1 think it should be done.

2 The issue of time raises its head as well. A

3 significant number of patients, it seems to me, from my own

4 looking in the literature, do not get resected, for good and

5 proper reasons. How do we know how safe this is over time?

6 Because lots of studies are being done off-label, we don't

7 get reports in the scientific literature; we get the reports

8 that describe the presurgical case.

9 So if we want to sort of investigate whether this

10 long-term occupation in tissue of this device is safe, I

11 think we should test for that, and I think it can be done.

12 There are experimental protocols like you are doing to

13 answer this question for longer periods of time, again, with

14 a range--maybe 100 percent in one case, 30 percent in the

15 other, of n-BCA--to make a reasonable assessment of the

16 safety and toxicity away from the, let us say, major use,

17 but testable limits that you know will be used by

18 clinicians.

19 So I think that some of the in vitro testing and

20 preclinical testing misses those opportunities, which I

21 think we should have.

22 So I think that we should be thinking about acute

23 biocompatibility testing with different formulations, and I

24 think we should be thinking about chronic testing on

25 formulations, different from what you are now doing and

1 different from the individual components. So I guess I am
2 underscoring the recommendation of the FDA to use a mixture
3 of the oil, the tantalum, and the glue, at wider ranges than
4 the FDA suggests, and for longer periods of time than the
5 FDA suggests. I don't think it is draconian, but I think
6 they are achievable goals, and there is no information like
7 that out there, and you have a model that could test it.
8 So as I look at the safety and toxicity issues
9 from the nonclinical perspective--I am not benefitting from
10 using this, as lots of folks do--but I see what happens when
11 you put this product in the hands of every clinician who
12 wants it, and we deserve to answer these kinds of questions
13 because you can.
14 What about the limits of the formulation's safety
15 and toxicity? And that actually relates to all the types of
16 testing that you are doing--the short-term and the long-
17 term. I think we can get the evidence, and I think we
18 should get it. I don't know what the outcome will be. We
19 can make some predictions, but I am not in the prediction
20 business.
21 So in conclusion, I think the preclinical testing
22 as you have done, and actually some of the experience
23 reported in the literature, is good as far as it goes. I
24 think it should be widened and deepened to include the
25 ranges of formulations and longer time. Seeing that, I

1 think, would assuage some concerns I have about the actual
2 clinical practice being different from what you are testing.
3 That's all I have to say, and I'll answer any
4 questions.
5 DR. WALKER: Thank you, Dr. MacLaughlin, for a
6 very thorough review.
7 Does any Panel member have questions for Dr.
8 MacLaughlin?
9 Sally?
10 MS. MAHER: I don't have a question, but I
11 actually have a comment. My comment goes toward Dr.
12 MacLaughlin's suggestion that the sponsor, while they are
13 labeling the product for a short-term preoperative use, is
14 under an obligatio to test this as a long-term implant. I
15 think that we as a Panel need to be careful at looking at
16 what the sponsor intends the device to be used for with how
17 the surgeons may sometimes use it, without putting an extra
18 burden on companies that cannot predict how they will always
19 be used and what's going on.
20 Maybe one of the issues needs to be making the
21 labeling stronger about the need to take the material out as
22 opposed to doing the long-term testing. It's just a
23 thought.
24 DR. MacLAUGHLIN: Yes, that's a very good thought.
25 I am being very practical here, because I look at what

1 reality looks like, and I look at the possibility of
2 achieving that answer.
3 In my opinion, if this were a really abstract
4 issue without a reasonable experimental model, it might be
5 really moot, wouldn't it, because you have a specified use
6 for the material, and that's it; you are not allowed, so to
7 speak, to use it above and beyond that. But I think
8 practice tells us that that is really true. We already know
9 people are using it for longer periods of time, an d we
10 already know people are using material that as one
11 component, just the n-BCA.
12 So I think that's my perspective of saying it
13 isn't, I don't think, unreasonable to address that, because
14 I think someone should, and this is an opportunity, because
15 the product would be approved for that use.
16 MS. MAHER: No--the product will be approved for a
17 short-term preoperative use; it would not be approved for a
18 long-term use. And yet, by having the sponsor obligated--
19 and again, I am not saying that they necessarily should or
20 should not do it, but obligated to do it--you are actually
21 forcing them to say that maybe this is okay when in fact
22 there may be other reasons why it is not okay as well
23 besides just the biocompatibility.
24 So I just think we should take that into
25 consideration.

1 DR. MacLAUGHLIN: You are correct, you are
2 correct. It also says, I think, in the package insert that
3 long-term testing hasn't been done. There is no data on
4 that.
5 MS. MAHER: Stronger labeling could also be
6 developed.
7 DR. MacLAUGHLIN: Certainly.
8 DR. WALKER: Are there any other questions for Dr.
9 MacLaughlin?
10 [No response.]
11 DR. WALKER: There being none, let me suggest that
12 we break for one hour. It is 11:45; let's come back at
13 12:45 promptly, at which time Dr. Hurst will continue with
14 the Panel presentations, and then Dr. Gatsonis.
15 We'll see you in an hour, and Dr. Canady and Dr.
16 Gatsonis, we'll call you back in about an hour.
17 DR. CANADY: Thank you very much.
18 DR. GATSONIS: Thank you.
19 DR. WALKER: Thank you.
20 [Whereupon, at 11:45 p.m., the proceedings were
21 recessed, to reconvene at 12:50 p.m. this same day.]

1 AFTERNOON SESSION

2 [12:50 p.m.]

3 DR. WALKER: Ladies and gentlemen, it is 12:50. I
4 think we should get started with the meeting.

5 This is the portion where the three reviewers from
6 the Panel give their perspectives on preclinical to clinical
7 and statistical evaluation. We heard from Dr. MacLaughlin
8 this morning on the preclinical evaluation; and Dr. Robert
9 Hurst will provide the clinician's perspective; and then
10 we'll hear from Dr. Gatsonis.

11 Dr. Hurst?

12 DR. HURST: Thanks very much.

13 I am going to be really low-tech and put out some
14 handouts. I have about 15 copies or so. We have 20 for the
15 Panel members, and we can pass the remainder out in the
16 audience as well. They will pretty much summarize what I
17 going to say.

18 I have been asked to clinically review the PMA
19 concerning the cyanoacrylate device for presurgical
20 embolization. Whenever we review treatment options for
21 brain AVMs, we have to keep in mind some very important
22 clinical perspectives. Some of these have been emphasized
23 in Dr. Hudson's memo at the beginning of the pack handed out
24 for the Panel members in which he indicates that this
25 history of this PMA has a number of interesting aspects.

1 First of all, this PMA was initiated in early
2 1996, and nearly 2 years later, in December of 1997, the
3 company decided to terminate the study because of slow
4 enrollment.
5 DR. GATSONIS: Speak up a bit, please.
6 DR. HURST: Absolutely, yes.
7 It may seem surprising that 13 of the largest U.S.
8 centers for AVM management, including several of the largest
9 centers in the world for AVM management, were unable to
10 rapidly collect large numbers of randomizable patients. But
11 in fact, this difficulty serves to remind us a little bit
12 about the disease of AVM.
13 First, there is no animal model for brain AVM, so
14 that virtually all treatment modalities have to be evaluated
15 in human subjects.
16 Second, brain AVMs are a rare type of
17 cerebrovascular disease. Less than 2,400 new brain AVMs are
18 diagnosed in the U.S. every year, and of these patients,
19 many of them are not surgical candidates, further reducing
20 the pool of patients available for enrollment in treatment
21 studies.
22 To put the rarity of this into perspective, the
23 FDA regulation, 21 CFR, Section 526, defines rare disease or
24 conditions as those affecting less than 200,000 people in
25 the United States. So that any way you look at this, AVM is

1 a very rare disease.

2 In addition to their rarity, AVMs are very

3 heterogeneous in their clinical manifestations. They may

4 affect any part of the brain and, therefore, any brain

5 function and therefore have widely varying risks of

6 treatment even for AVMs that look virtually identical.

7 AVMs may be symptomatic over a wide range of

8 sizes, from millimeters in diameter to multiple centimeters

9 in diameter, and they can cause dysfunction by a number of

10 types of pathophysiology, including hemorrhage, mass

11 effects, seizures, even ischemia and venous hypertension

12 involving brain not directly involved by the AVM.

13 In spite of their heterogeneity, there is one

14 clinical feature that is very homogeneous about AVMs. We

15 know that AVMs are over the long term universally

16 devastating to the brain. So if a person has an AVM, they

17 are eventually going to get into trouble with neurological

18 deficits and probably with shortening of their life. So

19 there is a very significant clinical imperative to treating

20 these lesions.

21 Nevertheless, when we have a rare heterogeneous

22 disorder like this, it makes it very difficult to collect

23 big, homogeneous groups of patients. And without large

24 homogeneous groups of patients, what we usually think of as

25 our most effective tool for evaluating a new treatment--that

1 is, statistical evaluation--in comparison becomes much more
2 limited in its applicability, and that is in fact what we
3 have here.
4 So when we evaluate this device, we need to focus
5 very carefully on specific clinical criteria very similar to
6 what we did when we evaluated the polyvinyl alcohol device.
7 And the question becomes: Does this device safely and
8 effectively close vessels in a presurgical situation?
9 The PMA is not really designed to evaluate the
10 clinical aspects of brain AVM or clinical judgment; we
11 should leave that up to the treating physician. And in fact
12 when we focus on these very important clinical aspects of
13 the device, we find the PMA indicates that there is very
14 satisfactory performance. The primary efficacy parameters
15 of the percent occlusion and the number of occluded vessels
16 are really not different between the cyanoacrylate device
17 and the polyvinyl alcohol device.
18 With respect to safety issues, the two most
19 critical parameters--procedure-related complications and
20 intracranial complications--again, there is very little if
21 any difference between these two devices.
22 So the information in the PMA clearly supports the
23 approval of the cyanoacrylate device for presurgical
24 treatment, presurgical embolization of brain AVMs.
25 Dr. Hudson's memo goes on to mention another very

1 important aspect of this PMA--that in March of 1998, the
2 clinical study was started again because of pressure from
3 the physicians involved in the trial. That is because the
4 U.S. lacks the availability of this device.
5 If we look at the list of centers, we find that
6 this group of physicians includes a number of interventional
7 neuroradiologists, neurosurgeons--in fact, those with the
8 most experience in treating brain AVMs not only in the U.S.
9 but also in the world. And the reason they wanted this PMA
10 to continue is because physicians in the United States
11 currently lack access to this device, which has in fact been
12 a standard of brain AVM treatment throughout Europe and
13 Canada since the 1970's.
14 The availability in the United States has been
15 severely limited by regulatory constraints, and in many
16 cases, most cases, reluctance by companies to pursue FDA
17 approval, because sales of a device like this are not
18 expected to be very big. This is a small market, and costs
19 of development are very high.
20 Nevertheless, when we take a look at the opinions
21 of these experts, when we look at standard textbooks of
22 neurosurgery, of interventional neuroradiology, we find that
23 cyanoacrylate is considered not only an important therapy
24 but often represents the current standard of care in the
25 treatment of brain AVMs.

1 So we need to evaluate this device recognizing all
2 of these factors associated with brain AVM and its clinical
3 management. I think the PMA data indicate that there is a
4 substantial equivalence between the cyanoacrylate device and
5 the already approved polyvinyl alcohol particle device.
6 This alone very, very strongly supports approval of the PMA.
7 But I think we also need to have an appreciation
8 of the viewpoint of the majority of interventional and
9 neurosurgical experts in the field that, based on 25 years
10 or so of clinical experience in the use of this device with
11 brain AVMs, there is a very significant need for FDA
12 approval to make this device available for treatment of
13 patients in the United States.
14 That is my evaluation of the PMA from the clinical
15 standpoint.
16 DR. WALKER: Thank you, Dr. Hurst.
17 Do any member of the Panel have questions on Dr.
18 Hurst's presentation?
19 DR. GATSONIS: Can I get the summary again? It
20 was difficult to hear Dr. Hurst at the end?
21 DR. WALKER: Certainly.
22 DR. HURST: Sure. I think that when we evaluate
23 this data, we have got to consider everything involving
24 brain AVMs. We have got to consider the complex clinical
25 picture and focus on the important clinical aspects of does

1 this safely and effectively close vessels in a preoperative
2 situation.
3 And I think the data from the PMA, when we look at
4 percent occlusion, when we look at number of vessels
5 occluded, at least to me appears to be substantially
6 equivalent between the cyanoacrylate device and the already
7 approved polyvinyl alcohol device.
8 When we look at some really important safety
9 parameters--and the two that I am looking at are really
10 intracranial complications and procedural complications.
11 Again, I think we discussed device complications. And many-
12 -perhaps most--of those device complications do not
13 translate into any meaning for the patient. There is no
14 real effect of many of these device complications.
15 So I think all of this has to be considered when
16 we evaluate this device. And again, the history of the
17 device did not start in 1996 when this PMA was initiated.
18 Again, I think we are looking at nearly 30 years of
19 experience worldwide with the use of this device, so in
20 spite of the fact that we may not have all of the studies
21 formally presented that we would like, there is a vast
22 amount of data on this device.
23 DR. WALKER: Are there any other questions for Dr.
24 Hurst from members of the Panel?
25 [No response.]

1 DR. WALKER: If not, Dr. Gatsonis, we have you on
2 the speaker phone, and I think one of the tricks for the
3 automatic level control on it is not to speak too quickly,
4 because it tends to truncate words.
5 So we would be delighted to hear from you if you
6 are ready.
7 DR. GATSONIS: Okay. Yes, I am ready, and I will
8 speak slowly.
9 I asked several questions this morning, and what I
10 would like to do now is raise a couple of additional sort of
11 technical questions and then raise two or three bigger-
12 picture questions that I have about the analysis.
13 When it comes to the technical questions, one item
14 that I wanted to find out was whether the bootstrapping that
15 was done was also done for the full model, the full analysis
16 of covariance model that was being used, or is it really
17 done just on the basis of the response data without taking
18 covariance into account? My sense is that it is probably
19 the latter, but I just want to make sure.
20 In terms of the bigger picture issues here, I
21 think the choice of what is a threshold for equivalence to
22 my mind has not yet been justified by anybody. This could
23 be because the phone doesn't work very well, but I am not
24 sure I have heard a very good, clear explanation as to why,
25 if two procedures are within 20 percent difference in the

1 average reduction, that would be considered equivalence. So
2 I would like to hear the rationale for that discussion.
3 Incidentally, the power for this type of analysis,
4 the statistical calculations, were not obviously the
5 original ones, because those were done for a different
6 endpoint and hence, for a different study. So for this
7 particular study, power calculations are given on page 16 of
8 Volume 1, I believe. I did not quite follow how these were
9 done, so if the sponsors have some additional explanation, I
10 would appreciate it, because there, they are trying to
11 compute the power now for the continuous endpoint, and they
12 do admittedly come up with a very ? figure if the
13 approach that they use is correct.
14 One other item that I think we have to bear in
15 mind as we evaluate this entire dataset and in particular as
16 we evaluate straight differences between the two arms is
17 that this is a study with 47 patients in each arm. If you
18 don't find a difference--in other words, if you find a
19 confidence interval for the difference that is large enough
20 to contain zero, that doesn't necessarily mean there is no
21 difference.
22 I understand that everybody in the room knows what
23 I am talking about, but I just wanted to raise this issue
24 because I don't want us to conclude from the fact that
25 several of these confidence intervals, say, for the

1 secondary endpoint are large--I do not want us to conclude
2 from that that there is no difference between the two
3 modalities.
4 For instance, for the safety endpoints that were
5 raised earlier, as they were being discussed, I was doing a
6 little calculation on my computer, testing that there is a
7 difference in the two rates, and it seemed that, for
8 instance, the P value was .1 or .12 or something like that.
9 But that was only on a rather limited set of patients.
10 Obviously, when you design a study, you cannot do
11 sample size calculations based on the secondary endpoints--I
12 agree--otherwise, you may have to run studies with lots and
13 lots of patients. On the other hand, you should interpret
14 the findings about the secondary studies in that light.
15 I think those are the two big picture items that I
16 would like to raise to the Panel, to the sponsors, and to
17 the FDA, and those items would give me a certain pause in
18 making statements to the effect that the two procedures are
19 equivalent.
20 Thanks.
21 DR. WALKER: Normally, we don't have sponsor
22 presentations as part of the Panel deliberations; but I
23 think that with the permission of the Panel, we will invite
24 the sponsor to come up and address the points that Dr.
25 Gatsonis raised, if there is no objection.

1 Please.

2 DR. HOY: This is Hoy Leung, a Statistical

3 Consultant for Cordis.

4 DR. WALKER: Please speak into the microphone so

5 that he can hear you all the way to Rhode Island?

6 DR. HOY: Okay. Can you hear me, Dr. Gatsonis?

7 DR. GATSONIS: Yes, I can hear you--and I am

8 actually in Boston.

9 DR. HOY: Thank you.

10 To answer your first question about the Bootstrap

11 method and whether it is used on the full analysis of

12 covariance models or on just the response data, the answer,

13 as you guessed correctly, was the latter. It is the

14 Bootstrap for the response data only.

15 The second question about the threshold for

16 equivalence of 20 percent and whether that would be a

17 tolerable delta is really a clinical question. But to my

18 knowledge, this number 20 percent has been used quite a bit

19 in other clinical trials to declare non-inferiority.

20 One example could be in the bioequivalence study,

21 where one used the confidence band of 80 to 125 percent

22 around the ratio of the mean, so that translated really

23 close to the plus or minus 20 percent, and 80 percent mean

24 response.

25 In terms of using the proportion of patients and

1 whether 20 percent is an acceptable delta for declaring the
2 equivalence when the response rate is 80 percent--and to my
3 knowledge, I know this number has been used a lot, both in
4 drugs and in some other devices--I can give you an example,
5 where the Anti-Infective Division in FDA actually has a
6 guideline to give the criteria for what is the meaning of
7 non-inferiority when the response rate is 80 percent and the
8 delta is exactly 20 percent.
9 This is all I can answer based on my limited
10 knowledge on this question.
11 On the third question about the power calculation
12 and how was it done, to do the postop power calculation, we
13 will need to use the pooled standard deviation of the two
14 treatment arms. What we did was to derive the pooled
15 standard deviation from the mean-squared error of the ?
16 from the analysis of covariance model, as we know that that
17 term is being used for doing tests on the ?
18 statistics, so we thought that that may be the most
19 appropriate term to use for the calculation of sample size.
20 Actually, based on this approach, during the
21 postop power calculation on the actual observed data, we
22 found that if the clinical delta is 20 percent, the sample
23 size of 47, and 47 in each group, would have 96 percent
24 power to detect a clinical difference of 20 percent.
25 The last question about the finding of

1 nonstatistical significance does not mean that there is no
2 difference--on this point, we all totally agree with you, a
3 nd that is why we also provide 95 percent confidence
4 intervals in conjunction with the nonsignificance, so that
5 the reviewer would have a chance to look at the bands of
6 confidence interval and render judgment.
7 I hope I have answered all the questions.
8 DR. CANADA: Can I ask a question?
9 DR. WALKER: Yes, please.
10 DR. CANADY: It is unclear, although for the
11 purposes of the PMA, we need to look at the comparison--is
12 it a fair statement from the discussion of the catheter
13 sizes that these options might be used in different
14 circumstances, that the PVA would require a larger catheter
15 for delivery?
16 DR. PURDY: This is Phil Purdy from Southwestern
17 Medical School.
18 I am not real positive that I understand the
19 question. As I understand it--
20 DR. CANADY: I'll restate it. The question is
21 since the PVA seems to require a larger catheter for
22 delivery, is it possible that the new methods would be more
23 effective in some cases?
24 DR. PURDY: Yes. There are situations where you
25 would like to perform an embolization in an AVM that has a

1 particularly tortuous and distal feeder which you cannot
2 catheterize adequately with a larger and stiffer catheter to
3 reach a point where you feel like you can embolize it
4 safely; and only through using one of the more flexible
5 devices can you get far enough into the feeder to feel that
6 you can embolize it safely. But if you don't have a glue
7 option with that small catheter, when you get out there, you
8 are severely constrained in terms of what device you have as
9 an option to use once you get there.
10 So it is absolutely correct, if I understand your
11 question, that the glue in that situation is actually an
12 enabling technology.
13 DR. CANADY: Thank you.
14 DR. WALKER: Dr. Roberts?
15 DR. ROBERTS: I was just going to say that I
16 suspect if you look at the incidence of procedure-related
17 complications, you will see that the inability to subselect
18 the vessel was twice as common or a little bit more in the
19 PVA group. There was about twice as much vasospasm, about
20 twice as much vessel perforation, and about the same amount
21 of vessel dissection, so I am assuming that that all means
22 that the catheter is a problem and that actually using the
23 glue and the smaller catheters would be a lot safer in those
24 patients.
25 DR. PURDY: That is correct.

1 DR. WALKER: We have now moved into the portion of
2 the meeting where Panel members can address any questions to
3 either FDA staff or members of the scientific team from the
4 sponsor.
5 Are there any other questions from members of the
6 Panel, either for FDA or for the sponsor?
7 MS. MAHER: I would just like to say one thing.
8 What we are doing here as a Panel is looking to make sure
9 the devices described by the sponsor have provided
10 reasonable assurance of safety and effectiveness. And while
11 their clinical study did state that they were looking at
12 equivalence, we are actually not looking at equivalence; we
13 are looking for scientific data that reasonably assures
14 safety and efficacy. So I just wanted to remind people of
15 that.
16 DR. WALKER: Thank you, Sally.
17 Are there any other questions from members of the
18 Panel for either FDA staff or the sponsor?
19 [No response.]
20 DR. WALKER: If not, we can move the focus of our
21 discussion to the five questions that have been propounded
22 to us by FDA scientific staff.
23 Dr. Hudson, did you have some slides or viewgraphs
24 with the five questions on them, so we can turn our
25 attention to those?

1 DR. HUDSON: Yes.

2 DR. WALKER: And what we'd like to do is read each
3 question and then go around the table, and each Panel member
4 who wishes to do so can contribute a part of the answer.
5 I'll try to summarize the answer to each of those questions
6 and give that to Dr. Witten and see if it is a satisfactory
7 answer for the question that was asked.

8 **Discussion of FDA Questions for Panel**

9 DR. HUDSON: These questions were revised so we
10 are down to four questions.

11 The first question is asking for your comment and
12 recommendation on appropriate labeling regarding of the
13 ratio of the components used in physician training and
14 whether other studies should be done.

15 "The sponsor recommends the use of ethiodized oil
16 in combination with their product. However, no predefined
17 ration of the three components was used in the clinical
18 study. The amount of n-BCA used in the study varied from 10
19 percent to 70 percent in 36 documented presurgical
20 embolizations. Please comment on the following: a) What
21 instructions for use would you recommend the sponsor provide
22 on their label regarding the appropriate ratio of the
23 components to be used for a given anatomic setting?"

24 Excuse me--do you want me to go through (a), (b),
25 and (c)?

1 DR. WALKER: Yes. Let's go through (a), (b), and
2 (c), and then we can address our answers to all three.
3 DR. HUDSON: Okay.
4 1(b) is: "The sponsor provides training to
5 physicians interested in using their product. What
6 recommendations do you have for how the physicians are
7 trained?"
8 And 1(c) is: "What preclinical and/or clinical
9 studies would you recommend the sponsor conduct to define
10 the ratios of the components that could be recommended for
11 use in the instructions for use for various AVM settings,
12 i.e., high flow, vessel tortuosity?"
13 DR. WALKER: Okay. Let's go around the room
14 clockwise, starting with Dr. Hurst--if you could address
15 those three.
16 DR. HURST: Okay. I'm going to start with 1(a),
17 and I first would like to say that I think the sponsor has
18 put some guidelines in the updated response, at least that I
19 have in front of me, as part of the training program. The
20 appropriate ratio of these components is very difficult to
21 reduce to a set of formulas, and I think that that is part
22 of the difficulty in coming to grips with this whole
23 question. The exact ratios of these things are going to be
24 determined not only by the features of the AVM and the
25 anatomy and the flow-through of the AVM, but where you can

1 get your catheter and how big that catheter is at the time
2 that you do the injection.
3 The guidelines that the sponsor has outlined here,
4 I think are perfectly appropriate and should in fact be
5 incorporated into a training program. We don't expect
6 people when they start using something like this to be as
7 good as somebody who has been using this for a number of
8 years, and this is clearly a judgment process where
9 guidelines have to be given, and I think those guidelines
10 are outlined here.
11 DR. WALKER: Is there any comment on the training
12 program itself?
13 DR. HURST: I think the training outlined in the
14 sponsor's package that I have in front of me here is
15 adequate. That was 1(b).
16 And for 1(c), in terms of preclinical studies, I
17 don't think that, again, you are going to get a lot more
18 information from doing preclinical studies, because each AVM
19 is so individually variable, and when you combine that with
20 your catheter position, what you need is good judgment and
21 judgment in the ability to judge flow by injecting through a
22 microcatheter. And again, the guidelines are perfectly
23 appropriate to set people on that course.
24 DR. WALKER: Thank you, Dr. Hurst.
25 Dr. Rosseau?

1 DR. ROSSEAU: Regarding 1(a) and the instructions
2 for labeling, it would be my recommendation that, rather
3 than requiring more or additional preclinical testing, I
4 would simply include that in the labeling that ratios
5 between 10 and 70 percent have been reported upon, known to
6 be effective. We can work with the labeling, but I would
7 include that in the labeling.
8 In terms of 1(b) and the training program, I would
9 view that as being well-designed as described. I see that
10 the entire area of dealing with AVMs is fraught with
11 problems of patient acquisition, so that I foresee a problem
12 with physician training in which a physician may spend the
13 required amount of time with you, become very proficient
14 after this course, and then not see a patient in whom this
15 education is applicable for a year or more. Therefore, I
16 would recommend but not require that a review course that
17 would hit the highlights, that would allow them to re-review
18 materials they already have, but have that lab or, more
19 importantly even the clinical discussion period, available
20 in a briefer re-review that could be done on a voluntary or
21 elective basis.
22 I have no further comments regarding 1(c).
23 DR. WALKER: Thank you, Dr. Rosseau.
24 Dr. MacLaughlin?
25 DR. MacLAUGHLIN: I am very much in favor of

1 giving the clinician all of the latitude they need to have
2 in this kind of setting. As I said, I am not a clinician,
3 but in my reading of the standard text and hearing folks
4 talk today, it really seems to me as though this is a
5 completely ad hoc kind of arrangement, and appropriately so.
6 So I am not in favor of having a specific set of
7 guidelines as might happen. I think I agree with you, Gail,
8 that it makes more sense to have the limits placed, as I
9 said before when I was talking about the technical aspects
10 of some of the preclinical testing. I think it makes more
11 sense to say A to B is what is clinically used, knowing that
12 that is not binding, but it is based in reality.
13 So I think that that is acceptable to me. I think
14 it is very hard to define what is appropriate in a setting.
15 With respect to the teaching component, if I'm not
16 mistaken, a hospital purchasing this material for its use is
17 predicated, if I heard you right, Ms. Wells, on somebody in
18 the hospital taking the course--the most qualified person or
19 a qualified person taking the course. That is nowhere
20 evident, and I would like to see that somewhere, that you
21 have a qualified person on board, or somebody from your
22 hospital comes and trains, somebody of your selection comes
23 and trains, and the flow starts. I do not know if there are
24 any legal implications to that, but I think it made sense
25 from what your perspective was on offering the training, as

1 far as entry into the training.

2 And I don't think there are any other preclinical

3 studies that would be useful for looking at this issue of

4 what is appropriate in a setting with respect to occluding

5 the vessels. As you all know, and as I assume will come up

6 later, I have other concerns about the preclinical testing.

7 But as far as this question goes, I would be happy to see

8 the outer and inner limits and some restriction on the

9 course.

10 DR. WALKER: Thank you.

11 MS. Wojner?

12 MS. WOJNER: It's nice to sit in the middle of the

13 table, because oftentimes your comments are already

14 summarized, and I think that has occurred, so I have nothing

15 further to add at this time.

16 DR. WALKER: Thank you.

17 Ms. Maher?

18 MS. MAHER: I have nothing further to add also.

19 DR. WALKER: Dr. Roberts?

20 DR. ROBERTS: What I was going to say was just

21 that I am sure for the FDA people, the idea that there is

22 going to be flexibility and not a set standard of how

23 something is put together is very nerve-wracking, but I

24 think you have got to go with the realities. And the

25 reality is that these AVMs, as has been discussed today, are

1 very variable, and you just cannot prescribe that we are
2 going to use this amount, we are going to use this ratio, we
3 are going to use this ratio and this and this and this. You
4 just cannot do it that way. So you are going to have to go
5 with a leap of faith and say we cannot orchestrate it the
6 way that we would like to be able to do it. We would like
7 to have a device that comes out of a package and looks
8 exactly like this and is going to do exactly this and there
9 won't be any two ways about it. It is not going to work
10 that way, and this does not work that way.
11 So I think you are going to have to just take a
12 deep breath and say that what we are really going to put our
13 efforts into is not trying to figure out exactly what the
14 ratio should be, but instead, trying to make sure that
15 physicians who are going to use this have been trained in
16 this material and have in fact seen how this material
17 polymerizes, what are the facts--if you've got a rapid flow
18 rate, what are you going to do; if you've got a big AV
19 portion of this, how are you going to deal with that. I
20 think that is the important thing.
21 One thing I would recommend in terms of the
22 training is that I honestly feel there probably should be
23 some sort of entrance criteria so that not just any
24 physician who wanders into Cordis and says "I would like to
25 know how to do this" gets trained with that. I think there

1 should be some evidence that someone who is going to do this
2 has significant catheter experience. These are not lesions
3 that should be lightly tackled. People who do this should
4 have good experience. We can see that even in this
5 particular trial where these are very experienced operators,
6 there are complications. So I think it is important that
7 there be recommendations that physicians being trained in
8 this should have catheter experience and familiarity working
9 in the brain prior to being trained in this.
10 In terms of preclinical or clinical studies, I
11 honestly don't think that is possible, so I wouldn't
12 recommend anything in terms of clinical studies.
13 DR. WALKER: Thank you, Dr. Roberts.
14 Dr. Gatsonis, you cannot see it, but the speaker
15 phone is next to Dr. Roberts. Could you give us your
16 comments now on those three questions?
17 DR. GATSONIS: I do not have any comments in
18 addition to what I have heard about this one.
19 DR. WALKER: Thank you.
20 Dr. Canady?
21 DR. CANADY: I have no additional comments.
22 DR. WALKER: All right. Let me see if I can
23 summarize for Dr. Witten.
24 On Question 1(a), I think the consensus of the
25 Panel is that the guidelines for ratios are difficult to

1 quantify, but as provided by the sponsor, they are adequate;
2 that some wording that ratios between 10 to 70 percent are
3 effective; and that the FDA should give the clinicians the
4 latitude that they feel they need.
5 On Question 1(b), I think the consensus of the
6 Panel is that the Cordis training program is already well-
7 designed and adequate; that the sponsor may wish to consider
8 adding some entrance criteria for that program since this is
9 a high-technology, high-risk procedure, and that it might
10 possibly be wise to recommend a periodic review course in
11 addition to the initial training course; and furthermore,
12 that the present policy of selling only to hospitals in
13 which someone has already trained is a good policy and
14 should be continued.
15 On Question 1(c), I think it was the consensus of
16 the Panel that no additional preclinical studies are called
17 for.
18 Dr. Witten, is that enough for an answer to
19 Question 1?
20 DR. WITTEN: Yes. Thank you.
21 DR. WALKER: All right.
22 Dr. Hudson, if you will flip us over to Question
23 2, we will now consider that.
24 DR. HUDSON: Okay. Question 2 is related to the
25 long-term implantation issue.

1 "The sponsor has not conducted long-term
2 implantation biocompatibility testing of the device.
3 Although this device is not intended for permanent
4 implantation, eight patients in the clinical study, four in
5 each group, did not have their AVM surgically resected. The
6 sponsor proposes to include in the label that the safety and
7 efficacy of the device as a long-term implant has not been
8 established. What recommendations if any do you have for
9 revising the label to caution the user about using the
10 device as a possible permanent implant? Are there
11 additional preclinical animal studies that you believe
12 should be performed to evaluate the long-term risk of
13 permanent device implantation?"
14 DR. WALKER: Dr. Witten?
15 DR. WITTEN: Yes. Before you go around asking
16 people for their answers, I would just like to take the
17 opportunity to provide some clarification about the
18 question; is that okay?
19 DR. WALKER: Yes.
20 DR. WITTEN: What Ms. Maher said is correct, that
21 we evaluate a product based on what the sponsor proposes is
22 its label indication. But I think one thing we are
23 struggling with which we would appreciate your help on is
24 that from the study it is not clear to us how well or how
25 you can identify those patients who are going to go on to

1 have surgical resection. So we would like your help in
2 determining how to best identify those patients and what
3 your opinion is of that warning or caution in the label.
4 DR. WALKER: For the guidance of the Panel
5 members, we have an option later on this afternoon of
6 suggesting to the FDA that they impose certain conditions on
7 the approval of this premarket approval application, and it
8 may be that we will want to start thinking about specific
9 wording to propose as a motion to go along with the answers
10 to these questions. So we don't necessarily have to propose
11 that wording now, while we are answering these questions;
12 we'll get another chance to do it later.
13 Dr. Hurst?
14 DR. HURST: I would simply say that we need to
15 rely very heavily on the labeling, that the labeling should
16 indicate the approved indication is for presurgical and
17 emphasize that there are no longer-term studies that have
18 yet been conducted on permanent implantation of the device.
19 So I think that a labeling would be the way to go.
20 DR. WALKER: Dr. Rosseau?
21 DR. ROSSEAU: I agree with that.
22 DR. WALKER: Dr. MacLaughlin?
23 DR. MacLAUGHLIN: I don't completely agree with my
24 two colleagues. I agree that the long-term study issue we
25 could--I am dividing this into two stories. One is the

1 long-term thing, which I agree is probably impossible to
2 predict in people. But what I am looking at is the
3 preclinical testing that was done for safety and toxicity of
4 the device. It does not encompass the known uses of the
5 device, which was my point this morning. So it seems to me
6 to be entirely consistent, it would make sense to test, and
7 it would be my suggestion to do the toxicity and the safety
8 studies already designed and underway using slightly
9 different formulations, including a 10/90 and a 90/10 as we
10 suggested earlier this morning, just so that it is
11 internally consistent, so the testing that was done for the
12 device that we know is being used--let's leave long-term off
13 the table--is in fact done. I think that is consistent. It
14 is different than looking at the outcomes and what happens
15 in the patients. It is saying, gee, let's test the product
16 as it could be used. And my concession to all the
17 combinations and permutations thereof is to take the limits,
18 and it is my suggestion to do that, to encompass in your
19 preclinical testing for safety and toxicity by well-done
20 studies the device that you know is used.
21 I don't think that is unreasonable, and I don't
22 think it is different from the spirit of the preclinical
23 testing, anyway. So that would be my suggestion.
24 DR. WALKER: Thank you.
25 Ms. Wojner?

1 MS. WOJNER: I am leaning back in the opposite
2 direction of my previous two colleagues, that I think we
3 have captured it with this statement. These cases are going
4 to be followed on a long-term basis anyway, and I think that
5 should the manufacturer decide that ultimately they want to
6 go in that direction, at that point, they can pursue that
7 process in similar fashion.
8 DR. WALKER: Thank you.
9 Ms. Maher?
10 Ms. MAHER: My comments have now been adequately
11 given.
12 DR. WALKER: Thank you.
13 Dr. Roberts?
14 DR. ROBERTS: Well, I guess one thing I would like
15 to ask just as a point of clarification is that I wasn't
16 clear whether--I sort of got two different thoughts or
17 flavors on this. One was that some of this longer-term
18 biocompatibility is being done, or it is not being done. I
19 mean, is it in process or is it not in process?
20 DR. HUDSON: The sponsor is doing the combined
21 device biocompatibility, but they don't have long-term
22 implantation studies going on.
23 DR. WALKER: Dr. MacLaughlin?
24 DR. MacLAUGHLIN: My understanding is that the 7-
25 and 30-day studies that we're talking about that have been

1 done with components, with the n-BCA or the metal, are being
2 done with a formulation which sort of hits the mark for a
3 lot of the cases that are being used. I think it is the 30
4 percent or something like that--I have forgotten the
5 specifics--so it is a value--should be done.
6 My suggestion is that we do a little bit more
7 testing, covering the range that we already know clinically
8 is being used, because we have to ask, if we don't think
9 about doing that, why not do that. Do you know what I mean?
10 It has to do with testing the device.
11 DR. ROBERTS: My question is--we were talking
12 about the fact that in a rabbit or a mouse or whatever it
13 was that we were looking at in terms of a subject, it was
14 basically a 90-day test. But then I sort of got the
15 impression that it was being done, but the results aren't
16 out yet--or is it not being done at all?
17 DR. WITTEN: Maybe we should let the sponsor
18 answer that.
19 DR. ROBERTS: Yes.
20 DR. CATO: My name is Pedro Cato, the current
21 Project Leader for the glue project.
22 To answer your question with regard to the long-
23 term, we are currently undergoing biocompatibility testing
24 of the three-component mixture; however, we have not
25 undergone any testing that would require a chronic toxicity

1 testing, which would be the 90-day, at this time.

2 DR. ROBERTS: So what are you doing?

3 DR. CATO: We are doing the biocompatibility

4 according to the ISO 10993; instead of the individual

5 components, we are doing it in situ, as it has been used by

6 the physicians, which would be the three-component system

7 all together.

8 DR. ROBERTS: So you are looking at all the

9 aspects--the cytotoxicity, the sensitization, the

10 irrigation, et cetera, et cetera--

11 DR. CATO: That is correct.

12 DR. ROBERTS: --but not the subchronic/chronic

13 toxicity.

14 DR. CATO: No subchronic--right. Exactly. That's

15 true.

16 MS. MAHER: So is it correct to say that

17 essentially, you are doing the short-term implant studies,

18 not the long-term implant studies, since this is designed to

19 be short-term?

20 DR. CATO: That's correct. We are doing it based

21 on the fact that the device is for greater than 24 hours and

22 less than 30 days, prolonged application.

23 MS. MAHER: Okay.

24 DR. WALKER: Dr. Gatsonis, we are on Question 2,

25 with the long-term implantation/biocompatibility.

1 DR. GATSONIS: I do not have anything to add to
2 that question.
3 DR. WALKER: Dr. Canady?
4 DR. CANADY: I guess I would only say that the
5 indication for the procedure would not imply long-term
6 implantation, so it is an unusual set of circumstances,
7 either a change of approach or perhaps complication at the
8 time of catheterization, or that rare case where there is no
9 AVM, and the patient is unwilling to go forward, where we
10 end up with long-term toxicity. So the indication is quite
11 clear to suggest that the chronic use is not indicated, but
12 it is not clearly stated.
13 DR. WALKER: Let me see if I can summarize what we
14 have heard around the table, then, for Dr. Witten.
15 What I have heard from the panel is that the
16 labeling should emphasize that this is a presurgical use
17 product only, but we recognize that long-term use is
18 impossible to predict, and there is certainly sentiment
19 within the panel that it is going to be used on a long-term
20 basis, and there is some concern among panel members about
21 the long-term bioeffects of this product if it is used in a
22 manner inconsistent but predictably with the labeling.
23 Is that sufficient for you?
24 DR. WITTEN: Yes. Thank you.
25 DR. CATO: Dr. Walker, may I just add one comment

1 related to the biocompatibility, to clarify for the Panel?

2 DR. WALKER: Yes.

3 DR. CATO: On the biocompatibility, with all the

4 sensitization, as you mentioned, the list that we go through

5 on the 10993, we are performing the genotoxicity testing

6 which includes the bacterial and the two mammalian tests on

7 the final product.

8 DR. WALKER: Thank you very much.

9 Dr. Hudson, will you put us up to Question 3?

10 DR. HUDSON: Yes.

11 Question 3: "21 CFR 860.7(e)(1) states that there

12 is a reasonable assurance that a device is effective when it

13 can be determined, based upon valid scientific evidence,

14 that in a significant portion of the target population, the

15 use of the device for its intended uses and conditions of

16 use, when accompanied by adequate directions for use and

17 warnings against unsafe use, will provide clinically

18 significant results. The reduction in blood flow observed

19 with the n-BCA embolic agent was proposed by Cordis to be

20 equivalent to the control if it was within a 20 percent

21 difference. Measurement error of AVM size determination may

22 be significant. Please discuss whether the effectiveness

23 data for the Trufill n-BCA Liquid Embolic Agent provides a

24 reasonable assurance that the device is effective for this

25 use."

1 DR. WALKER: Dr. Hurst?

2 DR. HURST: Yes, I think that it does provide that
3 assurance. I think that when we look at the primary
4 endpoints of safety and effectiveness--that is, its ability
5 to safely close blood vessels in a presurgical situation--I
6 believe that they have shown that.

7 DR. WALKER: Dr. Rosseau?

8 DR. ROSSEAU: I believe they have shown safety and
9 efficacy.

10 DR. WALKER: Dr. MacLaughlin?

11 DR. MacLAUGHLIN: I would agree.

12 DR. WALKER: Ms. Wojner?

13 MS. WOJNER: I agree.

14 DR. WALKER: Ms. Maher?

15 MS. MAHER: I agree.

16 DR. WALKER: Dr. Roberts?

17 DR. ROBERTS: I agree.

18 DR. WALKER: Dr. Gatsonis?

19 DR. GATSONIS: I will have to be the skeptic on
20 this. I think that the conduct of this equivalence study
21 has several of the things that you say never do in studies,
22 and I will mention two which have come up before; I will
23 just summarize them for the record.

24 Number one, the study was originally designed with
25 a different endpoint than what they actually used at the end

1 in the analysis, as far as I can tell. When you do
2 equivalence studies, you have got to be even more careful
3 about this than when you do other studies. Equivalence
4 studies tend to be somewhat more tricky in terms of the
5 findings. You do need, as in every study, to specify the
6 endpoints in advance and stick to them.
7 In equivalence studies, you also need to start
8 with a justifiable threshold for equivalence. The 20
9 percent that has been used so far to my mind has not been
10 justified by anybody. I don't think I would consider it a
11 strong argument to say there was another study in which a
12 figure of 20 percent was used. Every time you set a
13 threshold for equivalence, you have to justify it in the
14 context of the specific clinical realm that is addressed by
15 the study.
16 So for instance, if the threshold were actually 15
17 percent and not 20 percent, then even formally, they
18 wouldn't be equivalent. So I think this should give us
19 pause--namely, you start out with an endpoint, and you
20 change it; you don't define the threshold; at the end of the
21 study, you make a valiant effort, and you analyze it, and
22 you use a particular threshold. I think that these are sort
23 of the usual no-no's when we construct equivalence studies.
24 Hence, I will be a skeptic on this question.
25 DR. WALKER: Dr. Canady?

1 DR. CANADY: I think we have to look back at the
2 history of the study and not that it actually was a study
3 that was formulated at a different time, probably by
4 different people, and was abandoned and then reborn at the
5 request of the neuroradiologist, which I think is
6 significant. So I think that that plays into some of the
7 design issues here, and therefore some latitude may be
8 indicated.
9 DR. WALKER: Thank you, Dr. Canady.
10 Let me see if I can summarize the Panel's
11 sentiments for Dr. Witten.
12 I think it is the consensus of the Panel that the
13 20 percent bandwidth is adequate, that that is not a
14 problem, but that there is some sentiment that the fact that
15 the endpoint changing during the course of the study is
16 statistically a problem; however, it was also pointed out
17 that the study was stopped and then restarted and that that
18 should be reconsidered along with the changing of the
19 endpoint.
20 Dr. Witten, is that a sufficient answer to this
21 question?
22 DR. WITTEN: Yes.
23 DR. WALKER: Dr. Hudson, will you give us Question
24 4?
25 DR. HUDSON: "21 CFR 860.7(d)(1) states that there

1 is a reasonable assurance that a device is safe when it can
2 be determined that the probable benefits to health from use
3 of the device for its intended uses, when accompanied by
4 adequate instructions for use and warnings against unsafe
5 use, outweigh any probable risks. The clinical study
6 determined that there were more device-related complications
7 with the subject device. Please discuss whether the safety
8 data for the Trufill n-BCA Liquid Embolic Agent provide a
9 reasonable assurance that it is safe for this use."
10 DR. WALKER: So we covered effectiveness in
11 Question 3, and here we cover safety.
12 Dr. Hurst?
13 DR. HURST: I think this is fortunately a subject
14 that we mentioned earlier, that the device-related
15 complications rarely translated into real patient events. I
16 think that when we do look at the procedural complications
17 or the intracranial complications, they seem at least to be
18 equivalent, and I would consider this to be a safe device.
19 DR. WALKER: Dr. Rosseau?
20 DR. ROSSEAU: I would as well, and I would
21 highlight the fact that some of the complications with the
22 use of this device are catheter delivery-related as opposed
23 to the device itself.
24 DR. WALKER: Dr. MacLaughlin?
25 DR. MacLAUGHLIN: In substance, I agree. When you

1 look at this as the procedure of putting the material in and
2 getting the result, I agree. I view it as different from
3 the questions I raised earlier. But I would agree with that
4 statement.
5 DR. WALKER: Ms. Wojner?
6 MS. WOJNER: I think the device is safe, is
7 effective, and it is right for patients to get it out there.
8 DR. WALKER: Ms. Maher?
9 MS. MAHER: I agree.
10 DR. WALKER: Dr. Roberts?
11 DR. ROBERTS: I would basically agree. I also
12 would say that I think it would have been nice for the FDA
13 to actually have put in another sentence that said that the
14 procedural complications of the control device were 21
15 versus 14 for the experimental device, and for intracranial
16 events, the control device was 21 as opposed to 10 for the
17 experimental device. I think that makes it a little fairer,
18 rather than just concentrating on the device-related
19 complications, because I think we have to look at these
20 patients in a whole, not just simply at the device itself;
21 and quite frankly, as was pointed out before, some of these
22 device things, such as an occluded catheter, although I
23 think rightly put in as a complication of the device, is
24 actually not a patience complication; it just means the
25 catheter needs to be removed and replaced.

1 DR. WALKER: Dr. Gatsonis?

2 DR. GATSONIS: Let me just focus on the data

3 that are actually on this slide of the FDA, the 12 out of 52

4 and the 5 out of 50. That is a difference of 10 percentage

5 points; it is the difference between 23 percent and 10

6 percent. If you try to make a formal comparison on the

7 basis of this, the P value--I was just doing it again--is

8 something like .12 or something of this sort. This is with

9 a sample size of 50 per group.

10 So if these complications are important

11 complications, I think this number should again give us some

12 pause and should be looked at vis-a-vis the sample size that

13 was used to calculate it.

14 DR. ROBERTS: How about the P value on the

15 procedural complications and the intracranial events?

16 DR. GATSONIS: I did not do that. I was just

17 doing the one that was on that slide at this point.

18 DR. WALKER: Dr. Canady?

19 DR. CANADY: I have no additional comments.

20 DR. WALKER: Let me see if I can summarize.

21 The sentiment around the table seems to be that

22 while complications were noted, those complications did not

23 represent a danger or an unsafe aspect to the patients, and

24 in fact, some of those complications may be related to the

25 catheter system, which is not the subject of consideration

1 today, rather than to the device that we are considering
2 today.
3 Dr. Witten, is that an adequate answer for
4 Question 4?
5 DR. WITTEN: Yes. Thank you.
6 DR. WALKER: Having answered the FDA's four
7 questions, we can now move on to the second Open Public
8 Hearing on the Cordis Endovascular Systems PMA.
9 Is there anyone in the audience who wishes to
10 address the Panel now?
11 [No response.]
12 DR. WALKER: If not, we have an opportunity for
13 summations from FDA and from the sponsor prior to the
14 portion of the meeting in which the Panel deliberates and
15 votes on its recommendations to be passed up to the Food and
16 Drug Administration.
17 I would like to ask the Food and Drug
18 Administration, Dr. Hudson or Ms. Chen, if you have any
19 summation--this is not for the introduction of new data but
20 to clarify what has gone before.
21 **FDA and Sponsor Summations**
22 DR. HUDSON: No. I just want to thank the Panel
23 members for considering the PMA.
24 DR. WALKER: Thank you.
25 Does anyone from the sponsor want to make any

1 concluding clarifications or comments?

2 Ms. Wells?

3 MS. WELLS: I would like to mimic that. We would

4 like to thank you very, very much for your consideration.

5 It has been a long road.

6 Thank you very much.

7 **Concluding Deliberations and Vote**

8 DR. WALKER: Now we move to the point where the

9 rubber hits the road in this meeting. This is where we

10 begin to formulate a motion to pass to the FDA and then to

11 debate that motion.

12 We are here to make a recommendation to the FDA on

13 the sponsor's request for premarket approval.

14 Ms. Scudiero will now read the Panel

15 Recommendation Options to the Panel.

16 MS. SCUDIERO: These are the Panel Recommendation

17 Options for Premarket Approval Applications.

18 "The Medical Device Amendments to the Federal

19 Food, Drug, and Cosmetics Act, as amended by the Safe

20 Medical Devices Act of 1990, allow the Food and Drug

21 Administration to obtain a recommendation from an expert

22 advisory panel on designated Medical Device Premarket

23 Approval Applications that are filed with the agency. The

24 PMA must stand on its own merits, and your recommendation

25 must be supported by the safety and effectiveness data in

1 the application or by applicable publicly-available
2 information."
3 "Safety is defined in the Act as reasonable
4 assurance, based on valid scientific evidence, that the
5 probable benefits for health under the conditions of
6 intended use outweigh any probable risks. Effectiveness is
7 defined as reasonable assurance that in a significant
8 portion of the population, the use of the device for its
9 intended uses and conditions of use will provide clinically
10 significant results."
11 Your recommendation options for the vote are as
12 follows:
13 1) Approval--if there are no conditions attached.
14 2) Approvable with conditions. The Panel may
15 recommend that the PMA be found approvable subject to
16 specified conditions such as physician or patient labeling,
17 education, labeling changes, or further analysis of existing
18 data. Prior to voting, all the conditions should be
19 discussed by the Panel.
20 3) Not approvable. The Panel may recommend that
21 the PMA is not approvable if the data do not provide a
22 reasonable assurance that the device is safe, or if a
23 reasonable assurance has not been given that the device is
24 effective under the conditions of use prescribed,
25 recommended, or suggested in the labeling.

1 Following the voting, the chair will ask each
2 Panel member to present a brief statement outlining the
3 reasons for his or her vote.
4 DR. WALKER: So that we understand the ground
5 rules, the voting members of the Panel are Dr. Canady, Dr.
6 Hurst, Dr. Rosseau, Dr. Gatsonis, Dr. MacLaughlin, and Dr.
7 Roberts--that is six voting members, and we are required to
8 have a minimum of five. That is also an even number. As
9 chair, I am allowed to vote only in the case of a tie.
10 DR. GATSONIS: I don't think I am supposed to be
11 voting today.
12 MS. SCUDIERO: Dr. Gatsonis and Dr. Canady, we
13 have looked into what is written in the regulations as far
14 as directions on voting and decided that you are permitted
15 to vote.
16 DR. GATSONIS: Okay.
17 DR. WALKER: Dr. Hurst, as the lead reviewer,
18 would you like to introduce one of those three motions for
19 the Panel to consider?
20 DR. HURST: Yes. I move that the device be
21 approved.
22 DR. WALKER: Is that approval, or approval with
23 conditions?
24 DR. HURST: I think that we have talked about a
25 lot of conditions that to my eye have been pretty much met,

1 and I would move that it simply be approvable.

2 DR. WALKER: Okay. Is there a second for Dr.

3 Hurst's motion?

4 [No response.]

5 DR. WALKER: There being no second, is there

6 perhaps another motion that you would like to introduce?

7 DR. HURST: How about approvable with conditions?

8 DR. WALKER: Is there a second for Dr. Hurst's

9 motion?

10 DR. ROSSEAU: Second.

11 DR. WALKER: All right. Dr. Rosseau has seconded

12 that.

13 Now, let me pull out the flow chart and see what

14 we are supposed to do. As I understand it, we are having a

15 vote to approve with conditions and a second. Now we will

16 talk about the conditions and not talk about the main vote

17 until after all the conditions have been individually

18 introduced and individually debated. So for each condition,

19 we will introduce it, see if there is a second, talk about

20 it, vote on it, and then move on to the next condition.

21 Fair enough?

22 DR. CANADY: Fair enough.

23 DR. WALKER: Does anyone have any conditions that

24 they would like to add to the recommendation for approval?

25 DR. CANADY: I'd like to add a labeling condition.

1 DR. WALKER: Yes, Dr. Canady.

2 DR. CANADY: That would be a statement that the

3 biocompatibility long-term has not been established.

4 DR. WALKER: Is there a second for Dr. Canady's

5 motion?

6 DR. ROSSEAU: Second.

7 DR. WALKER: Dr. Rosseau seconded.

8 Is there any discussion?

9 [No response.]

10 DR. WALKER: There being no discussion on a motion

11 that the labeling be amended to discuss the long-term

12 biocompatibility, are we ready for a vote?

13 DR. ROSSEAU: Point of clarification.

14 If we want additional labeling conditions, should

15 this be considered now or as a separate condition?

16 DR. WALKER: As a separate condition. We can add

17 as many conditions as we want.

18 DR. ROSSEAU: Even if they are all regarding

19 labeling?

20 DR. WALKER: Yes, absolutely.

21 Are we ready for a vote?

22 MS. WOJNER: I have a question.

23 DR. WALKER: Yes, Ms. Wojner.

24 MS. WOJNER: I have the labeling right in front of

25 me, but isn't this already specified on the labeling?

1 DR. WALKER: Dr. Witten or somebody from FDA, do
2 you want to answer that?
3 DR. ROBERTS: But since the labeling really hasn't
4 been done until after--I mean, it won't be approved until
5 after this Panel meeting anyway--I think that to say it
6 would be approved with the condition that the labeling
7 specify that there has not been long-term biocompatibility
8 evidence--at least that way, they know that that has got to
9 be on there.
10 DR. WALKER: If I could offer, we are not
11 wordsmithing their labels, but we are conveying a sentiment
12 of the Panel to the FDA so that when the FDA wordsmiths with
13 the sponsor, they will know what we are thinking.
14 DR. ROSSEAU: Okay.
15 DR. WALKER: All those in favor--are we doing this
16 by ayes or by hands?
17 DR. MacLAUGHLIN: Are we voting on the conditions,
18 or--
19 DR. WALKER: Just on the conditions.
20 DR. MacLAUGHLIN: Just on the conditions.
21 DR. WALKER: Just on Dr. Canady's motion that we
22 add the condition with respect to labeling for long-term
23 biocompatibility and the fact that that is not known.
24 We are supposed to do it with hands. All right.
25 All in favor of this amendment, which is simply a

1 motion for approval with conditions, all who are in favor of
2 that amendment, please raise your hands.
3 [A show of hands.]
4 DR. WALKER: Dr. Gatsonis, is your hand up?
5 DR. GATSONIS: Yes, it is.
6 DR. WALKER: Dr. Canady?
7 DR. CANADY: Yes, it is up.
8 DR. WALKER: I believe this condition passes.
9 Are there any other conditions that members of the
10 Panel would like to add to the vote for approval with
11 conditions?
12 DR. ROSSEAU: I would recommend an additional
13 labeling condition, that being that there be language that
14 specifies that preclinical studies were done with amount of
15 n-BCA used varying from 10 to 70 percent, and that
16 information, therefore, on human use and these ratios is the
17 only experience that we have to date.
18 DR. WALKER: Is there a second for that motion?
19 DR. MacLAUGHLIN: I can second it and then discuss
20 it.
21 DR. WALKER: Surely.
22 DR. MacLAUGHLIN: Okay--I second it.
23 The discussion revolves around limiting this, I
24 think, to the clinical experience. When you're talking
25 about preclinical, I am a little confused. My preclinical

1 is in the animals, and your preclinical is in preapproval.

2 DR. ROSSEAU: Preapproval; premarket approval.

3 DR. MacLAUGHLIN: Right. So you are talking about

4 the 10 to 70 being used in patients; right?

5 DR. ROSSEAU: That's correct.

6 DR. MacLAUGHLIN: Okay. I understand.

7 DR. WALKER: Any other discussion on Dr. Rosseau's

8 motion with respect to including some language that 10 to 70

9 percent is the range that has been tested in preclinical

10 studies?

11 [No response.]

12 DR. WALKER: Are we ready to vote for approval or

13 disapproval of this condition?

14 All right. All in favor of including this

15 condition, please raise your hands.

16 [A show of hands.]

17 DR. WALKER: Dr. Canady?

18 DR. CANADY: Yes.

19 DR. WALKER: Dr. Gatsonis?

20 DR. GATSONIS: Yes.

21 DR. WALKER: I think the motion for this condition

22 passes.

23 Is there a third condition that we wish to add,

24 from any member of the Panel, either here or by phone?

25 DR. ROBERTS: We are talking about labeling now,

1 or just conditions?

2 DR. WALKER: We can add anything we want.

3 DR. ROBERTS: Well, I do think it's important, and

4 I'm not sure whether this has been decided--I assume it has

5 been--and that is that I think it is important that there be

6 a training program, that individuals under go training in a

7 very set program prior to being able to use this material.

8 DR. WALKER: Would you like to phrase that as a

9 motion?

10 DR. ROBERTS: Yes. So moved.

11 DR. WALKER: Does anybody want to second that?

12 DR. HURST: I'll second that.

13 DR. WALKER: Thank you, Dr. Hurst.

14 Is there any discussion on the motion to also

15 include as a condition in our recommendation that the

16 training program that is currently required be continued

17 after the device is approved. I think that's the sense of

18 what you are doing.

19 Discussion on that?

20 [No response.]

21 DR. WALKER: Hearing no discussion, let's vote on

22 it.

23 All in favor, hands up.

24 [A show of hands.]

25 DR. WALKER: Dr. Canady?

1 DR. CANADY: Yes.

2 DR. WALKER: Dr. Gatsonis?

3 DR. GATSONIS: Yes.

4 DR. WALKER: Is there any opposition?

5 [No response.]

6 DR. WALKER: I think the motion passes.

7 Is there any fourth language for conditions that

8 we wish to add for approval with conditions?

9 DR. ROBERTS: I guess the other thing that I would

10 add is that I am assuming that since there are studies that

11 are ongoing, that the results of those studies be made to

12 the FDA and that the FDA evaluate those, and assuming that

13 the combined product is no worse than what the single agents

14 showed in their testing, that that be considered sufficient

15 for the short-term testing of this device.

16 DR. WALKER: Is there a second to that?

17 DR. MacLAUGHLIN: I have a point of clarification.

18 Is that cricket, Dr. Witten? Can we do that?

19 DR. WITTEN: The recommendation that they not do

20 anymore testing?

21 DR. MacLAUGHLIN: No.

22 DR. ROBERTS: No, no. I recommended that the

23 testing that is already ongoing be reported to you and that

24 you evaluate that, and as long as it is no worse than what

25 we have already seen, we would assume that that would be

1 fine. But I don't want it to be that we pass this, so we
2 throw out the data that is already being collected.
3 DR. WITTEN: Yes, that's something that would
4 certainly--
5 DR. WALKER: Dr. Witten, wouldn't that happen
6 anyway, regardless of what we do?
7 DR. WITTEN: If you want to make a
8 recommendation,a nd you think it is important for us to
9 review the results before the product is approved, then you
10 are certainly free to put it in your conditions of approval.
11 Like all the recommendations, we take them back and look at
12 them with the sponsor, but it is certainly well within the
13 scope of what you can recommend.
14 DR. MacLAUGHLIN: Right, but--pardon m e--it is
15 only things underway, though; is that correct, Dr. Witten?
16 DR. WITTEN: You are not limited; you can
17 recommend anything. It is up to you. If that is what the
18 recommendation is, then that is what you are recommending.
19 You can recommend anything you want about this testing or
20 any other testing. We are really asking for your
21 recommendations about what you think we should do as we
22 carry forward with the review of the product.
23 DR. MacLAUGHLIN: I understand.
24 Then, I might broaden--I will second and broaden
25 the discussion to include perhaps a recommendation that the

1 data for the combined device covering the 10 percent and 90
2 percent range--just those two limits, let us say--be
3 included in that pending tox data, that short-term, not the
4 long-term data, be included, because you have studies
5 underway. I was recommending that we see the extremes of
6 the labeled product in those studies.
7 Just to be clear, I am not talking about the
8 chronic study. I am talking about expanding what is
9 underway.
10 DR. WALKER: Yes.
11 Is there any other discussion on this condition,
12 which speaks to the necessity of reporting the ongoing
13 testing results to the FDA, even though those studies aren't
14 yet finished, and including the dosage extremes in that
15 study?
16 DR. HURST: Would this delay the approval until
17 the new studies were finished?
18 DR. WITTEN: Yes, it probably would. I think
19 actually, if you are going to discuss this, it would be
20 better to leave it as two separate motions. Dr. Roberts had
21 the first motion of wanting the FDA to review the current
22 studies that are underway, and that should probably be voted
23 on; and then do a second motion, if Dr. MacLaughlin feels it
24 is important, to state that they should do it, and then let
25 the Panel have the right to vote on that, too, because it

1 would delay it, and it would increase the cost of developing
2 the product.
3 DR. MacLAUGHLIN: I agree with your suggestion. I
4 think we should do that. We should separate the two.
5 DR. WALKER: Do you want to withdraw your
6 amendment?
7 DR. MacLAUGHLIN: I will add it next if it gets
8 seconded after Dr. Roberts'.
9 DR. ROBERTS: I just want to make sure that the
10 testing that is already underway gets reported out--and I
11 don't want to delay things, and I am going to make an
12 assumption that it probably won't show anything different
13 than what we have already seen, because I think, quite
14 frankly, the combination is probably not going to be any
15 worse than the individual components, but I'd just like to
16 make sure we don't lose that information.
17 DR. WALKER: So our fourth condition that we are
18 discussing speaks to the necessity of ongoing testing that
19 is currently in progress being reported to the FDA and the
20 FDA considering the results of that testing.
21 Are we ready to vote? All in favor, please raise
22 your hands.
23 DR. MacLAUGHLIN: We need a second. I second.
24 DR. WALKER: Excuse me. I think Dr. MacLaughlin
25 seconded it, so we can do it.

1 All in favor, raise your hands.

2 [A show of hands.]

3 DR. WALKER: Dr. Canady?

4 DR. CANADY: Yes.

5 DR. WALKER: Dr. Gatsonis?

6 DR. GATSONIS: Could you repeat the thing that we

7 are voting on right now? I missed it.

8 DR. WALKER: Yes. There is some ongoing testing

9 that the sponsor is currently doing, and the results of that

10 testing are not ye available. Dr. Roberts' motion was that

11 that testing is important and that the results of that

12 testing should be reported to FDA and considered by them.

13 DR. GATSONIS: Yes.

14 DR. WALKER: Any opposed?

15 [No response.]

16 DR. WALKER: Is there any fifth condition that we

17 wish to add to this motion to approve?

18 Dr. MacLaughlin?

19 DR. MacLAUGHLIN: I would add as a fifth condition

20 the suggestion, the amendment I made to the amendment just a

21 minute ago, which was the extremes of dose response just in

22 the acute phase of the studies, exactly of the type being

23 conducted now on the combination--I think it is 35 percent

24 or 33 percent. That is what I would recommend.

25 DR. WALKER: So that would be at the level of 10

1 percent and 70 percent?

2 DR. MacLAUGHLIN: Yes. The extremes of the

3 currently--the labeling that we agreed to.

4 DR. WALKER: Is there a second to that motion?

5 [No response.]

6 DR. WALKER: If not, are there any other

7 conditions that the Panel wishes to add to the motion to

8 approve with conditions?

9 [No response.]

10 DR. WALKER: Okay. Then, at this point, it has

11 been moved and seconded that the Premarket Approval

12 Application P990040 for the Cordis Endovascular Systems,

13 Inc. Trufill n-Butyl Cyanoacrylate and Trufill Tantalum

14 Powder intended for presurgical treatment of AVMs be

15 conditionally approved with the four conditions of approval

16 that the Panel has just voted on.

17 We have a second for that main motion. Okay.

18 All in favor of this main motion with the

19 identified conditions of approval, please raise your hand,

20 and for this one, I need to go around and state for the

21 record first who is voting yes and then who is voting no.

22 So, raise your hands.

23 Voting yes are Dr. Hurst, Dr. Rosseau, Dr.

24 Roberts. And how about Dr. Canady and Dr. Gatsonis?

25 DR. CANADY: Yes.

1 DR. GATSONIS: I vote no.

2 DR. WALKER: Okay. So we have four yes votes, and
3 we have Dr. Gatsonis voting no.

4 Do we have any other no votes?

5 DR. MacLAUGHLIN: I am a no vote.

6 DR. WALKER: All right. So we have two no votes,
7 so the motion with conditions does in fact pass.

8 All right. It is the recommendation of the Panel
9 that the Premarket Approval Application for the Cordis
10 Endovascular Systems, Inc. Trufill n-Butyl Cyanoacrylate and
11 Trufill Tantalum Powder intended for the presurgical
12 treatment of arteriovenous malformations be conditionally
13 approved with the previously voted-upon conditions.

14 I am now going to ask each Panel member as we go
15 around the table to state the reason for his or her vote,
16 starting once again with Dr. Hurst.

17 DR. HURST: I voted for approval because I think
18 that this device is safe and effective for the indicated
19 use.

20 DR. WALKER: Dr. Rosseau?

21 DR. ROSSEAU: I not only agree, but I believe that
22 we have a proven need for it in the medical community, for
23 these difficult and extremely rare-to-treat lesions, and an
24 informal 30-year history of its human use.

25 DR. WALKER: Dr. MacLaughlin?

1 DR. MacLAUGHLIN: This was a difficult vote for
2 me, because I see the value on the one hand, and on the
3 other, the scientist in me says we need to be consistent
4 with the testing of the material that we have used; and for
5 that reason, actually only, I voted no.
6 DR. WALKER: Dr. Roberts?
7 DR. ROBERTS: I think this is an important advance
8 in patients who have a very difficult-to-treat lesion.
9 Informally, I would encourage the sponsor to perform long-
10 term chronic toxicity testing, because I think it would
11 certainly be information that would be important to all of
12 us. So I'll add that just as a personal request, but I think
13 it is a very important device for us to have in our
14 armamentarium.
15 DR. WALKER: Dr. Gatsonis?
16 DR. GATSONIS: In my view, the evidence for safety
17 and for equivalence is not convincing from a methodologic
18 point of view and from the point of view of just simply
19 looking at the results, and thus my "no" vote.
20 DR. WALKER: Thank you.
21 Dr. Canady?
22 DR. CANADY: I also think that this is a technique
23 that offers an important alternative to the neuroradiologist
24 in a very difficult problem that is almost an orphan
25 disease.

1 DR. WALKER: Thank you.

2 Dr. Witten, is there anything you need to add at

3 this time?

4 DR. WITTEN: No. I'd like to thank the Panel for

5 their thoughtful consideration of this application.

6 DR. WALKER: And so would I like to thank the

7 Panel for being cooperative with me when I am pinch-hitting

8 for Dr. Canady, who normally does such a wonderful job of

9 running these meetings.

10 This meeting of the Neurological Devices Panel is

11 now adjourned.

12 [Whereupon, at 2:08 p.m., the proceedings were

13 concluded.]

CERTIFICATE

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

Anne E. Hayes

ANNE E. HAYES