

1 difference in plasma versus serum, you might want to make a
2 little stronger pitch for using the plasma and that becomes
3 an issue, unless you are just going to let this go by the
4 wayside in the future and just use the quantitation.

5 MR. THOMAS: It is our firm hope that, at your
6 next panel meeting, we will be discussing that very matter.

7 DR. GUTEKUNST: I do just want to add a comment
8 that we, also, were surprised to see that we did not detect
9 differences between serum and plasma because, of course,
10 with our own HIV test, we did see differences. It is quite
11 possible that those do have something to do with the
12 biological nature of the virus.

13 Maybe some of the HIV gets trapped in a clot when
14 you purify serum. I really don't know. That is just,
15 obviously, speculation. But I think when you have the
16 opportunity to review our quantitative assay as well, you
17 will see that we really don't see that bias with these
18 tests. At least, we believe we don't see that bias.

19 DR. HOLLINGER: Does this have anything to do with
20 the use of the DMSO or some of the other things that were
21 added to the assay that is a little bit different?

22 DR. GUTEKUNST: I guess it is possible. I really
23 don't know the answer. But we really were not able to see
24 reproducible differences between the matrices in the studies
25 that we did.

1 DR. WILSON: Dr. Baron?

2 DR. BARON: Are we done? I have a comment about
3 the package insert in terms of instruction. Is this a good
4 time to say something about that?

5 DR. WILSON: Sure.

6 DR. BARON: On page 32 of the package insert for
7 the AMPLICOR, it says, on the top, "Record the positions of
8 the controls and specimens." And it basically doesn't say
9 anything about where you put a control, positive or
10 negative, in that specimen.

11 It clearly states in the COBAS instructions that
12 it doesn't matter where you put the positive control. I
13 agree with that. But I think when you are doing it by hand
14 in a microtiter plate that it might be useful to say
15 something like, "Put the positive control at the end," and,
16 "Put a negative control somewhere in the middle," as opposed
17 to just saying they could be anywhere.

18 It is just a thought.

19 DR. HOLLINGER: While we are doing that, this is
20 really more in the guise of practical suggestions for maybe
21 some instructions in the package insert, as you have
22 mentioned. A couple of things I was just curious about and
23 I don't know how important this is in terms of people doing
24 the assay, but you talk about the residual alcohol or
25 ethanol causing inhibition, particularly the ethanol.

1 My question was does the alcohol do so also and
2 how much alcohol or ethanol has to be left behind before you
3 have a problem on there. It gets back to the same thing
4 about the pellet, also. If there would be a little line
5 somewhere down at the bottom of the tube that says, you
6 know, "Suck it up to this point but don't go below this,"
7 particularly in the initial pellet where you can't see it
8 very well.

9 So those are all issues. And also about the
10 insoluble stuff that is left, how much of that contains
11 nucleic acid of the stuff that does not get redissolved when
12 you dislodge it there. Could you sort of give me some
13 feeling about that for just a minute?

14 DR. BARON: Could I add on to Dr. Hollinger's
15 question so you can answer all at once.

16 DR. GUTEKUNST: If I can remember them.

17 DR. BARON: It will be the same kind of thing. We
18 have differences in terms of our technologists and being
19 able to pull off the right amount but not too much. I know,
20 in some cases, some manufacturers have a training program
21 and an unknown set that have to be carefully done with
22 correct results before they certify a technologist to
23 perform a test.

24 I am wondering if we have that sort of thing going
25 on here.

1 DR. GUTEKUNST: To answer your question, we do
2 have a training program and we do require certification of a
3 laboratory before they are allowed to perform the test.

4 DR. BARON: Each person, or--

5 DR. GUTEKUNST: Each technologist. That's
6 correct. Each technologist does get validated. Now, it is
7 allowable, I believe, under our training program, for
8 another technologist in the laboratory to do the training of
9 subsequent technologists.

10 DR. BARON: Yes; because I have some that just
11 can't do it.

12 DR. GUTEKUNST: So do we, as a matter of fact.
13 And then, to answer some of Dr. Hollinger's questions, we
14 have shown, by direct spiking experiments, that if you have
15 greater than about 10 percent ethanol, 10 percent of the
16 70 percent ethanol, residual that you will get a complete
17 shutdown of the amplification reaction.

18 Now, we are not so concerned on the first
19 precipitation because we are going to do another one. So if
20 some is left behind, it is really that final step that is
21 critical.

22 I do agree with you absolutely that the manual
23 sample preparation is a critical part of the assay. That is
24 why we have the internal controls, so that it doesn't make
25 the technician feel good that they didn't get a result but

1 at least they are not reporting a result for samples where
2 they have lost that pellet.

3 We do try to emphasize proper techniques during
4 the training procedures and we make our trainees go through
5 three days of training and then two days of validation in
6 the hopes that they will become more familiar with it.

7 Then, of course, more and more automation down the
8 road will help to resolve some of those issues.

9 DR. HOLLINGER: One other thing. You said in the
10 insert, and I wasn't sure how this was interpreted--at one
11 point, you said, with the internal control, if it happens to
12 show inhibition, it said, at least in the control--I think
13 it is on page 33 or 34--

14 DR. BARON: Page 33 of the COBAS instructions.

15 DR. HOLLINGER: Yes; on page 33, it says, under
16 internal control. It says, "If the internal control
17 absorbance value of a specimen or control is less than
18 0.15," it says, "it would invalidate the run." I am not
19 sure--do you really mean the run, or invalidate that
20 specimen?

21 DR. GUTEKUNST: If the internal control is invalid
22 in either of the controls--if it is invalid in the controls,
23 it invalidates the entire run because the control result is
24 not valid. If it is invalid in a clinical specimen, then
25 only the result for that clinical specimen is considered

1 invalid. Perhaps, that is not clearly written in the
2 insert.

3 But the criteria for the controls is very strict,
4 and if either of those has an invalid target or internal
5 control result, then the entire run is invalidated.

6 DR. SPECTER: But it specifically says, "any
7 specimen, including the test specimen."

8 DR. GUTEKUNST: It does. It invalidates the whole
9 run.

10 DR. SPECTER: It says, "If the IC absorbance value
11 of a specimen or control is less than 0.15, the run is
12 invalid and the entire test procedure must be repeated."

13 DR. GUTEKUNST: I probably wrote that. I am sure
14 it is a mistake.

15 DR. HOLLINGER: It is really just the specimen
16 that has to be repeated; right?

17 DR. GUTEKUNST: That's correct. That is certainly
18 our intention.

19 DR. SPECTER: It needs to be stated separately.
20 If it is the internal control, it is everything. If it is
21 the specimen, it is only that specimen.

22 DR. GUTEKUNST: Right.

23 DR. SPECTER: So it has got to be blown up.

24 DR. GUTEKUNST: I will take credit for that.

25 DR. WILSON: Any further comments or questions

1 from the panel? If not, let's break now. Let's reconvene
2 at 3:20.

3 [Break.]

4 **Open Public Hearing**

5 DR. WILSON: At this point, I would like to
6 announce that we are now in an open public hearing, if any
7 members of the public would like to comment.

8 There being no comments, this portion of the
9 meeting is closed.

10 **FDA and Sponsor Response**

11 DR. WILSON: Does FDA have any last-minute
12 comments?

13 DR. GUTMAN: No; we have no further comments.

14 DR. WILSON: And industry; does the manufacturer
15 have any last-minute comments they would like to make?

16 MR. THOMAS: No, just that we would like to thank
17 the panel, since this has been an extremely useful
18 discussion from our point of view. If we didn't reinforce
19 it enough in the earlier session, we would like to, again,
20 thank the FDA staff. This has been an extraordinarily
21 productive collaboration for the information you have seen
22 here, and we are greatly appreciative of that.

23 DR. WILSON: Thank you.

24 **Final Recommendation and Vote**

25 DR. WILSON: We will move now into the final

1 recommendations and vote. Ms. Freddie Poole will read the
2 voting options to everyone so that this is clear.

3 MS. POOLE: These are the panel-recommendation
4 options for premarket approval applications. The Medical
5 Device Amendments to the Federal Food, Drug and Cosmetic
6 Act, as amended by the Safe Medical Devices Act of 1990,
7 allows the Food and Drug Administration to obtain a
8 recommendation from an expert advisory panel on designated
9 medical-device premarket-approval applications that are
10 filed with the agency.

11 The PMA must stand on its own merits, and your
12 recommendations must be supported by safety and
13 effectiveness data in the application or by applicable
14 publicly available information. Safety is defined in the
15 Act as reasonable assurance based on valid scientific
16 evidence that the probable benefits to health, under
17 conditions of intended use, outweighs any probable risk.

18 Effectiveness is defined as reasonable assurance
19 that, in a significant portion of the population, the use of
20 the device for its intended uses and conditions of use when
21 labeled will provide clinically significant results.

22 Your recommendation options for the vote are as
23 follows; approval if there are no conditions attached;
24 approvable with conditions. The panel may recommend that
25 the PMA be found approvable subject to specified conditions

1 such as physician or patient education, labeling changes or
2 a further analysis of existing data. Prior to voting, all
3 of the conditions should be discussed by the panel.

4 The third option; not approvable. The panel may
5 recommend that the PMA is not approvable if the data do not
6 provide a reasonable assurance that the device is safe or,
7 if a reasonable assurance has not been given, that the
8 device is defective under the conditions of use proscribed,
9 recommended or suggested in the proposed labeling.

10 Following the voting, the chair will ask each
11 panel member to present a brief statement outlining the
12 reasons for their vote.

13 The voting members for today are: Dr. Margaret
14 Hammerschlag, Dr. Carmelita Tuazon, Dr. Melvin Weinstein.
15 Appointed as temporary voting member for today is Steven C.
16 Specter.

17 I should read the statement that appointed him to
18 temporary voting status. Pursuant to the authority granted
19 under the Medical Devices Advisory Committee Charter dated
20 October 27, 1990, and as amended August 18, 1999, I appoint
21 the following member, Steven C. Specter, as a voting member
22 of the Microbiology Devices Panel for this meeting on
23 July 28, 2000.

24 For the are, he is a special government employee
25 and consultant to this panel under the Medical Devices

1 Advisory Committee. He has undergone the customary conflict
2 of interest review and has reviewed the material to be
3 considered at this meeting.

4 It is signed David W. Feigal, Jr., Director,
5 Center for Devices and Radiological Health, July 24, 2000.

6 DR. WILSON: Thank you.

7 At this point, then, we will entertain motions.
8 Dr. Specter?

9 DR. SPECTER: I will make a motion for approvable
10 with conditions.

11 DR. TUAZON: I second the motion.

12 DR. WILSON: The motion has been made and seconded
13 for approval with conditions. Is there any discussion at
14 this point? Would anyone like to introduce the first
15 condition?

16 DR. SPECTER: If we look under the first question,
17 we had talked about striking language from the first
18 warning. So the first condition would be that we take the
19 first bullet and delete everything after the second HCV in
20 the sentence; that is, "by enzyme immunoassay but were not
21 tested by immunoblot assay." I move that be stricken.

22 DR. WILSON: We have a motion.

23 DR. WEINSTEIN: Steve, for clarification, could
24 you read the sentence again?

25 DR. SPECTER: It says, "Performance has not been

1 demonstrated for diagnosis of individuals who one, were not
2 tested antibodies to HCV or two, had reactive results from
3 testing for antibodies to HCV."

4 DR. WEINSTEIN: Period.

5 DR. SPECTER: It is actually also up above. I
6 forgot about that. So, in the actual statement, it also
7 says the same thing and should be stricken. It should read,
8 "The AMPLICOR HCV test is indicated for patients who have
9 had liver disease and antibodies to HCV." And then we would
10 strike, "that were detected by enzyme immunoassay and
11 immunoblot," and leave in, "and who are suspected to have
12 active HCV infection," and the following sentence.

13 DR. HOLLINGER: I think, Steve, if I may, the
14 second part on the Warnings, I think we just struck the
15 whole two."

16 DR. SPECTER: Oh; that's right. Point two. So
17 just after the first HCV.

18 DR. HOLLINGER: So it is just, "Performance has
19 not been demonstrated for diagnosis of individuals who were
20 not tested for antibodies to HCV."

21 DR. SPECTER: Yes. I stand corrected.

22 DR. WILSON: So we have a motion to amend the main
23 motion. Do we have a second?

24 DR. HAMMERSCHLAG: I second.

25 DR. WILSON: Is there any discussion on this

1 condition? We have to take a vote on each of these as we go
2 through. I will start with Dr. Tuazon.

3 DR. TUAZON: I agree.

4 DR. WILSON: Dr. Hammerschlag?

5 DR. HAMMERSCHLAG: I agree.

6 DR. WILSON: Dr. Weinstein?

7 DR. WEINSTEIN: I'm sorry; I'm lost here. I don't
8 think I am going to be lost for long, but what we are
9 amending at the moment is the short introductory paragraph
10 that does not have a bullet?

11 DR. SPECTER: Correct.

12 DR. WEINSTEIN: And that is going to read, "The
13 AMPLICOR HCV test is indicated for patients who have liver
14 disease and antibodies to HCV and who are suspected to have
15 active HCV infection."

16 DR. SPECTER: And the next sentence.

17 DR. WEINSTEIN: And the next sentence is included
18 as well.

19 DR. SPECTER: Correct.

20 DR. WEINSTEIN: Fine. I vote in favor.

21 DR. WILSON: Dr. Specter?

22 DR. SPECTER: In favor.

23 DR. WILSON: Dr. Hollinger?

24 DR. HOLLINGER: Favor.

25 DR. WILSON: Are we ready for a main motion vote

1 or are there further conditions.

2 DR. SPECTER: I have one further condition. If we
3 look at the third bullet, I would like to see that changed
4 so that it now reads, and forgive me for going through all
5 of it, but, "A negative AMPLICOR HCV test result does not
6 exclude active HCV infection. Although a wide range of HCV
7 genotypes can be detected, analytical sensitivity and other
8 performance characteristics have not been determined for all
9 HCV genotypes."

10 So I am adding the word "all." And then I would
11 suggest that we leave whatever statement that is going to be
12 worked out to be worked out by the FDA and the company
13 rather than our trying to wordsmith something.

14 DR. WILSON: We have another motion to amend the
15 main motion. Do I have a second?

16 DR. TUAZON: Second.

17 DR. WILSON: Is there any discussion?

18 There being no discussion, we will take the vote.

19 Dr. Tuazon?

20 DR. TUAZON: I agree.

21 DR. WILSON: Dr. Hollinger?

22 DR. HOLLINGER: I agree.

23 DR. WILSON: Dr. Hammerschlag?

24 DR. HAMMERSCHLAG: I agree.

25 DR. WILSON: Dr. Weinstein?

1 DR. WEINSTEIN: I vote in favor.

2 DR. WILSON: Dr. Specter?

3 DR. SPECTER: Favor.

4 DR. WILSON: The motion moves. Again, are we
5 ready for the main motion vote or are there further
6 conditions?

7 DR. SPECTER: I have three more conditions that I
8 would like to see included.

9 DR. WILSON: Let's do them one at a time.

10 DR. SPECTER: Okay. They come under No. 2d where
11 it talks about HCV RNA not being detected. We talked about
12 three specific areas. The first one would be that there be
13 some kind of comment made about possibly the use of heparin
14 leading to this HCV not being detected. Again, for all
15 three of these motions that I am going to make, I would
16 leave the wording to be worked out between the FDA and the
17 company, but that there be a warning about heparin possibly
18 leading to a "HCV RNA not detected" result.

19 DR. WILSON: We have a further amendment to the
20 main motion. Do we have a second?

21 DR. HAMMERSCHLAG: Second.

22 DR. WILSON: Is there any discussion?
23 Clarification? There being none, we will take the vote.

24 Dr. Tuazon?

25 DR. TUAZON: In favor.

1 DR. WILSON: Dr. Hollinger?
2 DR. HOLLINGER: In favor.
3 DR. WILSON: Dr. Hammerschlag?
4 DR. HAMMERSCHLAG: In favor.
5 DR. WILSON: Dr. Weinstein?
6 DR. WEINSTEIN: In favor.
7 DR. WILSON: Dr. Specter?
8 DR. SPECTER: In favor.
9 DR. WILSON: The motion passes. I won't ask if
10 there is another one because I know there is.
11 DR. SPECTER: The next one would be a very similar
12 statement related to HCV RNA not detected in dialysis
13 patients, being associated with their clinical treatment.
14 DR. WEINSTEIN: Hemodialysis, or both?
15 DR. SPECTER: Hemodialysis patients, I believe.
16 Is that correct; it is just hemodialysis we are talking
17 about?
18 DR. WILSON: There is a motion to amend the main
19 motion. Do I have a second?
20 DR. HOLLINGER: Can you clarify that just a
21 minute, Steve?
22 DR. SPECTER: The point was raised that there have
23 been some false negatives in hemodialysis patients. Is that
24 correct? Was that the statement that was made?
25 DR. FRIED: If I may be allowed. I think the

1 issue of the hemodialysis patients is a very interesting one
2 and, in general, we consider that those patients are
3 actually immunosuppressed so that if you look at some of the
4 published studies, they actually are less likely to be
5 antibody-positive and have more RIBA-indeterminate cases, so
6 you would be more likely to detect HCV RNA by PCR than you
7 are by serologic tests.

8 I have a reference that I gave to Dr. Ticehurst to
9 that effect, and there are several others like that. So, in
10 fact, we actually say that in hemodialysis patients where
11 you have a strong clinical suspicion of HCV infection, we do
12 go to PCR testing.

13 So I would just like to clarify that. I don't
14 agree, necessarily, with that statement.

15 DR. SPECTER: Then that brings up an entirely
16 different issue about human dialysis patients and whether
17 they should be tested in the absence of HCV antibody which
18 is something--the recommendation is that this only be used
19 in the presence of HCV antibody.

20 DR. FRIED: Still, the majority of dialysis
21 patients will have anti-HCV antibody-positive, but there are
22 a number of patients who will not that we would go on to HCV
23 RNA testing in the absence of an antibody test.

24 DR. SPECTER: I will leave it alone.

25 DR. FRIED: Fine.

1 DR. SPECTER: It is an off-label test, then, and
2 that is a different issue. The other motion had to do with
3 retesting.

4 DR. WILSON: Are you withdrawing that motion?

5 DR. SPECTER: Yes; let's just let that go.

6 The next motion had to do with retesting and a
7 statement be made that when you have "HCV RNA not detected"
8 and you plan to retest that you not do this by diluting
9 specimens already in possession but that new specimens be
10 collected.

11 DR. WILSON: There is a motion to the main motion.
12 Do we have a second? Any discussion? There being none, we
13 will take the vote.

14 Dr. Tuazon?

15 DR. TUAZON: In favor.

16 DR. WILSON: Dr. Hollinger?

17 DR. HOLLINGER: In favor.

18 DR. WILSON: Dr. Hammerschlag?

19 DR. HAMMERSCHLAG: In favor.

20 DR. WILSON: Dr. Weinstein?

21 DR. WEINSTEIN: In favor.

22 DR. WILSON: Dr. Specter?

23 DR. SPECTER: Favor.

24 DR. WILSON: Are we ready for the main vote, are
25 there further conditions?

1 DR. SPECTER: I am shutting up.

2 DR. WILSON: Dr. Hammerschlag?

3 DR. HAMMERSCHLAG: Following through on that from
4 the earlier discussion we had about moving into 2d about
5 should any additional instructions be provided to
6 laboratories and primary-care clinicians for interpreting an
7 "HCV RNA not detected" result, which, actually, this is all
8 part of it but to probably point out that, then, perhaps,
9 additional testing would be done because another explanation
10 could be--it could be a false-positive ELISA.

11 Do we want to add a sentence to that effect, "and
12 further serologic testing may be indicated to confirm the
13 ELISA." You can have false positives and you can have false
14 negatives.

15 DR. TUAZON: Do you want to qualify--

16 DR. HAMMERSCHLAG: I mean, this could be a true
17 negative but the ELISA may be positive so that this may
18 indicate a false positive ELISA and suggest further testing.

19 DR. TUAZON: Would you do that on all positives or
20 in a subgroup like--

21 DR. HAMMERSCHLAG: It is for the reasons--it is
22 just another interpretation of what it means to have a
23 negative result, such as HCV RNA is negative. I just always
24 feel that it never hurts to be explicit.

25 DR. SPECTER: I think it is very difficult to give

1 guidance there. More than likely, if you had a negative
2 test, you would repeat it. So I don't know if you want to
3 recommend repeating it and then, if that is negative, doing
4 serology. I would like to stay away from that and let labs
5 develop their own procedures. My suspicion is that each lab
6 will decide to go and proceed if they get a negative.

7 DR. HAMMERSCHLAG: Okay.

8 DR. HOLLINGER: I guess, if they wanted to, and
9 what you are saying is I suppose they could say what a
10 negative HCV RNA and a positive anti-HCV might represent. I
11 guess, in a few sentences, they could say, "This could
12 represent a recovered individual or resolved infection. It
13 could represent a false-positive, anti-HCV test. A RIBA
14 test might be helpful in that regard. There could be some
15 things in there, and that is probably something they could
16 work out, I think, in the discussion, don't you think, FDA?

17 DR. GUTMAN: There is no question we could include
18 it with great facility in the package insert and then what
19 an individual lab decides to do with it in terms of the
20 reporting I think might be a practice of laboratory
21 medicine, unless you felt very strongly the need for it.

22 But to include--the discussion in the package
23 insert would be fairly straightforward and, frankly,
24 probably doesn't require recommendation from the group. We
25 have heard you.

1 DR. WILSON: Okay. So that is withdrawn?

2 DR. HAMMERSCHLAG: I will withdraw it.

3 DR. WILSON: The motion is withdrawn. Are there
4 further motions to amend the main motion?

5 DR. DURACK: This is a question, not a motion. It
6 is to do with the first paragraph on indications and the
7 structure of that. Is the second sentence not a warning,
8 rather than an indication, "detection of HCV RNA is," that
9 is an informational sentence and a warning, to me, rather
10 than part of the indication. I just raise it as a question.

11 DR. HAMMERSCHLAG: I think it could be interpreted
12 as an indication. It means that it cannot be used to
13 determine whether it is a chronic or an acute infection. It
14 is not its indication. Semantics.

15 DR. DURACK: It is a question of the structure of
16 that first paragraph.

17 DR. WILSON: Do you want to make a motion to
18 modify it?

19 DR. DURACK: I just raise it. I think it is a
20 warning, really. Detection does not distinguish between
21 acute and chronic infection. That is just for the group to
22 consider.

23 DR. BARON: It is almost repeated in the warnings.
24 It says, "It is not known if performance is affected by the
25 state, acute or chronic, of infection. So that is almost a

1 repetition of--

2 DR. WILSON: Dr. Tuazon?

3 DR. TUAZON: Just to be inclusive in terms of what
4 Dr. Durack has included in the warning, that performance has
5 been demonstrated for monitoring of progress of disease
6 and/or response to treatment in HCV-infected patients.

7 DR. WILSON: Under the second bullet, a more
8 comprehensive bullet.

9 DR. TUAZON: Right; a more comprehensive
10 statement; "Monitoring of progress of disease and/or
11 response to therapy in HCV-infected patients."

12 DR. WILSON: So we have another motion to amend
13 the main motion. Do I have a second?

14 DR. SPECTER: Second.

15 DR. HOLLINGER: Which bullet?

16 DR. SPECTER: No. 2. It was just clarifying what
17 monitor--

18 DR. HOLLINGER: Could you read it again,
19 completely, for the record?

20 DR. TUAZON: "Performance has not been
21 demonstrated for monitoring of progress of disease and/or
22 response to treatment in HCV-infected patients."

23 DR. WILSON: Do we have a second on the motion?

24 DR. SPECTER: Second.

25 DR. WILSON: Is there any discussion?

1 DR. HAMMERSCHLAG: Then, if that is the case, what
2 about Bullet No. 4 because they were getting redundant.
3 That says it is not known if performance is affected by the
4 state of infection.

5 DR. TUAZON: That is progress.

6 DR. HAMMERSCHLAG: Progress also could be
7 interpreted as a state--well; all right.

8 DR. WILSON: Any further discussion?

9 DR. WEINSTEIN: Could you repeat one more time the
10 revised warning for Bullet No. 2.

11 DR. TUAZON: "Performance that has not been
12 demonstrated for monitoring of progress of disease and/or
13 response to treatment of HCV-infected patients."

14 DR. WILSON: Is there any further discussion? We
15 will take the vote.

16 Dr. Specter?

17 DR. SPECTER: Favor.

18 DR. WILSON: Dr. Hollinger?

19 DR. HOLLINGER: In favor.

20 DR. WILSON: Dr. Hammerschlag?

21 DR. HAMMERSCHLAG: Favor.

22 DR. WILSON: Dr. Weinstein?

23 DR. WEINSTEIN: Favor.

24 DR. WILSON: Dr. Tuazon?

25 DR. TUAZON: Agree.

1 DR. WILSON: Are we ready for the main vote or are
2 there further conditions.

3 DR. HOLLINGER: Sorry; one more.

4 DR. WILSON: Dr. Hollinger?

5 DR. HOLLINGER: On the fourth part, I think we
6 should probably stipulate that whenever--I don't know how
7 this sentence is going to be so let me just sort of
8 verbalize it. Whenever quantitative data is stipulated in
9 the insert or somewhere else, such as for limits of
10 detection of analytical sensitivity, such as IU per ml, it
11 should be clearly stated that this is based on the WHO
12 genotype 1 standard 76/970 or something to that effect in
13 there so that it is clear that any IU per ml is based on
14 that particular standard alone and not just a general IU per
15 ml.

16 DR. WILSON: We have a further motion to amend the
17 main motion. Is there a second?

18 DR. SPECTER: I'll second.

19 DR. WILSON: Is there any discussion?

20 DR. WEINSTEIN: Where would that go? What is the
21 wording and where would it go? Would it go in the Warnings
22 or would it--

23 DR. HOLLINGER: Fifth paragraph, eighth page. No.
24 I have no idea.

25 DR. WEINSTEIN: You have made me into the scribe

1 here and I am trying to write this down.

2 DR. HOLLINGER: I have no idea where it is going
3 to go.

4 DR. TUAZON: Let the FDA worry about it.

5 DR. HOLLINGER: But somewhere. I mean, I think I
6 am just really trying to make the point that I think if we
7 are going to stipulate this, it needs to very clearly state
8 what it is based on, where this is in form of advertising,
9 the form of inserts or other things. It should stipulate
10 where it is coming from.

11 DR. SPECTER: It is really related to evaluating
12 the data that are in the insert because it is not a
13 quantitative test. So it is not for specimen evaluation.
14 It is for evaluating the data behind the test.

15 DR. WILSON: We have a motion to amend the main
16 motion. Is there a second?

17 [Second.]

18 DR. WILSON: Is there any further discussion?
19 There being no further discussion, we will take the vote.
20 Dr. Hammerschlag?

21 DR. HAMMERSCHLAG: Agree.

22 DR. WILSON: Dr. Weinstein?

23 DR. WEINSTEIN: In favor.

24 DR. WILSON: Dr. Specter.

25 DR. SPECTER: In favor.

1 DR. WILSON: Dr. Tuazon.

2 DR. TUAZON: In favor.

3 DR. WILSON: Dr. Hollinger?

4 DR. HOLLINGER: In favor.

5 DR. WILSON: The motion passes.

6 Are we ready for the main vote or are there
7 further conditions?

8 DR. HOLLINGER: Michael, I'm sorry. I have got a
9 7 o'clock flight, so I could care less about when I get out.
10 One thing we did not discuss, and I am sorry, and I don't
11 know where it goes in here, but there was a stipulation to
12 the effect that if you have one positive result and you
13 repeat it and you get a positive and a negative, that that
14 should be considered to be a positive result.

15 We never did discuss that. I have a problem with
16 that in a way because I wonder whether that ought to be
17 considered as an indeterminate result rather than a positive
18 result. There is an issue, I think, that needs to be
19 clarified here because, certainly, if you repeat it and the
20 replicate, the duplicates that are done afterwards, both of
21 those are positive, I have no--I mean, that is either a
22 positive or, if they are both negative, it is negative.

23 I have a problem if one is positive and one is
24 negative of, perhaps, calling that, at least on that
25 specimen, as a positive result rather than a indeterminate

1 result or equivocal. I don't care what it is called, but
2 something other than a positive result.

3 I would like to maybe just hear a little bit of
4 discussion on that, if you wouldn't mind.

5 DR. WILSON: Does the manufacturer have any
6 information about how to interpret those results?

7 MR. THOMAS: Yes; we do. Dr. Hollinger is
8 correct. In the draft package insert that you had, which
9 was sent to you rather early, we have continued to discuss
10 this with the agency and, in fact, our most recent proposal
11 which was July 6, we proposed that an equivocal result be
12 repeated in duplicate and simply the results of the
13 duplicate be taken as the final result.

14 For all the retesting we did, that seems to
15 resolve it quite nicely.

16 DR. WILSON: Is that wording in the insert now?

17 MR. THOMAS: It is not in the insert, but the
18 proposed wording is part of the PMA file with FDA.

19 DR. HOLLINGER: So how is that going to be
20 interpreted? How did you propose--

21 MR. THOMAS: Again, if a result is equivocal--that
22 is, it falls in whatever the zone turns out to be, then the
23 specimen is retested in duplicate and the results of the
24 retested specimens be taken as the final result, ignoring
25 the equivocal result.

1 DR. HOLLINGER: No; that is not quite it.

2 DR. SPECTER: He was trying to say they never get
3 a positive and a negative, then.

4 DR. HOLLINGER: You do the duplicate and you get a
5 positive and a negative.

6 MR. THOMAS: In which case it is still equivocal.

7 DR. HOLLINGER: Okay; because it did stay
8 positive. I'm glad to hear that.

9 DR. WILSON: If that wording has been worked on, I
10 don't think we need to vote, then, to amend it.

11 Are there any further conditions? If there are no
12 further conditions, then we are ready for the main motion.
13 The main motion was approvable with conditions.

14 Dr. Weinstein, could you just briefly summarize
15 those conditions?

16 DR. WEINSTEIN: Sure. Condition No. 1 is to
17 change the first sentence in the proposed indications such
18 that it will read, "The AMPLICOR HIV test is indicated for
19 patients who have liver disease and antibodies to HCV and
20 who are suspected to have active HCV infection." The second
21 sentence in that paragraph would remain unchanged.

22 Condition No. 2 is a revision in Bullet No. 3.
23 Under Warnings, the bracketed sentence would now read,
24 "Although a wide range of HCV genotypes can be detected,
25 analytical sensitivity and other performance characteristics

1 have not been determined for all HCV genotypes." I think
2 what would remain in there will be a list of genotypes and
3 subtype numbers. I think that still was left in there. The
4 last clause of that sentence would then be deleted.

5 Condition No. 3 was to add a warning regarding
6 interference of heparin with the assay as per Question No.
7 2d from the questions for the panel.

8 Condition No. 4 would indicate that when retesting
9 is needed, a new specimen should be obtained rather than
10 repeating the assay on the existing specimen.

11 Condition 5 is to revise Bullet No. 2 under the
12 Warnings. I did not write down the exact wording of that.

13 DR. TUAZON: I will read it for you.

14 DR. WEINSTEIN: Okay; thanks, Carmelita.

15 DR. TUAZON: This is only the third time I am
16 reading it. "Performance has not been demonstrated for
17 monitoring of progress of disease and/or response to therapy
18 in HCV-infected patients."

19 DR. WEINSTEIN: I did have it written down. I
20 just couldn't find it.

21 The last condition, No. 6, is when we are
22 addressing quantitative issues, the WHO International Units
23 should be referred to.

24 DR. WILSON: Does anyone need any clarification?

25 DR. SPECTER: Yes; we didn't cover, under Bullet

1 No. 1, that we had deleted point 2 as well as part of the
2 first motion.

3 DR. WEINSTEIN: So that is part of Condition No.
4 1, is--Steve, read it to me as it should be.

5 DR. SPECTER: It should just say, "Performance has
6 not been demonstrated for diagnosis of individuals who were
7 not tested for antibodies to HCV."

8 DR. WEINSTEIN: Period.

9 DR. SPECTER: Period.

10 DR. WILSON: Dr. Baron?

11 DR. BARON: As a nonvoting raconteur, can I
12 comment that the heparin wording--no, the second testing
13 wording was not exactly as Dr. Specter had intended, I don't
14 think, because he had said that the warnings should say you
15 mustn't dilute the specimen to retest. Dr. Weinstein didn't
16 say that exactly. He said get a new specimen.

17 In reality, what you usually do is go to your
18 frozen aliquot and test that one first, you know what I
19 mean? But I think the key here is not to dilute the
20 specimen to try to remove inhibitors.

21 DR. WILSON: Does anyone need any other
22 clarification, any other review of the conditions? We are
23 ready for the vote, then, on the main motion which is
24 approvable with the conditions as summarized by Dr.
25 Weinstein.

1 Dr. Specter?

2 DR. SPECTER: In favor.

3 DR. WILSON: Dr. Tuazon?

4 DR. TUAZON: In favor.

5 DR. WILSON: Dr. Hollinger?

6 DR. HOLLINGER: In favor.

7 DR. WILSON: Dr. Hammerschlag?

8 DR. HAMMERSCHLAG: In favor.

9 DR. WILSON: Dr. Weinstein?

10 DR. WEINSTEIN: In favor.

11 DR. WILSON: The motion passes. While Dr.

12 Weinstein is finishing his job as the scribe, we will go

13 around. Dr. Specter, we do need to have each of panel

14 members give their reasons for their vote.

15 DR. SPECTER: I voted in favor because I felt that

16 this would provide a safe and effective test for the

17 measurement of HCV.

18 DR. WILSON: Dr. Tuazon?

19 DR. TUAZON: I agree.

20 DR. WILSON: Dr. Hollinger?

21 DR. HOLLINGER: I liked what we decided.

22 DR. WILSON: Dr. Hammerschlag?

23 DR. HAMMERSCHLAG: I agree. I feel this was a

24 very well-put-together application that I actually could

25 follow, unlike others.

1 DR. WILSON: Dr. Weinstein, if you are done
2 writing?

3 DR. WEINSTEIN: I am done writing and I agree with
4 the earlier comments. I think this is a good assay and I
5 think that the changes and conditions that have been made
6 are constructive.

7 DR. WILSON: We are just reminded, of course, that
8 there are two PMAs today, the AMPLICOR and the AMPLICOR
9 COBAS. Technically, we have voted on one.

10 DR. TUAZON: Which one?

11 DR. WILSON: We can handle this fairly easily, the
12 second one, which is the AMPLICOR COBAS. Therefore, we can
13 entertain motions at this time.

14 DR. SPECTER: I make a motion that we make this
15 approvable with the identical conditions that we did for the
16 AMPLICOR test.

17 DR. TUAZON: Second the motion.

18 DR. WILSON: The motion has been moved and
19 seconded. Is there any discussion?

20 DR. BARON: Do you want to just take under
21 advisement my comments about for the AMPLICOR placement of
22 controls in the microwell plate.

23 DR. WILSON: Okay. Thank you. Is there any
24 further discussion? We will take the vote.

25 Dr. Weinstein?

- 1 DR. WEINSTEIN: In favor.
- 2 DR. WILSON: Dr. Hammerschlag.
- 3 DR. HAMMERSCHLAG: In favor.
- 4 DR. WILSON: Dr. Hollinger.
- 5 DR. HOLLINGER: In favor.
- 6 DR. WILSON: Dr. Tuazon?
- 7 DR. TUAZON: In favor.
- 8 DR. WILSON: Dr. Specter?
- 9 DR. SPECTER: In favor.
- 10 DR. WILSON: Again, we need to have each member
- 11 comment on the reasons for their vote.
- 12 Dr. Specter?
- 13 DR. SPECTER: I believe this is essentially
- 14 equivalent to the AMPLICOR in its performance and,
- 15 therefore, is safe and effective.
- 16 DR. WILSON: Dr. Tuazon?
- 17 DR. TUAZON: I agree with his comments.
- 18 DR. WILSON: Dr. Hollinger?
- 19 DR. HOLLINGER: I agree.
- 20 DR. WILSON: Dr. Hammerschlag?
- 21 DR. HAMMERSCHLAG: I concur.
- 22 DR. WILSON: Dr. Weinstein?
- 23 DR. WEINSTEIN: I agree.
- 24 DR. WILSON: I would like to thank everyone for
- 25 their participation, the members of the panel, the FDA for

1 the work that they have done, and for Roche for all the work
2 they have done. And I agree with Dr. Hammerschlag that this
3 has been one of the best submissions that we have seen to
4 date.

5 There being no further business, the meeting is
6 adjourned.

7 [Whereupon, at 4:00 p.m., the meeting was
8 adjourned.]

9

C E R T I F I C A T E

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


ALICE TOIGO