

1 and which should have correspondingly dramatically  
2 different criteria, judging sufficient evidence for making  
3 that particular indication-based claim, represent a huge  
4 step forward.

5           What I'm worried about is that if we insist on  
6 always showing rigorous data regarding the application in a  
7 specific clinical context, then aren't we really saying  
8 that we're always insisting on falling back to either the  
9 diagnostic category or the outcomes category of the  
10 indication, and I think we are saying that if we insist on  
11 that, aren't we?

12           I personally object to that. I think the whole  
13 point of having these different categories of indications  
14 is to permit drugs to be approved, marketed and used on  
15 label for things other than diagnosis and outcomes  
16 initially. It's the same thing with the development of CT  
17 NMR, where the applications and the evidence and the  
18 categories that you describe came after its approved use,  
19 not before its approved use.

20           DR. TULCHINSKY: Before we hear about MR and  
21 how that was cheated in the discussion, let me address the  
22 comments previously made by the two speakers.

23           To start with, this discussion has happened  
24 already, and the Congress directed us to take the  
25 functional indication and run with it. This has already

1 been addressed, and if you take the Congress as the voice  
2 of the American people, then the American people told us  
3 it's okay.

4           If you review the 1997 Act, it is in there, I  
5 believe. I would -- it is not? Ms. Axelrad is shaking her  
6 head.

7           MS. AXELRAD: I don't believe that it's in  
8 there.

9           DR. TULCHINSKY: I do believe that there is.  
10 While we're looking, I do believe that there is indication  
11 towards the functional use of those tracers. I think we  
12 need to keep that in mind if indeed that is true.

13           But if it is not, that was the basis of the  
14 move that brought the nuclear medicine community to  
15 Congress to seek this legislation. So that's one point  
16 that I wanted to make, and I think what we're doing today  
17 is a major milestone as far as the difference that has  
18 taken place in the way we assess those tracers.

19           It's in a way paradoxical to me that in the  
20 past, physicians sought less bureaucracy on the side of FDA  
21 in approval process and in the past have fallen on a deaf  
22 ear. Today, we see the reversal of things. I hear  
23 physicians objecting to a more scientifically-based, more  
24 creative approach to looking at diagnostic methods, and  
25 that is just an interesting observation personally.

1 Have we figured it out, Ms. Axelrad?

2 MS. AXELRAD: What I think what you were  
3 referring to is the reference in Section 122 of the  
4 Modernization Act.

5 DR. TULCHINSKY: Exactly.

6 MS. AXELRAD: On the requirements for  
7 radiopharmaceuticals.

8 DR. TULCHINSKY: Exactly.

9 MS. AXELRAD: Not for PET specifically.

10 DR. TULCHINSKY: That's correct.

11 MS. AXELRAD: And what --

12 DR. TULCHINSKY: Radiopharmaceuticals.

13 MS. AXELRAD: Right. But this was a separate  
14 section. PET was addressed in a separate section of the  
15 Modernization Act and was specifically excluded from the  
16 radiopharmaceutical section.

17 DR. TULCHINSKY: Understood. But PET choices  
18 are radiopharmaceuticals.

19 MS. AXELRAD: Right. But we were talking about  
20 what Congress did or didn't intend in the Modernization  
21 Act, and it was not addressed in the radiopharmaceutical  
22 section, but that being said, let me just read what the  
23 statute said.

24 It says there's a special rule in Section  
25 122(a) that says, "In the case of a radiopharmaceutical,

1 the indications for which such radiopharmaceutical is  
2 approved for marketing may in appropriate cases refer to  
3 manifestations of disease, such as biochemical,  
4 physiological, anatomic or pathological processes, common  
5 to or present in one or more disease states."

6 Then it defines the radiopharmaceutical as "an  
7 article that is intended for use in the diagnosis and  
8 monitoring of a disease or a manifestation of a disease in  
9 humans and that exhibits spontaneous disintegration of  
10 unstable nuclei," and it goes on with this other stuff.

11 DR. TULCHINSKY: Right. Therefore, I would  
12 stand with my statement that that's what they intended, for  
13 us to look at the physiology, biochemistry and so forth,  
14 across diseases, not specifically narrowed to one  
15 indication, one disease and how that changes things.

16 We ought to keep that in mind because that is  
17 the starting point for our discussion today. Without that,  
18 this discussion today would not have happened.

19 DR. LOVE: If I could just get in for just a  
20 second. A moment ago, I certainly hope I wasn't defensive.  
21 One of the concerns that we had when we were looking at the  
22 guidance document to discuss some of these issues is when  
23 you have a functional indication, what is the clinical  
24 setting in which that indication is going to be used, and  
25 that gets back to some of what you're talking about in

1 terms of the relevance to an individual patient.

2 Some of the things, principles we talked about  
3 there, are the apparent need to study at least the spectrum  
4 of patients, maybe those who are moderately ill or very  
5 severe if you're only going to look at a certain thing,  
6 like ejection fraction. If you're looking at a situation  
7 here where you have cerebral perfusion, it's going to be  
8 evaluated in a wide variety of patients as Dr. Conti  
9 presented, looking at a number of different things.

10 So what kind of information would be needed to  
11 show that there is relevance in this type of population?  
12 Is it studying a few? Looking at sensitivity and  
13 specificity? That might be an approach. Is it studying  
14 looking at a clinical outcome? That might be an approach.  
15 There might be others that would be relevant to provide the  
16 data to answer that question.

17 So I'd like to hear what the panel feels would  
18 be relevant in this kind of a consideration, both now today  
19 given the database that we have, and then if something else  
20 is needed, what would that be?

21 DR. RAMSEY: Dr. Choyke, did you have a  
22 comment?

23 DR. CHOYKE: Thanks. Yes. I agree actually  
24 with a lot of what was said. I didn't mean to appear to be  
25 reacting, but I think this is a kind of a unique situation

1 we have here. We have an agent that's been around for a  
2 fairly long time, and we have a huge track record. We have  
3 a mandate of some sort from Congress, and so it's very  
4 unusual, but in the future, if a sponsor came before us  
5 with an agent that promotes a functional assessment, I  
6 think what we'd really like to see is the theoretical  
7 underpinning, the animal models where you can do things you  
8 can't do in people, and then some clinical-based evidence  
9 of an example in essence of where the application looks  
10 strong, and from that, you can't obviously do those kind of  
11 complicated studies in a huge population of people, but in  
12 essence what we're doing here is taking a model of disease,  
13 the kind of evidence that you look at, and extrapolating  
14 from that to other kind of entities that are similar, and I  
15 think that's a very reasonable approach overall, and I  
16 think if a sponsor successfully documented the theory, the  
17 animal background and then one or two examples where it was  
18 convincingly similar to an animal model, that they would  
19 have a functional application that would be acceptable. So  
20 I'm very content with that kind of model.

21 DR. TULCHINSKY: I think that's a very well-  
22 positioned argument, and it is interesting that other  
23 imaging modalities would certainly derive a clear benefit  
24 from what has transpired.

25 The Congress specified those positions for PET

1 and radiopharmaceuticals. As we look at the draft  
2 document, and I hope that those committee members that came  
3 today have looked at that very carefully, and the draft  
4 guidance is for the imaging pharmaceuticals, not to  
5 radiopharmaceuticals.

6 I see Ms. Axelrad looking at the book again,  
7 and I think that that is very useful for the imaging  
8 community in general. On my personal level, I'm very  
9 pleased to see that.

10 DR. PONTO: This radiopharmaceutical represents  
11 a tool. It's a tool to measure blood flow. We already  
12 know that blood flow is a relevant parameter in the brain  
13 or we would not have approved HMPAO and ECD. We would not  
14 be using that.

15 So we need to look at the effectiveness of this  
16 particular tool to measure blood flow, and as anybody  
17 that's looked at my CV, you'll know that probably 90  
18 percent of my papers have been written on O-15 water, and  
19 they have not been limited to the brain only.

20 I have published work on the use of this tracer  
21 looking at blood flow in the bone marrow in normal patients  
22 and in people with leukemia and also in solid tumor, and I  
23 would advocate that looking at the mechanism of action, you  
24 presented a myocardial justification for a cerebral measure  
25 of blood flow, that if we could limit this indication to

1 looking at blood flow and then use it wherever it's  
2 relevant.

3 DR. TULCHINSKY: I would like to echo that  
4 comment and say that it would be appropriate in my view to  
5 specify that this tracer is useful for assessment of blood  
6 flow, including special clinical situations that it would  
7 seem to be demonstrated useful and list those. That would  
8 be by far more fair and coherent approach with what the  
9 statute is telling us in my personal belief as a  
10 professional.

11 DR. RAMSEY: Dr. Conti?

12 DR. CONTI: Two quick comments. One, I want to  
13 go back to what Dr. Choyke mentioned a few moments ago.  
14 His statement should be reread to the committee because I  
15 think this is the most key aspect of where we want to go  
16 with these types of radiopharmaceuticals.

17 These are inherently safe drugs for the most  
18 part, and the fact is if we can use animal data theoretical  
19 as a foundation for evaluating these drugs and cite  
20 examples, they don't have to be extensive examples in terms  
21 of outcome data necessarily for radiopharmaceuticals, again  
22 they are safe, if they do mimic what we've already proven  
23 in a validation study in animal models, then we should go  
24 ahead and approve these pharmaceuticals and get them out  
25 into the community so the data can be generated following

1 approval, much the same way as we do in devices.

2 So I think what he stated in his comments a few  
3 moments ago should be taken to heart by the committee and  
4 by the FDA.

5 The second point I'd like to make is that we  
6 were reluctant to pursue a general perfusion application  
7 for this pharmaceutical because of the limited nature in  
8 the body applications, but I actually believe that that's  
9 the appropriate way to go because this is a perfusion  
10 tracer that can be used in the heart. It can be used in  
11 the brain, and the data support it. It has been validated  
12 in a number of situations, and the data would support its  
13 use as a general perfusion imaging agent, and the community  
14 would support that.

15 DR. KONSTAM: You know, I actually am looking  
16 forward to us discussing the data. It sounds like we're  
17 spending an awful lot of time discussing whether it's  
18 relevant to discuss the data, and I'm frankly finding that  
19 discussion extremely disturbing.

20 I think that personally, I don't care what's in  
21 the law. Personally, I think comments like it's safe, I  
22 find very disturbing because the burden on the FDA is not  
23 only to show that it's safe but also to show that it's  
24 effective, and, you know, again I'm going to keep coming  
25 from a very different perspective, which is that I don't

1 think any of the physicians around the table really believe  
2 that we are in this business to treat biochemical processes  
3 or physiology, and therefore the public health really  
4 demands that we seek a standard of documenting that we're  
5 making a difference in patient care.

6 To me, the argument here is very different. To  
7 me, the argument here is to what extent are we willing to  
8 compromise on that standard because we know so much about  
9 the biochemical process or the physiologic process that  
10 we're studying, that we're fairly certain that if we study  
11 that process, we will make an impact on care, even though  
12 we haven't studied it.

13 Now, in this case, again I come in with a good  
14 deal of ignorance because I don't know much about the  
15 fields being discussed today, but I find it -- so maybe  
16 that's the limitation or maybe that's an asset because I  
17 find it personally very difficult to make the leap to  
18 simply say because I know something about cerebral blood  
19 flow, I know I have helped myself in managing the patient.

20 Now, I guess to me, I think really that's where  
21 this discussion sits. How much do we really know about the  
22 physiology? How much do we know about this agent's impact  
23 on the physiology, and on the basis of that, how much are  
24 we willing to compromise on the usual standards of holding  
25 an intervention or a drug to an extremely high level of

1 standard, to say I am impacting on care, the drug is doing  
2 clinically what I think it's doing, and I think that's  
3 where we're going to have to identify a compromise.

4 I think we're going to have to come out and  
5 say, well, in such a circumstance where the physiology's  
6 very well known and the agent on a physiologic basis is  
7 very well known, then maybe we don't need two 2,000-patient  
8 randomized clinical trials, each with a P value of less  
9 than .05 showing an effect on survival or something like  
10 that.

11 But we've got to decide what is the standard.  
12 There needs to be some clinical standard, and I look  
13 forward to discussing the data here and seeing whether the  
14 data here reach some acceptable level of standard based on  
15 what we know the agent does physiologically.

16 DR. TULCHINSKY: My light was first. Thank  
17 you.

18 I think the comment is well made, and you're  
19 right. Your ignorance has helped us today as we discuss  
20 different aspects of this matter, and specifically what  
21 you're bringing up is, the question is, is it effective?

22 One way to look at that same question is, is it  
23 effective in demonstrating blood flow in general, and I  
24 think that FDA has posed a very voluminous body of  
25 literature that points to the answer, yes, it is effective

1 in demonstrating blood flow. It's as close to the nature  
2 as you can come to demonstrating blood flow.

3 Now, is it useful in specific conditions? I  
4 think if you're looking to the package insert in finding  
5 that answer, you are simply looking in the wrong place.  
6 That belongs in the textbooks. That belongs in current  
7 articles, and that belongs also in some part to reside in  
8 your clinical judgment.

9 If you ask yourself, and I hope you will -- you  
10 might answer aloud so we can all hear. Among the  
11 medications that you use clinically, how many times out of  
12 all prescriptions that you write is it for package insert-  
13 directed indication, and if your answer is 90 percent, I'll  
14 be stunned. If it's 50 percent, I'll be surprised, but  
15 I'll believe it. If you say it's about 25 to 30 percent,  
16 that to me might be closer to the norm.

17 But what that tells you is that I think as the  
18 science progresses, that you modify your applicability of a  
19 particular medication, and it's specifically true for  
20 diagnostic agents, and that's how you practice medicine,  
21 but I think the way that we approach radiopharmaceuticals,  
22 and the way that has been discussed many times over and  
23 over again and very well put in written word is that I  
24 think we need to start thinking, as Jonathan was saying,  
25 about functional application, list specific conditions

1 where it has been shown but not limit the physician to  
2 that, and follow the data-driven therapeutic position or  
3 Harrison's textbook or whatever the specialty textbook that  
4 you have and your clinical judgment.

5 On that, I'll close.

6 DR. RAMSEY: Dr. Ziessman? I'm sorry, Dr.  
7 Houn. I know your light has been on for awhile, and I'll  
8 call on you next. Oh, okay.

9 DR. ZIESSMAN: I'm sympathetic with the FDA  
10 today because they're trying to find their way in how to  
11 look at a new approval process for radiopharmaceuticals, in  
12 this case particularly radiopharmaceuticals, and I think  
13 what's becoming evident is that I think most of us  
14 appreciate the data is there for approval of this  
15 radiopharmaceutical for blood flow, is the presentation, I  
16 think, today that has us bothered because I think your  
17 concern's appropriate, that we haven't discussed the data,  
18 and that the data that was presented probably isn't  
19 adequate for our approval. But I think we all know that  
20 it's there, and that's the problem I think we face.

21 I don't have a quick answer how we should  
22 proceed as a result.

23 DR. RAMSEY: Dr. Houn, I think, is next.

24 DR. HOUN: I just wanted to say that across the  
25 Center for Drugs, drugs are developed in a manner where

1 preclinical studies in animals are done first to try to  
2 assess safety and appropriate dosage and get an idea of  
3 what is the pharmacologic action of this drug. Then  
4 they're assessed in small numbers of humans for safety, and  
5 then larger numbers in terms of trying to test a hypothesis  
6 in terms of the drug action. So what was said by Dr. Conti  
7 really is not different from the drug model.

8 I think the reliance purely on biochemical  
9 information, I mean, we know sudinitil citrate inhibits  
10 degradation of CGMP. That's a biochemical indication.  
11 What does it do? Well, it's believed it vasodilates, and  
12 that's why it was being developed as a drug for  
13 hypertension. It turns out it causes erections. It's now,  
14 you know, Viagra. This is how, you know, biochemical  
15 activity needs to be tested in humans to define relevancy,  
16 and I don't think people are saying we're not going to be  
17 doing human drug trials.

18 I just want to emphasize how important that  
19 part of the information is for the drug development  
20 process.

21 DR. RAMSEY: Dr. Links?

22 DR. LINKS: I thought that Dr. Konstam  
23 beautifully identified what the central issue is we're  
24 discussing and bringing it back to the specific case we're  
25 trying to look at this morning.

1           It seems to me that if you have what I'll call  
2 a functional indication that it measures cerebral blood  
3 flow, then the primary evidence that should be presented to  
4 support that indication is evidence about the tracer's  
5 ability to measure blood flow, such as the dog heart study  
6 that was shown but obviously going beyond that single  
7 study.

8           Now, fortunately, in the literature, there are  
9 examples for O-15 water in other organs, in other species,  
10 that go beyond the dog heart. But if we're truly to  
11 embrace the new final rule that allows these different  
12 types of indications, then the primary data on which to  
13 support or not support the indication must be data having  
14 to do with that indication. So that's the first point I'd  
15 like to make.

16           The second point I'd like to make is that I  
17 really like the use of the word "example" that I think Dr.  
18 Konstam used, Dr. Choyke used. Obviously, it's insane to  
19 propose a drug for which there's no clinical application,  
20 and it's not helpful to not present any evidence clinically  
21 that the drug is making a difference in patient management  
22 one way or another.

23           What I'd like to emphasize, however, is that at  
24 least to me, the degree of evidence required for an example  
25 is significantly less than the degree of evidence required

1 if your indication is diagnosis- or outcome-based.

2 So the studies presented this morning in my  
3 opinion absolutely satisfy my criteria for example, whether  
4 or not they would be sufficient to satisfy the criteria of  
5 evidence if the indication itself was based on diagnosis or  
6 outcome.

7 DR. RAMSEY: Dr. Konstam?

8 DR. KONSTAM: Well, you know, I worry about the  
9 word "example" because I'm not sure what it means, and I  
10 mean, we've seen some beautiful examples of cases today,  
11 and I think they were very helpful to me because I've never  
12 seen them before, and again I don't know too much about it.  
13 So they're very helpful to me in terms of putting this in  
14 perspective and bringing this down to the real world.

15 On the other hand, I was very worried watching  
16 them because in my former days as a radiologist, I've seen  
17 many presentations of examples of cases, and people show  
18 their best cases, and even if they're not showing their  
19 best cases, what does it mean, and how do you translate  
20 that into statistics? How do you translate that into what  
21 the impact is on the patient, and so I don't know what  
22 example means.

23 I guess I think that -- well, I guess maybe we  
24 need to ask ourselves that question. If we say, well, the  
25 example is the Grubb study, it's not an example of a case

1 report. It's an example of a potential specific clinical  
2 indication. What's that indication? Prognosticating in  
3 the presence of carotid occlusion for subsequent stroke.  
4 Well, I think we actually should look at that article and  
5 start talking about that right now or soon because I have a  
6 1:00 flight, because to me, that was the closest thing in  
7 the data set that was actually evidence that the agent used  
8 for the biochemical or the physiologic indication that is  
9 being requested will mean something clinically.

10 I think we should tear apart that article and  
11 examine the statistics in it and examine the population and  
12 examine the validity because that's the one that will help  
13 me make a decision whether I think this agent should be  
14 approved or not.

15 I think that the rest of the body of data that  
16 Dr. Love presented, you know, I feel was really fairly  
17 weak. I feel that the supportive studies to the Grubb  
18 study seemed weak to me. They seemed duplicative. It's  
19 not clear that they're separate populations.

20 I think that the sickle cell case is exciting  
21 and interesting. It doesn't quite make it for me because  
22 it's not clear to me how that translates into influencing  
23 care, and so I get the sense that this could be a useful  
24 agent, but when it comes down to me asking the FDA to say  
25 this is safe and effective and ought to be used in clinical

1 practice, I want more than that, and, yes, physicians are  
2 going to use their own judgment and are going to use off-  
3 label applications all the time, but that's not the FDA's  
4 problem.

5 The FDA's problem is to declare that something  
6 is safe and effective, and so I think we'd better look at  
7 the data and ask ourselves whether it's safe and effective  
8 for examination of cerebral perfusion based on a  
9 clinically-relevant application.

10 DR. PONTO: I understand completely your  
11 concern. If this is all I knew about O-15 water, I would  
12 not want to approve it. The trouble is, I have a file  
13 drawer this big that literally has hundreds of articles in  
14 it. Dr. Herscovitch has done a validation back in '83,  
15 wasn't it, of this whole process, and knowing that, that's  
16 why I expressed confusion at why we were looking at these  
17 particular articles to approve this particular drug for  
18 this indication, and if we only had this data, I would also  
19 have the same concerns that you have.

20 DR. TULCHINSKY: But given the data we do have,  
21 again it's a good suggestion. We should look at the  
22 article, and I have looked at the article. We're talking  
23 about Grubb's article, of course. It's again in our hand-  
24 out, Volume 5, and what I'd like to hear instead of a  
25 general comment, what is the concern that you have about

1 that article?

2 DR. KONSTAM: Well, I don't have any concern.

3 DR. TULCHINSKY: So what is the comment then?  
4 I think it was very well presented by the FDA  
5 representative.

6 DR. KONSTAM: No, I guess my concern is that  
7 we're not discussing it. That's my concern.

8 DR. TULCHINSKY: That is our homework, is to  
9 look at it. If you have a concern, address it.

10 DR. KONSTAM: I thought you were saying that we  
11 don't even need to look at it.

12 DR. TULCHINSKY: Oh, no, no.

13 DR. KONSTAM: I thought you were saying that  
14 all we have to do is know that it has a physiologic effect  
15 and that's that.

16 DR. TULCHINSKY: Then my comment was taken out  
17 of place. My point is this, that you have a tracer that  
18 has a physiological indication. Say, like this one. You  
19 document that it's safe, and you study it in animals, then  
20 you proceed to the clinical model, and that has been done.

21 DR. KONSTAM: Right.

22 DR. TULCHINSKY: Hasn't it? I mean, this  
23 tracer went on to the clinical arena. Then it has shown to  
24 work in certain scenarios, not maybe to the same rigor as a  
25 commercial product that has a sponsor because again the

1 financial power to show that is just not behind that drug.

2           However, the scientific studies were well done.  
3 The Grubb article was published in JAMA, a publication that  
4 I hope will grow into respect tremendously. I'm not saying  
5 you should not show that it's useful in some clinical  
6 situations. It does show the blood flow in clinical  
7 scenarios in humans. No, that is not the point.

8           But the point is that once you have shown it in  
9 a number of clinical scenarios, that it does demonstrate  
10 the cerebral blood flow, then you approve it for cerebral  
11 blood flow, including situations -- and that's what I think  
12 I said in my first comment, including the situations in  
13 which it has specifically been studied, but --

14           DR. KONSTAM: Now, this is very --

15           DR. TULCHINSKY: -- don't the other one to it.

16           DR. KONSTAM: No. This is very helpful. So  
17 maybe we could, based on what you're saying, maybe you  
18 could or others around the table could quantify for the FDA  
19 a little bit more clearly, you know, in this circumstance,  
20 what are the standards of clinical data that we'd like to  
21 see? And then maybe we could look at this data set  
22 relative to that.

23           So for example, let's take the standard and  
24 work backwards from it. You know, the standard for drug  
25 approvability is two randomized clinical trials with P less

1 than .05 with the data set in hand by the FDA, that it's  
2 being used in a population, that it's been studied in the  
3 population in which it's likely to be used, that the data  
4 set is clean, that there was a preset protocol established,  
5 and that it was adhered to, and that we have good evidence  
6 that it was adhered to, and that the data set has validity  
7 and integrity.

8           So those are the starting points. So maybe you  
9 could articulate in this case which of those specifically  
10 would you be willing to compromise, and what specifically  
11 would be the standard of clinical investigation  
12 specifically that you would say that, short of that, that  
13 you would say when we come back and look at this data set,  
14 we could say yes, we can approve this agent?

15           DR. RAMSEY: Excuse me. I'm going to take the  
16 chair's prerogative. Dr. Herscovitch?

17           DR. HERSCOVITCH: Yes. I have a few comments,  
18 some of which may be repetitive, but I think have to be  
19 said, is that, firstly, in terms of O-15 water as a  
20 cerebral perfusion agent, it is an extremely good agent,  
21 probably the best agent there is on the basis of a  
22 tremendous amount of experience.

23           Secondly, I will say that none of that  
24 experience and none of those data are in this package. So  
25 I would have to disagree with Mark Tulchinsky who said that

1 this package shows that it's useful for measuring CBF. I  
2 would say that this package does not show that it's useful  
3 for measuring CBF at all, and this in part, I think,  
4 reflects to the approach that the FDA probably felt they  
5 had to use, especially not including all the animal  
6 validation studies, and also to their very restricted,  
7 perhaps unfortunately restricted, choice of papers, not  
8 doing a full literature search as was done yesterday with  
9 the myocardial blood flow agents and fludeoxyglucose.

10 I think the question is to a certain extent  
11 what is the question? For example, looking at the question  
12 we have to answer, Number 4, based on the presented review.  
13 Well, even forget about that. Just in general, the  
14 question is, do you think water is safe and effective to  
15 measure cerebral blood flow in patients with a variety of  
16 cerebral vascular diseases?

17 Well, the answer, I feel, is yes, because O-15  
18 water gives you excellent maps of cerebral perfusion. So  
19 is that the question? The answer is yes. It gives you  
20 excellent maps of cerebral perfusion in virtually any  
21 disease. So if that is the question, then a proposal could  
22 be designed to answer that.

23 Then there is another question. Is the  
24 assessment of cerebral blood flow by O-15 water or other  
25 methods useful in the diagnosis and management of specific

1 diseases, and surprisingly, the answer is not very many,  
2 and even in diseases like cerebral vascular disease, when  
3 the problem is by and large in the plumbing, isolated  
4 measurements of cerebral blood flow, either quantitatively  
5 or just a map, are not particularly useful in terms of  
6 making a decision about what to do with the patient.

7           The only other comment I'll make is concerning  
8 the Grubb paper which we seem to be giving a lot of stock  
9 to in this process, is that my opinion, and I think we  
10 should discuss it, is that's an extremely well-done paper,  
11 probably one of the best papers showing the clinical  
12 application of PET, but, on the other hand, it is not  
13 particularly relevant to deciding whether CBF is a useful  
14 perfusion agent because the main outcome measure there was  
15 the oxygen extraction fraction that was measured with a  
16 different tracer in conjunction with CBF. Actually one can  
17 even show, I believe, that if the CBF is off, it kind of  
18 cancels out, and you still get a good measure of the oxygen  
19 extraction fraction.

20           So if we were discussing the utility of those  
21 three O-15 tracers that one needs in this case to measure  
22 the oxygen extraction fraction, the Grubb paper is an  
23 extremely good place to start, and I would contend short of  
24 the NDA-type study that you mentioned, this is probably the  
25 best paper in the literature to meet requirements of a

1 committee such as this.

2           Unfortunately, I don't think it meets the  
3 requirements to answer the question about O-15 water. So I  
4 think we are really in a conundrum. We are in a  
5 philosophical conundrum about whether we are approving a  
6 perfusion agent or something that is useful for the  
7 diagnosis of a specific disease, and we are also in just a  
8 bit of a logistical conundrum because the FDA experts,  
9 unfortunately, and I think but for reasons which I totally  
10 understand, did an assessment which doesn't necessarily  
11 provide us with all the data we need. So we're really  
12 stuck here.

13           DR. RAMSEY: I just want to make one comment  
14 which I've tried not to make comments, but as a  
15 neuroradiologist, I know my surgeons do respond to the data  
16 obtained by regional cerebral blood flow when they look at  
17 those patients, and they use it to make clinical decisions,  
18 but that said, I thought at this point, I would jump in  
19 here and just read the question since we've alluded to it  
20 several times to see if we can then direct our attentions  
21 to that.

22           It's Question 4. "Based upon the presented  
23 literature review, do you think water O-15 injection is  
24 safe and effective in positron emission tomography (PET)  
25 imaging to measure cerebral blood flow in patients with

1 cerebral vascular disorders associated with ischemia,  
2 hemodynamic abnormalities, occlusion and other vascular  
3 abnormalities?"

4 DR. KONSTAM: Ruth, before we get into the  
5 question, I don't know whether this is appropriate or  
6 inappropriate, but I personally would like to hear some  
7 discussion on the panel with respect to the question I  
8 asked, which is, in this circumstance where the principle  
9 motivation for approvability is as a physiologic marker?

10 If we accept that people use the word  
11 "example," I think -- I don't like the word, but if we're  
12 to accept that even in those circumstances, we need to  
13 document that the agent has a role to play clinically,  
14 based on data that can be analyzed statistically and  
15 meaningfully -- I mean, I think it's worth having some  
16 discussion about what people think that means in terms of  
17 criteria.

18 Does it mean a single study? You know, what  
19 are the standards of that study? You know, what do we mean  
20 when we say example, and I for one would like to see -- let  
21 me throw something out. I'd like to see one extremely good  
22 study where the basic findings are beyond reproach based  
23 on, as best we can tell -- now, here we have, you know, an  
24 article in the literature. Ideally, the FDA would have the  
25 data set and the original protocol. So that's not here,

1 but those would be ideally.

2           Ideally, you'd have a study. You'd have the  
3 data. You'd be able to validate the data. You'd be able  
4 to validate the statistical approach, and that the study  
5 has some clinically-relevant impact on something,  
6 prognosis, relative to some other diagnostic method that we  
7 are very confident has a major impact on clinical outcome.

8           That is to say, what I'm trying to approach is  
9 to say basically this is analogous to having a  
10 process/outcome link, basically. It's saying that we're  
11 going to go through the process of measuring cerebral blood  
12 flow. What we really want is better patient outcome, and  
13 we're going to wind up being very confident that if we  
14 measure cerebral blood flow well, and we have the data to  
15 know that we were measuring it well, then that will impact  
16 on outcome.

17           I guess that's what I'm looking for. So now go  
18 back. A single study that does that, that somehow permits  
19 us to make that process/outcome link, to say yes, if I  
20 measure cerebral blood flow by this agent accurately, I  
21 will to a fairly good degree of confidence know that I have  
22 impacted on clinical care in some meaningful way.

23           Is one study enough? I'd probably like one  
24 study and at least a fair amount of support around that  
25 from other studies that may not be quite as good but at

1 least point in the same direction. Internal consistency  
2 within the study would be another thing that would be  
3 useful.

4 So that's my throwing out the idea about what  
5 I'd like to see, and maybe we could measure this data set  
6 against it. Maybe it meets it, maybe it doesn't. I don't  
7 know. I haven't decided yet, but maybe we could have some  
8 reaction of that.

9 DR. TULCHINSKY: I totally agree with the  
10 comment made, and that is, some standards need to be  
11 developed, and clearly there is great deal of room for  
12 making the process better.

13 This is just really a first step. I consider  
14 it to be a step in the right direction and a very good  
15 step. FDA has done an exceptionally good work, and with  
16 all due respect to the comment that maybe not all the  
17 papers were submitted, but please do realize that if all  
18 the papers were submitted, and Dr. Ponto pointed out that  
19 she has a whole drawer full, I would never be able to  
20 physically make it to this meeting.

21 I had a hard time dragging the five volumes,  
22 but I think as a member of the panel, one ought to look at  
23 what has been submitted, and if one looks again carefully  
24 at what has been placed in our package, there are  
25 references, although not xerox copied for us, but there are

1 references to fairly good number of basic papers, and it's  
2 a good array of papers.

3 If you look at the reference that has not been  
4 xeroxed, it has the original articles by Bergmann, for  
5 example, on Page 6 of the initial section in Volume 5.  
6 I've looked at that paper. I didn't have to have FDA make  
7 a xerox copy of it for me. I'm sure that there were some  
8 things missed.

9 Again, using my intellectual ability to  
10 synthesize, it seems to me that what has been proposed is  
11 very reasonable. What are the criteria, though? I think a  
12 separate meeting probably is worthwhile to talk about the  
13 criteria. I don't think we're going to resolve it today,  
14 but one good paper -- what is good? How many patients?  
15 How well would one statistically analyze it, and what are  
16 the methodologies to be applied?

17 It's all excellent questions. I think we need  
18 to spend some time thinking about it. 50 patients at least  
19 to make it a good paper. Statistical analysis, and that's  
20 a discussion that probably deserves different time and  
21 different place.

22 DR. AMENDOLA: Can I make a small comment? I  
23 was wondering why some of the seminal papers were not  
24 included in the review, and I was wondering if looking at  
25 these papers, they are fairly new, and I wonder if that is

1 because maybe 10-15 years old, that is the reason that the  
2 FDA didn't include it.

3 Looking at the Grubb paper, another thing  
4 caught my attention, that they had to end the study early  
5 because of lack of funding, and I was wondering if that,  
6 the lack of funding, is something that has to do with the  
7 dearth of material presented, that some of the other  
8 studies that didn't reach that critical number of 50  
9 patients to be accepted for the FDA review.

10 DR. RAMSEY: Dr. Conti?

11 DR. CONTI: Again, two quick comments. One, I  
12 wanted to just state as far as the literature was concerned  
13 that what was submitted to FDA from the ICP were  
14 representative articles, not the entire world's literature  
15 on 0-15. So this is an important distinction.

16 Secondly, I want to remind the committee that  
17 there are a number of perfusion-related agents that are  
18 currently with label. Okay. These are approved  
19 radiopharmaceuticals for perfusion imaging. There is  
20 precedent. There is data that supported those initial  
21 perfusion imaging agents for their approval.

22 I would also like to stress that there are  
23 other modalities that use the concept of perfusion imaging.  
24 So again, I don't think the committee, from the public's  
25 perspective, should spend a great deal of time on focusing

1 on the concept of whether or not perfusion is an important  
2 clinical question. This has already been addressed through  
3 other discussions with other approvals, but to focus on the  
4 equivalency of this particular tracer that has been  
5 validated in animal studies and has been shown in a number  
6 of representative articles to be clinically useful, that's  
7 where the focus should be.

8 DR. RAMSEY: Dr. Links?

9 DR. LINKS: In that regard, if we cast our mind  
10 back to previous agents that we've considered in this  
11 committee, what I would call the standard, even if you're  
12 just going to focus on diagnostic accuracy, the standard  
13 has changed from agent to agent because the context in  
14 which the agent was to be used has changed, and the  
15 competing choices were of either good quality or poor  
16 quality or non-existent in the different scenarios.

17 So I'm personally a little loathe to talk about  
18 standards of any type in that regard because, for example,  
19 it would only be natural to say, well, unless the  
20 indication is a diagnostic accuracy indication, unless the  
21 diagnostic accuracy is X, we're not going to approve it,  
22 and we've approved agents whose diagnostic accuracy was  
23 relatively low by most conventions but was sufficiently  
24 high to make a difference clinically because there was  
25 nothing else available to compete with the information.

1           In the same way, I'd be loathe to talk about P  
2 values, sample sizes, et cetera, for any kind of paper.  
3 For instance, let's say that we're talking about a  
4 perfusion agent, and the issue is one of a change in  
5 management based on the outcome of the imaging study.

6           I pose the question in what fraction of the  
7 patients would the management have to be changed in order  
8 for you to say that the agent was a useful agent? That  
9 would be a very --

10           DR. KONSTAM: Any patients. But I look to any  
11 patients. I mean, you could say one in a thousand. I  
12 mean, this is --

13           DR. LINKS: Then we're together.

14           DR. KONSTAM: Just a second. I don't think we  
15 are because this isn't a discussion about cost  
16 effectiveness. We're not getting into costs here.

17           So if you knew for sure that an agent was going  
18 to influence therapy one in a thousand cases, I think that  
19 that to me -- I don't know what the cut-off for that would  
20 be, but that would satisfy me.

21           The question is how do you know it? How do you  
22 know from a study of 50 patients or a hundred patients or a  
23 thousand patients or 10,000 patients that therapy was  
24 influenced in one of a thousand patients?

25           The way you know that is by statistics. That's

1 how you know that a finding is valid and correct. So the  
2 level of impact is not what we're discussing here. The  
3 issue really is -- and I accept Dr. Conti's point. I will  
4 state his point a different way.

5 I think what he is making a plea for is to say  
6 that, you know, we know so much about the impact of  
7 cerebral blood flow measurement and how that impacts on  
8 outcomes, that we don't have to remeasure outcome with this  
9 agent. Okay?

10 Now, I would challenge that that's really true,  
11 but then again I don't know anything about it. So maybe it  
12 is true. But I really am concerned when you say I don't  
13 need a P value because you do need a P value because if you  
14 don't have a P value, you don't know that the study is very  
15 likely to be correct or not.

16 DR. LINKS: Well, let me rephrase it then.  
17 Let's say that I do a study with 50 patients, and the  
18 outcome is changed in one. I can certainly express a  
19 confidence interval of what in the overall patient  
20 population the most likely or the range of percent of  
21 patients in which the outcome would be changed is, but a P  
22 value per se is not necessarily the most meaningful  
23 statistic.

24 In other words, maybe we're just quibbling, but  
25 I don't want to have standards that are so explicitly

1 defined for certain paradigms, that there's no way of  
2 fitting another paradigm into it. So if by P value, you're  
3 really not talking about necessarily a P value but rather  
4 some way of characterizing confidence, then we're together.

5           Even in a case like that, I would hope that we  
6 don't have to agree on a minimum fraction in which the  
7 outcome would be changed or a minimum diagnostic accuracy.  
8 Obviously we want to characterize the certainty with which  
9 we're saying that the outcome will be changed by thus and  
10 so or the accuracy is thus and so. We have no disagreement  
11 there, but the statistics they are characterizing are  
12 certainty rather than providing some sort of threshold  
13 operation for action or no action.

14           DR. RAMSEY: Ms. Beaman?

15           MS. BEAMAN: Well, I'm still floundering over  
16 here between the information that's presented and the  
17 information that may very well be out there.

18           From what I've read, the agent perhaps does  
19 indeed measure blood flow. It's a diagnostic tool, to be  
20 used as the diagnostic tool. There may be volumes upon  
21 volumes of information out there, some of which I'm sure  
22 people around this table have some knowledge of.

23           It isn't here. It wasn't presented, and from  
24 what is presented and even looking further into some of the  
25 indications referenced here, I didn't find some answers,

1 and one question that is still there is, if it's used as a  
2 diagnostic tool, is it necessarily of sound clinical  
3 application at the expense of the patient? So you know the  
4 blood flow, the degree of blood flow. What do you do?  
5 How do you use it? From a quality of life standpoint,  
6 please help me out here.

7 DR. TULCHINSKY: Yes, that's a tough question  
8 to answer. I don't think anyone around the table would  
9 have a clear-cut answer for you, but again, I would support  
10 my earlier statement that studies to show clinical  
11 effectiveness to that degree as to improving the quality of  
12 life are very energy- and finance-intense endeavors.

13 Not many medications that we use today would  
14 have that information in it, but I think it would be a good  
15 start to look at what we have in front of us and either  
16 agree or disagree. I personally agree that it does measure  
17 blood flow, cerebral blood flow in this case, and one would  
18 have to rely on clinical judgment as to how it will be used  
19 along with the information provided.

20 It will not be unlike 95 percent of what we do  
21 today. It will be very much along the lines of our medical  
22 practice, but it is not to say your question does not need  
23 one seeking answer. I think we are in pursuit of that  
24 answer, but the lack of it today at the table in my view  
25 should not preclude us proceeding.

1 DR. RAMSEY: Dr. Conti?

2 DR. CONTI: I apologize for having to walk a  
3 distance here, the delay, but I want you to ask the patient  
4 who had transfusion therapy and sickle cell whether it made  
5 a difference to that particular patient that we did a test  
6 on that child or his or her parents, and I want you to look  
7 at the data in the sickle cell paper and use that as an  
8 example of altered management.

9 A patient received a specific therapy on the  
10 basis of the PET findings. It's a very tangible evidence  
11 that that did occur. It's published.

12 I also want to point out that this committee,  
13 as far as I remember, yesterday approved a perfusion  
14 imaging agent for the heart called N-13 ammonia. So keep  
15 this in mind when you're doing these evaluations and keep  
16 in mind, as I said earlier, that perfusion imaging and  
17 perfusion-based assessments, whether it be with PET, SPECT,  
18 MRI, ultrasound, transcranial doppler, for example, are in  
19 fact there. They're approved, and they're used clinically,  
20 and decisions are made on them every day.

21 DR. AMENDOLA: I think that if you look at the  
22 Grubb article which I think most of us, if not all, agree  
23 that is a very sound article, it provides the answer to  
24 your question. They identify the set of patients which are  
25 at high-risk category of stroke, and their assessment of

1 these patients going to have surgery.

2 I think that if you read the other articles, I  
3 agree with Dr. Conti's opinion that this agent has a really  
4 valuable indication many times as an important impact on  
5 clinical decisionmaking.

6 DR. CHOYKE: Can I make a comment about, you  
7 know, this discussion, and, you know, I started out fairly  
8 happy with the evidence until I heard two O-15 experts say  
9 that they didn't really see the evidence here for cerebral  
10 blood flow, which is what the question talks about.

11 Yet, you know, we know they both -- I hasten to  
12 add that there's voluminous data outside this room that  
13 exists, and, you know, so, where my own thinking is, is  
14 that are we that rigid that we can't bring in expert  
15 opinion that hasn't been presented officially here?

16 I really think this agent should be approved,  
17 especially in view of what we did yesterday to be  
18 internally consistent, but on its own merits, I think it  
19 should be approved based on what I've heard and other  
20 comments, but, you know, I think we may be getting into  
21 almost a legalistic rigidity in terms of just considering  
22 what we have before us, and I think the common sense  
23 decision is to go forward with O-15, but, you know,  
24 legalistically, I don't think we have it. So that's where  
25 I am.

1 DR. RAMSEY: Dr. Ziessman?

2 DR. ZIESSMAN: Yes, I think that's right. I  
3 mean, I think the problem today is the process, and we're  
4 just trying to figure out and learn the proper process to  
5 approve radiopharmaceuticals for these new indications, and  
6 I think we all agree that if we had to do this over again,  
7 this would not have been the way we would have looked at  
8 this radiopharmaceutical today. We would have had stronger  
9 and more appropriate basic science information, more  
10 appropriate animal studies, and it seems to me then if we  
11 presented clinical data, I think we may have our own  
12 standards, but I don't think the standard has to be very  
13 rigid.

14 I think if we had expanded on what Dr. Conti  
15 presented, for example, had multiple experts come in and  
16 give us information like that or reviewed literature that  
17 gave similar type of information, that we had multiple  
18 examples that showed us how it impacted on clinical care,  
19 that that would have satisfied us for these -- they would  
20 have satisfied me for these indications, but I don't think  
21 we ought to penalize this radiopharmaceutical because of  
22 what's happened with this process because of the situation  
23 that we're floundering in trying to find the proper way to  
24 do this.

25 I think the radiopharmaceutical ought to be

1 approved. I think we all understand that this is an  
2 excellent radiopharmaceutical, that it has clinical  
3 utility. The process is what has suffered today.

4 DR. RAMSEY: Dr. Love?

5 DR. LOVE: If I could offer an approach that  
6 might help. We've certainly been talking ourselves on what  
7 is the best way to proceed that would help us in this, and  
8 I think it's quite clear that there are other data out  
9 there from your comments.

10 Yes, the committee is free to consider other  
11 opinions and information discussed on the panel. Obviously  
12 from our perspective, if you wanted to make some sort of  
13 conditional or preliminary type of vote, that would also be  
14 acceptable to us on perhaps the condition that these other  
15 articles are reviewed, and we can either get that  
16 information to you or develop some other mechanism, if you  
17 wish, if you want to see it, or you can give us a  
18 preliminary assessment and whatever recommendations you  
19 have for us in terms of looking at the other articles that  
20 are available.

21 So there are a number of other options that the  
22 committee could choose to follow, other than a strict vote.

23 DR. PONTO: I would like to propose a change in  
24 the question. I would say based upon the literature, do  
25 you think 0-15 water injection is safe and effective in

1 positron emission tomography imaging to measure blood flow?  
2 Limit it to that.

3 DR. RAMSEY: Mr. Hammes?

4 MR. HAMMES: I've just been sitting here taking  
5 this all in and trying to digest it, and what I call us to  
6 personally, you know, I believe, and I've done some  
7 literature review in this through the years, that oxygen-15  
8 water does measure blood flow.

9 I don't see that data here, you know, and based  
10 on the presented data, I couldn't say that's the case, but  
11 I do believe that's the case.

12 But, overall, when I look at the presentations  
13 yesterday and our deliberations and all the evidence, I had  
14 a comfort level in what we were doing yesterday that was  
15 orders of magnitude stronger than my comfort level with  
16 this drug today, and I just don't feel comfortable based on  
17 what I have to, say, answer this question yes, you know.

18 Laura's proposed question, I'd feel a little  
19 more comfortable with, but, you know, you still have to see  
20 the data, I guess. Without seeing the data, it's hard to  
21 say yes, and this is compounded somewhat by the knowledge  
22 that I have, that, hey, we have other cerebral blood flow  
23 tracers. I don't see the drastic need for approval of a  
24 third cerebral blood flow tracer based on flimsy evidence.  
25 So I feel uncomfortable with it.

1 DR. RAMSEY: Dr. Tulchinsky?

2 DR. TULCHINSKY: It would help me, I guess,  
3 with pondering myself on that same question, it would help  
4 me to understand why is it that we around the panel, people  
5 that are considered to be knowledgeable or should be  
6 knowledgeable in this topic, you may correct me at any  
7 point here, but we're supposed to be knowledgeable on the  
8 topic, and we have personally reviewed the data.

9 Now, I have reviewed the data. It didn't stop  
10 here. Dr. Ponto has reviewed the data, and that data is  
11 your baby really, quote unquote, not literally speaking.  
12 You want to say yes, but you are saying no. It sounds  
13 fairly schizophrenic to me for the lack of a better  
14 correlative term.

15 Now, if we have studied the data, we've worked  
16 with the drug, and we are comfortable with what the  
17 question is posing, why simply not answer the question?  
18 Why does it have to be the volumes right here piled up on  
19 the floor? Is there a particular point I'm overlooking?  
20 I'd like someone to point it out because we have looked at  
21 the data. We individually and professionally reviewed it.  
22 Some of us have spent a number of years writing about it.

23 What makes today different as far as you  
24 answering that question? In one situation, having that  
25 pile on the floor with those articles, and in the other

1 situation, not having that pile on the floor with the  
2 articles but just having -- being reviewed by your own  
3 self?

4 I'm lacking an understanding of this critical  
5 difference perceived by others.

6 DR. RAMSEY: Ms. Beaman?

7 MS. BEAMAN: I'll answer that by saying because  
8 this is not the Psychic Hotline. That's why.

9 DR. TULCHINSKY: Could you clarify?

10 MS. BEAMAN: You said, yes, the volumes may be  
11 out there, but why do we have to have them stacked here,  
12 because there are those of us who are not psychics. That's  
13 one reason why, and it is the responsibility of the  
14 presenters to have that information before us at some point  
15 if indeed we're going to be expected to act up on it.

16 We're seeing a perfect example here when  
17 specific guidelines are not set forth for recommending  
18 approval of drugs what can happen. Statements such as you  
19 recommended approval of ammonia yesterday, why not this one  
20 today. As long as we don't have some specific guidelines,  
21 and we have multiple interpretations, we're going to  
22 continue to have these kinds of dilemmas, and I'll follow  
23 that by also stating in reference to the gentleman here.

24 DR. LOVE: Dr. Sancho.

25 MS. BEAMAN: Dr. Sancho. I think it's pretty

1 elementary that there is some expected blockage and blood  
2 flow issues with sickle cell patients, and that also  
3 transfusions are indeed a help, a tremendous clinical help.  
4 I am a person who gives space to the patient as a cancer  
5 survivor here. I didn't quite follow your point as to  
6 thanking that patient who got a transfusion as a result of  
7 your use of this drug.

8 DR. LOVE: That was actually directed at Dr.  
9 Conti, not Sancho.

10 DR. RAMSEY: Dr. Tatum? Oh.

11 DR. CONTI: Peter Conti from USC. My point was  
12 simply to give you an example from the literature of how  
13 patient management was altered on the basis of the  
14 information provided from the diagnostic test, that there  
15 was question brought up within the committee discussion  
16 about outcomes and effect on patient management, keeping in  
17 mind, of course, that the word "alterations in management"  
18 may mean something simply from preparing the operating room  
19 for a potential bleed-out from a biopsy all the way down to  
20 something such as survival.

21 If something has been altered or changed in the  
22 work-up, the day-to-day activities of managing a patient,  
23 those are the things we need to be looking at, and those  
24 are very difficult necessarily to quantify with P values  
25 and specifics within the manuscript, but you can at least

1 glean from the literature, at least the perfusion  
2 literature, that there are changes in how we manage  
3 patients on the basis of the imaging data that's provided.

4 DR. LOVE: If I could interject, the discussion  
5 that has been taking place is very valuable to us, and we  
6 certainly appreciate it, and I think it's clear to us from  
7 listening that there are a number of different perspectives  
8 on the committee, and that it's mixed, and what I would ask  
9 the chair, your feeling, but we would be comfortable  
10 pulling the question at this point in time, not going  
11 forward with actually getting an answer and coming back and  
12 representing this at another advisory committee meeting.

13 But I certainly want to thank everybody for  
14 this discussion. It has been extremely relevant and  
15 helpful to hear the different perspectives.

16 DR. RAMSEY: I think Dr. Hertzberg was first.  
17 Well, actually Dr. Tatum, but --

18 DR. HERTZBERG: I happen to have some knowledge  
19 because I serve on an NIH study section where I was last  
20 week, through some of my relationships there, that one of  
21 the patient management aspects that they're going after,  
22 the Powers group, which Grubb and et cetera are members of,  
23 is they're going to be looking at bringing back EC/IC  
24 bypass in this specific group of patients that show this  
25 particular pattern in PET, and so I think that this

1 publication was just last year.

2           They're just now girding up to procure the  
3 funding to go investigate this, but I think that that's the  
4 kind of thing that you can see in terms of a change in  
5 patient management that will result in this.

6           DR. RAMSEY: Dr. Tatum?

7           DR. TATUM: This gets back to Dr. Love and  
8 yesterday. I think it's a good for clarification points  
9 that what I understand about how this process is going  
10 forward. This is like doing a step to bring forward  
11 sponsors, and my understanding was that what's going to go  
12 in the Federal Register is going to be based on what we  
13 basically have here.

14           Therefore, trying to introduce documents or  
15 other information that is not part of this would not  
16 include necessarily in what's going to go forward.  
17 Therefore, we do need to do, I think, what you're saying,  
18 so that that information can be included in what I  
19 understand the process to be.

20           DR. LOVE: Right. We would have to have the  
21 additional literature in order to move forward to reference  
22 it in the FR notice.

23           DR. RAMSEY: Dr. Ziessman?

24           DR. ZIESSMAN: As I understand, we are just an  
25 advisory committee, and the FDA can take our advice or not

1 take our advice.

2 I think that we can give advice to say that we  
3 don't feel we have the data to approve this  
4 radiopharmaceutical based on what was presented. Many of  
5 us have the feeling there is the data out there and would  
6 say if the FDA would review that data, we think they would  
7 find that this is approvable and therefore take it from  
8 there without having to come back to the advisory  
9 committee.

10 DR. LOVE: That would be at the committee's  
11 pleasure. We certainly do intend to review the other data,  
12 but whether it comes back is the committee's pleasure.

13 DR. TULCHINSKY: Right. As a note, I would  
14 like to make a small one here, that I believe that FDA, as  
15 this process began, I'm talking about two years ago and up  
16 to date, and if you look at the November meeting notes, one  
17 of the potential mechanisms of dealing with this same  
18 situation of non-supported drug application, no sponsor for  
19 the drug application.

20 One suggested approach was to have an  
21 organization actually review the literature and present  
22 that at the FDA meeting. If you'll recall the November  
23 meeting in 1998, that was a favored approach, and the  
24 thought back then was let's see how it works, if FDA would  
25 do it, as a first step and maybe that can be generalized

1 later into us professionals doing this with FDA having the  
2 final look-over and checkmark.

3 I do believe today we are a bit reverting, and  
4 I personally would favor to proceed today with voting on  
5 this question. I do feel that the members have been  
6 irreversibly altered by this discussion, and I'm not  
7 ignoring the comments made by the patient advocate.

8 I think those comments are very appropriate,  
9 very good, and those comments do pertain to everything  
10 we've done yesterday, and I'm not saying do it just because  
11 we did it yesterday. I think we did yesterday the right  
12 thing. Let's do the right thing today is my simple point.

13 I'll give the floor to Jonathan.

14 DR. LINKS: Well, it's up to you to give the  
15 floor to me.

16 DR. RAMSEY: I'm not sure who was next. I  
17 think Dr. Hertzberg, actually.

18 DR. HERTZBERG: But, yesterday, with all due  
19 respect, I think we had a different standard of evidence.  
20 We had different quality of evidence in terms of what was  
21 presented, and that's why it was right to do it yesterday,  
22 and that's why it is questionable whether it would be right  
23 to do it today at best.

24 DR. LINKS: For all of us who love nuclear  
25 medicine, it seems to me that if the only way the

1 literature that we know for 100 percent certain is there  
2 and supports the use of this tracer, if the only way for  
3 that literature to get into the FR is to do the process Dr.  
4 Love suggested, then especially if you love nuclear  
5 medicine, we need to follow that process.

6 DR. TULCHINSKY: It's not going to get in  
7 there. The literature will not decide it.

8 DR. LOVE: No. We will have literature  
9 references listed in the FR notice.

10 DR. TULCHINSKY: In the FR?

11 DR. LOVE: Yes, and so the basic --

12 DR. TULCHINSKY: This entire literature list?

13 DR. LOVE: Not all of it.

14 DR. TULCHINSKY: Okay.

15 DR. LOVE: Those references --

16 DR. LINKS: Only if we don't act on it will it  
17 get in there, right?

18 DR. LOVE: The references that are forming the  
19 basis of the decision would be the ones that are listed.  
20 There are a couple of approaches that we could probably  
21 take at this point in time.

22 One is what was mentioned. We can not vote  
23 today, look at the rest of the information, bring it back  
24 to the committee for presentations. The other would be  
25 whether or not we wanted to do the review and send it to

1 the panel without a full meeting, and each of you can send  
2 back your individual comments to us. That's another  
3 approach, without actually doing a meeting.

4           Someone on the committee could review the rest  
5 of the information. That's an option. There's several  
6 ways to approach this without having to take a vote today,  
7 and it seems to us from what we're hearing, is that there  
8 is a mixed sense on this, and clearly that there are other  
9 data that were not considered, and we're perfectly happy to  
10 do that.

11           DR. MALCOLM: May I? We're going around in  
12 circles. May I make a motion, please? May I make a  
13 motion, number 1, that this question today be pulled? We  
14 get that answered, and if we can get a vote on that.

15           PARTICIPANT: Second.

16           DR. MALCOLM: Okay.

17           DR. RAMSEY: Discussion? We had the discussion  
18 on whether it should be pulled or not. I guess we vote.

19           DR. TULCHINSKY: As a preponderant for not  
20 pulling it, I would say for the sanity of this meeting,  
21 yes, that will be fine.

22           DR. RAMSEY: So the question before us is if we  
23 should pull the question for the present time. All those  
24 in favor?

25           (Show of hands.)

1 DR. RAMSEY: Opposed?

2 (No response.)

3 DR. RAMSEY: None opposed.

4 MR. MADOO: Question pulled.

5 DR. MALCOLM: Okay. The next is how do we  
6 handle this?

7 MS. AXELRAD: Let me address that for a second.  
8 I do not think it's a good idea for us to simply pull  
9 literature together and submit it to you and get comments  
10 back in the mail. I think that this needs a public airing,  
11 especially given the different views expressed by committee  
12 members.

13 So what I would suggest is that we review the  
14 literature. We may ask the Institute for Clinical PET to  
15 provide us a better selection from the literature, and  
16 we'll do a review like we did for FDG and ammonia, and we  
17 will present it to the committee at a future meeting.

18 DR. RAMSEY: Dr. Herscovitch?

19 DR. HERSCOVITCH: Perhaps we should stress that  
20 the different views expressed by committee members related  
21 more to the process and the evidence that was presented and  
22 not to the nature of the tracer which I am convinced when  
23 we do have the data will demonstrate that it is an  
24 excellent perfusion agent and perhaps just a minor point,  
25 but picking up on something the gentleman said down the

1 way, that although there are other perfusion agents, such  
2 as HMPAO and ECD, which have been approved, they really  
3 don't do the job for at least one of the applications that  
4 was discussed, and that is functional brain mapping as a  
5 prelude to surgery and defining eloquent cortex. That  
6 really can't be done. So even though there are other  
7 perfusion agents which might do the job in certain types of  
8 cerebral vascular disease, there isn't an agent which does  
9 the job in functional brain mapping.

10 Finally, not to anthropomorphize this agent,  
11 but Dr. Ziessman did already, it really is too bad that the  
12 agent is being blamed because of the nature of the  
13 presentation and the difficulty of clarifying the process,  
14 but I do have to agree with everybody who did say that they  
15 feel uncomfortable approving it because they feel they  
16 didn't have the literature, and perhaps I was in a somewhat  
17 better position to be very optimistic because I am more  
18 familiar with the literature as is perhaps Dr. Links and  
19 Dr. Ponto.

20 DR. KONSTAM: You know, I agree with what we've  
21 decided to do, and I also agree that I think it would be a  
22 mistake just to send this out and get our comments back. I  
23 think we need to reconvene. I think there's a dynamic here  
24 that has to be fleshed out, and I think that would be very  
25 valuable.

1           I do think I'm still a little bit stuck, and I  
2 wonder what to do to unstick myself and perhaps other  
3 panelists regarding, you know, defining a little bit more  
4 clearly what is the standard of evidence that we'd like to  
5 see here, and maybe this does exist in terms of criteria,  
6 and we haven't looked at it carefully enough or thought  
7 about it carefully enough, but listening to my colleagues  
8 around the table, I think we've been applying very  
9 different standards across the table, and I think it would  
10 be worthwhile taking a shot at agreeing about what that  
11 might be.

12           Again, I think the goal is going to have to be  
13 if we're going to approve an agent for a biologic process,  
14 physiologic process, biochemical process, you know, to my  
15 mind, we're going to need to do that on the basis of a very  
16 strong data set supporting what I will continue to call a  
17 process/outcome link, and that is that if we use a  
18 particular agent to measure a particular process, we'd like  
19 to have some way of coming to a strong conclusion that that  
20 will influence patient care, and I don't think that's a lot  
21 to ask.

22           I think there are a variety of different lines  
23 of evidence that can be brought to bear on that type of  
24 subject. For example, I think to me in this particular  
25 case, other evidence related to the impact of cerebral

1 blood flow measurement on clinical outcomes or patient  
2 management with other agents, I think, could come to bear  
3 on this discussion.

4           So if I were convinced that an agent was the  
5 perfect cerebral blood flow mapping agent and was safe, and  
6 I had an extensive knowledge base that measuring cerebral  
7 blood flow impacted upon patient care in some way, I would  
8 be much more lenient on the clinical data relevant to this  
9 particular agent. I still would like some, but I'd be more  
10 lenient.

11           So some of these ideas, I think, are worthy of  
12 being fleshed out and written down and agreed upon as we go  
13 forward with the discussions.

14           DR. RAMSEY: Dr. Tulchinsky?

15           DR. TULCHINSKY: I was wondering if it would be  
16 appropriate to make a motion to have ICP present the data  
17 for our next meeting. I would like to make that motion.

18           DR. RAMSEY: Is there a second?

19           DR. AMENDOLA: Second.

20           DR. RAMSEY: Discussion? Is that appropriate  
21 or I don't know what the rules are?

22           MS. AXELRAD: ICP can certainly make a  
23 presentation. In fact, they made a presentation here. I  
24 think that the FDA would also be making a presentation  
25 because what we're going to be asking you to vote on is our

1 assessment of the literature, and what we're going to be  
2 publishing in the Federal Register is going to be our  
3 assessment of the literature.

4 So while we could do that, it would be fine,  
5 but I think that we would intend to make an assessment and  
6 a presentation ourselves.

7 DR. TULCHINSKY: Oh, certainly. That goes  
8 without saying. The point is that why don't we have ICP  
9 compile the evidence, the one that was lacking today, and  
10 have the FDA review it, just like any other time that you  
11 have sponsored submission.

12 MS. AXELRAD: Right. That's what we were sort  
13 of hoping would happen in any event for the drug.

14 DR. TULCHINSKY: Well, I would like to  
15 formalize that.

16 DR. KONSTAM: Well, I think we have to remember  
17 that we are here at the service of the FDA, not vice versa,  
18 that the FDA is going to have to make this decision. As  
19 somebody pointed out, the FDA can in its wisdom choose to  
20 go against the panel under some circumstances.

21 We're here serving them. I think what they've  
22 expressed to us is their concern that they haven't provided  
23 us today with sufficient data to help them, and so I think  
24 the onus is on them to decide what they'd like to do to  
25 help us come to our deliberation, not for us to tell them

1 how to do that.

2 DR. RAMSEY: Could you maybe amend the motion  
3 in that way? Something like if they would like a  
4 presentation?

5 DR. TULCHINSKY: I'm not sure that it's  
6 necessary because, yes, we all understand that we're here  
7 to help FDA, and we're not serving them. Certainly we're  
8 serving to the public if you look at the things that you  
9 signed when you accepted this appointment, but I think it's  
10 appropriate to have ICP compile the literature in a way  
11 that they feel is complete, and just like any other time,  
12 radiopharmaceutical will be compiled, the literature, by  
13 the sponsor.

14 It would be fairly common process, and I think  
15 that the folks that know most about this tracer are members  
16 of ICP. Dr. Hertzberg.

17 DR. RAMSEY: No. My only concern is directing  
18 the FDA to have them make a presentation. I don't object  
19 to them collecting the information.

20 DR. TULCHINSKY: Even FDA can make the  
21 presentation. That would be fine. But I think the  
22 information needs to be collected and submitted to FDA by  
23 ICP in the form that they would feel would fulfill our  
24 overall requirements today for the lack of the literature,  
25 and FDA can either choose to have them present it. Again,

1 it's their prerogative.

2           The point is not who's going to be standing at  
3 a podium. The point is what's going to be in front of us  
4 as far as the data is concerned. That is the critical  
5 point, and I'll leave it up to the FDA to decide how they  
6 wanted it verbalized and flown out from that point on. But  
7 the key is it was felt that the data is lacking. All the  
8 experts is within the realm of ICP. They know all the  
9 data. I would suggest that we give them the opportunity to  
10 compile it, have the FDA review it as they always do, and  
11 decide who wants to present it.

12           DR. RAMSEY: Can we use that as the motion  
13 then?

14           DR. ZIESSMAN: Do we need a motion? I mean,  
15 the FDA knows what is needed.

16           MR. MADOO: Yes, I think it might be of benefit  
17 for just the lay audience, for people reading the  
18 transcript, if Dr. Conti could in a nutshell define what  
19 ICP is.

20           DR. CONTI: As the President-elect of the ICP,  
21 I probably should be able to do that. This is an  
22 organization primarily of nuclear medicine physicians who  
23 happen to use positron emission tomography. One of the  
24 founding purposes of the organization was to obtain  
25 reimbursement for PET radiotracers and was formed over a

1 decade ago to do that.

2 We're currently involved in a number of  
3 activities, including the working with the FDA to come up  
4 with an acceptable regulatory process as well as approvals  
5 of these clinical tracers.

6 In addition to obviously Medicare  
7 reimbursement, we're primarily interested in the primary  
8 sector reimbursement, and so we work with a number of  
9 insurance companies to educate the community on the value  
10 of these tracers.

11 I would like to actually begin our presentation  
12 for ICP for the approval of this drug by having our two  
13 experts, Dr. Ponto and Dr. Herscovitch, who are here, who  
14 are the world's experts on this tracer use. Dr.  
15 Herscovitch is actually a consultant for this medical  
16 advisory board. He was brought in specifically to look at  
17 these PET radiotracers, one of the leading experts in the  
18 field.

19 So I'm a little bit astonished that the medical  
20 advisory board hasn't taken advantage of this expertise in  
21 this deliberation.

22 DR. LOVE: Right. I think what you're talking  
23 about now is essentially what we would certainly be  
24 comfortable going ahead and completing the review, getting  
25 the other information. It's clear that Dr. Herscovitch and

1 Dr. Ponto have additional information, and I'm sure that  
2 ICP will work with them to get those other articles that  
3 they have identified as well, and I think we'll be able to  
4 bring back another review shortly.

5 DR. RAMSEY: I think Ms. Axelrad was actually  
6 first.

7 MS. AXELRAD: Well, I wanted to go back to  
8 several points earlier and address Dr. Konstam's point  
9 regarding the standards that would be used by the committee  
10 when we we make the presentation the next time, and I think  
11 that one of the things that hasn't been mentioned at all in  
12 the discussions is the final rule that was published on  
13 radiopharmaceuticals implementing the section of the  
14 Modernization Act that addresses the issues that Dr.  
15 Tulchinsky raised, and in that section, it's 21 Code of  
16 Federal Regulations, Section 315.5, it says that "the claim  
17 of functional, physiological, or biochemical assessment is  
18 established by demonstrating in a defined clinical setting  
19 reliable measurement of functions or physiological,  
20 biochemical or molecular processes."

21 So it does say that it has to be in a defined  
22 clinical setting, and we have, you know, the draft guidance  
23 document on medical imaging drugs that addresses what is  
24 meant in the rule by defined clinical setting.

25 So what I am thinking is that by the time we

1 finish doing the review of the literature of O-15 water, I  
2 think we will have also made a fair amount of progress in  
3 finishing up that draft guidance document, and that we may  
4 have the opportunity when we make the new presentation to  
5 clarify some of the thinking in terms of what the standards  
6 ought to be that should be used in evaluating these by the  
7 committee.

8 DR. RAMSEY: Dr. Herscovitch, did you still  
9 want to make a comment?

10 DR. HERSCOVITCH: Yes, and this is a totally  
11 personal comment which I feel I have to make. I have to  
12 correct the previous statement. I am not a member of the  
13 ICP, and although I appreciate your comment about my  
14 expertise in O-15 water, I came here and all my  
15 participation here was at the behest of the FDA, and all  
16 the questions that I answered or volunteered answers for  
17 were at the behest of the FDA as the government's employee.  
18 I am not associated with the ICP as a member or in any way  
19 as their representative.

20 MS. AXELRAD: Well, maybe either we or the ICP  
21 can take advantage of your expertise in conducting the  
22 further review of the literature. Maybe both.

23 DR. HERSCOVITCH: Maybe that's why we have  
24 lawyers, as yourself.

25 DR. RAMSEY: Okay. Any other questions?

1       Comments?

2                       (No response.)

3                       DR. RAMSEY: Well, I want to thank you all. I  
4 want to thank the FDA for a lot of work in putting the  
5 papers before us and doing everything in preparation for  
6 this, and as usual, Mr. Madoo, for getting us all together  
7 for this meeting, and I guess we'll see you all again, and  
8 have a good, safe trip home.

9                       Thank you all.

10                      (Whereupon, at 11:14 a.m., the meeting was  
11 adjourned.)

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