

1 inhibitory sample, that you would take another sample from
2 the patient, so we would certainly not recommend diluting
3 the sample and testing. We would suggest either retesting
4 the sample, first of all, and then if that doesn't give you
5 a clear-cut answer, getting a second specimen from the same
6 patient.

7 DR. HOLLINGER: It is always good to get a second
8 specimen. Don't even know if it's from the same patient.

9 DR. MURRAY: The point about the retesting is that
10 you have got to start from the very beginning, you have got
11 to take the raw specimen and do a full, brand-new specimen
12 prep because one of the things that you don't want to do is
13 use something that has already been through the specimen
14 prep and given you an inhibitory result.

15 You have to start from the full specimen and do
16 the full procedure right from the beginning all over again.

17 DR. HOLLINGER: The second thing has to do with
18 amplicon contamination. Can you tell us how much of a
19 problem this is? You know, this was obviously a major
20 problem initially when people were not used to doing
21 testing, when they were doing detection and amplification in
22 the same labs, and a variety of things like this, but is
23 this really much of a problem at the present time, and is
24 the amplification efficiency for each genotype equivalent to
25 what is seen in the internal control?

1 DR. GUTEKUNST: For your first question on
2 amplicon contamination, I think that we have come a long
3 way. People, as you say, are much more experienced, they
4 appreciate that good laboratory practices have to be
5 followed.

6 I think it is not as much of an issue as it had
7 been initially, but we still feel it is important to include
8 as many precautions as we can in the product in order to
9 minimize that.

10 With regard to the genotype amplification, the
11 internal control is most similar to a genotype 1 specimen.
12 It was designed that way, as was our positive control, and
13 so we believe that the other genotypes are amplified
14 relatively comparably to that.

15 DR. HOLLINGER: Does the AmpErase decrease the
16 sensitivity of the assay? Have you tested it with and
17 without the AmpErase to see if there is any changes in the
18 concentration?

19 DR. GUTEKUNST: We have not done that experiment.
20 The characteristics that we have described are with AmpErase
21 in the assay.

22 DR. HOLLINGER: So, you are not whether--

23 DR. GUTEKUNST: I don't know the answer.

24 DR. HOLLINGER: Just a question on the
25 specificity. I looked to see. You did add several things

1 to look at, and I think these are very good in looking at
2 different viruses, and so on, and I think the comment about
3 Flaviviruses was a good one.

4 You also said you looked for HAV and HBV as
5 potential inhibitors in the assay, but as I understood it,
6 for your HAV assay, you really just used IgM anti-HAV
7 positive specimen.

8 DR. GUTEKUNST: Right.

9 DR. HOLLINGER: You didn't really show that you
10 had HAV in it.

11 DR. GUTEKUNST: That's correct.

12 DR. HOLLINGER: It would have been better to use
13 HAV RNA, and the same with HBV, you use HBsAG positive
14 specimens, and not all of those always contain HBV DNA, so
15 to make those statements, really, one should really use HAV
16 RNA and HBV DNA along with EBV DNA, I don't think was used
17 either.

18 DR. GUTEKUNST: We did have in the panel of viral
19 isolates, I believe we did have at least one plasmid from
20 HBV, so we did have HBV DNA in that study, and then there
21 was also an HAV isolate from ATCC, but the clinical
22 specimens, you are absolutely correct, they were serology
23 positive. We did not demonstrate directly in those
24 specimens that nucleic acid from the other viruses was
25 present.

1 DR. HOLLINGER: By the way, I wasn't implying
2 about--a lot of these questions I think Roche has really
3 been a leader in adding some of these things I think to the
4 test like the internal controls and the AmpErase I think are
5 always good measures anyway. I think that is a real plus
6 anyway.

7 I couple of other things. In the reproducibility
8 at the sites, you tended to ignore site 1, which had 4 to 8,
9 I think, negative samples. You seemed to indicate that
10 these 4 samples you excluded because the internal control
11 was negative, if I remember right. I can't remember if it
12 was 4 or 8, it was something like that.

13 I was a little concerned by that because these
14 apparently were identical samples tested at every site, all
15 the four sites.

16 DR. GUTEKUNST: That's correct.

17 DR. HOLLINGER: If they were identical samples
18 tested at every four sites, and the assays were all the
19 same, then, each of the sites on those samples should have
20 an internal control that was inhibitory.

21 So, I was a little concerned about that, and my
22 feeling would be that they probably sucked up the pellet,
23 but I mean that would be the other thing, but I would like
24 to hear your comment, because you didn't mention that at
25 all, and you just seemed to sort of exclude it when it could

1 have been considered a false negative.

2 MR. THOMAS: Yes. Of course, that is a completely
3 independent study from the clinical trial, although it
4 happens to have been done at the same sites, and we are
5 using spiked specimens as the panel.

6 You are correct that the major reason for not
7 presenting that is I think FDA has indicated to the
8 committee that we are in the process of redefining that
9 study and intend to redo it with more information on lots
10 and genotypes, and a variety of parameters.

11 In the particular study, there was simply an error
12 in study design in that the study didn't allow for the
13 replacement of panel members, so that if there was, for
14 instance, an IC inhibition in a negative sample, such as
15 occurred at that site, we couldn't replace it, so
16 analytically, we were stuck. We won't make that mistake
17 again. It is conjecture what happened, of course, but you
18 are right, it did happen in four cases.

19 It was whether, you know, there was a very large
20 number of replicates run, and, you know, from a statistical
21 point of view, I doubt that 4 in 1,000, which is about what
22 we are talking about, would show a statistical difference
23 across sites, but I guess it is interesting that it happened
24 to occur in one site, but I don't know that we can interpret
25 any more than that.

1 DR. HOLLINGER: While you are there, the assays
2 that were set up with the clinical specimens, did the people
3 doing the test know whether these were anti-HCV positive or
4 not when they did the assay?

5 MR. THOMAS: No, PCR was run blinded to serology.

6 DR. HOLLINGER: So, they were all blinded.

7 MR. THOMAS: Yes.

8 DR. HOLLINGER: And were there any repeats that
9 were done? I mean in the protocol, what was set up to
10 prevent someone from repeating an assay? You know,
11 generally speaking, in a laboratory, you get a specimen, you
12 test it, it is gone.

13 MR. THOMAS: Yes.

14 DR. HOLLINGER: You send the results back. You
15 don't have the opportunity to say, oh, gee, this was anti-
16 HCV positive, maybe we had better go back and repeat this to
17 see, and then do it a second or third time, and they have
18 enough in the panels to do that, I mean to really to set it
19 up properly, you would send them just absolutely enough to
20 do one assay, and have none left to do any repeat.

21 So, tell me how this was controlled for and if I
22 were to tell you that some of them repeated it on several
23 cases, what would you say?

24 MR. THOMAS: Well, they may or may not have. The
25 way we protect the database, which I think is what is in

1 question, is remember that these are automated instruments
2 and we will be able to electronically draw down all of the
3 information, so the data were screened by the sponsor in our
4 database looking for the first valid test of any specimen,
5 and once that occurred, then, any future testing would be
6 ignored.

7 There were a couple of cases. I have no reason to
8 think anyone was doing anything odd, trying to gain the
9 results, but simply that people, for instance, they have
10 these reagents running, and they have some space left on the
11 instrument, and so, hey, let's put these samples in the well
12 is more likely what happened. Regardless, that has not
13 effect on the results you have seen.

14 DR. HOLLINGER: Can you tell me a little bit about
15 this equivocal zone that goes from 0.15 up to, let's say, 3.
16 In many assays, you go very quickly from what is a negative
17 to a positive, and there is not much concentration level
18 there until you reach a plateau, and so what I would like to
19 know is if the cutoff at the lower limit of detection is 50,
20 let's say, IU's per mL, at one level does this test reach an
21 optical density of 3?

22 MR. THOMAS: Well, we have looked at this many
23 times, and the correlation between sample titer and optical
24 density or absorbance is not very good, nor is it intended
25 to be since we are deliberately overamplifying since it is a

1 qualitative test.

2 The distributions that you saw there indicates, of
3 course, a very large separation. In the Cobas instrument
4 that was shown in the display, it actually goes up to an OD
5 of 4.0. We truncated it 3.0 just so you could see the rest
6 of the distribution.

7 Over what was probably 6- or 700 samples in the
8 graph that you saw, there were 3 samples in the equivocal
9 zone, and Dr. Murray gave you the results of retesting of
10 those, and then the rest of the way across, until you get to
11 3.0, there was only 3 other samples.

12 DR. HOLLINGER: I guess what I was asking, if you
13 have something to 1,000 IU's per mL, is that always over 3?

14 MR. THOMAS: Well, we have data on that.

15 DR. HOLLINGER: I mean at a certain level, that is
16 always over 3, and I am trying to see where that--and I
17 understand there is variation, I mean a fair amount or
18 variation in these tests to repeat from one day to the next,
19 but I am trying to get an idea about where this level is in
20 the equivocal zone.

21 DR. GUTEKUNST: I would say certainly--I think
22 with confidence I could say that at 100 IU's, those values
23 will be greater than 3. At 50, we are starting to get to
24 where maybe they are not always, they are greater than 1,
25 but maybe not always greater than 3.

1 In fact, I think Dr. Ticehurst may present some
2 information looking at very near or at the limit of
3 detection, but there does seem to be some unexpected
4 variability in the OD's that the assay generates.

5 DR. HOLLINGER: I think that is enough for right
6 now. I have got some other questions, but I will close a
7 little later.

8 DR. WILSON: We can ask questions a little bit
9 later. We are going to have a very short break at this
10 time, so those people who need to check out can do so.

11 We will reconvene at 20 minutes before the hour.

12 [Break.]

13 **Open Public Hearing**

14 DR. WILSON: At this point we would like to
15 announce that we are now in an open public hearing. Anyone
16 from the public who has a comment to make, please step
17 forward to the podium, identify yourself.

18 [No response.]

19 DR. WILSON: There being no public comments, the
20 open public hearing is closed.

21 The next presentation is by the FDA. I would like
22 to introduce Dr. John Ticehurst, medical officer for the
23 Microbiology Branch for the Division of Clinical Laboratory
24 Devices.

25 Dr. Ticehurst.

1 FDA Presentation

2 Clinical Issues & FDA Questions

3 John R. Ticehurst, M.D.

4 DR. TICEHURST: While we are getting set up here,
5 I wanted to take just a second to address several of the
6 questions that came up from the panel before.

7 One, there was a question that pertained to
8 retesting that Dr. Hollinger had raised and Dr. Thomas
9 answered quite well. We have done some analysis that I
10 think pertains to that a little bit, and also it explains
11 some other things that is worth bringing up.

12 Over the past few days, Dr. Kat Whitaker has
13 looked at the study results for some concordance
14 information. In case this wasn't clear, most of the
15 specimens that were plasmid specimens in these studies have
16 matching serum specimens from the same patients, these that
17 are in the clinical studies.

18 What she did was look through the results for
19 concordance of the Amplicor results in those, and, in
20 general, it's very, very high. So, I think that is useful
21 information for a number of things. It partly addresses Dr.
22 Hollinger's question, but it is useful information.

23 Back to the two questions that pertain to
24 inhibitors and the inhibitor control, one is that I have
25 looked at the sort of real-time running data from the Cobas

1 version of this assay as it is performed in the Johns
2 Hopkins clinical microbiology lab where I am a part-time
3 faculty member, and the rate of inhibitory specimens, there
4 is roughly 10 percent, which is quite distinct from what Dr.
5 Thomas mentioned.

6 I have talked with a technologists who run the
7 assay there, and one of the possible explanations for that
8 is that they think that a lot of the specimens from dialysis
9 patients, which is similar to what was being discussed
10 before.

11 I think there is another point where this might be
12 relevant, is that the vast majority of the specimens that
13 were tested in the clinical studies were frozen before they
14 were tested, and it has been our experience with many other
15 similar assays, not these, we don't know yet, but freezing
16 and thawing often has an effect to remove inhibitors even
17 though they are not characterized as to what they are.

18 On the other side, again, the 10 percent figure
19 that came from Hopkins, we don't know if that is a matched
20 population at all to what was studied here, in fact, it may
21 not be matched at all, and dialysis patients may not be the
22 indicated type of patient for these studies.

23 Finally, there was a lot of discussion back and
24 forth, particularly with Dr. Fried--oh, I am not supposed to
25 do this?

1 DR. WILSON: No. Go ahead.

2 DR. TICEHURST: Excuse me, sorry.

3 I will go into my formal presentation.

4 [Slide.]

5 The statement in yellow here actually does
6 encapsule a lot of what Dr. Fried said, the hepatitis C
7 virus RNA is the only practical marker of active infection,
8 and that really states the clinical utility of it. There is
9 no other practical way to determine whether the virus is
10 present in a target organ or in another form, as Dr.
11 Gutekunst indicated.

12 As a result of that, there have been calls and a
13 perceived public health need for standardized, reliable
14 assays, and as an example, the '97 Consensus Conference that
15 was held at NIH. This was one of the major areas of concern
16 from that conference.

17 However, there is still no licensed or approved
18 HCV RNA assay in this country.

19 [Slide.]

20 So, there have been challenges put before any
21 manufacturer seeking a first approval, before us at FDA, and
22 before you as a panel today, and that is what is the
23 appropriate basis for the first approval.

24 The same statement. Currently, HCV RNA is the
25 only practical marker of HCV replication. There is no

1 reference out there. It has been pointed out before. It
2 makes it very hard do the right studies.

3 Another challenge is that these assays, as again
4 Dr. Fried mentioned, in general, these assays, and I think
5 in particular these Roche assays, are already a standard of
6 practice for diagnosis and for monitoring of HCV infection
7 and HCV associated disease.

8 So, there is at least some perception of validity
9 to them which should be paid attention to, and at the same
10 time we have to consider if we set the threshold for
11 approving these too high, it will look kind of silly because
12 we are plotting against a standard of practice. We will
13 also never get an approved assay.

14 If we set it too low, we may be hiding some
15 problems in the assays that people should know about, and
16 this gets to the last point about that the first approved
17 assay is going to be a standard for assessing performance of
18 other assays as they come down the line.

19 They also become a standard for other things like
20 when sister parts of FDA are looking at therapeutics, these
21 assays are often used in evaluation of them.

22 [Slide.]

23 So, there are several areas that I want to focus
24 on here. One is Roche's claim for equivalent detection of
25 the HCV genotypes. We are going to be asking for your help

1 in developing an appropriate threshold for determining the
2 performance of an assay that doesn't intend to detect
3 different genotypes specifically, but needs to detect a
4 variety of different genotypes to be useful

5 I also want to talk some about the appropriate use
6 of the WHO genotype 1 Standard and its quantifier, which is
7 International Units, and finally, to talk some about the
8 clinical studies and their analyses, and the proposed
9 indication for use that was developed interactively between
10 the company and FDA.

11 [Slide.]

12 Before doing that, I want to give you a little
13 information that is pertinent.

14 [Slide.]

15 These submissions were granted Expedited Review
16 status because of their public health significance. What
17 that means is they always get pushed at the top of the queue
18 internally, and we have been working very hard, as indicated
19 in the third bullet here, both our colleagues from Roche
20 Molecular and us have worked together very actively and very
21 interactively on these submissions.

22 It is also worth noting that the review group from
23 FDA has included contributions from two of the other
24 centers, Drugs Evaluation and Research, and two branches of
25 the Center for Biologics Evaluation and Research.

1 I want to note that we are continuing to work
2 closely with Roche Molecular, so that they reach an
3 appropriate threshold of data analyses for several areas
4 that we are not going to discuss in detail today.

5 These include the cutoffs for both viral RNA and
6 the internal control RNA, the equivocal zones which were
7 described as grey zones in Dr. Murray's talk, the different
8 matrices that have been proposed for use, which are ACD
9 plasma, EDTA plasma, and serum, and whether those are used
10 in either a fresh or frozen state, on reproducibility and on
11 analytical specificity.

12 [Slide.]

13 Now, I am going to spend the rest of the time
14 reading each one of these person's names and telling you how
15 they contributed.

16 [Laughter.]

17 DR. TICEHURST: Actually, what is not on here are
18 the contributors from Roche Molecular. You have heard from
19 three of them today. One person who doesn't get to talk,
20 but serves a lot of commendation is Meredith Tallās, who is
21 sitting next to Dr. Thomas. These folks have worked very
22 closely with us, and we really appreciate that.

23 We have had a number of different kinds of
24 contributions from these various people on here. There are
25 four that are highlighted in green - Don St. Pierre and

1 Woody Dubois have been real facilitators, if not catalyzers,
2 to move this expedited review along.

3 Freddie Poole and Kat Whitaker have really done an
4 enormous amount of work that I certainly want to acknowledge
5 them for, Freddie, a lot of administrative aspects that I am
6 not familiar with, and Kat has done just a terrific job with
7 a lot of the scientific aspects here.

8 [Slide.]

9 I want to spend just a minute here talking about
10 the quantifiers that have been used in these submissions
11 because it does get a little daunting sometimes when you see
12 one set of data that has one name next to a number versus
13 another.

14 First, with regard to the WHO Standard, taking
15 data from the Saldanha paper that describes this standard,
16 according to the data in this paper, by endpoint dilution
17 PCR--most of the methods were PCR whether an in-house method
18 or a Roche method--1 International Unit corresponds to
19 approximately 2 copies, which I am going to call PCR copies
20 because they use that methodology.

21 If you use same data that was submitted to us by
22 Roche, and these correspond similar to some of the studies
23 that were described, subgenomic DNAs made from cloned cDNA,
24 representing two of the subtypes of genotype 1, which were
25 quantified by UV spectroscopy, and then with their not

1 approved quantitative assay, an International Unit
2 corresponds to about 2.5 molecules of RNA quantified in that
3 way, so that a PCR copy is roughly equivalent to a little
4 more than A_{260} molecule, which makes sense.

5 There are several points to be made here. One is
6 these numbers differ from what is in that package that you
7 were given, I think yesterday, and that is because as a
8 result of the numbers that were calculated, folks from Roche
9 went back and determined that there were some errors in the
10 numbers that had been given to us.

11 I felt it was important to correct these because
12 they do make things a lot more clear having recalculated
13 these. There is another point, that these numbers, a lot of
14 times these quantitative values are expressed and
15 interpreted logarithmically. They really don't differ by
16 very much.

17 I think one of the reasons the log values are used
18 goes back to the points about imprecision in these numbers
19 that come out. I think the bottom line to take away from
20 all this is that these numbers are all rather close, okay.

21 [Slide.]

22 Now, there has also been some discussion of this
23 previously today, that the Roche endproduct absorbance
24 values, which go in this range of roughly zero to 3 or zero
25 to 4, depending on the instrument that is used, these are

1 measuring the colored product of a horseradish peroxidase-
2 catalyzed reaction, but they don't directly represent HCV
3 RNA.

4 The point I am mentioning that is that there is a
5 sort of biologic possibility that if you have got a positive
6 result, that that means that there is RNA present, and we
7 don't always know that with these assay results, because
8 that's not what is actually being detected. I mean the
9 assay is set up, so that is what it should be, and as Dr.
10 Murray showed in her presentation, some of the discussion
11 after the presentations, most of the data that have been
12 presented to us are consistent with the theoretical concept
13 that when you have effective amplification, you get a very
14 high absorbance value. It is sort of all or none.

15 When there is no amplification, the values
16 approach zero, and as Dr. Thomas said, very few results from
17 human specimens, whether in the clinical studies or in the
18 non-clinical studies, yield the intermediate values in
19 between there that include the equivocal zone.

20 However, there are certain non-clinical studies,
21 they are a bit confusing here because they do show at least
22 in our analysis a semi-proportional relationship between the
23 absorbance values and the concentration of HCV RNA that
24 started, and we don't really understand those at this point.

25 [Slide.]

1 Shifting to talking about these assays, detection
2 of genotypes and subtypes. Why is this relevant?

3 If there were suboptimal detection of different
4 HCVs, this could yield false negative results, it could be
5 interpreted as absence of active infection, and it could
6 lead to inappropriate management.

7 One thing to consider is whether it matters with
8 all these subtypes. As Dr. Fried pointed out, genotype 1
9 accounts for the vast majority of infections in this
10 country, but it should be considered these assays are likely
11 to be used in centers, either in this country or elsewhere,
12 where the proportions of infrequent subtypes are much
13 higher.

14 Certain centers in this country might be, for
15 example, more like to have patients from Egypt where
16 genotype 4 is very, very common. Even in a sort of standard
17 center in this country, well, overall, many individuals with
18 infrequent subtypes are likely to be tested.

19 For example, is subtype 3a represented 5 percent
20 of infections in this country--which is proximate from the
21 data I have seen--and 100,000 viruses were tested, which is
22 I think a very conservative estimate for how these assays
23 might be used, 5,000 of those would represent 3a.

24 I think the bottom line is it is less important
25 that the assays detect equivalently than we know what the

1 differences are, so that users can make adjustments in how
2 they use these assays.

3 [Slide.]

4 Well, what about suboptimal detection of certain
5 genotypes? In a way, it doesn't make sense, as Dr.
6 Gutekunst showed you, there is very high conservation in the
7 5-prime non-translated regions of different HCVs and
8 particularly within this amplified segment.

9 She also mentioned or alluded to the fact that
10 these differences were recognized with a number of different
11 assays in older versions including the Version 1 of these
12 assays. She also mentioned that RNA structure may
13 contribute to the inability to suboptimally detect and that
14 there is also the possibility that mismatches with reagent
15 oligonucleotides could contribute to that.

16 Again, the Roche Version 2 assays have included
17 changes to optimize cDNA synthesis and amplification to the
18 company's credit.

19 [Slide.]

20 So, here is their claim. They claim that
21 genotypes 1 to 6, including certain subtypes, are detected
22 to endpoints that correspond to a level of approximately 100
23 International Units per mL of the WHO genotype a standard.

24 [Slide.]

25 Several comments. There was not a single method

1 used for genotyping for those specimens that were
2 characterized according to the genotype. It varied from
3 study to study.

4 In a study of 17 human specimens that represented
5 11 subtypes, all yielded predicted-size amplicon, Dr.
6 Gutekunst showed you that. None of these specimens, they
7 are all quantified, but none of them had less than 50,000
8 International Units per mL according to the standard.

9 In another study that was mentioned, of 87 human
10 specimens, all of which yielded 100 percent results, these
11 specimens were not quantified.

12 There was no genotyping done during the clinical
13 studies, nor was there quantitation of any assessments
14 during the clinical studies.

15 [Slide.]

16 There were no experiments that were specifically
17 designed to determine if the internal control competed with
18 HCV RNA of any type, and again with the various genotypes.

19 The reproducibility data that has been generated
20 so far was only done with genotype 1.

21 The data from serially diluted specimens are felt
22 to be insufficient because they correspond to a small number
23 of specimens, and they are somewhat conflicting. If you
24 look at what was given to you yesterday, the word was
25 conflicting, but because of the numerical changes and the

1 recalculations that have been done, the data actually looked
2 better than what the panel received in the handout.

3 These next two slides allude to some of the points
4 that Dr. Gutekunst is making in the discussion.

5 [Slide.]

6 This is our analysis of some data from the semi-
7 automated Cobas assay where we are looking at concentrations
8 of HCV RNA corresponding to about that limit that is being
9 claimed across genotype, and there is just a few
10 representative results displayed here for these four
11 subtypes.

12 There is two sets of data from two sets of
13 experiments here. One was with human specimens and the other
14 was with subgenomic RNA molecules. There are roughly the
15 same amounts of molecules in each assay, and we are looking
16 at the percent of results that either gave an absorbance
17 value greater than the lower cutoff, which is the cutoff
18 that the company proposes for the assay, which is the lower
19 end of the end of the equivocal zone or greater than the
20 upper end of the equivocal zone.

21 When you look at these results, there are at least
22 with the lower equivocal zone cutoff, when you get to
23 genotype 5, you fall below the 95 percent threshold that is
24 normally accepted as sort of a standard for qualitative
25 detection limit.

1 [Slide.]

2 This is the same analysis now with a manual assay,
3 and the numbers are slightly different, but the data are
4 basically the same, that is, with genotype 5, you fall below
5 the 95 percent threshold for anything above the lower cutoff
6 and with genotypes 3a and 5 for the higher cutoff.

7 Again, I want to point out that the company is not
8 proposing this. They are proposing that all results greater
9 than this value, when retested above that value, would be
10 considered positive.

11 [Slide.]

12 I talked a little bit about the WHO Standard.

13 [Slide.]

14 A little bit about their data. Both of their
15 essays demonstrated 100 percent detection of the actual
16 standard when it was serially diluted down to 50
17 International Units per mL, which corresponds again back to
18 those calculations I showed you, about 90 PCR-copies per mL.

19 In their limited reproducibility study, the lowest
20 concentration of another genotype 1 virus that was studied
21 was 200 PCR copies per mL, and at that level, there was 100
22 percent detection.

23 Summarizing a bunch of other data in a very
24 cursory way, where there was concentrations corresponding to
25 approximately 40 to 80 International Units per mL--again,

1 these numbers changed from what you were handed yesterday
2 because of the recalculations--there are some of these
3 studies where there were results less than 95 percent cutoff
4 sort of threshold.

5 [Slide.]

6 Now, the company has proposed using this
7 terminology in certain data as has been expressed to you,
8 including genotypes other than 1, quantitative data have
9 been converted to International Units.

10 The point to be made is that at least at this
11 point in time--this may not be the case in the future--at
12 this point in time, that International Unit quantifier
13 pertains only to genotype 1, and it may no pertain to all
14 genotype 1 viruses.

15 I think the intent, as other International
16 Standards are developed, and they are in development, that
17 hopefully, 1 International Unit will be the same as another,
18 but we don't know that at this point in time, and whatever
19 terminology that is being used for these assays is going to
20 set a precedent for results in other data pertaining to
21 qualitative and quantitative assays.

22 Again, we need quantitative data to analyze the
23 performance of even the qualitative assays.

24 [Slide.]

25 Talking a little bit about the clinical studies

1 for a diagnostic indication.

2 [Slide.]

3 Some points under clinical studies. All the
4 patients that were studied had disease. They either had
5 biochemical or some other clinical evidence of liver disease
6 that wasn't specified in the study. Some of them were known
7 to have hepatitis C although we don't know exactly what that
8 means.

9 Many of these people had a physician's diagnosis
10 of chronic hepatitis C. As was pointed out earlier, none of
11 them were thought to have acute hepatitis C, but in general,
12 in the studies, there were no uniform diagnostic criteria
13 that were developed for establishing that people had
14 hepatitis C or any of the other causes of liver disease that
15 were described.

16 All these people were characterized according to a
17 single time point, and that is the date the specimens were
18 collected for detecting anti-HCV, for alanine
19 aminotransferase, and for studying with the Roche assays.

20 There were no data from earlier dates that would
21 enable patients to be categorized either as acutely or
22 chronically infected according to the so-called 6-month
23 "rule," which for those that were here six months ago, would
24 know what this meant.

25 The panel that met in January felt it was quite

1 important to categorize people as having acute or chronic
2 hepatitis, in this case C, it was important that you had
3 evidence that they had that viral infection six months prior
4 to be called chronic, and they didn't have it six months
5 prior to be called acute.

6 There is no data from later dates that could
7 demonstrate anti-HCV seroconversion or for which additional
8 RNA testing could be done to try to explain some results
9 that didn't always make sense.

10 [Slide.]

11 As I mentioned earlier, no specimens were
12 characterized via quantitation or genotyping.

13 As Dr. Murray presented, there are certain
14 patients--and I think it was roughly two-thirds of them--for
15 which liver tissue had been studied for histopathologic
16 changes.

17 It is important to note that the interval from the
18 time of collecting that liver tissue to the time the study
19 specimen is collected was variable, in many cases years, so
20 that the changes may not be representative of disease that
21 was present when the HCV RNA was studied for.

22 It is also important to know, as the panel did in
23 January, that the changes, histopathologic changes of
24 hepatitis, of course, are not specific for any etiologic
25 agent.

1 The clinical studies were not designed to
2 determine assay performance in individuals without apparent
3 disease, and that is not a criticism, it is just a note, and
4 it pertains to the indication for use.

5 [Slide.]

6 Now, there are challenges that any company, and
7 FDA, and you all have to face when the first assay would be
8 considered for approval, and these again are not a point of
9 criticism, it's just something that we all have to deal with
10 here.

11 Again, there is no reference method for
12 establishing that HCV RNA is present, and every other sort
13 of reference technique that would be used to establish
14 whether or to propose there was acute or inactive infection
15 present, or HCV-associated disease has shortcomings in them.

16 We recognize that it is very difficult to generate
17 data that enable categorization of patients according to the
18 6-month "rule" that I just discussed.

19 In general, there are no reference specimen banks
20 that could be used that fit these criteria.

21 The seroconversion panels of the type that Dr.
22 Gutekunst described this morning are very unusual, and
23 because they often come from commercial suppliers, the
24 quality of them is uncertain. It is extremely difficult, if
25 not impossible, to do prospective studies of acute

1 infections now because the incidence of acute infections is
2 greatly declining, and to do serial sampling is very
3 expensive even when you are dealing with chronic infections.

4 [Slide.]

5 As an example of one of these challenges, this is
6 a particular thought as applied to the Roche data of
7 thinking about specificity and when we are using anti-HCV as
8 the primary reference marker.

9 The first part of this pertains to what might be
10 considered a very important part of specificity, and that is
11 considering the kinds of things that Dr. Fried mentioned
12 about the utility of these results, that if the results of
13 one of these assays were false positive in people who had
14 high risk of hepatitis C, that could have profound effects
15 on management.

16 I think the other thing to balance that, it should
17 be considered that one of the things that is different about
18 approving these assays versus licensing them, for example,
19 for blood product use, is that people can be retested, you
20 can go back and retest people.

21 However, just to consider some of the points,
22 among those people that were EIA positive and RIBA positive,
23 or EIA positive and RIBA indeterminate, the Roche assays
24 yield a higher percent RNA positive than those described--
25 maybe for different assays--but in the scientific

1 literature, with either hospital or donor populations.

2 These results aren't surprising because we know
3 that the study selected for patients with disease, and it
4 was probably enriched for people who had known HCV
5 infection, therefore, there was a high pre-test probability
6 here, and we know that assays, these particular assays have
7 high analytical sensitivity, but again the endproducts of
8 these assays are not amplified HCV cDNA.

9 A similar sort of thought here, there were some
10 HCV RNA positive results among EIA negative specimens, and
11 they could represent so-called "serosilent" chronic HCV
12 infections which are thought to occur, or false positivity.

13 [Slide.]

14 To come to some conclusions.

15 [Slide.]

16 With regard to the area of genotype detection, if
17 one method had been used for determining genotyping, it
18 would have eliminated the variability among different
19 methods. This is recognized, it is a difficult area because
20 the whole area of genotype and relation to HCV and HCV
21 disease has been evolving over years, and none of the
22 methods, of course, are FDA-approved or licensed, but it is
23 recognized there is variability in them and that one method
24 would have eliminated that.

25 In terms of the numbers of specimens that were

1 characterized, in all the studies that were performed, it is
2 our conclusion that these were insufficient for establishing
3 that claim.

4 I pointed out to you some of the results that were
5 conflicting the serial-dilution studies. They don't appear
6 to conflict as much as they did yesterday, than they did
7 today when we have had some numerical corrections.

8 [Slide.]

9 Here are some considerations, then, I am going to
10 come to us asking you for appropriate thresholds.

11 Rigorous demonstration of genotype detectability
12 could be impossible or unreasonable at this point.

13 A less rigorous demonstration could be based on
14 sort of multiplied probabilities or building the case. Here
15 is an example. In indicated populations, if the proportions
16 of subtypes were known or approximated, if low
17 concentrations of anti-HCV were very infrequent, and false
18 negative results were very infrequent, small differences
19 between detectability of subtypes might be insignificant.

20 [Slide.]

21 Thinking about the genotype 1 Standard and the
22 International Unit quantifier, well, of course, the standard
23 should be used, but it should be used to determine one limit
24 of detection, and that is the limit of detection for that
25 particular standard, and we commend Roche for doing that.

1 Our concern at this point is that the
2 International Unit quantifier could imply accuracy for
3 uncharacterized HCV.

4 We should recognize that at least at this point in
5 time, the Standard's limitations and especially those
6 pertaining to variability of HCV genomes and the current
7 methods for quantifying viral RNA.

8 If analytical sensitivity were simply described as
9 50 International Units per mL, it could imply that these
10 assays detect as few as 100 PCR-copies per mL for all HCVs,
11 and at this point in time, our thinking is that most
12 quantitative data should not be expressed directly as IU/mL.

13 As an example for a possible way of dealing with
14 this, would be to express the data as corresponding to [n]
15 where n is the number, IU/mL, the International Standard for
16 HCV genotype.

17 Well, that is cumbersome. You might have noticed
18 I tried to do that on all these slides. It is cumbersome.
19 It may not be the solution. It may be unnecessary as other
20 standards are being developed, but I think it is something
21 we are considering right now.

22 [Slide.]

23 Now, with regard to the clinical studies, the
24 analyses, particularly those for specificity, would be more
25 exacting if data from a verified HCV RNA assay were

1 available for enough specimens to represent a valid subset
2 of the study populations.

3 To the company's credit, they did have data from
4 an alternative PCR assay to support the results that they
5 refer to as discrepant, but we don't have the information at
6 this point in time to determine that that is a verified
7 assay, so those data have not been presented to you at this
8 time.

9 Even without that, the current data and analyses
10 appear to support at least one diagnostic indication for
11 use, and you will be seeing that indication if you haven't
12 read through things already in a few minutes.

13 We will reassess these considerations as
14 additional data and analyses are submitted and also in
15 concert with your recommendations.

16 [Slide.]

17 The indication for use that has been proposed was
18 one that was developed interactively between Roche and FDA,
19 and I want point out some features to it.

20 It would be indicated for evidence of active
21 infection but not directly indicated for the diagnosis of a
22 disease. So, in that sense, it is sort of a laboratory
23 diagnosis, and not indicated for an actual clinical
24 diagnosis.

25 That may seem like a moot point, but most of the

1 time the way CDRH does things is that when assays are
2 approved for an indication, it's a diagnostic indication,
3 whereas, detection of infection is not truly diagnostic.

4 It would not be explicitly indicated for evidence
5 of acute infection or for evidence of chronic infection
6 because, by the nature of the clinical studies that were
7 done, it was not possible to determine whether people were
8 actually acutely or chronically infected according to strict
9 diagnostic criteria, so performance couldn't be demonstrated
10 for either.

11 These considerations go back to some thoughts that
12 were again discussed in the January 2000 Microbiology Panel
13 meeting, we put forward an analogous proposal with regard to
14 an anti-HCV assay.

15 The points that were made at that time, I think
16 are relevant here, are as follows: One is the likelihood is
17 that these studies do represent chronic infections. The
18 vast majority of patients that are going to be studied to
19 support any of these assays are going to be mostly chronic
20 infections. The vast majority of people who would be tested
21 with these assays, if they were approved, would be
22 chronically infected.

23 So, even though there is not a perfect rigid
24 definition of who is being studied, there is a correlation
25 between the types of people who would be studied and the

1 typical types of people for whom they would be indicated.

2 So, we feel it is appropriate without having clear
3 evidence of performance for the classic indications, acute
4 infection or chronic infection, that it would be appropriate
5 to approve for a more generic indication of evidence of
6 active infection.

7 Again, although populations without evident
8 disease were studied, the indication is limited to patients
9 with liver disease.

10 The indication is also limited to patients with
11 EIA and immunoblot evidence of antibodies to HCV.

12 Even though the studies have not been done to look
13 to see how these assays would perform if only EIA were done,
14 so that we could see what would be the performance if we did
15 RNA testing after EIA, these are analyses that probably
16 could be done on the data they have been submitted, but
17 these just haven't been done yet.

18 [Slide.]

19 Again, these clinical studies were most likely to
20 represent chronic infections and were unlikely to have
21 included any acute infections, but the decision was made, at
22 least to this point, not to explicitly warn their
23 performance was not demonstrated for providing evidence of
24 acute infection, because it was felt that that could imply
25 that performance was demonstrated for chronic infection.

1 Again, why the distinction? The data from the
2 scientific literature clearly established that people with
3 acute infections, first of all, take a while to start
4 cranking out HCV RNA and have detectable levels, the levels
5 may be lower than during chronic infections, they may be
6 sporadic. That is still a somewhat controversial area, but
7 this is where we are at this point.

8 Finally, although no data were submitted for what
9 would be a major potential use--that would be monitoring of
10 chronic more so than acute infections--we would consider
11 approval for only the diagnostic indication and provide a
12 warning about monitoring indications.

13 With that, I am ready to present the question
14 unless--do I present the questions or do I stop for your
15 questions?

16 Exclude me for a technological interlude.

17 The information quotes here--and this is all in
18 the actual questions that everybody has at the end of the
19 sort of agenda for today's meeting--that this indication for
20 use information is excerpted from a draft intended use
21 statement, the intent of which was agreed upon between Roche
22 and FDA earlier this week.

23 You have already heard the indication for use
24 statement. I will read it again.

25 "The Amplicor HCV Test is indicated for patients

1 who have liver disease and antibodies to HCV that were
2 detected by enzyme immunoassay and by immunoblot assay, and
3 who are suspected to have active HCV infection. Detection
4 of HCV RNA is evidence of active HCV infection but does not
5 distinguish between acute and chronic states of infection."

6 What is also part of this intended use statement
7 are these warnings: Performance has not been demonstrated
8 for diagnosis of individuals who (i) were not tested for
9 antibodies to HCV or ([inaudible]) had reactive results from
10 testing for antibodies to HCV by enzyme immunoassay but were
11 not tested by immunoblot assay.

12 Second. Performance has not been demonstrated for
13 monitoring of HCV-infected patients.

14 Third. A negative Amplicor HCV Test result does
15 not exclude active HCV infection.

16 This next statement in brackets here is sort of a
17 real draft that would be revised according to data and input
18 from the Microbiology Panel. [Although a wide range of HCV
19 genotypes can be detected, analytical sensitivity and other
20 performance characteristics have not been determined for HCV
21 genotypes (list: genotype/subtype numbers); these genotypes
22 might be more likely to yield false negative results.]

23 Fourth. It is not known if performance is
24 affected by the state (acute or chronic) of infection.

25 Fifth. It is not know if performance is affected

1 by the presence or absence of disease. Detection of HCV
2 RNA, by itself, does not indicate the presence of liver
3 disease.

4 Finally, there will be a warning about testing of
5 donors and the wording of this is something that doesn't
6 need to be discussed today and it gets worked out in
7 collaboration with the Center for Biologics, Evaluation, and
8 Research.

9 The first question pertains to the appropriateness
10 of this indication, and that is not the first question.

11 Is the proposed indication for use appropriate
12 with, more specifically, is it appropriate to consider
13 approval of these assays that would be indicated for
14 evidence of infection, but not directly indicated for
15 diagnosis, not be explicitly indicated for evidence of acute
16 infection or chronic infection, and if so, are the proposed
17 cautions adequate, which I just read to you, just a point
18 back as to what those were, would not explicitly warn about
19 use for acutely infected individuals, again in terms of a
20 statement like performance not demonstrated for providing
21 evidence of acute infection, and fourth, warn about major
22 potential off-label uses such as monitoring, because there
23 were no pertinent data submitted.

24 I am going to ask you as you discuss these
25 questions to consider, please, again, this widely perceived

1 the public health need for standard infections and the lack
2 of an FDA-approved or licensed HCV RNA assay, and the
3 diagnostic testing algorithm that was put together by CDC
4 consultants and federal government liaisons, which proposes
5 the use of HCV RNA's assays, either after detection by EIA
6 and immunoblot or after presumptive detection of anti-HCV by
7 EIA.

8 You have seen at least one version of that today.
9 It's in the questions, specifically, but here it is. This
10 is right out of the MMWR recommendation and reports from
11 October 1998. I won't go through that now.

12 The second question which becomes moot if that
13 indication isn't considered appropriate, is to consider the
14 data that were supported for this proposed indication for
15 use, and specifically asks: Are the data from patients who
16 were treated with antivirals or who received a liver
17 transplant appropriate for evaluating this diagnostic
18 indication for use?

19 Part of the point is that people who are treated
20 are not being evaluated for diagnosis. They have the
21 diagnosis. The same is true for liver transplants.

22 Some other considerations are whether, in spite of
23 that, they would be representative of the kinds of people
24 who would be tested, especially in terms of the
25 characteristics of the viruses that were circulating in

1 them.

2 Were the clinical data appropriately analyzed?

3 Are data sufficient for determining or
4 approximating specificity in appropriate populations?

5 Should any additional instructions be provided to
6 laboratories and primary care clinicians for interpreting a
7 negative result?

8 Do the data support the proposed indication? If
9 not, can the Panel recommend an alternative diagnostic
10 indication for using both versions of this assay that is
11 supported by the data?

12 We will ask you, please, to consider for these
13 last four subquestions if there should be separate
14 considerations that pertain to the two different versions of
15 the assay.

16 The third question must have gone into a
17 thermocycler because it amplified over the past several
18 days. It really is overkill in detail, but I think that the
19 concepts are here, and that the major concept is that we
20 would really appreciate the Panel's input with regard to how
21 we deal with this difficult problem of assay's ability to
22 detect different genotypes. I am not saying it's Roche's
23 difficult problem, it's everybody's difficult problem.

24 Based on data submitted for detecting HCV
25 genotypes and subtypes, and to verify Roche's claim that

1 performance is equivalent for each subtype, to a limit
2 corresponding to 100 International Units per mL of the
3 Standard:

4 Are certain approaches appropriate for all studies
5 to support the claim? More specifically:

6 Should all genotyping be performed by using a
7 single approach, that is, nucleotide-sequence determination
8 of a coding region, followed by phylogenic percent identity
9 analysis with a database of HCV sequences? If not, what
10 does the Panel recommend?

11 For quantifying HCV RNA, should methods that are
12 independent of PCR be used whenever possible? If so, can
13 the Panel recommend practical methods for quantifying HCV
14 RNA in clinical specimens?

15 There have been two methods discussed in the
16 studies that have been presented today. One is Roche's own
17 assay which uses the same amplifying reagents in terms of
18 oligonucleotides, and those are unapproved assays.

19 The other version is UV spectroscopy, which is
20 independent and a sort of chemical way of quantifying, but
21 it is really only useful for specimens that contain or
22 samples that contain RNA concentrations vastly in excess of
23 10^{13} copies or molecules per mL. So, it is not practical
24 for any clinical specimen.

25 Was an appropriate range of subtypes studied in

1 the analytical studies? If not, what additional subtypes
2 should be studied? This is for basically all studies.

3 And are there any other such approaches that the
4 Panel would recommend?

5 I put these up out of order. I am sorry, that was
6 Part (b). This is Part (a).

7 Are the proposed warnings and limitations
8 appropriate? If not, what should be modified or added?
9 Again, the panel consider if there are differences between
10 the two assays, they should be addressed separately. I
11 apologize for putting those up in reverse order.

12 Lastly, Part (c). To support the claim, what
13 additional studies should be performed?

14 There is a lot of detail here. The bottom line is
15 there are a number of different types of studies that could
16 be performed. There is a range of rigor that could be
17 applied in each of these types of studies.

18 We have provided these as multiple choice to try
19 to simplify it to some degree, and if, in fact, it has
20 complicated it, you can avoid it, but hopefully, you
21 understand the intent of what we are asking for.

22 We are trying get the appropriate threshold here,
23 so that we are asking for the right amount of rigor, and not
24 too much.

25 But just as an example, considering submitted

1 information and data from the clinical study, is it
2 appropriate to assume that appropriate ranges of subtypes
3 and HCV RNA concentrations were sampled. As Roche has
4 pointed out, they have four sites, one in the Northwest,
5 three in the South and the Southeast part of the country.
6 It be appropriate to assume that they are representative of
7 what would be tested in this country.

8 Should genotype and HCV RNA concentration be
9 determined from statistically appropriate subsets of
10 specimens representing each study site? Or should genotype
11 and HCV RNA concentration be determined for all studies that
12 contain HCV RNA?

13 Obviously, again, you can't genotype if you don't
14 have RNA, but this would be another instance where a
15 verified alternative assay would be very helpful. Or is
16 there another approach that you would recommend?

17 The rest of the questions follow that theme.
18 Should I take the time to read through them in detail,
19 because they follow that theme, and I think, hopefully, that
20 the intent is clear, and your input will be greatly
21 appreciated.

22 Thank you very much for your attention.

23 **Open Committee Discussion**

24 DR. WILSON: Thank you. There is time for a few
25 questions. Dr. Durack.

1 DR. DURACK: Can we address the presenters?

2 DR. WILSON: Yes.

3 DR. DURACK: I have a question for Dr. Murray on
4 the patient population.

5 Dr. Murray, you told us about the three subgroups
6 of HCV positive patients, but I notice in Table 13, there
7 are 12 percent of the patients who are listed under Other
8 Diagnoses. Now, they were all investigated for liver
9 disease, I guess, to get enrolled.

10 Could you tell us a little bit about the 12
11 percent or 106 Others?

12 DR. MURRAY: The Other category is take from the
13 demographic table, which is the table that I think you are
14 referring to in the panel booklet, and the categorization on
15 that table was actually a separate categorization to the one
16 that we did to separate the patients into the three
17 subgroups.

18 Essentially, that table was based on the history
19 that the investigator had at the time that he interviewed
20 the patient, what the most likely diagnosis was that he
21 thought the patient had.

22 In fact, what we know, having looked at the biopsy
23 data on the subset of patients who do have biopsies, the
24 Others were things like autoimmune hepatitis, non-alcoholic
25 steatohepatitis, hepatitis B, hepatitis A, primary biliary

1 cirrhosis, various other types of biliary pathology.

2 So, there is other diseases that are quite a large
3 and mixed bag of different diseases.

4 DR. DURACK: Of the 106 patients, are there some
5 who end up having no liver disease at all or not?

6 DR. MURRAY: I think that almost every patient had
7 liver disease. I can't think of any patients, certainly
8 none of the biopsy patients. There was one biopsy where
9 there was no discernible liver disease on the biopsy, but
10 the other patients all had some evidence of liver disease.
11 That is why they were being investigated.

12 If they didn't have evidence of liver disease in
13 the form of an elevated ALT or some other abnormality on
14 biopsy, they had hepatitis C serology that had brought them
15 in to the clinic, but the majority of them, I think Dr.
16 Ticehurst's points about the fact that this is essentially a
17 group of patients who have liver disease, I think it is fair
18 to say that the vast majority of the patients in the study
19 have liver disease. This is the population they
20 investigated. They all had liver disease.

21 DR. SMITH: I have a question as far as the false
22 positives. You mentioned that it looked like they were
23 people who had primarily biliary disease.

24 My concern is for primary care physicians who will
25 be using this test--

1 DR. MURRAY: I am sorry. The false positive what?

2 DR. SMITH: The false positive, the actual
3 Amplicor test that was used in those patients, that woman
4 who had primary biliary cirrhosis?

5 DR. MURRAY: The one case?

6 DR. SMITH: Yes. As this test gets used more and
7 more, and they are going to be in the hands of people who
8 are less experienced, and they are just looking at liver
9 disease in general, have you data on more of those patients
10 who might be false positives based on their primary biliary
11 cirrhosis or other biliary disease?

12 DR. MURRAY: We don't, and what is interesting
13 about that case, in fact, the test was positive on both the
14 Amplicor and the Cobas test, which is sort of interesting,
15 and the patient had a history of chronic hepatitis C,
16 although no evidence that we could find of chronic hepatitis
17 C.

18 You know, looking at all the cases who had primary
19 biliary cirrhosis or other biliary pathology on histology,
20 they are all negative on both anti-HCV serology and on our
21 PCR test. So, what we have is the patient's set that was
22 included and, you know, all the primary biliary cirrhosis
23 cases were negative.

24 Mike has a comment on this.

25 DR. FRIED: I would just like to add one thing.

1 Primary biliary cirrhosis is a very specific diagnosis, and
2 we are not talking about confusing that with gallbladder
3 disease, cholelithiasis, choledocholithiasis. So, this is
4 biopsy-proven primary biliary cirrhosis with appropriate
5 serologies, et cetera.

6 DR. HOLLINGER: On this same question, about the
7 false positives, if I remember right, when they were looking
8 at interfering substances, and other things, they used
9 bilirubin. I think there were two patients in the bilirubin
10 group that were actually positive, and the assumption that
11 you made was--or that was made at least--was that these were
12 true positives, probably in the window period.

13 Do you, in fact, have data that those patients
14 ultimately went on and developed anti-HCV, so that this
15 could be established as really true, and this was not really
16 a false positive test?

17 DR. MURRAY: The samples that had very high levels
18 of bilirubin that were tested for interfering substances,
19 where bilirubin was tested as an interfering substance,
20 there were one or two positive cases detected there.
21 Unfortunately, those samples were from sample repositories
22 where we don't get a great deal of history on the cases.

23 Those samples were actually sent out for
24 additional evaluation. They were sent to the University of
25 Washington who have three alternative PCR assays that they

1 run. Those are the unvalidated assays that Dr. Ticehurst
2 was talking about. In fact, they were positive on all three
3 of the assays at the University of Washington using
4 alternative PCR primers, and I think they could be
5 genotyped, as well. So, there was additional supportive
6 data which is from an unvalidated, unregistered test, but we
7 assume that HCV RNA was present in those samples.

8 We don't have any follow-up because they were
9 samples from sample banks where we don't have recourse to go
10 back and follow up the patient.

11 DR. HOLLINGER: You said they were genotyped.
12 What were their genotypes?

13 DR. MURRAY: I am sorry. We can check that over
14 lunch for you and get back to you if you like.

15 DR. WILSON: Any additional questions? If not,
16 let's break for lunch now. Because we are running a little
17 bit behind schedule, let's reconvene at 1:30, but promptly.

18 Thank you.

19 [Whereupon, at 12:39 a.m., the proceedings were
20 recessed, to be resumed at 1:00 p.m.]

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

[1:30 p.m.]

Committee Discussion

DR. WILSON: I would like to reconvene the meeting. If we could have someone from FDA put up the first question. This is the open committee discussion. This portion of the meeting is open to public observers. However, public observers may not participate except at the specific request of the Chairperson.

I would like to invite the panel to begin their discussion of the questions as we move through this. One thing that, in discussing this a little bit with Dr. Gutman, is that we would all try to keep in mind that it is not our role to discuss the finer academic points of the assays or the field of study but, rather, to help FDA to determine what is a least-burdensome approach for the manufacturers and to stay focused on the issue of today which are the two PMAs.

The first question that Dr. Ticehurst has put up. Is the proposed indication for use appropriate as follows with the subpart. At this point, I would like to open this up for discussion among the panel members.

Dr. Baron?

DR. BARON: Many laboratories do not perform RIBA in-house. So explain to me, if the indications were for

1 patient samples that had antibodies and RIBA and you were to
2 use it without RIBA, would you then be using it with the FDA
3 disclaimer commentary on it? Is that how that would work?

4 DR. WILSON: Steve?

5 DR. GUTMAN: Yes. This product, in all candor,
6 could be used off-label with no particular commentary. We
7 don't anticipate we can predict the configuration of all
8 labs or what the testing pattern is. So I would focus on
9 what you see and actually not worry about--unless you think
10 there is an incredible health hazard in a potential off-
11 label use that might be devastating, I would focus on what
12 you see.

13 DR. WILSON: Dr. Hollinger?

14 DR. HOLLINGER: I think I would agree with what
15 was mentioned here. I saw that, too. I see no benefit of
16 having that as an indication and to just say, "The AMPLICOR
17 is indicated for patients who have liver disease and
18 antibodies to HCV that were detected by enzyme immunoassay,"
19 and take out, "by immunoblot assay."

20 Not very many people use RIBA except under those
21 unusual circumstances which are anti-HCV-positive and HCV-
22 RNA-negative when you are trying to determine where this
23 might be a false positive or an old disease or something
24 else for insurance purposes and a variety of other things.

25 I don't think because the tests were done with

1 RIBA and anti-HCV is, to me, not a particular indication to
2 add that. I could just argue the other thing, that if you
3 did anti-HCV and they did an HCV RNA, then you use the RIBA
4 to sort of determine if the positives has a relationship to
5 infection, and sometimes it did. In a patient population,
6 most likely it did. In a low-prevalence population, it may
7 not have.

8 So I think, by putting that in there, it does seem
9 to suggest that you are going to have to do both--or you
10 probably should do both of those tests. I think that is the
11 wrong message to send.

12 DR. DURACK: Would it make sense, then, to just
13 say antibodies to HCV without any further qualification?

14 DR. HOLLINGER: Yes. I would just take out, "and
15 by immunoblot assay."

16 DR. DURACK: What about taking out, "and by enzyme
17 immunoassay?" Just say, "antibodies to HCV."

18 DR. BARON: Because we can't predict what new
19 kinds of tests may come along.

20 DR. HOLLINGER: That would be okay. It would be
21 more generic.

22 DR. BARON: I also believe that it would be useful
23 to list the genotypes that have not been well-determined.
24 My understanding is that they are up to twelve now. One of
25 my hospitals just has a 7a. So I think it would be

1 important to change those warnings as more experience with
2 the kit becomes available over time.

3 DR. STEWART: Wouldn't it be just indicated which
4 one have shown to be positive and not bother saying what
5 haven't?

6 DR. BARON: Say, one?

7 DR. STEWART: One, and the ones that were checked.

8 DR. BARON: I am not sure I buy how many of those
9 others were checked as sufficient to put it in here.

10 DR. HOLLINGER: Again, I just want to walk back a
11 little bit to that about the immunoblot assay because, under
12 the Warnings, it has a similar kind of a thing, again, which
13 I would take out that, 2, the whole section of 2 there and
14 just leave it, "Performance has not been demonstrated for
15 diagnosis of individuals who were not tested for antibodies
16 to HCV," and leave out the rest of that.

17 Does the panel think that the genotyping tests are
18 not sufficient to pick up--I mean, that this test was not
19 sufficient to pick up all the genotypes, at least 1 through
20 6, I guess it was, that were done. Do they feel it is not
21 sufficient? I thought the data looked reasonably good, to
22 me, for picking up these genotypes.

23 I agree; there are other genotypes that are being
24 determined. More common, of course, are 1, 2, 3, 4 and
25 sometimes 5 and 6.

1 DR. WILSON: Dr. Specter?

2 DR. SPECTER: I would agree completely with that
3 statement, especially in light of the fact that we do have
4 sequencing data that shows that the probe region is
5 homogenous throughout the different genotypes. Until we see
6 it for new genotypes, I think we can say that the ones that
7 we have seen are fine and we should leave it at that.

8 DR. HOLLINGER: I just might ask John Ticehurst;
9 was it your feeling, or the FDA's feeling, that there wasn't
10 enough evidence that, perhaps, it was able to pick up all
11 the genotypes that were out there? I know that was a real
12 issue with some of the earlier assays with 2 and 3,
13 particularly.

14 But it seems like now with the addition of the
15 DMSO and a few other things that a lot of these things have
16 been resolved.

17 DR. TICEHURST: Thanks, Dr. Hollinger. I think
18 your point that you mentioned just a second ago that there
19 were recognized problems with earlier assays including
20 earlier versions of these. They are well-described in the
21 literature. I think that raises a flag that makes people at
22 least pay particular attention to what has been done here.

23 I think that there was some discrepancy between
24 two of the analytical studies, at least one of them
25 indicated, the one on subgenomic RNAs, that the subgenomic

1 RNAs that represented genotypes 4 and 5 were not detected to
2 the same level as the clinical specimens that were tested.

3 You asked the question, if you do these signs of
4 serial dilution studies with, I think, it was a total of
5 eight specimens representing eight different subtypes.
6 There were the other nonclinical studies that were done--
7 they are called "nonclinical" in the sense that they were
8 done in-house, not in the context of the clinical studies,
9 but they are with clinical specimens, 87 specimens and then
10 another 13 or so--I guess it was 17--that were quantified.

11 There are data there. The question is are these
12 sufficient. I think the assessment from FDA was that these
13 are not a--they leave a lot of room for variability there.
14 But we are really getting into the third question here as to
15 what is the right threshold. Where do we decide enough is
16 enough? Can we borrow from the scientific literature here?

17 But we are looking at the performance of these
18 assays and it really boils down to what the right threshold
19 is. We will appreciate your advice on that.

20 DR. HOLLINGER: I guess that is why I asked the
21 question about where this equivocal zone was in there with
22 the EIUs and so on because--I mean, most of us have looked
23 at patients over a long period of time here and done
24 quantitative assays. We rarely see a patient with HCV RNA
25 concentrations that are below 10,000, 20,000, or so.

1 It is very unusual to find a naive individual, not
2 a treated patient but the naive individual, who is
3 circulating virus at that level. So we make the assumption
4 that all the genotypes are the same. Perhaps, that is the
5 wrong assumption and perhaps some of these anti-HCV-
6 positive, RNA-negative, may, indeed, potentially infect.

7 You could always argue that fact, but I think it
8 is probably less likely and I think that most patients with
9 disease do circulate very high concentrations of virus.
10 What are your thoughts, John?

11 DR. TICEHURST: I am aware with regard to what you
12 were just saying about patients circulating high
13 concentrations. Dr. Fried showed some data. The company
14 provided us with a lot of papers. I had always been at
15 least aware of that notion from other stuff I have read and
16 so forth, that people who are not treated, who are
17 chronically infected, with a couple of years following their
18 acute infection, they tend to reach a set point that does
19 not vary very much over time that is generally high in terms
20 of these infections, generally in the 10^5 to 10^7 range per
21 ml.

22 When I have looked very hard to find what is the
23 frequency of individuals untreated who are less than 10^4 ,
24 that is kind of hard to find. The kinds of data that were
25 presented here earlier today were means. I know, when I

1 have looked for distributions, what I have found are they
2 are not bell-shaped distributions. They do tail off as you
3 go down.

4 One study I found where it did have a distribution
5 was--this was a study of perinatal transmission in The
6 Journal of Infectious Diseases in 1998 from Dave Thomas at
7 Johns Hopkins. There have been 142 samples there and
8 roughly 5 to 10 percent of them were less than 10^4 per ml.

9 That is the only time I have ever seen where that
10 question--I mean, they weren't asking that question in that
11 paper where I could directly answer that question. I think,
12 however, it is probably a pretty valid notion that the
13 number of people who have concentrations of virus where we
14 really start to worry about getting down to that real of the
15 analytical limit of detection is not that pertinent for the
16 indication that is being sought for today.

17 So I think that is a very helpful point in
18 thinking about appropriate thresholds.

19 What comes up as something to consider, perhaps,
20 is if and when a company wants to claim a monitoring
21 indication, and they have already been approved for this
22 type of indication, then that consideration of high
23 sensitivity is extremely important. Would it be, then,
24 appropriate to go back and ask for more rigid verification
25 that this kind of analytical sensitivity can be routinely

1 detected in a clinical setting?

2 It is just something to consider, but I think it
3 is something to consider that if we were to lower the
4 threshold for this kind of indication, and I am not saying
5 we should or shouldn't, would it then be appropriate to
6 reconsider that threshold when we go to a different
7 indication where the clinical parameters, the virological
8 parameters in the clinical setting are different.

9 DR. WILSON: Dr. Specter?

10 DR. SPECTER: John, just to clarify that a little
11 bit further, the thresholds varied some but they were still
12 in the range of about a two- to four-fold variation so that
13 you were still less than a thousand genome equivalents.

14 DR. TICEHURST: Way, less; yes.

15 DR. SPECTER: The question that you raise, then,
16 is what is going to be a clinical threshold that is going to
17 be meaningful. My suspicion is that, if you are below a
18 thousand, and any of these would be detected, that is going
19 to be meaningful decrease that will work well if you look at
20 what is going on with HIV and what is considered to be a
21 threshold level of significance in HIV.

22 We don't know that for HCV yet.

23 DR. TICEHURST: Perhaps it might be appropriate to
24 ask Dr. Fried or Dr. Hollinger or other people on the panel
25 who are practicing clinicians in this area, but my

1 understanding is that, in monitoring people with disease,
2 whether or not on treatment, that it is not the reduction
3 that is important so much as the eradication, so that you
4 are really looking for ultimate sensitivity in that setting.

5 I would be happy if anybody wants to dispute that
6 point.

7 DR. FRIED: I think at the end of treatment, you
8 want eradication. I think we are going to start seeing
9 data, and since you brought up the issue of monitoring, that
10 changes are also going to be important in terms of being a
11 negative predictive value for a sustained response.

12 But getting back to the point that Dr. Ticehurst
13 first had mentioned, I think it is very important to realize
14 that we are dealing with the diagnosis here of untreated
15 patients with hepatitis C so that the likelihood of finding
16 patients at these very, very low levels where genotype-
17 specific differences might make a difference, as I have
18 shown, from some of the papers, it did have ranges ranging
19 from 300,000 to over 2 million.

20 It is pretty small, and I think that is also
21 important to realize.

22 Thanks.

23 DR. TICEHURST: Blaine, if I could go back, you
24 were asking about equivocal before, and I think it was Dr.
25 Thomas that responded to your question earlier today. That

1 is a very tricky issue to analyze, to deal with, because, as
2 they showed you, in the clinical studies, there are very few
3 such results.

4 It is very hard to create experiments where you
5 get those kinds of results. The real issue is when you get
6 an absorbance value out of one of these assays that is
7 somewhat less than the high value that indicates full
8 amplification, what does it mean? Does it mean there is HCV
9 RNA present or not?

10 That is the tough question to answer. The only
11 time we have had any kind of--as I mentioned in one of my
12 slides, most of the studies that have been submitted to us
13 support what Dr. Thomas said, that there were very few
14 results that fall into that sort of range of uncertainty.

15 In a couple of the analytical studies that were
16 done, for reasons that certainly are not clear to us at FDA,
17 there were a lot of such results. I am specifically
18 referring to the studies that were done where subgenomic
19 RNAs were serially diluted and then tested.

20 You see, as you decrease the concentration of HCV
21 RNA input, you see more and more results at lower absorbance
22 values. The same thing happened in another study that was
23 presented to us where matched specimens of serum, EDTA and
24 ACD plasma were serially diluted and then tested in
25 triplicate.

1 As the concentration of HCV RNA declined, we saw
2 the same pattern of more and more results shifting into this
3 zone of uncertainty. So it is at least unclear to us at
4 this point exactly what the meaning is and the proper
5 interpretation of the equivocal zone.

6 I think that, going back to the consideration of
7 the indication for use, however, the data that are presented
8 indicate that the equivocal zone has very little impact on
9 this indication for use because, frequencywise, they are
10 very, very low.

11 DR. WILSON: Any other comments about the
12 Warnings? There was a specific question earlier from the
13 FDA about whether the proposed cautions are adequate and
14 specifically about the issue of distinguishing between acute
15 and chronic states of infection.

16 As was alluded to earlier, it was felt that most
17 of these specimens came from patients with chronic
18 infection. So I would be interested if the panel has any
19 thoughts about that.

20 DR. HOLLINGER: On which one, Mike?

21 DR. WILSON: It would be 1b.

22 Dr. Specter?

23 DR. SPECTER: In terms of the acute, I don't think
24 there is much you can say. It is very hard to identify when
25 somebody become acute with HCV infection. So the real

1 question becomes chronic. You can clearly establish
2 somebody has a chronic infection when you look at it in the
3 context of what was alluded to earlier, if they have had
4 evidence of infection and clinical disease for six months or
5 longer, then we know that it is a chronic infection.

6 So you can establish that at some point in time if
7 some comment is made about looking at clinical and other
8 laboratory parameters in addition to this test. I don't
9 know if that is intuitive or if that needs to be stated,
10 but, clearly, one can establish the use of this in chronic
11 infection if one uses the six-month criterion that we
12 alluded to earlier.

13 I thought, when we had that discussion, that there
14 was a statement made about things being done in the context
15 of other parameters. Maybe John can clarify that for me,
16 but it is my recollection that did come up as part of the
17 discussion.

18 DR. TICEHURST: My recollection of it--we have the
19 transcript but it is not in front of me right now--

20 DR. SPECTER: I am a lot older than you, John.

21 DR. TICEHURST: I don't know about that. The
22 panel very clearly stated that, in the context of clinical
23 studies and evaluating data--not in terms of use, but in the
24 context of evaluating data--that if somebody was going to be
25 said to have--it probably came up more in the discussion of

1 hepatitis B, but it can be extrapolated.

2 If somebody is said to have chronic hepatitis B in
3 the context of a study, that they should be shown to have
4 HBsAg at timepoint 1, and when their study specimen is
5 collected, it has HBsAg and it has to be at least six months
6 later. You could do the same thing with anti-HCV.

7 So it doesn't really apply to how they are used.
8 It is for showing that, if you use them for people that you
9 think have chronic hepatitis C, we know that, when we study
10 them, people, by very strict criteria, have chronic
11 hepatitis C, this is how they perform.

12 DR. WILSON: Dr. Hollinger?

13 DR. HOLLINGER: The other thing, too, you have
14 indicated here on one of your questions about the fact that
15 this is evidence for infection and it is not indicated for
16 the diagnosis of disease. I think that is a good point
17 because that is exactly what it does look for. It finds
18 virus in the blood, but that doesn't necessarily say whether
19 the patient has, really, clinical disease.

20 The other thing, though, about acute and chronic,
21 we have moved a little bit further along than these criteria
22 which were arbitrarily set at six months for C and other
23 things, and that we have biopsies now.

24 Most of the time, we see a patient, they have gone
25 into the blood bank, they have found that they were positive

1 and pretty much you move along very quickly in these
2 patients in their workup, and you end up doing a biopsy
3 fairly quickly. If they have got stage 3 liver disease or
4 cirrhosis or severe fibrosis or something, I think it is
5 pretty clear you have got chronic disease.

6 I, personally, don't need to follow that patient
7 for six months to establish that he has got chronic disease.
8 So I think, at least from my viewpoint, that is a
9 difference.

10 DR. WILSON: Dr. Durack?

11 DR. DURACK: Are we still working on Warnings?

12 DR. WILSON: Yes.

13 DR. DURACK: Just a couple of points about
14 wording. In Bullet Point No. 2, the word "monitoring," I
15 think, is obviously very important because the users will be
16 looking at that and it has economic implications.

17 To some people, monitoring suggests progress of
18 disease. To others, a little more specifically, monitoring
19 of therapeutic response, response to treatment, which may or
20 may not be the same thing. I would suggest, if you agree
21 with it, that we might say, "monitoring progress of disease
22 and/or response to treatment," if that is the intent of the
23 panel, progress of the disease and/or response to treatment.

24 Also, in the last bullet point, "donors." I
25 presume that is meant to cover both blood and organ donors

1 and, if so, does that need to be specified under Warnings?
2 Is it the intent that that covers blood and organ donors?

3 DR. GUTMAN: We will negotiate that language with
4 CBER. I think it does take into account at least tissues.
5 I am not sure how--since organs are regulated by a different
6 agency, I am not sure whether that is accounted for as well,
7 but we will make sure that is appropriately broad.

8 DR. WILSON: Further comments about the Warnings?
9 Dr. Tuazon?

10 DR. TUAZON: Just one question regarding the
11 monitoring of progress of disease. Has it been shown that
12 the viral load correlates with progression of disease? It
13 may not be the right thing to include here, just because I
14 think we don't have any data to show that the viral load
15 correlates with the severity of disease.

16 DR. DURACK: My comment was about performance has
17 not been demonstrated for monitoring of--

18 DR. TUAZON: Okay.

19 DR. WILSON: Dr. Weinstein?

20 DR. WEINSTEIN: I had just one question or
21 possible suggestion with regard to Bullet No. 3 and the
22 bracketed statement. I wondered whether it might be better
23 to delete the last clause of that statement and say,
24 instead, "Although a wide range of HCV genotypes can be
25 detected, analytical sensitivity and other performance

1 characteristics have not been determined for all HCV
2 genotypes."

3 DR. DURACK: Actually, I had the same thought. I
4 wonder if we might add, "Have not been adequately determined
5 for all genotypes."

6 DR. WEINSTEIN: Sure.

7 DR. DURACK: Because there has been some
8 determination. It may not be that it is not adequate for
9 all.

10 DR. WEINSTEIN: Sure.

11 DR. DURACK: And then delete the rest.

12 DR. WEINSTEIN: Yes.

13 DR. SPECTER: My question would be how useful is
14 that if you don't let them know what the genotypes are. Why
15 not indicate that it has been adequately determined and
16 indicate the genotypes for which it has been determined so
17 that you give real guidance as opposed to saying, "Well, you
18 guys figure it out, but it is not good for everything."

19 DR. BARON: Wouldn't that pose a burden on the
20 company to keep updating it as soon as they get more data
21 with new genotype?

22 DR. WILSON: Steve? Which way would you normally
23 go? Would it be an inclusion or an exclusion on the
24 statement?

25 DR. GUTMAN: I am not sure we have a clear

1 precedent. We could go either way. You can specify, I
2 guess, the genotypes that you feel are adequate. I actually
3 think we will come back--the question, you sort of jumped
4 the gun in terms of what is adequate. That really is a very
5 important question to us.

6 You can specify in a positive way and then the
7 company can add additional information through supplements
8 and expand that or choose not to if they decide that is not
9 an important scientific or marketing issue.

10 DR. DURACK: This is a moving target so I think it
11 is good to write it in a way that does not need continual
12 rewriting, if that is possible.

13 DR. GUTMAN: If you specify what is or is not and
14 the genotypes change, or the information about the genotypes
15 changes, then you can't have your cake and eat it, too,
16 here. You have to recommend one path.

17 DR. WILSON: What is the feeling of the panel?
18 Would you rather have a statement of inclusion or exclusion?

19 DR. BARON: Given that if it is missing a genotype
20 that it doesn't detect, you probably won't know anyway
21 because it is the only test you have. I think you would be
22 better to have a more general sort of statement which says
23 that the company appreciates the fact that there are some
24 genotypes, perhaps, that may not be detected and leave the
25 burden to--you know, so that you can put some kind of

1 qualifying language in your results when you send them out
2 to physicians, because some day you are going to get that
3 patient with 12b or whatever it is that it missed, and you
4 can just say, "Well, we told you so."

5 DR. HOLLINGER: How often do manufacturers change
6 their package inserts?

7 DR. GUTMAN: In the context of the kind of
8 submission that you are looking at, it is a bit more
9 challenging in that they have to provide a supplement.
10 Again, the supplements--we have much better turnaround time
11 and there are a variety of tools for dealing with the
12 supplements which, at one extreme, can be actually a real-
13 time interaction depending on data requirements.

14 But the number of times they change, frankly, is
15 very variable and depends on the product line. When they
16 change, you have to realize, they have to redo their
17 labeling. That is a big deal for some companies because
18 they have stuff in storage.

19 So companies do it frequently but not daily or
20 weekly or monthly.

21 DR. HOLLINGER: I would like to see the genotypes
22 listed with, as I said, some notice that there may be other
23 genotypes that have not been--or other genotypes maybe
24 haven't been tested. It doesn't mean you can't detect them.
25 Those kinds of things can be worked out appropriately.

1 DR. SPECTER: I think the big factor is we know
2 that the vast majority of the isolates we see are going to
3 be covered and people are going to be comfortable. If they
4 have got an oddball genotype, then they have got concerns
5 because it is an oddball genotype to begin with.

6 But if you have listed what constitutes 98 percent
7 of the genotypes that are going to be encountered, then
8 people are comfortable and they know, "I can depend on this
9 test." If you say some genotypes are not detected, and you
10 don't indicate which they are, every physician who has got a
11 negative test is saying, "Well, was this that genotype?"
12 They have no clue.

13 DR. HOLLINGER: If they are going to put the
14 genotypes in, I think it would be useful to even say that
15 this represents a fair proportion, or the largest
16 proportion, of the cases of hepatitis C around, anyway.

17 DR. WILSON: Dr. Baron?

18 DR. BARON: Is that true only for the United
19 States? What about hepatitis C in other countries?

20 DR. SPECTER: They have tested fifteen genotypes
21 and that probably constitutes 99.5 percent of what is in the
22 world today. We know this virus is going to mutate so there
23 may be some new ones that come up that it is not going to
24 cover. I don't think that is a serious issue. They have
25 got the field covered now. Why leave people scratching

1 their head?

2 DR. WILSON: It sounds like, then, there is a
3 consensus. We are not taking a vote yet, but there is a
4 consensus to list the genotypes that have been tested and
5 use that with a more generic comment that Dr. Weinstein and
6 Dr. Durack have proposed.

7 DR. DURACK: Just a question. It was my
8 impression that some of those fifteen genotypes, there was
9 only one specimen tested. So it is a question of adequacy
10 of numbers as well as having covered the spectrum.

11 DR. SPECTER: I presume the FDA and the company
12 will work out what is covered.

13 DR. GUTMAN: Actually, the FDA would specifically-
14 -again, we are very concerned about getting the minimum
15 threshold here and so the third question is a very detailed
16 question. We hope to help truncate it, but that question is
17 very much directed at what is the minimum threshold for
18 genotypes.

19 That might be related to the claim in that you
20 might be able to craft a lower threshold of data with a less
21 specific claim. That may not suit the panel or it may or
22 may not suit the company, but I don't want you to start
23 specifying things in this label that would make the company
24 have to do additional work, unless you thought it was really
25 important that you made those specifications and the company

1 did that additional work.

2 So you might want to defer the discussion of what
3 is an appropriate label until we get through Question 3 and
4 then come back and decide, based on your answer to Question
5 3, what choices we ought to offer the company.

6 DR. WILSON: I agree.

7 Are there any further comments about the first
8 question?

9 DR. GUTMAN: I have a question of clarification,
10 just to make sure I am hearing what you are saying. What I
11 gather has been suggested here, because it more parallels
12 what the company's clinician has suggested and what many of
13 you are concurring with, is that the claim not be linked to
14 the requirement for immunoblot assay.

15 The dataset that we have looked at, obviously, is
16 dataset which has immunoassay and immunoblot assay. As John
17 mentioned in his presentation, it would be very easy to
18 analyze the data in both contexts. We already have it with
19 the immunoblot. You could subtract the immunoblot and look
20 at it in the context of the immunoassay.

21 Does that matter to this group? Are you saying,
22 "Gee; it doesn't matter, the fact that it wasn't analyzed
23 this way. We think the claim ought to be reconfigured in
24 the context of the existing data." Or should we sit down
25 with the company and, in fact, go back and revisit the data

1 and reanalyze it so that it matches more closely the altered
2 claim that you suggest?

3 Does anybody follow what I just said?

4 DR. SPECTER: I think, in a lot of ways, you have
5 analyzed the data already because you have those that were
6 ELISA-positive, RIBA-negative or RIBA-indeterminate. So the
7 data are there. You can look at it and see if it is upheld,
8 and I think it is because there were a number of those
9 specimens that were, in fact, HCV-RNA-positive when they
10 were RIBA-negative.

11 So it doesn't take anything away from that.

12 DR. GUTMAN: Okay; thank you.

13 DR. WILSON: There were some questions earlier
14 about specimens collected, plasma specimens, whether there
15 were sufficient numbers. Does anyone think that there
16 should be a warning about use of EDTA or other types of
17 preservatives?

18 DR. HAMMERSCHLAG: I think the numbers of the
19 specimens are relatively small. They can probably state
20 that the data are really insufficient, perhaps, to recommend
21 the use of those specimens.

22 DR. GUTMAN: We are interacting with the company
23 and I do believe they are planning to do larger studies both
24 for precision and for matrices. So I frankly think--if we
25 get into trouble, we will come back to the panel, but we are

1 hoping to negotiate some path with them.

2 DR. WILSON: Any further comments about the first
3 question? If not, then, Dr. Ticehurst, could you put up the
4 second question, please.

5 The second question is; "Based on data submitted
6 to support the proposed indication for use, are the data
7 from patients who were treated with antivirals or who
8 received a liver transplant appropriate for evaluating this
9 diagnostic indication for use?"

10 The second part; "Were clinical data appropriately
11 analyzed?" The third part; "Are data sufficient for
12 determining or approximating specificity in appropriate
13 populations?" The fourth part; "Should any additional
14 instructions be provided to laboratories and primary-care
15 clinicians for interpreting an 'HCV RNA not detected'
16 result?"

17 The last question; "Do the data support the
18 proposed indication," which I think we have already covered,
19 "versus an alternative indication?" They would like us to
20 look at all these parts both for the AMPLICOR and the COBAS.

21 Any comments? That is a lot to digest.

22 Dr. Hollinger?

23 DR. HOLLINGER: Can we be refreshed again about--
24 if I recall, there really wasn't much data on liver-
25 transplant patients, seven or eight. I just don't know the

1 numbers right now. Can somebody refresh us how many
2 transplant patients were actually looked?

3 DR. WEINSTEIN: I think it was 31.

4 DR. HOLLINGER: And also antiviral.

5 DR. WEINSTEIN: I think it was 31 transplant
6 patients.

7 DR. HOLLINGER: And the genotype of those
8 transplant patients?

9 DR. MURRAY: It was 31 transplant patients so it
10 is a small dataset, the transplant dataset. And we didn't
11 genotype those transplant patients unless they were
12 discrepant results with serology. So that is a very small
13 number.

14 DR. HOLLINGER: Personally, I don't think there is
15 probably much difference in looking at them. But if you
16 looked at it just from a numbers standpoint, they really
17 don't have enough numbers to make a claim, I don't think,
18 for transplant patients. I don't know about the antiviral,
19 the patients treated with antivirals. I think that is
20 another issue. Transplant patients, I just don't think
21 there is enough data although I don't doubt that the
22 information would be equally as appropriate.

23 DR. WILSON: Other comments?

24 DR. DURACK: Inasmuch as the numbers are small,
25 you could argue that they should be left out. But, on the

1 other hand, the results are not divergent. The results are
2 quite parallel with the other group. So I think, as a
3 clinician looking at this, it might be of some interest to
4 have the treated group and the transplant group, even though
5 the numbers are small.

6 My suggestion would be if you don't see the
7 results as divergent that they be included, even though they
8 are numerically small.

9 DR. WILSON: Dr. Stewart?

10 DR. STEWART: The indication of use that we just
11 went over did not include that as an indication of use. So
12 I guess the only question is whether you allow the data
13 about the transplant patients to go into the product
14 brochure.

15 DR. GUTMAN: Yes; that is the essence. You have
16 just asked the question.

17 DR. WILSON: Dr. Baron?

18 DR. BARON: I think it is useful to have that
19 information available in the product brochure.

20 DR. WEINSTEIN: Just clarify for me, is there a
21 difference between what is the product brochure as
22 information and a formal indication? I guess I am still a
23 little bit concerned.

24 DR. GUTMAN: There can be. You can have datasets
25 to illuminate things without making specific claims.

1 DR. WEINSTEIN: I think having the information in
2 the package insert would be useful but I am a little bit
3 reluctant to go forward with a formal indication when the n
4 is too small.

5 DR. GUTMAN: That would be an acceptable
6 recommendation.

7 DR. WILSON: Any comments about whether the
8 clinical data were appropriately analyzed? No comment?
9 Does the panel feel that the data were sufficient for
10 determining or approximating specificity in the appropriate
11 populations? I am seeing nodding and shaking. Dr. Baron?

12 DR. BARON: I don't think 31 patients is
13 sufficient to make those kinds of distinctions but I think
14 the information is there for informational purposes. When
15 you train students, you say, "Here is what the company says
16 about this product." But we have already said what the
17 indications for the use of the product are, so I am not sure
18 these questions are important in that context because that
19 is not one of the stated uses that the product is being
20 approved for.

21 MR. REYNOLDS: Everybody keeps commenting that
22 they are not happy with the 31. I agree that is a small
23 number. Anybody have a suggestion as to the minimum number
24 they should have?

25 DR. HOLLINGER: 32?

1 DR. TUAZON: I think we have to remember that
2 those patients are hard to come by, the combination of liver
3 transplant and hepatitis C. So the company can just add on
4 to their database when they accumulate the--

5 MR. REYNOLDS: That is why my question. What is
6 an appropriate number?

7 DR. SPECTER: Just to not specifically answer your
8 comment, Stan, but to make a point about it is that none of
9 here could answer that question, but a statistician could
10 readily answer that question. In determining what the right
11 number is, they take a lot of things into consideration.
12 Only a good statistician can answer that question, and it
13 has a very specific answer based on specific factors.

14 DR. WILSON: Dr. Gutman?

15 DR. GUTMAN: The intellectual force that drives
16 this line of questions, especially in this particular
17 patient population, is our reading, from at least some
18 background literature, there may actually be some
19 quantitative differences in this patient subtype to some
20 either variable extent might be appropriate to recognize.

21 That is why the question is on the table. It is
22 not necessarily just the small size of the numbers. It
23 actually has to deal with concern about the biological
24 profile of the subset.

25 DR. HOLLINGER: Is that question that is answered

1 c) here, I interpret that as being a question for the whole
2 group, not just the transplant patients.

3 DR. GUTMAN: I think you honed in on our favorite,
4 which is a), but you are correct.

5 DR. HOLLINGER: I always look at that as, "Data
6 sufficient for determining approximate specificity in an
7 appropriate population, the clinical population," and other
8 things; is that right, John? Or are you really limiting
9 that to the antivirals and the transplant?

10 DR. TICEHURST: I apologize. It seems that we are
11 mixing two questions here. I thought there was some
12 discussion going back to subquestion a) here. It has been
13 our perception, at least our understanding of the scientific
14 literature, that people who have been treated with
15 antivirals and go back to being viremic again tend to go
16 back to a setpoint very much like that before treatment, so
17 that they very well might be representative, in a virologic
18 way, of the kinds of people who are presenting for diagnosis
19 even though they are not presenting for diagnosis, they
20 already have a diagnosis.

21 In contrast, people who have received a liver
22 transplant, almost all of them who become reinfected again,
23 tend to go to a higher setpoint so that the range of viral
24 concentrations of them might not be representative of the
25 types of people who would be indicated for using this assay

1 and, therefore, they might not be an appropriate subgroup to
2 include in the analysis.

3 I apologize if we are off your discussion of
4 subquestion c).

5 DR. HOLLINGER: On the other hand, John, and I
6 agree with you, I think it does go to a higher level because
7 of our immunosuppression. If this is just a test for
8 diagnosis, not for quantitation, then it should detect all
9 of them. Therefore, if the idea is did this patient get
10 reinfected, then it should not pose a problem.

11 DR. TICEHURST: But the indications for people who
12 were getting an antibody test first, now, you can say, well,
13 they did have one at some point in time. But, in terms of
14 the immediate time of testing, they will not be getting an
15 antibody test first. So this assay result is standing on
16 its own.

17 Again, the question is, in terms of the
18 indications proposed, which is after antibody testing, if,
19 in fact, they do have a distribution that is a higher level,
20 are they going to be likely to bias in terms of not
21 capturing false negatives because they tend to be at a
22 higher concentration. That is why the question is there.

23 DR. WILSON: Outside of patients who have had a
24 transplantation, is there any comment about whether the data
25 are sufficient for determining specificity?

1 Okay; subpart d); "Should any additional
2 instructions be provided to laboratories and primary-care
3 clinicians for interpreting a result of 'HCV RNA not
4 detected?'"

5 DR. SMITH: Should the heparin issue be brought up
6 here since dialysis patients are--a primary-care clinician
7 taking care of someone in dialysis may not be aware of that
8 and they probably should know.

9 DR. WILSON: Dr. Tuazon?

10 DR. TUAZON: Is this question after you are EIA-
11 positive and HCV-RNA-negative? Is that what this is?

12 DR. WILSON: Presumably; yes.

13 DR. TUAZON: So then you have to have the caveat
14 that the RIBA should be done in patients who are blood
15 donors.

16 DR. WILSON: The product is not intended for use
17 in blood donors.

18 DR. GUTMAN: There will be explicit language
19 indicating it is not for use in blood screening programs.

20 DR. TUAZON: But you are warning laboratories and
21 primary-care clinicians who have this as HCV-RNA-negative.

22 DR. HAMMERSCHLAG: I think you may need something
23 like an algorithm. For instance, if the patient, assuming
24 that everybody is going to have a antibody test, the EIA
25 done first, and then that the HCV is negative, it could be

1 negative because it is truly negative, not there, or it
2 could have been a false positive EIA. Therefore, the next
3 step down the line, do the RIBA. And then start listing
4 other reasons that can give you negatives, which would be
5 inhibitors, heparin, a genotype we don't know about that
6 isn't picked up, recommend further testing.

7 There is a way of dealing with this.

8 DR. WILSON: Dr. Specter.

9 DR. SPECTER: My question would be, we have talked
10 about heparin and we have talked about dialysis patients.
11 What I have not heard is that the problem with dialysis
12 patients is is it definitely due to heparin and are these
13 two separate issues and should they both be included
14 separately, which I think they should.

15 DR. WILSON: Dr. Ticehurst, could you give us any
16 more information about the dialysis patients? Do you have
17 that or would the manufacturer have that?

18 DR. MURRAY: We don't have any data in dialysis
19 patients. I am not sure of any studies that have been done
20 specifically in that group of patients. Karen, yours is
21 anecdotal data from a couple of phone calls with customers
22 and I think, John, yours was anecdotal data as well from
23 discussions with the lab personnel.

24 So I think essentially we don't have any strong
25 data on which to hold a discussion.

1 DR. TICEHURST: I guess I might ask the question,
2 again, of people who would be involved in this clinically,
3 how much is that going to apply to a diagnostic indication
4 as opposed to a monitoring indication? Certainly, there
5 probably are going to be people who are going to realize
6 that they are infected while they are on dialysis, but that
7 might be something to consider.

8 DR. WILSON: But, Steve, please clarify. We can't
9 ask the company to introduce data into the insert when there
10 are no data.

11 DR. GUTMAN: No, no. I think what you are
12 discussing here is whether there are appropriate labeling
13 caveats of if there is uncertainty, that might have an
14 impact, how strong or you can make the recommendation we put
15 that labeling in and we can work with the company to make
16 sure there are appropriate limitations or warning that there
17 is this potential.

18 I am not sure, since the scope of the potential
19 isn't well-defined, I don't how strong you want to actually
20 make that language. If you thought it was an interesting
21 enough phenomenon, we could try and do some kind of
22 postmarket surveillance to see if it is a problem.

23 DR. WILSON: The data on the heparin are clear,
24 but the dialysis--I think that would be burden on the
25 company to do at this point.

1 DR. GUTMAN: I think we could deal with that in
2 some statement indicating limitations or questions.

3 DR. BARON: I haven't read a ton of product
4 inserts with this thought in mind, but I don't remember
5 seeing a lot of algorithms in product inserts as to what
6 test to do next. So I sort of tend to think would should
7 not put in there an algorithm that includes a RIBA because I
8 think that is up to the physician what sort of test a
9 physician wants to use to help resolve a problem.

10 I think you would put in something about potential
11 reasons for false negatives, but I wouldn't give them--

12 DR. HAMMERSCHLAG: There is not really much of a
13 choice as far as the tests that we have now. If you are
14 going to have a discrepant that way, there are only certain
15 ways it could be resolved. It is a suggestion and it may
16 not--I was just saying, in the list, you would have to say
17 that it might represent that this is truly negative and it
18 is a false-positive ELISA. And then you have to go ahead
19 and resolve it. One way to do that is with the RIBA.

20 But I think it should be in there somewhere. It
21 is not like there are a panoply of other serologic tests to
22 be used.

23 DR. HOLLINGER: I agree. No physician is going to
24 read these package inserts anyway. But they are going to
25 call the laboratory. Hopefully, the lab will read them.

1 That is where it is really helpful, for somebody in the
2 laboratory to read these. They should read these package
3 inserts. This, at least, helps them to provide a service
4 somewhat to the laboratory.

5 I agree. I think, some way or other, there might
6 be some benefit to having that information, if we know it.
7 Right now, we just don't know where that is an issue.

8 DR. GUTMAN: We would be happy to do that. I can
9 assure you, whether they are read or not, we review them as
10 though they are going to be.

11 DR. HAMMERSCHLAG: Sometimes, with some labs, they
12 do give you, at least some of the commercial labs, a
13 printout saying that this is an interpretation of what the
14 test means often with the suggestion of what to do next,
15 which may be right or wrong under certain circumstances.
16 But the information should be there.

17 DR. WILSON: Dr. Specter?

18 DR. SPECTER: The question that came up before
19 about HCV RNA undetected was that you don't want to take a
20 sample like that and dilute it to try and get rid of an
21 inhibitor. You want to take a new sample. I guess my
22 question really is should there be some kind of statement
23 there about not diluting specimens to try and get rid of
24 inhibitors as opposed to collecting a new specimen.

25 DR. WILSON: Any other comments?

1 DR. BARON: It seems like a good idea.

2 DR. HAMMERSCHLAG: I have got one question. I
3 know that sometimes in running PCR you can get sort like a
4 pro-zone if you have a lot of DNA. Sometimes you run it 1
5 to 10. Does this apply to RT PCR as well?

6 DR. GUTEKUNST: We haven't seen any evidence of
7 that with these tests. And I am not aware of any in the
8 literature with other RTC PCR tests for HCV either.

9 DR. WILSON: Any further comments? Subsection e),
10 we have already dealt with in Question 1, basically. Part
11 f), the question is are there any specific differences
12 between the AMPLICOR and AMPLICOR COBAS that the panel would
13 like to highlight or are we just treating these as the same?

14 DR. SPECTER: Treating them the same.

15 DR. WILSON: Any further comments on Question No.
16 2? John, if you could put up the third question, please.
17 If we could get you to come back up to the podium. These
18 are fairly long questions. Rather than trying to read all
19 of it and go through every one of the points, if you could
20 summarize for us what are the main points that you would
21 like to get from the panel on this question.

22 DR. TICEHURST: Let's consider the sort of three
23 parts to the question. There has already been some
24 discussion that alluded to some of these three parts. The
25 first one kind of addresses some of the things in a similar

1 vein to what you were just talking about with regard to a
2 negative result or a positive result, what kinds of
3 interpretation should be provided in the package insert that
4 will help laboratories.

5 This first part a) about proposed warnings and
6 limitations, obviously it has to apply, in terms of the
7 data, if it were to be approved, with the data that have
8 been submitted thus far, specifically, with regard to the
9 data that have been provided for genotypes. Again, I think
10 you have had some discussion.

11 The second part, are certain approaches
12 appropriate for all studies to support the claim, and the
13 third part about additional studies that should be done, are
14 interrelated. It goes back to a point that I think Dr.
15 Gutman made earlier that I tried to make in the talk that I
16 gave this morning.

17 This is an evolving area. It is a tough area. It
18 is an area, for those people who don't have to do the work--
19 it is very easy to be rigorous and say, you have got all
20 these different subviruses, some of which may be really
21 different viruses, but that may be detected by this assay,
22 what do you need to do to show with reasonable assurance of
23 safety and effectiveness what it does--not necessarily that
24 it does, but what it does.

25 So the b) focuses in on a point of should there be

1 some baseline when a company wants to go through what it
2 does that, if all the studies that are done in the realm of
3 what it does start from a baseline of certain types of
4 studies that are done, certain principles, is that a good
5 idea? Does it provide some assurance that at least you are
6 starting from that threshold.

7 What c) talks about is whether or not you have
8 such a baseline. Given the data that have been submitted,
9 and you think about the different kinds of studies that can
10 be done, the categories of clinical studies, reproducibility
11 studies, analytical studies, there is a whole range, in
12 terms of the rigor, that could be applied to each one of
13 those areas.

14 In terms of helping us decide what is the right
15 threshold to use here, where should we put the emphasis? Is
16 this not an important area at all that we don't need to put
17 much emphasis on rigor, that we can put a lot of faith in
18 things like looking at database searches that show that the
19 primers match up across the all the databases of HCV
20 sequences, then, going from that to the point of--to another
21 extreme of characterizing, to the nth degree, every specimen
22 in a clinical study and having another assay that shows the
23 ones that were not detected and characterizing those, too.

24 There is a wide range of what can be done here.
25 Is it important to put more emphasis on reproducibility, for

1 example, or more emphasis on dilutional studies like those
2 that were done, or more emphasis on clinical studies? The
3 point of having all those different choices in each of those
4 subquestions is to give you an idea of the range of the ways
5 that could be gone.

6 Does that help?

7 DR. WILSON: I agree that, on part a), we have
8 largely covered that in questions 1 and 2. In part b), are
9 certain approaches appropriate for all studies to support
10 the claim? I think the FDA is looking for help in this area
11 because, as has mentioned earlier, this is the first product
12 coming for this type of approval and we are dealing with an
13 organism that we can't see, we can't grow.

14 The question, then, is what are sufficient data
15 for the manufacturers to be able to make their claim, also
16 keeping in mind using the least burdensome approach.

17 I would like to hear comments on that from anyone
18 on the panel. Dr. Hollinger?

19 DR. HOLLINGER: I guess I am really happy with the
20 subtype data, the way it is presented here. I always figure
21 that the marketplace is going to--if there is a real problem
22 coming out here either with new assays coming in or so on,
23 if there is a problem, this is going to be picked up, just
24 like the initial genotype 2s and 3s were soon recognized
25 that the earlier tests were not detecting those.

1 Since this is a diagnostic test to just detect yes
2 or no in here, I haven't seen anything that makes me
3 uncomfortable that this assay is not going to pick up, if
4 not everything, certainly the vast majority of them. There
5 would be only a few things that would slip through.

6 So, from that standpoint, the burdens are the same
7 and so on. I don't have a problem with that, myself.

8 DR. WILSON: Dr. Specter?

9 DR. SPECTER: I would agree with that and I would
10 say we have really addressed it in talking about making a
11 statement about some genotypes may not be picked up.

12 DR. WILSON: How about for future submissions? Is
13 there anything that you would like to see?

14 DR. BARON: I think the FDA has suggested that,
15 perhaps, genotyping be performed using a single approach. I
16 would agree that at least the same area of the gene be
17 sequenced for that indication as opposed to one group
18 looking at an untranslated region, somebody else looking at
19 a translated region. I don't have great confidence that you
20 are always going to have the same answer.

21 DR. WILSON: Dr. Weinstein?

22 DR. WEINSTEIN: I actually had sort of a corollary
23 question which is what is the degree of agreement that
24 occurs if you are using different methods to determine
25 subtypes? In other words, I don't have a clue. So I don't

1 know whether you need to do it all one way.

2 John, I am asking you and the other virologists.

3 DR. TICEHURST: I am going to have a hard time
4 giving you a quantitative answer to that. I will give you a
5 qualitative answer that is based part on literature reading,
6 it is based part on the research group that I am involved
7 in, and it is based part on what I have heard.

8 That is that, in general, there are a number of
9 different technological approaches. A lot of sources will
10 say that sequencing a coding region and then doing
11 phylogenic analysis of that is the sort of gold standard. I
12 actually have posed it to a number of colleagues, this
13 question to a number of colleagues last week, and they said,
14 "Yeah; that's fine. But sequencing is very insensitive for
15 mixed infections so you probably need to accompany that with
16 one of the other technologies that is more sensitive for a
17 mixed infection."

18 So I said, "So we are going to ask all
19 manufacturers to do sequencing and another approach?" And
20 that got a big chuckle from everybody.

21 The other approaches provide less detailed
22 information. For example, one that is used widely is a non-
23 approved assay called line-probe. Basically, what it is is
24 reversed hybridization so that you amplify a region. I
25 think, in some of them, they actually may use the same

1 AMPLICOR or one very similar to it and then hybridize that
2 to a probe that is immobilized in a solid state, that are
3 nucleic acid, that, by design, should have enough sequence
4 that allow you to call based on what the AMPLICOR hybridizes
5 to. You can call the subtype from that.

6 My understanding is that there is quite a bit of
7 concordance between these different approaches. There are a
8 lot of in-house assays with restriction fragment-length
9 polymorphism, and that kind of thing. But everything but
10 sequencing tends to have problems when you go to subtyping.
11 That is where you get the inaccuracy.

12 But there is imperfect concordance about
13 sequencing, although it is thought, in general, that, in a
14 sense, sequencing 5-prime noncoding region is less
15 sensitive. Because it is more conserved region, which makes
16 it valuable for this kind of assay, you are going to tend
17 not to see the differences that you would see in the coding
18 region as much. So that is why, again, this concept that
19 sequencing the coding region, and some places will do
20 CoreE1, some will do NS5, and so forth, is the gold
21 standard.

22 DR. WILSON: Dr. Stewart?

23 DR. STEWART: I don't think our indication is here
24 to say that 1 or 2a, b, c, d are all--the thing is every one
25 of these tests, no matter what it is, is showing this is a

1 genotypic different isolate. So I think that makes no
2 reason that they all have to be tested by the same test.

3 They are showing they are different from 1 and
4 still being detected. I think that is the point of what the
5 tests were done, to show that these different ones, whether
6 this person says 2a and this says 2a is the same thing or
7 not, that is really not the question that is before us.

8 DR. WILSON: Other comments from the panel?

9 DR. BARON: I am just thinking in terms of the
10 future. If you are going to make specific claims for
11 specific genotypes, my most experience is with HIV. You
12 will find new ones that were not there before. So I think
13 if you are going to be comparing genotypes and genotypes
14 that, if you want to make claims in that way, that you
15 probably should do the confirmatory test in the same way
16 because, otherwise, you will find discrepancies in the
17 future and then how do you resolve them?

18 I don't think it is important for the indication,
19 at all, but it is important for your question.

20 DR. GUTMAN: But it would shape--now is the time
21 to go back to the Intended Use, that section on the Intended
22 Use because it seems to me that what I am hearing you say is
23 that you are perfectly comfortable with the status to
24 support a more general specific use but perhaps not to
25 support a genotype-specific discussion.

1 Am I mishearing you?

2 DR. WILSON: One of the subparts to this question
3 is can a particular subtype be used to represent all HCVs or
4 should certain subtypes be represented in all such studies--
5 that is, should there be reference strain that can be used?
6 Anyone have any comments on that?

7 Dr. Specter?

8 DR. SPECTER: I guess the real issue is not what
9 groups or subtypes are involved but whether isolate is there
10 contains the probe region. Who cares what genotype it gets
11 called. If it contains the probe region which seems to be
12 highly conserved, it is going to be detected. If it
13 doesn't, it is not going to be detected.

14 I don't know that we are ever going to ascertain
15 that. Clearly, if you use a singular method which is in a
16 region away from the probe region, it is not going to tell
17 you anything about whether this is going to be detected or
18 not by this test, no matter what genotype you call it,
19 unless you find a genotype that always lack this region.

20 But I think that is a long time coming and when
21 you get to other genotypes thirty years from now, maybe some
22 will and some won't and then it will be a different issue.

23 But in the current view that we have of HCV, this
24 region is totally unrelated to the region that is being used
25 for genotyping and, therefore, information about genotyping

1 tells you nothing about this test.

2 DR. WILSON: Other comments? Any further comments
3 about Question No. 3? Dr. Ticehurst, is there anything in
4 there that you would like us to cover before we move on?

5 DR. TICEHURST: I think we would really appreciate
6 some input on b(i). Are there any methods that--well, you
7 have to answer the first part of b(ii) to get to the second
8 part about quantifying about, having PCR-independent methods
9 and if there are any other methods that might be
10 recommended.

11 DR. WILSON: So you are looking for a confirmatory
12 method other than PCR; is that how we interpret that?

13 DR. TICEHURST: Yes. Again, this is another
14 technologically difficult area. UV spectroscopy is not
15 applicable here. There are some other chemical approaches
16 that can be applied but I don't think they are practical
17 here. We are fishing here, asking from experience either
18 with HCV or with other nucleic acid systems, that there are
19 other methods that could be used to give an independent
20 number.

21 We are heavily reliant in evaluating these
22 submissions on data that come from an unapproved assay.

23 DR. WILSON: Anyone have any comments on that?
24 Any further comments on the third question?

25 If not, could we put the fourth question up,

1 please. The fourth question states; "With regard to
2 standard reference materials, how should quantitative data
3 such as limits of detection for analytical sensitivity be
4 expressed with reference to the World Health Organization
5 Genotype 1 Standard when samples do not contain this
6 Standard?"

7 Dr. Specter?

8 DR. SPECTER: One could simply say you could do it
9 in genome equivalents. But it seems to me we have a fairly
10 good idea of what genome equivalents translate to in terms
11 of international units. Now, Dr. Ticehurst made the point
12 that this may not hold up for every genotype, but I am not
13 sure if there is any other data out there that, although it
14 has not officially be reported, I don't know if it is known
15 or not. If somebody has some insight, I would like to hear
16 if other genotypes hold up to have similar equivalents.

17 If you put it in genome equivalents, there is no
18 misunderstanding about what that is.

19 DR. WILSON: Other comments? Does anyone from the
20 manufacturer know the answer to that question?

21 DR. GUTEKUNST: I think the answer to that
22 question is not known at this time. I know that the NIBSC
23 is working to prepare a panel of genotype specimens that
24 will be characterized in reference to the WHO Standard. So
25 we are close. But I don't think we are quite there yet.

1 DR. SPECTER: I guess the question I would ask is
2 you used international units. I presume you base that on
3 numbers of genome equivalents to come up with international
4 units when you just use the other genotypes.

5 DR. GUTEKUNST: The way we have sort of calibrated
6 our quantitative PCR test to international units is to
7 actually use the WHO Standard as a reference standard and
8 then to calibrate our quantitation standard in reference to
9 that material so that we generate international units that
10 correlate with the WHO Standard.

11 DR. SPECTER: Right. But that is based on the
12 number of genome equivalents for each genotype.

13 DR. GUTEKUNST: That's correct.

14 DR. SPECTER: So you could use that because you
15 have that information.

16 DR. GUTEKUNST: When that information is
17 available.

18 DR. SPECTER: No. I mean, you know the actual
19 genome equivalents. You just don't know if they are
20 international units or not because you are just basing on
21 Type 1 using the same formula.

22 DR. GUTEKUNST: Yes; that's correct, assuming that
23 the other method that was used to quantitate those specimens
24 is genotype-independent, which we believe it is.

25 DR. WILSON: Dr. Hollinger?

1 DR. HOLLINGER: I was just looking at what the
2 Saldanha article about--I had forgotten what it said about
3 genomic equivalents. I know it reported that this is the
4 standard they are talking about here. Does anyone recall if
5 they had that based on the genomic equivalents also?

6 DR. WILSON: Dr. Ticehurst?

7 DR. TICEHURST: Anybody can correct me if I am
8 wrong. I have reviewed that paper several times in the past
9 few days. The context of that paper was basically it
10 described the studies that were done, and I think, actually,
11 Karen Gutekunst summarized some of them this morning, the
12 studies that were done and how they arrived at a definition
13 of an international unit and how they picked a certain
14 specimen which was something they had in large quantity that
15 could be in international standard.

16 They had 22 different laboratories. They had a
17 number of different methods that were used. Some of them
18 were strictly qualitative. Some of them were quantitative.
19 Some of them were in-house methods. I am pretty sure that
20 the only commercial-based methods that were used there were
21 Roche methods, either qualitative or quantitative, and a
22 couple of laboratories used TMA, which probably means they
23 were GenProbe methods.

24 The way that the relationship was made to some
25 other quantifier was twofold. The quantitative methods

1 diluted out to an endpoint and so there was a sort of
2 number-by-endpoint titration. That was that figure I showed
3 you earlier of 1.8 PCR copies. That was the endpoint
4 titration.

5 The quantitative methods, which, without dilution,
6 gave a number, had a mean of I think it was 6.6 whatever
7 per International Unit. So there is a slight discrepancy
8 between those two numbers. But that is basically what the
9 paper said.

10 DR. HOLLINGER: John, in the paper, it just says
11 the standard was made from a sample that was apparently, it
12 said, contained 10^5 genome equivalents per ml. But they
13 never do say how that was determined. I am sure that
14 somebody knows about that, but it was never in the paper.

15 DR. TICEHURST: It was determined, as I told you--
16 these are the data that--the thing in the abstract, that
17 10^5 , that is an approximate figure and that is why they
18 decided to make it 10^5 International Units per ml.

19 But the summary of the data are actually shown
20 here. Sample AA became the international standard, so
21 forget BB and CC. The endpoint mean shown there was the
22 mean of all the laboratories. But they ended up doing
23 another calculation where they tossed out two or three of
24 the laboratories that gave vastly different endpoints, and
25 that mean, I think, was, like, 5.2 or so.

1 That is where the 1.8 copies per International
2 Unit came from. The next line there, quantitative, is the
3 mean of all the quantitative assays that were done. Again,
4 most of them were Roche COBAS monitor. There were some in-
5 house assays.

6 If you take that figure and compared it to 10^5 ,
7 you would come up with 6.6 copies per International Unit.

8 Does that answer your question?

9 DR. HOLLINGER: It is all right to have an
10 international standard. I think this is good because if you
11 have one, then everybody can make a comparison against that
12 international standard, particularly one that is done by a
13 variety of tests, not just a single test.

14 The question is, if you are going to use this in
15 the package insert, again, from my standpoint, I don't mind
16 if this gives a lower limit of detection of certain
17 international units per ml as long as it states, in this
18 case "based on the WHO genotype 1 standard." And then you
19 could put a parenthesis, 77-970, which stipulates what it
20 is.

21 I think that is okay. We did that with albumin.
22 Many times, when you are looking at other proteins, albumin
23 was used a standard even though it is not the protein you
24 were looking for. We do this all the time when we were
25 trying to determine concentration of HBsAg. So this is just

1 another standard that can be used and then come to a
2 conclusion here that this is what we are making comparisons
3 with.

4 DR. WILSON: The second part of Question 4. It
5 says; "Other than the World Health Organization Genotype 1
6 Standard, are there other reference materials from different
7 organizations that the panel recommends for analytical
8 studies--for example, NIBSC genotype 3--and what are the
9 strengths and limitations of such materials when they have
10 not been accepted by international consensus?"

11 Does anyone have any recommendations? Comments?
12 Dr. Gutman and Dr. Ticehurst, is there any information
13 within the four questions that we have not covered that you
14 would like us to discuss?

15 DR. GUTMAN: There are no other questions, but I
16 may have inadvertently truncated a part of the discussion.
17 Actually, when Maggie raised a precision issue, I was
18 focused on the fact that we are planning to work with the
19 company to expand the analytical precision--not the
20 precision; the matrixes. And we are planning to work with
21 the company to expand the analytical foundation of the
22 assay.

23 I wasn't focused on the clinical studies, per se.
24 If you have a particular concern about the matrix, at least
25 in the clinical studies, I may have inadvertently cut off

1 some interest in discussion there.

2 DR. HAMMERSCHLAG: I really thought it was a
3 question, again, of specifying what is the appropriate
4 specimen, whether it is going to be coagulated serum or
5 plasma. At this point, I think we have more information on
6 serum than we do on plasma. So I would have to state that
7 is a preferable specimen.

8 It never hurts to be as explicit as possible
9 because--and then many problems with other assay, with other
10 companies, where things are omitted and they figure, by
11 exclusion, that it would be implied that you are not
12 supposed to do something. I think you need to be explicit
13 and say what does work and what we have insufficient
14 information to recommend at this point, not leave it up to
15 that if it isn't mentioned, it means you shouldn't do it.

16 DR. GUTMAN: The expectation was, and again I
17 guess it is to be seen, that there be an expanded analytical
18 dataset on which the claim could be carried over to the
19 other matrices. It was our belief, at least analytically,
20 they weren't there yet. We had not focused on the need for
21 additional clinical studies. We were really talking to them
22 about additional analytical studies in the matrices.

23 DR. HOLLINGER: Can I ask just anyone from the
24 company--I was surprised to see that there was no
25 differences between serum plasma and EDTA because it is so

1 different from what we have seen with HIV and even what has
2 been reported for HCV. When you use serum--I mean, it
3 looked like it was about 50 percent, often as much as
4 50 percent decrease in the concentration of the RNA from
5 when you compare serum with EDTA.

6 For HIV, I know, the ACTG and others have pretty
7 much settled on the fact that all of the studies are going
8 to be used--are being used--with EDTA plasma and not with
9 serum for that very reason. So I was really very much
10 surprised to see that there didn't seem to be, at least in
11 this data here, very much difference between serum and
12 plasma.

13 MR. THOMAS: You are making a comparison, then,
14 between a quantitative assay and a qualitative assay. In
15 this case, rather than trying to calibrate the
16 quantification, we are deliberately oversampling. So, for
17 that reason, perhaps, it is not surprising.

18 But if you are satisfied with the confidence
19 limits of the point estimates, then, apparently, there is no
20 difference. As I say, for that technological reason, it is
21 probably not surprising that these differences, if they
22 exist, don't show up.

23 DR. HOLLINGER: I am just thinking that, in the
24 future, obviously, you are going to move toward
25 quantitation. To avoid confusion, and so on, if there is a