there is
10 hepatitis present or not.

11 It was our impression, based on the perceived
12 difficulty in getting a lot of the specimens for what would
13 normally be assumed to be the usual indications for use--
14 acute hepatitis C, chronic hepatitis C, and so forth--that
15 there would not be major public health concerns by allowing
16 a general indication which would say this assay can be used
17 for evidence of HCV infection, but recognizing that that in
18 itself is not a diagnosis.

19 DR. GATES: And then, how would that be congruent
20 with some of the recommendations yesterday?

21 DR. TICEHURST: I think that where it could be
22 congruent--one could entertain--the obvious assay one might
23 apply that to that was discussed yesterday would be an HBSAG
24 assay. Then you'd have to start thinking, okay, if you were
25 to allow such a general indication that an HBSAG assay would

1 provide evidence of HBV infection or lack thereof, without
2 designating a particular state of infection, I think then
3 the appropriate thing is, okay, that's an idea. Then, I
4 think you'd have to go through the different particular
5 states of infection and ask the question: Given the state
6 of HBV infections in this country today, given the
7 implications of the various indications for use of an HBSAG
8 assay, are there public health concerns by lumping it all
9 together in one?

10 When we lump them together with anti-HCV, the
11 overriding concept was that there aren't a lot of acute
12 infections; the vast majority are chronic, and that's where
13 the vast majority of the application would be once it's on
14 the market. We haven't gone through that kind of detailed
15 analysis for HBV, but based on the discussion yesterday, I
16 would preliminarily conclude that you couldn't come to that
17 same conclusion for HBSAG.

18 DR. GATES: Because it's better to find that
19 there's more of a public health issue in terms of defining
20 acute versus chronic.

21 Dr. TICEHURST: And the testing in pregnant women
22 and so forth.

23 DR. GATES: Yes.

24 DR. CHARACHE: Dr. Alter?

25 DR. ALTER: Not to mention--and I have no idea if

1 this has anything to do with the way FDA makes its
2 decisions--but for HBV, we have serologic markers that can
3 distinguish between acute and chronic. For HCV, we don't.
4 This is it.

5 DR. CHARACHE: Thank you very much.

6 Are there any other questions? Yes?

7 MR. REYNOLDS: Stan Reynolds again, consumer rep.

8 Dr. Alter, you mentioned the algorithm, the
9 suggested algorithm. I do lots of HIV testing, and of
10 course, I am used to using this algorithm for HIV testing.
11 In your experience in talking with other public health
12 laboratories--because I come from a public health laboratory
13 setting, and I know we don't do hepatitis testing, but the
14 City of Philadelphia does and Allegheny County does, so
15 we're still talking large volumes, and they both employ a
16 similar algorithm. They would not report a positive based
17 solely on the RAA, because again, in a clinical setting, you
18 really don't have histories, they don't have a
19 gastroenterologist, they don't have a hepatologist to
20 counsel these people.

21 What is your experience in other large public
22 health laboratories?

23 DR. ALTER: My experience is that most public
24 health laboratories and in fact most clinical laboratories
25 only do the EIA, and that's what they report out. So if

1 someone requests an anti-HCV, they report out the results of
2 the EIA; they don't do RIBA, and most public health
3 laboratories don't even have the capacity to do it. And a
4 political laboratory would probably only do it if it were
5 requested specifically by the physician.

6 DR. CHARACHE: Thank you.

7 We're going to take the next two items on the
8 agenda out-of-turn and ask first for the open public
9 hearing, if anyone wishes to address the panel at this time.

10 Then we'll go on to the open committee discussion
11 and begin the questions prior to lunch if time permits.

12 Do we have anyone from the public who would like
13 to speak at this time?

14 [No response.]

15 DR. CHARACHE: Thank you very much.

16 I think, then, at this time, we'll go on with the
17 open committee discussion and initiate consideration of the
18 four questions that the FDA has asked for advice on.

19 I wonder if we could put up the questions that
20 were asked--first, Question Number 1.

21 The sponsor has suggested the following intended
22 use: "AxSYM HCV is a Microparticle Enzyme ImmunoAssay for
23 the qualitative detection of antibody to hepatitis C virus
24 in human serum or plasma. The detection of anti-HCV is
25 evidence of HCV infection. Although not indicative of a

1 particular HCV-associated disease state, antibodies to HCV
2 are detected in HCV-infected individuals with asymptomatic,
3 acute, and chronic hepatitis. An HCV antibody result, the
4 patient's clinical presentation, history, and other
5 laboratory results are used to diagnose HCV-associated
6 disease." That's the intended use.

7 Does the data support this general indication for
8 use?

9 Let's address that first, and then, if not, what
10 additional data are needed or what changes in the indication
11 would be appropriate?

12 Can we hear comments from the panel--and please
13 identify yourself.

14 I beg your pardon. We're going to call first on
15 the primary reviewers. First is Dr. Paul Edelstein.

16 DR. EDELSTEIN: Yes. I believe that the data does
17 support the general indication for use and that no
18 additional data or changes in the indication are
19 appropriate--or, needed or appropriate.

20 DR. CHARACHE: Dr. Tuazon?

21 DR. TUAZON: I agree. I think the data, after
22 review, support the general indications for its use, and no
23 additional data are needed.

24 DR. CHARACHE: Dr. Seeff?

25 DR. SEEFF: I was going to agree; assuming that

1 we're talking about repeatedly reactive confirmed results, I
2 completely agree with what the sponsor proposes.

3 DR. CHARACHE: Let me ask the reviewers--would you
4 for requiring in the indicated use the repeated testing, or
5 how would you like to address confirmatory--or do you feel
6 that's required?

7 DR. EDELSTEIN: I can address that, actually. I'm
8 skipping ahead to what I want to list as a condition. Would
9 you like me to go ahead and list those?

10 DR. CHARACHE: No. Indicate if you think there
11 needs to be a change?

12 DR. EDELSTEIN: No, I don't think that there needs
13 to be a change--well, I do think that there needs to be a
14 change in the indication for use, and the only indication
15 for use that I would suggest is that a bolded statement be
16 included that states, as the sponsor has said, under
17 "Interpretations," "It is recommended that reactive
18 specimens be investigated by additional, more specific or
19 supplemental tests."

20 DR. CHARACHE: Okay.

21 DR. TUAZON: I agree with that. That's the only
22 additional information that we could include--not there, but
23 I think where they have it in the interpretation of results.

24 DR. CHARACHE: Dr. Reller?

25 DR. RELLER: In the draft of the package insert

1 that we have, the warning about not for use in blood or
2 plasma donor screening, there is a warning, and that is
3 duplicated in the limitations of the procedure, and the
4 wording is clear and I think adequate. Simply taking the
5 statement that Dr. Edelstein read, the sentence just before
6 the limitations of the procedure, if that were also
7 duplicated and right up under the intended use, it would
8 make everything crystal clear, and it would be appropriately
9 in the limitations to interpretation, and it would be how
10 one would confirm this anti-HCV evidence of HCV infection.

11 DR. CHARACHE: Are you suggesting that that should
12 be under this warning header under indication of use, or--

13 DR. RELLER: I don't think that it needs to be
14 under the warning--rather than confusing things, the warning
15 applies to the currently suggested use of this product as
16 not being appropriate because it hasn't been cleared for
17 donors, but it would be a natural follow-through that this
18 is a test for detecting antibody, and that after one has
19 detected antibody by this test, the positives would be
20 confirmed, which is clearly delineated in the interpretation
21 section, but I think that getting that statement up in the
22 intended use with the wording that is already there would
23 make the whole package say what we want it to say.

24 DR. CHARACHE: Dr. Specter?

25 DR. SPECTER: We still have not addressed--and I

1 agree that those are good ideas--but we still have not
2 addressed the idea of whether there needs to be a repeat
3 test before a different confirmation test. That question
4 has been raised, but it wasn't addressed here, and I'm
5 wondering if that should be part of that statement or not.

6 DR. CHARACHE: Are there any comments or thoughts
7 on that point? It is stated that there should be a
8 confirmation test. Should there be advice in that setting
9 for a repeat test prior to other additional tests?

10 Dr. Edelstein?

11 DR. EDELSTEIN: Well, I am a little bit split
12 about this for a couple of reasons. One is if we require in
13 the indications for this test as opposed to the other
14 already licensed or cleared EIA tests that repeat testing
15 be done, that creates an unlevel playing field. What I
16 would wonder if there were some more general way for FDA,
17 for all HCV tests currently licensed or cleared, to include
18 that for all of them at the same time.

19 The second consideration is that if we consider
20 the reproducibility of this assay, just looking at that, the
21 reproducibility is fine. The question is was the wrong
22 specimen tested. That's basically the issue of
23 reproducibility. Is that what you think the issue is, Dr.
24 Seeff?

25 DR. SEEFF: It's my understanding that the

1 current, to coin a phrase, reference test does require
2 repeated positivity in order to present as truly positive.

3 The issue about whether you have the wrong
4 specimen I guess brings us to the question of whether you
5 should test two separate specimens from the same person, or
6 the same specimen twice, and that's something else
7 altogether.

8 If I could go back to this issue of repeated
9 reactivity--we have heard, I think, the intended use here is
10 for people with presumably established illness--acute,
11 chronic--is that correct?

12 DR. CHARACHE: No, no. It is everybody. It is
13 any use.

14 DR. SEEFF: As I guess the hepatologists will tell
15 you here, being on the receiving end of patients calling you
16 to say they are hepatitis C-positive, and the intense panic
17 and anxiety that that provokes, it is essential that a
18 person be informed of a true positive result.

19 So if we are talking about a routine screen and
20 particularly of low-risk populations, if that's included, it
21 is in my view mandatory that that be part of the test
22 requirement, that it be tested, repeated, and confirmed to
23 be positive, and then one can take the next steps.

24 It becomes less of a problem when you are dealing
25 with people who are acute, as we heard, with acute disease

1 or even with chronic disease with abnormal enzymes, in which
2 case, it is usually a true positive. But in low-risk
3 groups, I think it is essential that we do have a repeated
4 reactive.

5 The question is should we then distinguish between
6 low-risk and high-risk. Probably not. I think that we
7 should require that this be repeated positive.

8 The issue about whether we have a different sample
9 in order to be absolutely certain that we're dealing with
10 the right sample from the right person, well, that was
11 discussed recently by the Institute of Medicine, which says
12 we have to be careful that we don't cause more trouble than
13 we're worth as physicians and health care workers. We have
14 to take that into account, and I guess this does happen
15 sometimes, but I'm not sure that that is sufficient to
16 require that there be two entirely separate samples, and I
17 would leave that to those who are smarter than I am.

18 DR. CHARACHE: I'm going to ask Dr. Gutman for a
19 clarification. The previously approved test, was that CBER
20 approval for blood bank purposes, so there, the only use
21 that--

22 DR. GUTMAN: It was CBER approval. I believe the
23 CBER approval, however, extended into diagnostic claims as
24 well.

25 DR. CHARACHE: So it was for both; okay, fine.

1 DR. GUTMAN: It would be awkward to go back and
2 start making changes to products that were licensed, and I
3 would remind you that the data set we are looking at, I
4 don't object to any changes or recommendations in
5 performance, but the data set that we are looking at
6 actually wouldn't provide insight into how repeat testing
7 would in fact affect the overall performance. That could
8 probably be dealt with in a post-market study and probably a
9 fairly simple one. But you're not sitting on a data set
10 that would actually--you're giving us your best clinical and
11 laboratory judgment, but it is driven by data outside the
12 context of the submission.

13 The sponsor might be able to--

14 MR. KLAMERZINSKY: Matt Klamorzinsky [ph.], Abbott
15 Laboratories, Director of Regulatory Affairs.

16 CIBER screening tests are also licensed for
17 diagnostic use. They have a dual claim for screening and
18 diagnosis. Just one other comment. Following the
19 regulations as far as repeat testing and recommendations for
20 supplemental testing, 21 CFR 809(b) indicates that that type
21 of information should be in the interpretation of the
22 results. It doesn't say it shouldn't be in the intended
23 use, but that's where it belongs.

24 DR. CHARACHE: So it could be in both, but it has
25 to be in interpretation.

1 DR. GUTMAN: Well, actually, the discussion about
2 where it should be or how strong it should be stated, or
3 should it be bold, or what kinds of educational--it is not a
4 trivial or unimportant discussion. I listened to Miriam in
5 particular talk today about the educational challenge, and
6 I'm frankly not sure you will solve that educational problem
7 by putting it in the intended use, but if you thought that
8 was a noble idea, I wouldn't personally object to it.

9 DR. CHARACHE: Dr. Thrupp?

10 DR. THRUPP: Just to make sure that we're clear--
11 the presently licensed products, most of which come through
12 CBER, require repeat test and confirmatory test, and there
13 is no distinction between diagnostic or blood bank
14 screening; is that correct?

15 DR. GUTMAN: I believe that's correct, but I'll
16 ask Abbott, since they know their labeling better than I.

17 That's not correct, John? Well, we can try to
18 clarify that.

19 Dr. THRUPP: Because we do want to have a level
20 playing field with these products.

21 DR. CHARACHE: While they are clarifying that,
22 we'll go on.

23 Dr. Sanders?

24 DR. SANDERS: Actually, I have a question for the
25 FDA as to why this is a question. I want to be sure that we

1 are addressing what the real issue is here.

2 Is the issue the fact that the three disease
3 states are listed, and therefore, that should be struck from
4 the intended use? I need some clarification that.

5 DR. CHARACHE: Okay, we'll come back to that when
6 our clarifier is here.

7 Dr. Reller?

8 DR. RELLER: I recognize from Dr. Alter's comments
9 how far we have to go in terms of education. I like this
10 brief intended use as it is written in this draft, with the
11 addition of the confirmatory testing concept that Dr. Seeff
12 emphasized so clearly. By putting it in both places,
13 recognizing that it must be in the interpretation--it should
14 be there, up front--it gets the real message across that the
15 initial detection of antibodies by this test, the positives
16 need to be confirmed by supplemental testing so that the
17 laboratory reports a true positive.

18 This, we have heard, is not being done in all
19 public health laboratories, and it is not being done in all
20 clinical laboratories; and it should be done to avert the
21 public health indications, costs, et cetera, that Dr. Seeff
22 has alluded to, and to have the shorter indications for use
23 with that up front is a very useful tool around which one
24 can have the fiduciary aspect of directing a laboratory put
25 into effect, because it's right there in black and white,

1 this is what should be done, and then all of the people
2 involved in this process can utilize that intended use, the
3 confirmatory testing, right up front, of reporting only
4 truly positive samples, and we've got a goal in which to get
5 this done right, because without going into details, there
6 is a lot of mischief that can come about from many
7 directions when the confirmatory testing is not done and the
8 inappropriate use in this test in low-risk population groups
9 for lots of different reasons. I'll leave it at that.

10 DR. CHARACHE: Do we have an answer to our
11 previous question?

12 MR. KLAMERZINSKY: Yes. Typically, CBER tests are
13 positive, repeated in duplicate. In the case of HCV, it is
14 just a recommendation to use an additional supplemental test
15 or more specific test for further information.

16 DR. CHARACHE: Thank you.

17 We had a question of Dr. Sanders for further
18 clarification of this particular question. Specifically,
19 does the FDA want to know whether the panel thinks that the
20 data supports the fact that this test should be use din
21 asymptomatic, acute, and chronic hepatitis patients in all
22 three groups? Is that one of the questions?

23 DR. GUTMAN: That's implicit in the questions--is
24 that a reasonable span of activity for this test.

25 DR. CHARACHE: Okay. Can we get the opinion,

1 statement, by the panel to that particular question? Does
2 the panel feel that the data presented suggest that this
3 would be appropriate for all types of HCV infection,
4 regardless of clinical expression at the time of testing?

5 Dr. Seeff?

6 DR. SEEFF: I think that the data presented have
7 impressed me sufficiently that I will agree with it.

8 DR. CHARACHE: Dr. Edelstein?

9 DR. EDELSTEIN: Asked and answered, would be my
10 response.

11 DR. CHARACHE: And Dr. Tuazon?

12 Dr. TUAZON: I think the data supports that.

13 DR. CHARACHE: All right. Is there anyone who
14 would like to see any other answer? I think the panel is
15 very comfortable with that.

16 DR. SANDERS: The only reason I raise it is
17 because this intended use is different from the intended use
18 that was provided in the original packet. And that's where
19 the difference is, is articulation of the disease states.

20 DR. CHARACHE: Okay. So I think the panel has
21 felt that there should be perhaps at the end of this a
22 statement of the need for supplemental testing based on its
23 use in a wide range of populations, knowing that it need not
24 be used in a high-prevalence population, but these can't be
25 necessarily predicted.

1 Are there any other comments on Question 1, or any
2 other information the FDA would like on that?

3 DR. THRUPP: Yes. The motion, or whatever it was,
4 was for repeat as well as confirmatory.

5 DR. CHARACHE: We can come back to that when we
6 discuss further. Does anyone want to speak to that at this
7 time? No.

8 DR. THRUPP: Well, that's what we--

9 DR. CHARACHE: This wasn't a motion. This is just
10 a discussion of the question at this time.

11 Dr. Nolte?

12 DR. NOLTE: Yes. We also heard today from several
13 of the speakers that there may not be a need to confirm an
14 EIA result in a high-prevalence patient population, so we
15 are talking about an indication that really does not speak
16 to whether it's an acute or chronic infection, and yet I'm
17 hearing the panel saying that we are going to make
18 recommendations that the package insert essentially tell the
19 user that they have to do repeat testing and confirmation
20 regardless of the clinical state. Is that--there are a
21 number of--

22 DR. SEEFF: Well, in the clinical setting, I don't
23 think necessarily that confirmation has to be RIBA; I think
24 that when you are dealing with patients who are chronically
25 infected, you have to consider the question of treatment.

1 You're not going to treat people who are PCR-negative. So I
2 think the next step, routinely, in anyone who is found to be
3 anti-HCV-positive, even if they are in the high-risk group,
4 is to do a PCR to make sure that they either recognize this
5 or approve, and I wish the FDA would approve it--that's the
6 second issue.

7 DR. CHARACHE: Can we make that one of our
8 recommendations?

9 [Laughter.]

10 DR. SEEFF: I think that's the next step, because
11 you are going to have to make a decision about treatment,
12 are you going to treat or not.

13 I agree that you probably don't need it in a high-
14 risk group, and the question is can we in fact separate it
15 and say only in low-risk groups are we going to ask for
16 confirmation, but not in high-risk groups, when in fact in
17 the high-risk group, we are going to require confirmation if
18 we don't consider treatment. When we eventually reach the
19 point that I hope we will, that we'll be able to tell when
20 we see a patient for the first time and do the test, and
21 say, "Aha, you are not going to progress, and therefore,
22 don't worry about treatment," or "You are going to progress,
23 and therefore, we are going to treat," then we have a
24 different situation, because we all know this has been the
25 struggle with the natural history. It's all very well

1 saying that the natural history tells us that a lot of
2 people don't do badly, but how do we translate that to the
3 individual patient that we see, and at this moment, we
4 can't. Dr. Dienstag is going to give us the answer in 10
5 years' time from some studies he's doing and will be able to
6 tell us how to make that distinction.

7 DR. NOLTE: Clearly, the practical problem that
8 this raises is that if you put it in the package insert,
9 that obliges the laboratory to either follow that or have
10 some information that documents that they shouldn't. And
11 I'm not sure that we want to get that directed in terms of
12 instructions or indications or whatever you want to call it
13 in terms of the package insert.

14 DR. EDELSTEIN: My suggestion was to what it
15 already says, "It is recommended," rather than it should be
16 or it must be.

17 DR. CHARACHE: We can come back to that, I think,
18 later this afternoon.

19 Are there any other items on Question 1?

20 Dr. Reller, the last word.

21 DR. RELLER: I wanted to ask Dr. Seeff, is it a
22 fair statement that these patients who are positive in this
23 test, given that they may be in different risk groups, but
24 the reality is that for most if not all, the confirmatory
25 testing is important, although it may be important for

1 different reasons--nonetheless, you want a confirmatory
2 test.

3 DR. SEEFF: I guess that's what I was trying to
4 say, that in the low-risk group, we have to confirm it,
5 because we're going to report on a patient who has no
6 knowledge of this, and that's what going to be found in most
7 of the instances where we find this illness, is that people
8 are coming to donate blood, or they have a physical exam, or
9 they have an insurance policy done, and they get back a note
10 saying that you have an abnormal enzyme, or an ALT
11 immunoblot--anti-HCV if you are positive. And I think that
12 it is cruel for people to get that information without this
13 being absolutely confirmed, particularly when we learn that
14 under certain circumstances, in 50 percent of the instances,
15 this is a false positive.

16 So I believe that that is mandatory, and I
17 recommend it. I think that when it comes to the clinical
18 situation, the question as I understand from the laboratory-
19 -and I am not a laboratory person--it is tougher for the
20 laboratory person to be told you have to do it. On the
21 other hand, we really do need to go to that as the next
22 step. We would do that, I think, or clinicians would do it-
23 -it's not so much that we're confirming it, but that we have
24 to take that next step to make a decision for treatment.

25 The reason why I think this is important is the

1 issue that Dr. Alter has been raising. I think that not
2 only CDC but every organization that is interested in liver
3 disease has been sending out notifications to physicians,
4 and it doesn't matter how many times you do that, people
5 just don't seem to understand that general physicians don't
6 do the things that she is asking. She sent out videotapes,
7 she sent out tapes, she sent out notifications, and it is
8 not done.

9 If it becomes mandatory that the laboratory test
10 it, then the physician doesn't have to do that, because he
11 or she will get the result only if it's positive, and it's
12 truly positive. So that in essence is a form of education
13 which is mandatory.

14 DR. RELLER: I ask you the question because I
15 think it would help the laboratory to help the public to
16 have this in there.

17 DR. SEEFF: That's right.

18 DR. RELLER: That's the real point I'm driving at
19 over and over again.

20 DR. SEEFF: That's right.

21 DR. CHARACHE: Thank you.

22 Going on to Question 2: "Single-site studies were
23 performed for each of three HCV-infected categories
24 (asymptomatic, acute and chronic) that pertain to a
25 potential indication for use. The company does not claim

1 that their assay is indicated for diagnosis of any
2 particular state of HCV infection or disease but proposes to
3 present in the package insert the data sets obtained from
4 each population category. Is this appropriate?"

5 Dr. Edelstein?

6 DR. EDELSTEIN: Yes. I don't have a problem with
7 it.

8 DR. CHARACHE: Dr. Tuazon?

9 DR. TUAZON: I don't have any problem with that.

10 DR. CHARACHE: Others?

11 Dr. Thrupp?

12 DR. THRUPP: It says in the printing that it is
13 from a single site. As long as it is disclosed that it is a
14 single site, I don't have any problem with it.

15 DR. CHARACHE: Others?

16 [No response.]

17 DR. CHARACHE: The panel does not have a problem
18 if the information is provided. Is that the consensus? I
19 am seeing heads shaking at almost every seat.

20 Dr. Sanders?

21 DR. SANDERS: I agree--I am satisfied with the
22 data. But I think the reason the question was asked goes
23 back to what Dr. Ticehurst was saying, and I don't remember
24 all of the details, but there has been an attempt to
25 encourage multiple sites for data submission, and in this

1 instance, even though we are all satisfied with it, it is
2 one site.

3 So for me, that seems to raise the issue of how do
4 you decide when one site is good enough, as opposed to
5 multiple sites. I'd just throw that out.

6 DR. CHARACHE: So you are questioning whether this
7 is precedent-setting to permit a single site as opposed to
8 multiple sites for information that is being provided,
9 because I think everybody is comfortable with the sum total
10 of the information that has been presented.

11 DR. GUTMAN: I'd be happy to give you a little
12 perspective on the requirement for multiple sites. There
13 really are two different issues that make the agency want
14 multiple sites, and there is frankly not much that is
15 magical about three as opposed to four or five, or the
16 reason they picked three instead of two is that if two are
17 nondiscordant, then you can pick two out of three, so you
18 break the tie.

19 One of the issues about multiple sites is to get
20 the heterogeneity of sampling, and the second issue about
21 multiple sites is to get experience analytically across
22 multiple sites. The issue here would be whether, in the way
23 this study is put together, you get the biologic sample
24 variability and the analytical variability in performance
25 even though you don't have each population of specific

1 indication for use study at three unique sites.

2 So it may not be quite as precedent-setting, but
3 it was interesting enough and different enough from what we
4 have historically done that we wanted to pose the question.

5 DR. CHARACHE: May I ask for clarification, and
6 then we'll call on Dr. Thrupp--does it present a problem to
7 the FDA, and if so, what is the nature of any concern, if
8 multiple sites are required for data presentation and
9 analysis, but only a single site is required for the
10 labeling and the package insert? Does that dichotomy
11 present any difficulty for the--

12 DR. GUTMAN: I'm not sure--could you rephrase that
13 question?

14 DR. CHARACHE: Yes. Here, the single site data
15 does not affect the overall intentions for use that are
16 being presented. My questions is whether permitting a
17 single site to be used in the labeling of the package insert
18 presents any problem to the FDA for future precedent in
19 requiring multiple sites for decisionmaking as to
20 indications of use.

21 DR. GUTMAN: I don't think so. I think our
22 interpretation of this would be if the sponsor, for example,
23 decided to come back and make a specific claim that they had
24 a test for detection of acute states of hepatitis, we
25 probably would try to push them toward three sites again.

1 It's sort of the general nature of the claim that probably
2 makes us comfortable with deviating from our past practice.

3 DR. CHARACHE: Dr. Thrupp?

4 DR. THRUPP: One other alternative might be--and
5 we would wonder what the FDA would think about this--the
6 condition or a suggestion could be made that a post-
7 marketing expanded database be reported to the FDA, with
8 perhaps a recommendation that at some point in time, the
9 package insert be updated to include a broader sampling base
10 as an information update for the user.

11 DR. CHARACHE: Any other thoughts?

12 [No response.]

13 DR. CHARACHE: I think the panel is comfortable
14 with seeing this data provided and will consider further if
15 there will be a recommendation for subsequent additional
16 information.

17 Question 3: "Are the criteria appropriate for
18 categorizing individuals as being acutely infected with HCV?
19 If not, what changes should be made in these criteria?"

20 We have heard that they are not making claims for
21 acute versus chronic, so we have to ask for guidance as to
22 whether this is still of concern.

23 DR. THRUPP: Can you repeat that?

24 DR. CHARACHE: Yes. This question asks if the
25 criteria are "appropriate for categorizing individuals as

1 being acutely infected," the category being that they have a
2 c100 without added bands on the RIBA, and the question is if
3 those criteria are not considered appropriate, what
4 additional changes should be made.

5 And my question is is that question still of
6 interest if there are no specific claims being made.

7 [Pause.]

8 DR. CHARACHE: We are five minutes early for a
9 break for lunch, but perhaps this might be a good time.

10 Dr. Thrupp?

11 DR. THRUPP: Was the original intent of this
12 question wondering about some cautionary statement about the
13 window for very early after inoculation? That might be the
14 only possible way that they might want a cautionary
15 statement.

16 DR. CHARACHE: Well, perhaps we should break for
17 lunch at this time and come back to Questions 3 and 4 after
18 lunch.

19 We'll reconvene at 1:30.

20 [Whereupon, at 12:30 p.m., the proceedings were
21 recessed, to convene at 1:37 p.m. this same day.]

A F T E R N O O N S E S S I O N

[1:37 p.m.]

DR. CHARACHE: If we could come to order, please.

During the lunch break, there was some discussion on the part of the FDA if they could help us understand the specific questions a little more clearly than we did earlier, and I'm going to call on Dr. Gutman to help us.

DR. GUTMAN: Yes. I'd like to start with the specific issues of Questions 3 and 4. In light of the fact that the information based on the criteria will appear in the labeling, it probably would be helpful to have the committee deliberate on the criteria in 3 and 4. It will also help the agency in terms of looking at either this sponsor or other sponsors that might want to make more specific claims and/or claims of this nature with new technologies that might come knocking at the door, so it has both the practical value to us in labeling the product and the theoretical value to us in looking at future submissions.

But I want to re-answer the question that Dr. Charache asked about the regulatory implications of the decisionmaking that's going on, and it's a theme that actually underlies all four questions that maybe we didn't phrase as well as we could have phrased, or maybe we didn't posit in the discussions as we could have posited, and that

1 is what is precedent-setting or what is a little bit
2 different about the submissions than most submissions we
3 have brought to the panel before that we have entered in the
4 context of either our 510(k) or our PMA regulatory program--
5 certainly, the PMA regulatory program.

6 What is different is this notion of carrying a
7 product over the regulatory threshold to a general intended
8 use, and not adding specificity to the intended use, and
9 that's not starting or bad, and we are allowed to re-
10 engineer and find new ways of being least burdensome, so we
11 are not particularly bothered by that, and it didn't seem to
12 me like you folks were particularly bothered by that.

13 And we think of other ways. The most common way
14 that we deal with companies that might have new technology
15 in which data is hard to gather is we will often work with
16 companies to establish a narrow claim structure at first,
17 and then, frankly, allow that narrow claim structure to
18 support the product knowing that it will be used off-label
19 or in broader context and hoping that if there is some
20 scientific or marketing advantage that wider claims will
21 come back in knocking at our door.

22 The tension that exists here is the fact that
23 Abbott does have interesting datasets based on the criteria
24 which we hope you will comment on and which they intend or
25 would like to put in the package insert and that we probably

1 concur might have some value being put in the package
2 insert. And the issue that does concern us in terms of
3 regulatory implications is whether there--and frankly, I
4 think there is--the potential for perception of this as
5 being an implied intended use, or an underlying implied
6 intended use.

7 And there are ways to deal with that, the most
8 draconian way being not to have the data in the package
9 insert at all, to suppress the data or to generalize the
10 data in a way that it couldn't be interpreted that way. I
11 would ask for your fair and square appraisal of that. I am
12 not particularly supporting that because I think you degrade
13 and lose some potentially valuable information to the user.
14 But there may be other ways of taking the data that they
15 have and either having some kind of explanatory or
16 cautionary language or some movement away from perhaps
17 calling the data sensitivity data to agreement or positivity
18 or simply have numbers. There may be other labeling ways to
19 be able to move forward with the general claim to allow this
20 data to be in the package insert and to live with the
21 ambiguity of having a potential implied use here, and I
22 don't know if you want to go back and revisit Question 1 or
23 if you want to wait and address that in the context of your
24 decision about the product overall, or if you want to have a
25 new question, make your own question, have me cast the

1 question, or do that in the context of 3 or 4. But that is
2 the precedent-setting part of this deal, and that is
3 probably the only issue of real angst about anything, that
4 the issue of multiple sites could probably either be glossed
5 over or dealt with in the easy post-market study. But
6 that's the underlying issue that I think the review team is
7 fundamentally concerned with and what is new and different
8 about this.

9 DR. CHARACHE: I think that's very helpful.
10 Perhaps I could ask one more question of clarification along
11 the lines you have just discussed. Personally, I was aware
12 of the impact, which I felt was no problem along with the
13 rest of the panel, of recommending approval of the material
14 presented to say that this test was appropriate for acute,
15 or for any stage of hepatitis C.

16 I was not aware that this was a change in that
17 specificity was not considered to be important, which you
18 just mentioned.

19 DR. GUTMAN: Oh, I didn't mean to imply that. I
20 apologize. I didn't suggest that.

21 DR. CHARACHE: Okay. So the precedent-setting
22 question from the FDA's perspective is not having to
23 stipulate which stage of hepatitis C disease this is
24 targeted at?

25 DR. GUTMAN: What is interesting and what is

1 different about this is that we are using as sort of the
2 endpoint, the surrogate endpoint or the gold standard, is
3 the state of infection. The presence of serologic evidence
4 of infection is really the endpoint, not the type of disease
5 that that infection represents. That is what is interesting
6 about this.

7 DR. CHARACHE: Right, but this does not impact on
8 the need for the specificity--

9 DR. GUTMAN: No, I'm not suggesting that you
10 should decide how to posit specificity or any labeling
11 recommendations or additional studies--whatever you think is
12 appropriate.

13 DR. CHARACHE: So I think that with that question
14 in mind, perhaps we should take a moment to think back on
15 Questions 1 and 2, and we can just look at them and see if
16 we have any further comments to offer for them--if we could
17 see Question 1, please.

18 As I think the material you are speaking about is
19 the tables in the back of the package insert. There are
20 really three sets of tables. One is the precision table,
21 and that's divided into three--Tables 1, 2, and 3. That is
22 in Appendix 2 of Volume I of the books that we have. And
23 that precision--it just states the three sites.

24 So the question really pertains to Table 4 and
25 Table 5 and to Table 6.

1 DR. GUTMAN: That's correct.

2 DR. CHARACHE: Can we be reminded of which items
3 in Tables 4, 5, and 6 are single site studies, just as a
4 reminder for that issue? Perhaps Abbott can help us with
5 that.

6 MR.: If you look at Table 5, lines 3, 4, and 5.

7 DR. CHARACHE: "Acute HCV infection, chronic HCV
8 infection, and asymptomatic infection"--

9 DR. GUTMAN: All three of those are single sites;
10 is that correct?

11 DR. CHARACHE: Those are three that are single
12 sites.

13 DR. GUTMAN: We believe so, but we'll let Abbott
14 quality control--

15 DR. CHARACHE: Thank you.

16 DR. HOJVAT: This is looking at the categories
17 that we have.

18 DR. CHARACHE: Okay.

19 DR. HOJVAT: We'll have to take this and look at
20 the individual tables. So if we are looking at Table 4, for
21 example, random hospital patients, there were two sources of
22 the specimens, and they were tested at two sites.

23 DR. CHARACHE: Okay.

24 DR. HOJVAT: The first-time volunteer whole blood
25 donors, there were actually five sources of specimens, and

1 they were tested at four sites.

2 The random volunteer whole blood donors, two
3 sources of those specimens, and they were tested at two
4 sites.

5 If we go to Table 5, the HCV antibody-positive
6 individuals had a single source and were tested at one site.

7 The acute HCV infection, if we use that category
8 now by saying that we are including the seroconversion
9 specimens, there are going to be multiple sources, and the
10 other acutes, the eight, were from Dr. Thiele's lab. So
11 there are actually multiple sources in that category of
12 acute HCV infection.

13 DR. CHARACHE: So there were multiple sources in
14 the conversion group--

15 DR. HOJVAT: Yes. There were 15 different panels
16 from different sources.

17 DR. CHARACHE: --and then there was the one
18 population that was a nonconversion group that we heard
19 about subsequently from Dr. Thiele.

20 DR. HOJVAT: Well, we did include, if you
21 remember, there were two populations in our acute HCV
22 infection category, one with the seroconversion panels, and
23 the others were the eight specimens, I believe, from Dr.
24 Thiele's lab that did not have c100 reactivity. So those
25 are still the ones in the acute HCV infection.

1 DR. CHARACHE: And they were tested at--

2 DR. HOJVAT: They were tested at probably--I'll
3 have to check--I'm sorry--we do have the seroconversion
4 panels up there. So in fact, if you add those two together,
5 source of acutes is four, tested at two plus one--three
6 sites--two sites, okay.

7 DR. THRUPP: In terms of the total number of sites
8 that we're testing, was the one site all the same lab--

9 DR. HOJVAT: No.

10 DR. THRUPP: --and the two, same plus one, or
11 multiple--

12 DR. HOJVAT: No. They are not numbered. We are
13 just putting "n" there.

14 DR. THRUPP: Right, but the total number of
15 different sites utilizing--

16 DR. HOJVAT: It depended. We did have some that
17 tested the specimens they sourced at their site; we had
18 others where it was an independent source that was tested at
19 an independent testing site, and some of them had a
20 combination.

21 DR. THRUPP: But the total number of sites is,
22 like, seven?

23 DR. HOJVAT: The total number of sites tested is
24 seven.

25 DR. THRUPP: Okay.

1 DR. HOJVAT: I just want to add here, too, if
2 we're looking--are we going down through these?

3 DR. CHARACHE: Yes, let's just run through.

4 DR. HOJVAT: Let's finish that up, because I would
5 also like to bring another factor in, and that is that we
6 are talking about an automated instrument, and maybe we are
7 discussing here heterogeneity at the source of the different
8 specimens, but if we are looking at the number of sites, we
9 have an automated instrument here which I think you have
10 seen by looking at the precision data. This requires very
11 little input from the operator. So I think the issue of how
12 many testing sites, if we're looking at operator
13 variability, we can address that if we look at the precision
14 data and the fact that this is an automated instrument.

15 DR. CHARACHE: Okay. So if we go on to the
16 chronic--

17 DR. HOJVAT: Okay. We have done the acutes. The
18 chronic HCV infection--these were from one source and tested
19 at one site.

20 DR. CHARACHE: And asymptomatic?

21 DR. HOJVAT: Asymptomatic HCV infection, again,
22 one source, tested at one site.

23 The hospital patients, I think we mentioned there
24 was Stanford, and of course, they were fresh draws and
25 tested in real-time at that laboratory site.

1 Individuals at increased risk for HCV infection,
2 we had four sources for those specimens, and they were taken
3 to a different site where they were tested.

4 DR. CHARACHE: Just one other question there. The
5 acute, chronic and asymptomatic where there was one site for
6 the two of them, and for the acute, there was a different
7 site--two sites. Was the one site for the chronic and the
8 asymptomatic the same?

9 DR. HOJVAT: No.

10 DR. CHARACHE: So these were all separate studies-

11 -

12 DR. HOJVAT: Yes. The chronic HCV infections were
13 from Memphis, and the asymptomatic HCV infections were from
14 Sacramento.

15 DR. CHARACHE: Thank you for that clarification.

16 Then, the last one that was questioned was Table
17 6.

18 DR. HOJVAT: And I think those were the same
19 categories as you had in the previous tables.

20 DR. CHARACHE: The same patients.

21 Are there any other questions about the tabular
22 data that we are being asked to address?

23 Dr. Specter?

24 DR. SPECTER: The one point that I'd make is that
25 you have lumped the increased risk for HCV infection

1 patients, but in fact, when you look at them, one group
2 stands out as being different from the other two, and I'm
3 wondering if it wouldn't be best to separate--this still is
4 a whole issue whether hemodialysis patients are a special
5 group, and I wonder if that might not be separated out just
6 to make sure that people see that maybe there is something
7 different about this group of patients.

8 DR. HOJVAT: Yes. And actually, I did have that
9 breakout which we could put into the package insert if
10 required.

11 DR. CHARACHE: Dr. Reller?

12 DR. RELLER: To address the issues brought up
13 after lunch head-on but efficiently, I wonder if, for
14 discussion, to be dealt with specifically when it comes to
15 votes later, if one way to achieve our ends might be to have
16 the data presented under sensitivity and specificity and
17 clinical sensitivity, including the tables just discussed,
18 to have in the package insert something along these lines?

19 "These data are included to be descriptive of the
20 population studied and not as a basis for specific claims
21 for categorization or staging or timing of infection"--
22 something like that. The wording could be worked on. But
23 that way, one would include these data, which I think are
24 helpful. I am thinking of yesterday, we had prolonged
25 discussions of not knowing in a massive information what the

1 characteristics of the population were--were there people
2 who had other kinds of infection, like in Table 7 here,
3 those who were HIV-positive or those who had antibodies to
4 other infectious agents. It would be an opportunity to
5 include the descriptive information for what it's worth and
6 yet to have it clearly delineated that the intent of
7 inclusion is not to imply, directly or indirectly, that this
8 test that is so clearly delineated in intended use is an
9 assessment of HCV antibody status--we'll get into the
10 confirmation later--and that's it, and not to pigeonhole
11 patients based on this single test into any of these
12 particular clinical groups.

13 What do other panel members think about that as a
14 possible recommendation?

15 DR. STEWART: As I look through the information
16 given here in the tables, I don't see any criteria given
17 there at all, and I don't even see what the necessity is of
18 doing that, Barth. I don't think they are making any
19 claims. They are saying they have looked at different
20 patient groups and find them positive, but you are going to
21 only make that diagnosis as a physician reviewing all the
22 data. I don't think there is the implication there that you
23 can just look at a result and say it is acute, chronic, or
24 anything else. I don't think there are any criteria
25 included here.

1 DR. CHARACHE: I think some people would look at
2 this and say, oh, this works for asymptomatic patients, or
3 this works for patients with acute and chronic disease. I
4 think that's the question we're being asked, whether without
5 some warning, that these are examples and not claims,
6 whether they would be read quickly by somebody as a claim
7 even though Abbott is very carefully not making a claim.

8 DR. STEWART: I think they have done it very well.
9 I don't think there is claim there.

10 DR. EDELSTEIN: I think that if someone is going
11 to misread the indications as stated, then they may misread
12 any warnings that may be there. I don't see any problem
13 with it being presented as is. I don't really have a
14 problem. You're afraid that people overinterpret that.

15 DR. CHARACHE: Well, that's the question that the
16 panel is being asked to address--and there are two parts to
17 this. One is should you make such a line listing if there
18 is only one site and therefore perhaps not apply it to
19 another in terms of collection; and the other question is
20 should it be specified as clearly as this what these
21 populations are.

22 DR. GUTMAN: Yes. I have shed our angst. The
23 reason we brought you here today is to provide outside
24 perspective, not necessarily to agree or disagree with the
25 FDA. So we want your fair and square answer.

1 DR. SEEFF: The problem we have, to be perfectly
2 frank, is that I don't know how to diagnose acute hepatitis
3 C. The only way to really diagnose acute hepatitis C is to
4 have somebody who has normal enzymes, who doesn't have
5 antibody, who then develops abnormal enzymes and develops
6 antibody in conjunction with that, and then you can make a
7 diagnosis of acute hepatitis C.

8 What we have come to here is something that I was
9 really not aware of--it is a new approach to me. I am
10 convinced that the cases presented as acute hepatitis C were
11 acute hepatitis C. The reason for that is not because I was
12 told that one of the antibodies was not present in the
13 beginning and then came up later, because I was not aware of
14 that as a specific diagnostic category, but maybe you are
15 right. What I was impressed with in most cases is that they
16 were virtually all, with one exception, jaundiced, and
17 virtually nobody with chronic hepatitis C except in the
18 late stages have jaundice. These patients were jaundiced,
19 and they had high enzymes. Their jaundice disappeared, the
20 enzymes came down to normal or near normal, and all the
21 characteristics that were presented to us were very clearly
22 in my mind acute hepatitis. But those characteristics are
23 not what is stated. The features that have been used in
24 here to make a diagnosis of acute hepatitis C are the height
25 of the transaminases--10 times the upper limit of normal--

1 the presence of antibody, and the absence of c100. Is that
2 correct, Duane?

3 DR. THIELE: Yes.

4 DR. SEEFF: Okay. If that's the case, then, as I
5 say, I don't know of that as specific diagnostic criteria.
6 I think I tend to agree that what these tables should be
7 saying is that they have been tested in certain
8 circumstances that would suggest that this was acute disease
9 or chronic disease, and here are the data. I agree with Dr.
10 Reller that this should probably not be linked to say that
11 here, we have not been able to show that they are clearly
12 positive and acute or chronic hepatitis, but that here are
13 examples of tests that have been done in certain categories,
14 and the results appear to be pretty good.

15 So I don't know how to use this test for acute or
16 chronic disease. Virtually every patient that I see is
17 chronic the first time I see them. I wish I had eight cases
18 of acute hepatitis, because I am trying to study that
19 disease, and I cannot seem to find such cases.

20 DR. ALTER: I have them.

21 DR. SEEFF: So we are looking for such cases.
22 Virtually every time we see cases--this is not like
23 hepatitis B at all. IT is so difficult in hepatitis B; it's
24 a different category. This is a disease which is a
25 complicated disease. It has no symptoms associated with it.

1 You don't know when it begins. You don't know when it
2 becomes chronic. You have to wait for 30 years before
3 people die of this disease, if they do die of it. And the
4 only test we have to make a diagnosis or to identify it is
5 antibody to hepatitis C, and who can--I guess we were
6 talking about this at lunch time--we are using an antibody
7 to make a diagnosis of acute illness, and usually, used like
8 to have the antigen, and in this case, the antibody may miss
9 the very early acute disease.

10 So my feeling is that I would tend to agree that
11 these should be used as examples of where it has been
12 tested, but that there should be a broad category that this
13 test appears to be effective in all the settings in which it
14 has been looked at.

15 DR. CHARACHE: Would you feel it was advisable or
16 not necessary to perhaps decrease the number of categories
17 in Table 5 such that you had, going from the bottom up,
18 individuals with increased risk, hospital patients with
19 physicians' orders, and then perhaps presumed HCV infection
20 without stipulating whether they are acute, chronic, or
21 asymptomatic. And the top one would be proven HCV
22 positives. Would that be advisable or not necessary?

23 DR. SEEFF: You'd like to take these last three
24 categories and divide them?

25 DR. CHARACHE: That's my question, whether that

1 would be advisable or unnecessary.

2 DR. SEEFF: I don't have an opinion on that. I
3 think it's interesting to see those categories, but I don't
4 know whether they should be--I don't have an answer to that.

5 DR. THRUPP: That's where the data came from. It
6 doesn't hurt.

7 DR. EDELSTEIN: And you cannot collapse it because
8 the last two have specificity data.

9 DR. SANDERS: Madam Chair, I just want to remind
10 us all that in the limitations of the procedure, they
11 actually do state in the first bullet point, "Recognizing
12 that presently-available methods for the detection of
13 antibody to HCV may not detect all infected individuals."
14 So they made us aware that the acute people may not be
15 detected. And they go on to say, "A nonreactive test result
16 does not exclude the possibility of exposure to HCV or early
17 acute infection with HCV." So they tell us that that is a
18 limitation of the test.

19 And then they go on to say in the second bullet
20 point that the positive test does not discriminate between
21 active or inactive disease, and they mention a few more
22 categories. So it is stated there. And I think that anyone
23 who is reviewing the data, anyone in the clinical laboratory
24 who is reviewing the data with the same alacrity that we
25 have, would probably also read those limitations.

1 DR. EDELSTEIN: Most people don't read them.

2 DR. CHARACHE: Dr. Thrupp?

3 DR. THRUPP: I certainly agree that the
4 limitations of the procedures section have these very nice
5 clinical limitations, if you will, written there. I think--
6 this is coming back to what we discussed previously--the
7 importance of those limitations, I would think, and as very
8 nicely stated by Dr. Reller, that we are trying to provide
9 better guidance for the laboratory to better guide the
10 clinician, that is may be well worth bringing perhaps the
11 second sentence, or perhaps the second and third sentence,
12 of that bullet on page 7 up to the Intended Use paragraph,
13 as well as leaving it where it is--stating it both places.
14 And in addition, into that Intended Use introductory
15 paragraph on the first page, add the comment about repeat
16 testing, as Dr. Seeff has proposed.

17 DR. CHARACHE: Okay. I think I am hearing a
18 consensus on the panel that there is an advantage in
19 continuing to show the specific populations that have been
20 presumed tested. Does that reflect the consensus of the
21 panel--perhaps with Dr. Reller's addition of warning people
22 that this is not associated with claims, but it provides an
23 understanding of the populations tested.

24 Is there any objection to that consensus
25 statement? I am seeing general agreement.

1 And then, is there any problem with the repeat of
2 the three in the middle on Table 6, which is the same data
3 plus some additional analytical data?

4 DR. RELLER: Pat, do you want comments, or do you
5 want motions to solidify things, or do we only solidify at
6 the time of the vote?

7 DR. CHARACHE: We solidify at the time of the
8 vote, but if you think it would help, we can take a vote now
9 on the recommendations to the FDA. Let's do that. I think
10 that might help.

11 DR. RELLER: I move that in the package insert--

12 DR. CHARACHE: You recommend--not you move--you
13 move to recommend.

14 DR. RELLER: That's what I meant. I move to
15 consider to recommend, in the fullness of time--

16 [Laughter.]

17 DR. RELLER: --when the appropriate talented
18 parties are gathered together to consider the above.

19 DR. CHARACHE: Did you get that?

20 [Laughter.]

21 DR. RELLER: That something along the lines of the
22 following verbiage be put into the places discussing
23 sensitivity and specificity--where the populations described
24 or categorized as acute or chronic, that the wording "that
25 these categories are descriptive of populations studied and

1 not the basis for specific claims for categorization"--
2 something along those lines.

3 I don't think this is the time, but that message
4 should be forwarded on from the Advisory Committee for
5 consideration by the agency in their final working with the
6 sponsor about the wording that goes into the package insert.

7 DR. CHARACHE: And would you include with that the
8 fact, then, that the tables should stay?

9 DR. RELLER: I believe the tables should stay,
10 because they are helpful descriptors of the patients
11 studied. This is what Dr. Gutman was getting at earlier.
12 And I think that as one looks to the future, it reinforces
13 that there may be diagnostic products or tests in the future
14 that would be of use in helping better early to categorize
15 patients for whatever, whether it is prognosis, public
16 health reasons, therapeutic interventions, research studies,
17 et cetera, et cetera, and that conceptually, if there be
18 clinical research or public health utility in categorizing
19 patients, and one has tests that enable one to do that based
20 on the testing itself, that one has to have sufficient
21 numbers and adequate evidence from properly-done studies
22 that one can accurately do that. And to have the categories
23 at this point, and yet to delineate them as descriptive and
24 not supportive of a claim, I think is sending just the right
25 balance of the messages to what one has and what one would

1 look for in the future.

2 DR. CHARACHE: All right. We have a motion to
3 recommend to the FDA that the tables remain in the form that
4 they are presented and--

5 DR. SPECTER: Can I comment on that, because if
6 you are going to vote for them in the form that they are, I
7 still would like to bring up this point about the last line
8 being split out into the three subgroups that were actually
9 tested.

10 DR. CHARACHE: Could you--

11 DR. SPECTER: These are the individuals at
12 increased risk of HCV infection where--I don't know how many
13 people have this table, but there's a table that shows--

14 DR. CHARACHE: Yes.. So you would like to see that
15 last group separated into the three high-risk populations.

16 DR. SPECTER: Right.

17 DR. RELLER: So, Steve, you would put in there,
18 like those 150, something like an asterisk or whatever that
19 said "including 50 patients in hemodialysis, 50 patients
20 with intravenous drug use," et cetera.

21 DR. SPECTER: No. I would leave the 150 exactly
22 as it is and then below it, break out the three groups.

23 DR. RELLER: As subcategories.

24 DR. SPECTER: As subcategories. The important
25 thing being under the specificity data where it shows 51 of

1 57, it actually is--I don't know why it says that, actually-
2 -I thought it was 91 of 97--I think they perhaps--I don't
3 know what they've done there. But the important thing is
4 that for the hemodialysis, it was 26 out of 32, or 81
5 percent where there was concordance with the confirmatory
6 test, whereas with the other two categories, it was 100
7 percent. So there is a very distinct difference between
8 that one category and the others. I think that that point
9 should be made.

10 DR. CHARACHE: Let's vote first on Dr. Reller's
11 recommendation and then come to the question whether the
12 high-risk should be presented with each line displayed.

13 DR. EDELSTEIN: May I ask for a clarification? It
14 seems to me that we are discussing the conditions that we
15 are going to apply--

16 DR. CHARACHE: I don't think so--I'm sorry.

17 DR. EDELSTEIN: --because are we going to have
18 this discussion over again after we take the vote?

19 DR. CHARACHE: No. I think that at this point, we
20 are voting on what we recommend to the FDA as opposed to a
21 condition.

22 DR. EDELSTEIN: And do we need to vote on
23 recommendations, answers to questions? We haven't done that
24 before.

25 DR. CHARACHE: No, we haven't, and we don't have

1 to vote to make a recommendation. I was trying to help
2 clarify the consensus if we have one. So this is not a vote
3 for recommendation; this is a clarification of consensus.
4 And based on that, I will ask for a show of hands of those
5 who would like to make the recommendation as delineated by
6 Dr. Reller.

7 DR. THRUPP: With the modification by Dr. Specter.

8 DR. CHARACHE: Do you want to add that right now?

9 DR. THRUPP: Sure.

10 DR. CHARACHE: All right. With the modifications
11 made by Dr. Specter. Okay.

12 All those who would like to make that
13 recommendation to the FDA, please raise your hands.
14 Consultants can raise their hands, too. This is not a vote,
15 this is a recommendation.

16 [A show of hands.]

17 DR. CHARACHE: Seven.

18 All those who would rather not make that
19 recommendation.

20 [A show of hands.]

21 DR. CHARACHE: Okay. So you see where the
22 consensus lies. And that is not a vote, that is a display
23 of where the consensus lies.

24 Okay. Now let's come back. Is there anything
25 else on Question 1 on which you would like guidance that we

1 have not provided?

2 [No response.]

3 DR. CHARACHE: Okay. Is there anything on
4 Question 2?

5 [No response.]

6 DR. CHARACHE: All right. Let's go to Question 3.

7 We have been asked to--still, even though it's not
8 a current part of this application--assist in providing
9 guidance to the FDA on the definition of an acute infection.
10 Now, the definition as presented by Abbott is in the book
11 that we got this morning. The last exhibit on 7, the last
12 slide that was presented this morning, which is on page 7,
13 and the slide at the top of page 8. So an acute HIV
14 infection, n equals 23, two populations. Physician
15 diagnosis of acute hepatitis; unspecified signs and symptoms
16 of acute hepatitis; serum transaminase levels greater than
17 10-fold upper limits of normal; positive for anti-HCV but
18 not the c100 antigen band; nonreactive to hepatitis B and
19 hepatitis A; negative history for drug- or toxin-induced
20 liver disease; cholelithiasis, serologic evidence of other
21 viral illnesses, and congestive failure.

22 The definition on the top of page 8, which is a
23 continuation, commercial available HCV panels demonstrate
24 seroconversion; elevated serum transaminase levels--in this
25 case, ALT greater than 80.

1 Comments on this definition of acute disease--yes?

2 DR. STEWART: This information isn't going in the
3 package insert; this was to support the information that
4 these were acute cases to look at, and I see no indication
5 that there are any criteria that they are putting forward.
6 They are telling us what word criteria.

7 DR. CHARACHE: We were asked anyway in terms of
8 future reference to say whether we feel that this would be
9 an appropriate categorization of acute hepatitis C.

10 DR. STEWART: So this has nothing to do with
11 what's in the package insert.

12 DR. CHARACHE: No. This is separate.

13 DR. STEWART: Okay.

14 DR. CHARACHE: This is for future reference, or
15 perhaps future application.

16 Yes?

17 DR. THRUPP: Dr. Seeff just a few minutes ago
18 again made the comment that in relationship to this list,
19 the first two bullets, physician diagnosis and the
20 unspecified signs and symptoms--in his experience,
21 unspecified signs and symptoms would not be enough; he would
22 like to see jaundice. Is that being too restrictive?

23 DR. SEEFF: I'd like to comment on this in detail
24 when you are done.

25 DR. THRUPP: Well, I was bouncing it to you,

1 because I'm not sure--this looks pretty nonspecific.

2 DR. SEEFF: Before I do, I would just like to ask
3 a question. There is nothing as far as I can see in this
4 slide on page 7 which tells me that this is acute hepatitis.
5 This could just as well be chronic hepatitis. The only
6 reason I believe it's acute hepatitis is because an expert
7 told us that the cases they looked at also had jaundice
8 which disappeared. That's not in here. But the other
9 question that I have, if you turn to the next page, it says
10 "demonstrates seroconversion"--are we talking about
11 seroconversion from negativity to positivity or from--what
12 do we mean by "seroconversion"? So in other words, you had
13 to have somebody who was seronegative for antibody, develops
14 all of these, and then, in the appropriate time frame,
15 seroconverts. Is that--

16 DR. NOLTE: It's two separate populations, isn't
17 it? The two slides are two separate patient populations?

18 DR. SEEFF: Based on what we've seen in this one
19 slide, I don't see anything here that tells me that this is
20 unequivocally acute hepatitis. It is not uncommon to see
21 patients with chronic hepatitis with transaminase of 400 and
22 go up to 1,000. You can have flares and go up to 1,000.

23 So the physician diagnosis--if it's Dr. Thiele,
24 then it's okay, but if it's somebody else out in practice
25 who has never seen a case of acute hepatitis, the signs and

1 symptoms mean nothing. Transaminase levels could be like
2 this for both acute and chronic, positive for anti-HCV. As
3 I said, the only way that I know to diagnose acute hepatitis
4 unequivocally is to see somebody who had everything normal
5 and then, under observation, had developed abnormal enzymes-
6 -this is hepatitis C, not hepatitis B. There is no test
7 that I know of that will identify acute hepatitis C for me,
8 and I'm not sure that that should be our job, you know, if
9 the FDA would like that. I do think that you need to have a
10 group of hepatologists get together and see what they would
11 do. I think the addition of jaundice is helpful, but of
12 course, there are lots of people with acute hepatitis who
13 are not jaundiced. So you may need to have another panel of
14 people come up with a diagnosis of acute hepatitis C. I'm
15 not sure we can do that. So that represents my problem in
16 the diagnostic criteria, because I don't know if there's a
17 certain way of setting it that you can say to the next group
18 who come in, here, we have the diagnosis. We just can't do
19 that.

20 DR. CHARACHE: All right. I'm hearing Dr. Seeff
21 say that the definition which begins on page 7 and continues
22 on page 8 would be problematic for him. Is there anyone who
23 would like to make an additional comment?

24 Dr. Specter?

25 DR. SPECTER: Just very quickly, I think the

1 important issue here is the c100 story and how that fits
2 with other things, and I think there are two issues related
3 to that--one, where did it come from; and two, if there is
4 good scientific evidence to support it, it may be valid.
5 And I think that that's what we have to find out.

6 DR. SEEFF: Let me agree with you. As I said, I
7 heard about this today for the first time as specific
8 diagnostic criteria for acute hepatitis, and if there is
9 enough data to support that, published data, then maybe
10 that's sufficient. That would be very meaningful, and for
11 me, it would be very interesting and something I have
12 learned today.

13 DR. CHARACHE: Okay. Let's look at Question 4. I
14 think we've answered both parts of Question 3.

15 "Are the criteria appropriate for categorizing
16 individuals as being chronically infected with HCV? If not,
17 what changes should be made in these criteria?"

18 We have seen a categorization of the chronic group
19 into separate categories. The definitions that were shown
20 this morning follow the acute, also beginning on page 8.
21 Evidence of chronic HCV infection greater than 6 months; HCV
22 RNA before study specimen collected, or greater than 6
23 months HCV antibody-positive, and evidence of HCV activity;
24 disease most likely to be HCV-associated histopathologic
25 changes or Interferon therapy at any time, or replication

1 HCV RNA same date or later.

2 Let's look at that group, and then we can come to
3 another group. Is there a sense of the accuracy of those
4 criteria being diagnostic of chronic HCV infection?

5 Again, Dr. Seeff.

6 DR. SEEFF: This is entitled, "Chronic HCV
7 infection," and that's what has been stated. And all you
8 need is the presence of HCV RNA or the antibody for 6
9 months. The histology is only helpful if that is chronic
10 hepatitis, and we know that of all people who are HCV RNA-
11 positive, half of them are going to have to be normal
12 enzymes if you biopsy that group; some of them have minimal
13 evidence of inflammation.

14 So the first thing, if it's going to be called
15 chronic HCV infection, all you need, I think, is the
16 presence and persistence of anti-HCV or HCV RNA for 6
17 months.

18 The second category will be individuals with
19 chronic hepatitis C which would require, then, presumably
20 abnormal enzymes plus histology. That would be helpful.

21 DR. CHARACHE: Are there any other thoughts or
22 comments?

23 DR. SPECTER: I would hesitate a little on the
24 presence of the antibody because we have already heard that
25 up to 15 percent will have antibody and will not have

1 DR. SPECTER: It's irrelevant. I Mean, we're
2 trying to use an inclusion criterion, and if we miss some
3 samples, so what? What we want to know is that the samples
4 we have are good samples. So it really doesn't matter if we
5 miss some. We're talking about samples that can be included
6 in the study, so it's not important for what we are going to
7 make the criteria if we miss a few of those.

8 DR. CHARACHE: Thank you.

9 Next is the HCV infection, state not determined;
10 HCV antibody-positive more than 6 months before study
11 specimen collected; and no histologic evidence of chronic
12 hepatitis at any time. That's HCV infection, state not
13 determined.

14 DR. SPECTER: Again, this isn't really addressing
15 the question, and I don't think we need to discuss it.

16 DR. CHARACHE: Are there any other comments about
17 chronic categories, and have we addressed your questions?

18 Okay. So we have answered the four questions, and
19 I thank the group.

20 The next issue--we have continued our open
21 committee discussion--will be a brief break, and then the
22 public hearing--unless you'd like to go on--does the group--

23 DR. SPECTER: Let's go on.

24 DR. SEEFF: Let's go on.

25 DR. CHARACHE: You want to go on. All right.

1 Open public hearing. Is there any member of the
2 public who would like to comment?

3 [No response.]

4 DR. CHARACHE: Hearing none, the next item is
5 Industry Response.

6 Comments from Abbott on anything you've heard--or
7 anything we should know that we may not know? This is
8 scheduled as 5 minutes.

9 DR. HOJVAT: I'll talk very, very fast.

10 There was a question of the rate of false
11 positives, looking at the EIA against the AxSYM. If we look
12 at all of the categories that we tested where we had both
13 sets of data, we had a total of 20 false positives as we
14 have defined it in the EIA, and 18 in the AxSYM.

15 DR. CHARACHE: So they are very parallel.

16 Any other information that you'd like to share?

17 MR. KLYMERZINSKY: Matt Klymerzinsky, Abbott.

18 In regard to the addition of supplemental testing
19 mandated in the Intended Use, as I said before, it is not in
20 keeping with the current regulations, but we could work that
21 out with FDA, and as a sponsor, I don't think we object to
22 the labeling considerations.

23 The tables were placed in the package insert to
24 let the user know that the test works in the intended
25 populations. And again, with what we have heard today,

1 certainly, there was no intent on our part to make a claim
2 for acute chronics, but again, just to demonstrate that the
3 test does work in the intended populations.

4 There are tests now on the market for the
5 detection of hepatitis C for both blood screening and
6 diagnosis that have similar tables in the package insert
7 without any disclaimer or qualifier for those tables. So
8 this will be precedent-setting to impose it on one test and
9 allow users to sort of shop around for what tests they are
10 going to buy based on the amount of disclaimers or financial
11 considerations based on the amount of testing or whatever
12 would be required.

13 So I'll just leave it at that, but I did want to
14 make a point that what you are deciding here is precedent-
15 setting from the standpoint of other manufacturers' tests.

16 Thank you.

17 DR. HOJVAT: I did have one last piece of
18 information. At one point in the discussions, I believe we
19 heard an opinion that perhaps we should be doing repeat
20 testing on a positive. I think that if you look in
21 Amendment Number 10--I think it was information sent to you
22 earlier than this morning--you'll see that we did address
23 this issue with the FDA, and we did demonstrate to them
24 statistically that there was no difference between initial
25 testing and final interpretation if it was using, for

1 example, all three, if you did initial and then repeat
2 testing. And we did demonstrate that as justification to
3 not require additional retesting of initially reactive
4 specimens.

5 And if you notice, we did ask for retesting in an
6 equivocal zone which is close to the cutoff, around the
7 cutoff. We did recommend that you did retest a single in
8 that one.

9 For your information, we did actually only have, I
10 think, about 17 specimens that fell in that equivocal zone,
11 and when they were retested, all but three stayed exactly
12 the same. Only three of them flipped from the gray zone to
13 a negative.

14 So we feel that it would not be a risk to state in
15 the package insert the positive results above the equivocal
16 zone did not need to be retested in duplicate, and that
17 statistical justification was given to the FDA in our final
18 amendment and agreed upon by the FDA.

19 DR. CHARACHE: Any further questions?

20 DR. SEEFF: This was in low-risk groups?

21 DR. HOJVAT: This was overall.

22 DR. CHARACHE: Oh--so this would include those in
23 which they were proven ahead of time to be positive HCVs?

24 DR. HOJVAT: Uh-huh.

25 DR. CHARACHE: There was a large group of them.

1 DR. HOJVAT: Right.

2 DR. CHARACHE: Do you have that information in the
3 group that had the primary testing that were not known ahead
4 of time to be HCV positive?

5 DR. HOJVAT: Correct. In fact, on major--

6 DR. CHARACHE: In terms of the gray zones, did
7 they have more gray zones than the previously defined group?

8 DR. HOJVAT: I'd have to look to define what the
9 gray zones were.

10 DR. CHARACHE: Okay. Dr. Thrupp?

11 DR. THRUPP: While they are looking for that, this
12 issue could be looked at from another standpoint--from two
13 other standpoints. Number one, in order to agree that the
14 repeat testing is not necessary, that might be dependent on
15 the number of population cohorts studied, and we have
16 already discussed that it's nice they've got a number of
17 them, but many of them were one site only. So that could be
18 a precaution.

19 And the second thing relates to the level playing
20 field. There is a requirement out there for the reference
21 method, so to speak, that a repeat test is necessary, and
22 what would repeating of the other tests show--maybe they
23 would have a similar low rate of discrepancies, and this
24 might be an unlevel playing field. I don't know the answer
25 to these questions.

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1 DR. CHARACHE: Yes. I think that in one sense,
2 though, we have to remember that this is a very different
3 test, and therefore, the rules may not be the same in that
4 this is an automated system, and a lot of the problem with
5 the other test is the manual manipulation as well.

6 DR. HOJVAT: It does appear that most of those
7 gray zone or equivocal specimens are from the prevalent
8 studies; therefore, I would call that the low-risk-type
9 populations, which is similar to the screening test at a
10 blood bank, and there you can see the necessity for perhaps
11 doing retest. But they are within the low-risk population.

12 DR. THRUPP: But then, in response to the second
13 part of that, this is a different test, it is automated; the
14 sponsor--I think it would be relevant to have information
15 presented, not necessarily as a condition, but to indicate
16 that the repeat testing, as they have already indicated with
17 their test, shows very few discordant results, whereas the
18 reference method, which is not automated, is going to show
19 greater discordance rates, and therefore, that justifies
20 their not having to do it.

21 DR. CHARACHE: Yes, and I think that if that were
22 done, it would be important that they not be on the
23 previously-defined positive group, but rather on the group
24 that's going to be used in the future.

25 Let us then ask the panel whether--we have two

1 more things to do. One is any final discussion and a vote,
2 and the second is to take about 15 minutes to address the
3 issue that we didn't cover yesterday. So let me ask if you
4 would like to have a break at this time or if you would like
5 to continue.

6 DR. EDELSTEIN: Let's continue.

7 DR. STEWART: Let's continue.

8 DR. CHARACHE: All right. I think it's unanimous.
9 We will continue.

10 Freddie?

11 MS. POOLE: I'm going to provide some information
12 on panel recommendations options. For premarket approval
13 applications, the Medical Device Amendments to the Federal
14 Food, Drug and Cosmetic Act, as amended by the Safe Medical
15 Devices Act of 1990, allow the Food and Drug Administration
16 to obtain a recommendation from an expert advisory panel on
17 designated medical device premarket approval applications
18 that are filed with the agency. The PMA must stand on its
19 own merits, and your recommendation must be supported by
20 safety and effectiveness data in the application or by
21 applicable, publicly available information.

22 "Safety" is defined in the Act as "reasonable
23 assurance, based on valid scientific evidence, that the
24 probable benefits to health under conditions on intended use
25 outweigh any probable risk."

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1 "Effectiveness" is defined as "reasonable
2 assurance that in a significant portion of the population,
3 the use of the device for its intended uses and conditions
4 of use, when labeled, will provide clinically significant
5 results."

6 Your recommendation options for the vote are as
7 follows: 1) approval, if there are no conditions attached;
8 2) Approvable with conditions; the panel may
9 recommend that the PMA be found approvable subject to
10 specified conditions such as physician or patient education,
11 labeling changes, or a further analysis of existing data.
12 Prior to voting, all of the conditions should be discussed
13 by the panel.

14 3) Not approvable. The panel may recommend that
15 the PMA is not approvable if the data do not provide a
16 reasonable assurance that the device is safe or if a
17 reasonable assurance has not been given that the device is
18 effective under the conditions of use prescribed,
19 recommended, or suggested in the proposed labeling.

20 Following the voting, the Chair will ask each
21 panel member to present a brief statement outlining the
22 reasons for their vote.

23 Our voting members today are Dr. Natalie Sanders,
24 Dr. Carmelita Tuazon, Dr. Michael Wilson, and appointed to
25 temporary voting status pursuant to the authority granted

1 under the Medical Devices Advisory Committee charter dated
2 October 27, 1990 and as amended August 18, 1999, I hereby
3 appoint L. Barth Reller, M.D., Leonard B. Seeff, M.D.,
4 Steven C. Specter, Ph.D., and Lauri D. Thrupp, M.D. as
5 voting members of the Microbiology Devices Panel for this
6 meeting.

7 For the record, they are Special Government
8 Employees and consultants to this panel or other panels
9 under the Medical Devices Advisory Committee. They have
10 undergone the customary conflict of interest review and have
11 reviewed the material to be considered at this meeting.

12 This appointment is signed by David W. Feigel,
13 Jr., Director of the Center for Devices and Radiological
14 Health.

15 DR. CHARACHE: All right. We will now entertain a
16 motion for approval, approval with conditions, or not
17 approvable.

18 Dr. Reller?

19 DR. EDELSTEIN: I'd like to make a motion; I can't
20 vote.

21 DR. RELLER: I move that we recommend to the
22 agency for the PMA before us approvable for the intended use
23 stated, with two modest conditions or provisos which are--

24 DR. CHARACHE: Let's stop there and just say you
25 recommend for approval, and then we'll come back to the

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1 conditions--approval with conditions, and then come back--if
2 that's all right with you.

3 DR. RELLER: As you wish.

4 DR. SPECTER: Second.

5 DR. CHARACHE: It is moved and seconded approval
6 with conditions. We'll vote on that and then, as yesterday,
7 we'll consider the conditions beginning with the two that
8 Dr. Reller would like to have us considered and others that
9 anyone else may wish to have discussed.

10 So we'll go around, and we'll start with Dr.
11 Seeff.

12 DR. SEEFF: I agree.

13 DR. WILSON: I agree.

14 DR. THRUPP: Agree.

15 DR. SPECTER: I agree.

16 DR. TUAZON: I agree.

17 DR. SANDERS: I agree.

18 DR. CHARACHE: So it's unanimous agreement.

19 Dr. Reller, can you give us the conditions you'd
20 like discussed?

21 DR. RELLER: They are two, and they are changes in
22 the proposed labeling for the purpose of education of those
23 who perform, interpret and use the tests.

24 First, that the penultimate sentence in the first
25 column on page 7, the wording be revised and be included

1 there and immediately following the intended use as stated,
2 the following: "Reactive specimens should be confirmed by
3 an additional more specific or supplemental test such as
4 strip immunoblot assay or nucleic acid amplification assay
5 for HCV RNA."

6 DR. CHARACHE: Could you repeat that once more--
7 your statement--that immediately following the intended use--

8 -

9 DR. RELLER: Immediately following the intended
10 use statement, "Reactive specimens should be confirmed by an
11 additional more specific or supplemental test such as the
12 strip immunoblot assay or nucleic acid amplification assay
13 for HCV RNA."

14 There is the suggestion that this might be bolded.
15 The details of how attention is brought to this issue, I
16 leave with the agency, but the sense is that this test,
17 intended for the use of documenting the presence of antibody
18 to HCV be confirmed before being reported as a positive for
19 appropriate interpretation by the user.

20 DR. CHARACHE: Let's discuss that.

21 DR. RELLER: Do you want the second one, as a
22 package, or do you want to go one-by-one?

23 DR. CHARACHE: Let's go one-by-one.

24 DR. RELLER: All right.

25 DR. CHARACHE: And anyone else who has anything

1 they want on the table, please make sure you note it.

2 Are there any comments in terms of that particular
3 recommendation?

4 Dr. Specter?

5 DR. SPECTER: I am supportive of the language and
6 making it more recognizable. I am ambivalent on the idea of
7 moving it up front, out of custom with what is done with
8 package inserts for this type of testing. I think it should
9 be consistent with what is done.

10 DR. CHARACHE: All right.

11 Dr. Thrupp?

12 DR. THRUPP: Could I just make a comment
13 concerning the issue of where such comments should be
14 placed? If one looks at page 7 under the section,
15 "Limitations of the Procedure," and you start from the
16 bottom, the last bullet, all of the bullets, with the
17 exception of the second-to-the-last and the first two, the
18 rest of the bullets do relate to procedural details in
19 handling of specimens.

20 The first, second and second-to-the-last bullet
21 refer to, really, interpretation and intended use. Now, one
22 could suggest a separate section where these are brought out
23 as limitations of interpretation as opposed to limitations
24 of procedure, but that complicates our task, and maybe that
25 might be one answer. But I would support the--due to the

1 importance of this issue, I would support Dr. Reller's
2 motion as the simplest way to get the job done.

3 DR. CHARACHE: We have one support and point out
4 that in its current location, it is lost among the
5 procedures. I must confess that's why I didn't find it; I
6 thought it had to do with the testing itself.

7 Dr. Seeff?

8 DR. SEEFF: I am not exactly sure what the motion
9 is. You want to move it somewhere else, or--

10 DR. CHARACHE: The motion is to have it where it
11 is but to also put it in the very front under "Indications
12 for Testing."

13 DR. RELLER: The details are for the agency. The
14 main concept is getting right up front the importance
15 concept that we discussed in great detail earlier that
16 positives with this test should be confirmed before
17 reporting.

18 DR. GUTMAN: The sponsor has pointed out already,
19 but I'll be their voice here and point out again that this
20 is a departure in strength--it may be a warranted, or it may
21 be an unwarranted or a welcome or an unwelcome departure,
22 but it's a departure from the traditional recommendation.
23 "Should" is stronger, and "must," of course, would be the
24 strongest and probably might be stronger than we could even
25 entertain.

1 I don't wish to be leading, because we want your
2 advisory, so we'll do the best we can with your advice, and
3 we'll have to negotiate this with CBER, the worry about the
4 consistency problem. But you might give pause to whether
5 you in fact do think it should be a recommended, because
6 that will make a difference to the sponsor, and that will
7 make a difference to the FDA as we negotiate labeling.

8 DR. RELLER: To me, there is a distinctive
9 difference for what might be done with a very sensitive test
10 to exclude inappropriate donors from the Nation's blood
11 supply as opposed to what is necessary to, in my view and
12 from the discussions that I have heard, decide for
13 diagnostic purposes what constitutes a true positive for
14 potential therapeutic intervention, for prognostic--for
15 whatever purpose--that in reality, these need to be
16 confirmed to appropriately care for patients. And it is a
17 different issue as to whether they must be confirmed or
18 should be confirmed in terms of a screening of a blood donor
19 where you simply want to err on the side of not making a
20 mistake with giving someone blood. This is a different
21 issue--you don't want to make a mistake.

22 To me, it is very analogous to what it means for
23 the individual patient, an initiation of therapy and so on
24 of an HIV test, with confirmation versus simply excluding a
25 unit of blood. There are just very much different

1 implications for the individual patient, and since what is
2 before us is diagnostic use, I think that this is an
3 opportunity to make that distinction very clearly in accord
4 with recommendations from Dr. Alter what the CDC is doing
5 and Dr. Seeff's earlier, very cogent and very explicit
6 comments.

7 DR. CHARACHE: Dr. Wilson?

8 DR. WILSON: I agree with Dr. Reller. We have
9 seen in low-prevalence populations that the false positive
10 rate can be very high, and I think one can make a strong
11 argument for this test to be safe and effective that one
12 would need to do replicate testing on positive specimens;
13 otherwise, it is very difficult if not impossible to
14 interpret the test result.

15 DR. CHARACHE: Dr. Thrupp?

16 DR. THRUPP: I think Dr. Reller's motion--or
17 suggested recommendation--used the term "confirmed." We
18 have heard that a lot of data on repeat testing may not be
19 necessary. It may be that that might be an option, but what
20 I am hearing is that it is the confirmed test--confirmation
21 is what is important.

22 DR. RELLER: May--I was very careful in my choice
23 of words because I think it is an important distinction. I
24 haven't heard anything that makes me uncomfortable with the
25 data presented about the need to do repeat testing, and it

1 becomes superfluous if one has confirmatory testing. You
2 have a positive, and you see whether it is real.

3 So all of the things that would be wasted by just
4 doing the same thing twice could be saved by going to what
5 you really need for a diagnostic test for the individual
6 patient, which is what we are talking about here.

7 DR. CHARACHE: I think what I'm hearing is a
8 conflict between the belief that patients should not be told
9 the result without a supplemental test and the desire to
10 ensure that a company with a good test is not penalized by
11 being put at a financial disadvantage with their
12 competitors. And I think we have to remember that are tests
13 that CBER has approved for diagnostic as well as blood bank
14 use in which it was recommended, but the word "should" be
15 followed was not used.

16 So I think this is what we have to resolve. I
17 don't know whether you want to waffle and say "It is
18 strongly recommended," as opposed to "should," or whether we
19 can work this through so that our new recognition that this
20 is important isn't totally lost to precedent.

21 DR. RELLER: Well, there is a motion, and I don't
22 know if anyone seconded it, and if people don't think we
23 should add "should"--

24 DR. CHARACHE: It was seconded.

25 DR. RELLER: If people don't think we should have

1 "should," they can defeat the motion. It's conceivable that
2 this is an opportunity to do what is right in the public
3 interest, and maybe, is it possible that even though that's
4 the way it was and is in tests that are cleared for both
5 screening and diagnostic purposes, that there is in that
6 twin use some ambiguity that this affords a chance to clear
7 up in the public interest. I said "should," and that's what
8 I meant.

9 DR. CHARACHE: Dr. Edelstein?

10 DR. EDELSTEIN: I have to say I disagree with you,
11 Barth, for a couple of reasons. One is I'm not sure that
12 even in the product insert for the HIV antibody test that it
13 specifically states that the test result may not be released
14 without confirmatory testing. I'm not positive on that, but
15 I wonder about that, and that is done because of current
16 guidelines from various public health agencies.

17 The other is what about the situation in which
18 someone is having repeat testing done to confirm a prior
19 positive; would you then require that confirmatory testing
20 be done on that specimen as well?

21 One suggestion perhaps as a compromise might be to
22 qualify a positive result without doing confirmatory testing
23 with some sort of statement saying that depending on
24 clinical circumstances and prior laboratory results, it may
25 be indicated to confirm this test with a supplemental test.

1 What I'm worried about is disallowing release of
2 the test results without doing the confirmatory testing. I'm
3 not saying that it shouldn't be done in most cases, but I
4 wonder about saying specifically that you have to do the
5 confirmatory test before releasing it.

6 DR. RELLER: That wasn't part of the motion. I
7 took the exact wording that is already in this package
8 insert and suggested that it be moved up front for
9 educational purposes, plus the wording "should" instead of
10 "recommended" because I think it should be done.

11 Now, if the agency wants to put "should be"--and I
12 agree with you totally, if the test is done over and over,
13 you don't have to do this every time, but maybe on initial
14 testing, it should be--there is some room there--but the
15 main thing is to capture the intent or to forward the
16 intent--and what the agency does with it is their
17 responsibility--but forward the intent that when you first
18 find someone positive for HCV by this test for diagnostic
19 purposes for the individual patient, that that should be
20 confirmed with one of these other tests.

21 Dr. Seeff, what do you think?

22 DR. SEEFF: You know, I was much more comfortable
23 until I heard the data presented a month ago saying that
24 when repeats were done, they found no discrepancies--is that
25 correct?

1 DR. CHARACHE: No, we're not talking about
2 repeats.

3 DR. RELLER: We're talking about RIBA or nucleic
4 acid tests.

5 DR. SEEFF: I would be perfectly happy to leave it
6 where it is. I would bold it, because I think it should
7 stand out. Ideally, I would like to have it up front as
8 well as an educational thing--I agree with you--in order to
9 overcome the problems that they are having. The trouble is
10 I don't know--there is a question of penalizing the company
11 versus the issue of getting the information out, which I
12 think is very important.

13 DR. CHARACHE: Dr. Seeff, let me highlight, I
14 think, one key question here even more important than
15 position--should it be "recommended," should it be "strongly
16 recommended," should it be "should"?

17 DR. SANDERS: I'd like to make a comment about
18 that.

19 DR. CHARACHE: Let's hear from him first.

20 DR. SEEFF: Is "is" is?

21 DR. CHARACHE: Do you want to think about it while
22 we ask Dr. Sanders?

23 DR. SEEFF: I'm a compromiser. I would be willing
24 to say "strongly recommended."

25 DR. CHARACHE: Dr. Sanders?

1 DR. SANDERS: To me, this is an instance where we
2 as an advisory panel have the opportunity to let the FDA
3 understand our concerns, and we find that this is a really
4 key issue. However, we are sort of like the CEOs
5 micromanaging. Why can't we let the FDA staff take these
6 concerns specifically regarding this issue and work out the
7 details of the wording with Abbott? Why do we actually have
8 to articulate the actual words here?

9 DR. CHARACHE: I think we're struggling with what
10 they are going to have to struggle with, which is how
11 forceful we want to be in making this recommendation.

12 Let's hear from Dr. Gates, Dr. Thrupp, and Dr.
13 Wilson, and then let's vote on Barth's recommendation as it
14 was stated, and then, if we don't agree with that, let's see
15 what else we want to substitute.

16 Dr. Gates?

17 DR. GATES: Just from an industry perspective,
18 what's under discussion here is a particular package insert
19 for a particular product, which is ostensibly how to use
20 that product in whatever the intended use is for it.

21 I think that what we're talking about here is more
22 a general clinical practice in terms of when a particular
23 type of test ought to be confirmed, and I don't know that
24 the form of the particular package insert is the place for
25 that sort of education. I think it should be broader.

1 DR. CHARACHE: Dr. Thrupp?

2 DR. THRUPP: Again, I would support the motion and
3 just make this additional comment. Again, package insert
4 semantics notwithstanding, "should" is a little less strong
5 than "must," and "should" is a little bit stronger in my
6 view even than "strongly recommended". It may be silly, but
7 that's kind of why I would support the wording "should"
8 because--I disagree with Dr. Gates--I think the message
9 should be right up front for the lab to help the end-user.

10 As a matter of fact, I was perhaps a little
11 surprised that Dr. Reller didn't go one step further and
12 also included in the motion that it be bolded, but that's
13 another thing still.

14 DR. RELLER: I tried to be reasonable.

15 [Laughter.]

16 DR. CHARACHE: Dr. Wilson?

17 DR. WILSON: In the interest of expediting this,
18 there is a motion on the floor, but there isn't a second--

19 DR. CHARACHE: No--it was seconded.

20 DR. WILSON: Was it? Okay. Do you want to move
21 the question?

22 DR. CHARACHE: All right. Let's move the
23 question. The discussion that we are going to vote on
24 advising the FDA is to take the statement from the bottom
25 of page 7, change one word so that "recommended" becomes

1 "should," and also include it at the front under
2 "Indications for Use."

3 DR. SEEFF: Can you read that sentence?

4 DR. CHARACHE: Yes.

5 "Reactive specimens should be confirmed by a
6 specific or supplemental test such as a strip immunoblot or
7 nucleic acid amplification assay."

8 That's what we're voting on.

9 Dr. Specter?

10 DR. SPECTER: I support it.

11 DR. CHARACHE: Dr. Reller?

12 DR. RELLER: Yes.

13 DR. CHARACHE: Dr. Tuazon?

14 DR. TUAZON: Abstain.

15 DR. SANDERS: No.

16 DR. CHARACHE: Dr. Seeff?

17 DR. SEEFF: Let me think about it.

18 DR. CHARACHE: Do you wish to abstain, or would
19 you like to abstain from abstaining?

20 DR. SEEFF: Let me think about it a moment.

21 DR. CHARACHE: Okay. Dr. Wilson?

22 DR. WILSON: I support.

23 DR. CHARACHE: Dr. Thrupp?

24 DR. THRUPP: Yes.

25 DR. SEEFF: It's back to me. I abstain.

1 DR. CHARACHE: Okay. Then, let's have a show of
2 hands of those who voted for.

3 [A show of hands.]

4 DR. CHARACHE: There were four; there were two
5 abstentions and one opposed.

6 Would anyone like to make a second recommendation
7 that may provide more support? Dr. Tuazon?

8 DR. TUAZON: I would just like to make the
9 recommendation that the last statement that was modified
10 should be bold, remain in the same place, with the wording
11 that it is "strongly recommended" rather than "should".

12 DR. CHARACHE: All right. Let's first vote on the
13 statement and the on its placement. I think that that would
14 be easier. Is that all right?

15 DR. TUAZON: Well, I think it comes as a package,
16 where it should be in what is recommended. That's why I
17 wanted to have it bolded and then stay in the same place.

18 DR. SPECTER: May I please comment?

19 DR. CHARACHE: Please.

20 DR. SPECTER: We are making a recommendation here
21 to the FDA to uphold, and the vote that was just taken I
22 think clearly shows them that we all are in favor that this
23 clearly be put in a place where it is going to be
24 educational, where it is going to be very clear that this
25 needs to be done. And I think we have made the message, and

1 I don't think we need to vote seven times on whether it
2 should be bold or unbold or placed up or down or in or out.
3 The message has gotten through, we have made a
4 recommendation, and I think they have guidance from us, and
5 I think we can move on to other topics.

6 DR. CHARACHE: Okay. So you are recommending that
7 we make clear to the FDA that the group feels that this
8 should be put forth clearly and strongly and that there is a
9 consensus on that.

10 DR. SPECTER: The specifics is left to them.

11 DR. CHARACHE: And the specifics should be decided
12 by the FDA--

13 DR. SPECTER: Yes.

14 DR. CHARACHE: --with the sponsor.

15 DR. SPECTER: Yes.

16 DR. CHARACHE: Let's assume that's a motion.

17 DR. SPECTER: Sure.

18 DR. SANDERS: And I'll second it.

19 DR. CHARACHE: All right. That's seconded.

20 Can we say all in favor raise your hands.

21 [A show of hands.]

22 DR. CHARACHE: Opposed?

23 [No response.]

24 DR. CHARACHE: None.

25 Abstain?

1 [No response.]

2 DR. CHARACHE: None. Okay.

3 And I think probably that previous discussion may
4 have helped in seeing some of the thinking of the group.

5 Dr. Reller, you had a second point?

6 DR. RELLER: I did, and this is simply to capture
7 the sense with the wording that the delineation of the
8 inclusion of the categories be--that the wording be in there
9 that these are descriptive of the populations studied and
10 not the basis for specific claims. Again, it's the sense of
11 that, not the detail of the wording, which is the
12 prerogative and the responsibility of the agency, that is an
13 affirmation--what I am getting at is an affirmation by the
14 committee, a recommendation for retention of the tables and
15 delineating them as descriptive of the populations studied,
16 which we discussed earlier and agreed to as a package and a
17 concept, but this is getting it into the second--and final,
18 from my viewpoint--condition for the approvability of this
19 PMA before us.

20 DR. SPECTER: Can I restate it very simply?

21 DR. CHARACHE: Yes.

22 DR. SPECTER: That the previous discussion agreed
23 upon as pertains to Table 5 be moved as part of this change
24 to the package insert.

25 DR. CHARACHE: Could you--

1 DR. SPECTER: We have already discussed it and
2 agreed to something. All I am moving is that this be in
3 part of our official recommendations, and it specifically
4 referred to Table 5 and the data listed there--because there
5 were a couple of things we already--

6 DR. CHARACHE: Can you resolve that--

7 DR. RELLER: We are in agreement. That's what
8 we're talking about. We have already been through this; we
9 said that we liked it, and this is a matter of capturing it
10 where it needs to be, because Paul had earlier asked,
11 doesn't this come up as a condition, and it is a condition--
12 it's just that we captured it there so we didn't have to go
13 over this again. And all I am saying is I want that as
14 condition number two.

15 DR. CHARACHE: I'm going to have to say what it is
16 we have agreed to, so I'm just trying to think of how to
17 word it.

18 DR. SPECTER: Okay. Very simply, we agree to two
19 things, so that it's not unclear. We agreed 1) to include
20 language that was put forth by Dr. Reller earlier, and I
21 know you have that; and 2) that we delineate the three
22 subcategories under the increased risk groups.

23 DR. CHARACHE: All right. Let's take a vote.

24 Is there any further discussion? We have already
25 discussed it.