

1 increase in infection with an explicit warning that
2 the use of this device may be associated with
3 increased risk of an infection, and that the
4 infections not be separated out as they were in the
5 data we saw, but as overall infection risk, not listed
6 as bacterial meningitis, deep surgical infection,
7 superficial infection, but this is potential infection
8 rate.

9 DR. CANADY: And that has the additional
10 hammer of that if you do sufficient postmarket
11 surveillance to show that that's not there, then you
12 could apply for relabeling, which would be an
13 incentive to complete the study.

14 DR. MacLAUGHLIN: Pardon me. This is Dave
15 MacLaughlin.

16 Could you please repeat that comment? I
17 didn't hear it.

18 DR. CANADY: That the specific warning
19 would be an additional incentive to complete the study
20 which would allow them to apply for relabeling.

21 DR. MacLAUGHLIN: Thank you.

22 CHAIRPERSON BECKER: So at this point

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1 let's take a vote on the second condition for
2 approval, which is a change in the labeling for the
3 device to express concern about the risk of an
4 infection, making it an explicit warning, and that the
5 infections be listed as a conglomerate whole risk of
6 infection and not separate out as individual types of
7 infections.

8 So everybody in favor of this labeling
9 change, please raise your hand.

10 (Show of hands.)

11 CHAIRPERSON BECKER: So it's Dr. Loftus,
12 Dr. Egnor, Dr. Jensen, Dr. Canady, Dr. Haines, Dr.
13 MacLaughlin, Dr. Jayam-Trouth.

14 Everybody against this labeling change?

15 (No response.)

16 CHAIRPERSON BECKER: Everybody abstaining
17 from the vote.

18 (Show of hands.)

19 CHAIRPERSON BECKER: Dr. Ellenberg and Dr.
20 Germano.

21 The third condition that was brought
22 forward was that this product be used after every

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1 reasonable attempt has been made to close the dura.
2 So in addition to closing the dura, not as opposed to
3 closing the dura.

4 Did anybody want to second that motion?

5 DR. EGNOR: Second.

6 CHAIRPERSON BECKER: Okay. Dr. Egnor.

7 Any discussion regarding that?

8 DR. LOFTUS: Yes, I think that's an
9 inappropriate condition to impose because I think that
10 implies that surgical decision making is being
11 dictated by this panel, which is inappropriate.

12 Now, if indeed my opposition is sustained,
13 I would propose another labeling issue that might
14 supplant this one.

15 DR. HAINES: Well, in fact, the indication
16 says that it's intended as an adjunct to dural
17 closure. So I think that's already in the label.

18 DR. MacLAUGHLIN: That was going to be my
19 point, too. It's already on there. That was their
20 indication for use, was an adjunct to suture.

21 DR. JAYAM-TROUTH: It should be emphasized
22 though to me.

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1 DR. EGNOR: Yeah, it should be emphasized
2 because people are going to use this for the tough
3 cases regardless of what the label says, but that
4 should be stressed on the label that you've got to get
5 watertight closure. That's the only way it's
6 contested, is with a closure that's nearly watertight.

7 CHAIRPERSON BECKER: So it sounds like
8 maybe we should take a vote on this particular
9 condition, that the labeling be changed to emphasize
10 the fact that every reasonable attempt needs to be
11 made to get closure prior to application of the
12 device.

13 So everybody in favor of this condition,
14 may I see your hands?

15 DR. CANADY: Could I reword that?

16 CHAIRPERSON BECKER: Sure.

17 DR. CANADY: You know, just because as a
18 surgeon already your hackles are up when you hear that
19 one.

20 That this is to be used only as a adjuvant
21 to primary dural closure.

22 CHAIRPERSON BECKER: Okay. So to change

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1 the labeling to state that the DuraSeal device be used
2 only as an adjunct to primary dural closure.

3 Everybody in favor of that condition for
4 approval, may I see your hands?

5 (Show of hands.)

6 CHAIRPERSON BECKER: Drs. Loftus, Egnor,
7 Jensen, Canady, MacLaughlin, Jayam-Trouth.

8 Everybody opposed to that change in
9 labeling, may I see your hands?

10 (Show of hands.)

11 CHAIRPERSON BECKER: Dr. Haines.

12 And everybody abstaining from the vote?

13 (Show of hands.)

14 CHAIRPERSON BECKER: Drs. Ellenberg and
15 Germano.

16 Okay. So that's three conditions now. Is
17 there a motion for a fourth condition?

18 DR. LOFTUS: Yes, I would propose a motion
19 for a fourth condition, and it would state in some
20 word crafted way, wordsmithed way the following: that
21 this device has been demonstrated effective only in
22 cases where overt, spontaneous CSF leak or CSF leak

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1 documented by Valsalva maneuver has been demonstrated
2 and that it should not be considered as standard
3 therapy for primary closed dura where no leak is
4 evident.

5 CHAIRPERSON BECKER: Is there a second for
6 that condition?

7 DR. EGNOR: Second.

8 CHAIRPERSON BECKER: Dr. Egnor. Okay.
9 Any discussion points surrounding this
10 condition?

11 DR. CANADY: Every case leaked.

12 CHAIRPERSON BECKER: Dr. Canady makes the
13 point that every case that was treated here leaks.

14 DR. LOFTUS: Well, every case in the
15 trial, but that may not be someone else's clinical
16 experience.

17 CHAIRPERSON BECKER: Any further
18 discussion on this condition?

19 (No response.)

20 CHAIRPERSON BECKER: So let's take a vote
21 then on the fourth condition, which is that the device
22 should only be used in cases of overt CSF leakage or

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1 in leakage associated with Valsalva maneuver.
2 Everybody in favor of that condition, may I see your
3 hands?

4 (Show of hands.)

5 CHAIRPERSON BECKER: Dr. Jayam-Trouth, Dr.
6 MacLaughlin, Drs. Loftus, Egnor and Jensen.

7 Everybody opposed to that condition?

8 (Show of hands.)

9 CHAIRPERSON BECKER: Dr. Canady and Dr.
10 Haines.

11 And everybody abstaining from voting?

12 (Show of hands.)

13 CHAIRPERSON BECKER: Dr. Ellenberg and Dr.
14 Germano.

15 Any motions for further conditions for
16 approval?

17 DR. MacLAUGHLIN: I have one, Madam
18 Chairman, that was brought up in relation to the fact
19 that the device is radiopaque. I think that was
20 mentioned. You know, it should be stated somewhere
21 that it is so that clinicians know that if they do
22 some studies that that's what they're looking at.

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1 The MRI study.

2 DR. GERMANO: It is not necessarily
3 radiopaque, but it does show on the MRI as an
4 increased -- the MRI that was shown, it looked like an
5 area of increased signal intensity on T2 weighted
6 images. So it should be specified what to look for on
7 those postoperative cases, and I don't know if the
8 sponsor did any study with and without gadolinium, and
9 that would be also very interesting to know because
10 obviously one of the ways to check for infections is
11 to inject gadolinium, and I don't know if this
12 substance will or will not have an increased uptake
13 after gadolinium.

14 DR. JENSEN: Well, they stated in the
15 canine imagines that there was a homogeneous
16 enhancement along the edge, which diminished over
17 time.

18 DR. GERMANO: With gadolinium? I don't
19 think so.

20 DR. JENSEN: Well, to enhance something
21 you've got to give something. So you would have to
22 have gadolinium. If it was an MR, and they talked

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1 about hyperintensity. So I assume it was MR. You're
2 correct that they did not go into great detail about
3 what the actual imaging parameters were, and they
4 didn't talk about the different sequences that were
5 used, but I think it would be appropriate to have a
6 statement in there that talks about the fact that this
7 device can be imaged. They saw both CT and MR, and
8 what those imaging characteristics are.

9 Look at the dog study.

10 DR. GERMANO: Was that enhancement or was
11 it increased signal on T2 weighted?

12 DR. CANADY: No, it had increased signal,
13 plus it had enhancement at the margins.

14 DR. GERMANO: Both. Thank you.

15 DR. MacLAUGHLIN: I think you got the
16 spirit of what I wanted. I don't know how you word
17 it, just so that the others know that it will appear
18 on imaging of whatever type.

19 CHAIRPERSON BECKER: And I think it would
20 also be important to know the time or the duration of
21 that signal abnormality because, you know, a month or
22 two months out you're going to be faced with a patient

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1 who may have an infection. You don't know if this is
2 really infection or we're still seeing the end of this
3 abnormal signal from the DuraSeal. So I think that's
4 going to be important.

5 DR. JAYAM-TROUTH: One other question. Is
6 it different on the CAT scan? Is it radio-opaque? Is
7 it hyper dense or hypo dense?

8 DR. JENSEN: Well, if it's primarily
9 water, it's going to look closer to --

10 DR. JAYAM-TROUTH: So it would be hypo.

11 DR. JENSEN: -- CSF I would think on CT.

12 Again, we didn't get much in the way of
13 radiographic data, and that is something that the
14 sponsor is going to have to have specific imaging
15 characteristics of.

16 DR. GERMANO: So on page 8 of the material
17 that was provided, there is an MRI of a dog, and it
18 looks like a T2 weighted image, and it looks like an
19 area of increased signal on T2 weighted imagine, and I
20 think Dr. Jayam-Trouth's comments are very important
21 because it is possible that the patients undergo CT
22 instead of MR, and it would be important to know what

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1 their appearance is on a standard, conventional
2 emergency room admission CT.

3 CHAIRPERSON BECKER: So it sounds like the
4 condition that was put forth and not yet seconded has
5 to do with the change in the labeling to reflect the
6 fact that there are abnormal radiographic
7 characteristics associated with the use of DuraSeal,
8 definitely on MR, perhaps on CT, that aren't well
9 defined.

10 So I guess is there a second for the
11 motion that the labeling for this device be changed to
12 reflect the fact that there is changes in MR and
13 perhaps CT signal characteristics associated with the
14 use of this and that should be made very apparent to
15 the clinicians using it? Is there a second for that?

16 DR. JAYAM-TROUTH: It should be not only
17 defined, but also the time frame that it's present
18 should be defined.

19 DR. EGNOR: Second.

20 DR. JENSEN: Yeah, and I wouldn't call it
21 abnormal because there's just certain imaging
22 characteristics this material has on both CT and MR

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1 which would be clearly defined.

2 CHAIRPERSON BECKER: So can I actually
3 step back and say that maybe there are two conditions
4 here. One is that the sponsor further study the
5 imaging characteristics associated with the DuraSeal
6 and then secondly the labeling reflect that.

7 So I'm going to put out a motion that --

8 MS. SCUDIERO: We have a motion on the
9 floor though.

10 CHAIRPERSON BECKER: I think that they
11 need to be separated, and first we need to know what
12 the imaging characteristics are before we can change
13 the labeling to reflect them.

14 So I would actually make a motion,
15 supplant -- do we have to do them in the order they're
16 brought up or can we kind of table the one?

17 MS. SCUDIERO: Well, we have the motion on
18 the floor now.

19 CHAIRPERSON BECKER: Right. We have a
20 motion on the floor which is to change the labeling
21 characteristics or change the label to reflect the
22 fact that there are radiographic characteristics

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1 associated with the use of DuraSeal.

2 Is there a second to the motion to change
3 the labeling characteristics in that regard?

4 DR. JENSEN: Second.

5 CHAIRPERSON BECKER: The second is Dr.
6 Jensen.

7 So we've already discussed it, I think, in
8 great detail, and so we should take a vote now for
9 this condition, that the labeling for the device be
10 changed to reflect the fact that there are CT and MR
11 changes associated with DuraSeal.

12 Everybody in favor of changing the
13 labeling in that regard?

14 DR. JAYAM-TROUTH: Were you going to add
15 the --

16 CHAIRPERSON BECKER: Yeah, we're going to
17 go back and add where they need to define what those
18 changes are. They went a little out of order, but
19 we're following protocol.

20 (Show of hands.)

21 CHAIRPERSON BECKER: Dr. Jayam-Trouth, Dr.
22 MacLaughlin, Dr. Haines, Dr. Canady, Dr. Jensen, Dr.

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1 Loftus.

2 Everybody opposed to changing the labeling
3 to reflect this?

4 (No response.)

5 CHAIRPERSON BECKER: And everybody
6 abstaining from the label characteristic changes or
7 the radiographic changes?

8 (Show of hands.)

9 CHAIRPERSON BECKER: Dr. Egnor, Dr.
10 Ellenberg, and Dr. Germano.

11 So now the next motion put forward, I'm
12 not allowed to make. Does someone else want to take
13 up my motion to define what those MR and CT --

14 DR. GERMANO: Could I shed some light?
15 Because I found the piece of paper with some sentences
16 provided by the sponsor. This came in a blue folder
17 and has holes in it and page 21, and it does say that
18 DuraSeal MR and CT imaging.

19 So following recovery both animals -- this
20 is talking about two dogs where the craniotomy was
21 done -- both animals underwent MR and CT images at
22 three days, two, four, six, eight, and ten weeks. Gel

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1 appearance at each time point was characterized and
2 compared with pathological finding obtained 14 weeks
3 following implantation.

4 Results: the investigator found that the
5 sealant could be viewed with MRI and CT and could be
6 distinguished from CSF.

7 There's no note of gadolinium. There is
8 no characterization on how the images look like. The
9 only mention is that --

10 DR. JENSEN: But look further down.

11 DR. GERMANO: -- is that it's different
12 from CSF.

13 DR. JENSEN: Right, but look further down
14 where it says with MR/CT imaging investigators note
15 the following resorption characteristics, and they
16 talk about on page 22 homogeneous circumferential
17 marginal enhancement.

18 So, again, the sponsor did not provide us
19 with enough information to say exactly what type of
20 scanning was performed with what parameters and with
21 and without enhancement, although mention of
22 enhancement indicates to me that they gave gadolinium.

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1 However, part of your protocol had
2 imaging. So you should have that data, and the
3 sponsor has neuroradiologists on their board. So I
4 think that information -- but I think the time points
5 that were given in the dog are very important.

6 DR. GERMANO: I just point out that they
7 are in the dog.

8 DR. JENSEN: That's right.

9 DR. ELLENBERG: Point of order.

10 CHAIRPERSON BECKER: Dr. Ellenberg.

11 DR. ELLENBERG: My sense is that we're
12 going to be asked our opinions and --

13 DR. WITTEN: Mic, please.

14 DR. ELLENBERG: My sense is that this will
15 be asked for in humans, and I would like to get the
16 advice of FDA on the issue of this requiring
17 additional work from the sponsor pre-approval. How do
18 you want us to handle this particular recommendation
19 for a condition?

20 DR. WITTEN: Information that's additional
21 data that you think needs to be provided pre-approval
22 would be not a condition of approval, but would be

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1 a -- that would be a recommendation for not approval.

2 If there's information that you think the sponsor
3 should provide but could be provided after approval,
4 then that's a condition of approval.

5 So if there's an additional study you want
6 performed prior to approval, then that's not really a
7 condition of approval.

8 DR. ELLENBERG: So then how do we get past
9 the issue of labeling?

10 DR. WITTEN: Well, that's where you have
11 to decide how critical it is. If it's something
12 that's an additional study you think needs to be
13 performed prior to approval and the sponsor doesn't
14 have that data in hand, that is, it's an additional
15 study, then that would be a recommendation for not
16 approval.

17 If it's something where you think they
18 should get the information later and can add it to the
19 label later, then that could be a condition of
20 approval.

21 DR. ELLENBERG: Okay.

22 DR. WITTEN: Does that -- yeah.

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1 DR. CANADY: You know, in the outline of
2 the study they have CTs on everybody at six weeks and
3 three months. So it's a matter of analysis rather
4 than collection. We really want a characterization.
5 We don't want just a descriptive statement.

6 So I don't see the need for additional
7 studies.

8 CHAIRPERSON BECKER: But additional data
9 perhaps.

10 DR. CANADY: We're going to ask them for
11 the labeling and they've got the data. They'll just
12 put it in the label.

13 CHAIRPERSON BECKER: Okay. So there was a
14 motion then for better defining the radiographic
15 characteristics of the DuraSeal. Is there a second
16 for that motion?

17 Dr. Jensen. Dr. MacLaughlin.

18 Okay. So everybody in favor of the
19 sponsor looking at the data that has been collected
20 and defining the CT characteristics of DuraSeal and
21 the MR characteristics where they have it following
22 approval, may I see your hands?

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1 (Show of hands.)

2 CHAIRPERSON BECKER: Dr. Jayam-Trouth, Dr.
3 MacLaughlin, Dr. Haines, Dr. Jensen, Dr. Egnor, and
4 Dr. Loftus.

5 Everybody opposed to this condition?

6 (No response.)

7 CHAIRPERSON BECKER: Everybody abstaining
8 from the vote?

9 (Show of hands.)

10 CHAIRPERSON BECKER: Dr. Germano and Dr.
11 Ellenberg.

12 Do I have a motion for any other
13 conditions for approval? No further motions?

14 Okay. So then as I see it there has been
15 a motion made for approval with conditions, and there
16 are six conditions laid out. Let me see if I can
17 remember what those six are, and then we'll vote on
18 those as a group.

19 The first condition is that there be post
20 approval surveillance studies done for the risk of
21 infection.

22 These second condition is that there be

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1 explicit labeling warning about the risk of infection
2 with this product, that the risk may be increased, and
3 that the change in labeling reflect the total
4 infection rate and not separate out the different
5 kinds of infection.

6 The third condition for approval is that
7 this device be used as an adjunct to dural closure.
8 Make that very explicit.

9 The fourth condition is that this device
10 be used only in patients where there is overt CSF
11 leakage interoperatively after dural closure or where
12 the CSF leakage is induced by Valsalva
13 interoperatively after dural closure.

14 The fifth condition --

15 DR. LOFTUS: May I? That wasn't exactly
16 what I said.

17 CHAIRPERSON BECKER: I'm sorry.

18 DR. LOFTUS: I want to make sure. What I
19 said, I believe, if I stated it right, was that the
20 device has shown to be effective only in cases
21 where --

22 CHAIRPERSON BECKER: Okay.

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1 DR. LOFTUS: And the meaning is quit
2 different.

3 CHAIRPERSON BECKER: Yeah, you're right.

4 DR. LOFTUS: And the corollary was but
5 should not be considered standard of care where no CSF
6 leak can be identified.

7 CHAIRPERSON BECKER: So to restate
8 condition four then, that the device should be
9 effective in patients who had overt CSF leakage
10 interoperatively or who had Valsalva induced CSF
11 leakage interoperatively. It's not considered the
12 standard of care, but it is shown to be effective only
13 in a specific patient population.

14 DR. LOFTUS: But I wouldn't use standard
15 of care. I wouldn't use that terminology.

16 CHAIRPERSON BECKER: That it's not
17 standard of care?

18 DR. LOFTUS: Because it implies that
19 otherwise it is.

20 CHAIRPERSON BECKER: For other patient
21 populations it's not standard of care.

22 DR. LOFTUS: Right.

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1 DR. GERMANO: Also it raises the question
2 that Valsalva maneuver now is standard of care for all
3 craniotomies, supratentorial, infratentorial; is that
4 correct? We're not here to determine standard of care
5 today.

6 CHAIRPERSON BECKER: So maybe we should
7 just leave out the whole standard of care part and
8 just state that it's show to be effective only in
9 patients with overt CSF leakage or Valsalva induced
10 CSF leakage interoperatively.

11 DR. LOFTUS: I could accept that.

12 DR. EGNOR: Or say the data supports its
13 use only.

14 CHAIRPERSON BECKER: Fair enough.

15 DR. JAYAM-TROUTH: Can you restate it,
16 please?

17 CHAIRPERSON BECKER: So the fourth
18 condition was that the device has been shown to be
19 effective in patients with overt or Valsalva induced
20 CSF leakage interoperatively.

21 DR. ELLENBERG: Only.

22 DR. JAYAM-TROUTH: Only.

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1 CHAIRPERSON BECKER: Only. Okay. The
2 fifth condition is --

3 DR. GERMANO: Effective in doing what?

4 CHAIRPERSON BECKER: I'm sorry?

5 DR. GERMANO: Effective in doing what?

6 CHAIRPERSON BECKER: Effective in
7 closing --

8 DR. GERMANO: Of interoperative CSF leak
9 cessation.

10 CHAIRPERSON BECKER: So let me see if I
11 can restate that correctly. So the device has been
12 shown to be effective in stopping interoperative CSF
13 leaks in patients who have overt CSF or Valsalva
14 induced CSF leaks --

15 DR. LOFTUS: Do you know what? It's
16 totally redundant because the other patients didn't
17 have a leak. Maybe I should just withdraw the motion
18 altogether because that's totally redundant.

19 CHAIRPERSON BECKER: So let's take another
20 vote on this motion just to be sure that everybody is
21 clear.

22 DR. LOFTUS: You see what I'm driving at.

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1 I wanted to get a motion that protects the
2 neurosurgeon who chooses not to use this from being
3 accused of a violation of the standard of care.
4 That's what I'm trying to achieve, as a protective
5 mechanism, you know, for our profession.

6 DR. JAYAM-TROUTH: How would you word it?

7 DR. LOFTUS: Well, I've made every attempt
8 I can think of.

9 (Laughter.)

10 DR. EGNOR: I mean, could one say that the
11 use or lack of use of this material is not reflected
12 in the standard of care?

13 CHAIRPERSON BECKER: It was just made
14 apparent to me that the FDA can actually help the
15 sponsor work out this wording and we probably don't
16 need to fret about that too much.

17 So now the fourth condition, since we've
18 gotten rid of the previous fourth condition, is that
19 the labeling be changed to reflect that there are
20 imaging characteristics associated with the use of
21 this device and that the clinician should be warned
22 about that.

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1 And then the fifth condition, the new
2 fifth condition, is that the sponsor actually do a
3 little bit of research with the data that's already
4 been collected, a little analysis of the data that's
5 already been collected to help us define exactly what
6 those changes are in humans and how long they last.

7 DR. ELLENBERG: Point of order. I'm
8 sorry. I'm confused. Have we deleted as a condition
9 for approval the limitations on what has been shown in
10 terms of the usefulness in a certain patient
11 population or have we put it into another area of the
12 labeling?

13 CHAIRPERSON BECKER: I think it's my
14 impression that it's actually very clearly laid out in
15 the indications for labeling that this is where the
16 device has been shown to be effective. All right? So
17 it's not actually in the --

18 DR. ELLENBERG: Why would they state that
19 this is shown to be effective in X, Y, Z populations
20 in the label if we don't put it in as a condition of
21 approval? That's a major limitation that we've been
22 talking about all day.

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1 CHAIRPERSON BECKER: So, Dr. Witten, can
2 we have a little help with that one?

3 DR. WITTEN: Yes. If we don't specify in
4 the label the statement who it's used for, and there's
5 no specific contraindications, which I don't think is
6 what you're talking about anyway --

7 DR. ELLENBERG: No.

8 DR. WITTEN: -- then the only way that it
9 would be described in the label would be under the
10 clinical study where we describe the patients in whom
11 it is studied.

12 Now, what I could say is if there's some
13 concept you're trying to get across, then rather than
14 try to work out the specific wording here, you could
15 just explain what the concept is and then if you all
16 agree on that concept, whatever it is we'll try to get
17 it to show up in the label in some reasonable fashion,
18 recognizable fashion.

19 CHAIRPERSON BECKER: Dr. Loftus.

20 DR. LOFTUS: Yes. The concept that I'm
21 trying to address is that there is not enough efficacy
22 from this particular trial design to say that this

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1 needs to be used in every case where a patient is
2 operated on and a durotomy is performed, and it would
3 be remiss not to use the product. That's what I'm
4 trying to get across.

5 DR. GERMANO: Second.

6 CHAIRPERSON BECKER: Dr. Haines.

7 DR. HAINES: And I would say that since
8 the indication clearly states that it's intended for
9 use as an adjunct, it's not required. I mean somebody
10 will try to infer things regardless of what the
11 wording is, but it says adjunct. This is clearly not
12 intended as a primary, as stated, as being essential
13 to closure of the dura.

14 DR. GERMANO: But, Steven, those are two
15 different concepts. What you are saying is that this
16 is not the only way we close dura.

17 What I think we're trying to say is that
18 not only this is not the only way we close dura with,
19 but if we don't use it, it's only because now it's
20 going to be the only FDA approved product, and so then
21 if you have a question in your mind that the dura is
22 leaking, then you have to use it unless we state that

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1 there is not enough evidence today that this is
2 actually efficacious down the line.

3 There is evidence, 90 percent, 98 percent
4 of the time of the surgery, but whether or not that
5 has any clinical meaning we don't have.

6 DR. CANADY: What you really want to say
7 is that we have demonstrated interoperative
8 effectiveness, but we have not yet demonstrated the
9 clinical prevention of CSF leaks.

10 DR. GERMANO: Correct. Thank you.

11 DR. EGNOR: So why don't you say an
12 optional adjunct?

13 CHAIRPERSON BECKER: So it sounds like
14 there's a motion for another labeling. We'll let Dr.
15 Loftus make a comment and then we'll --

16 DR. LOFTUS: Yeah, I'm not changing the
17 motion. It really is important to me emotionally
18 because we have had tangible, serious questions about
19 safety issues here today that we have, you know, to
20 some extent overcome, and yet it needs to be very
21 clear that this is not a treatment without risk, and
22 that it's not mandatory in routine surgery.

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1 DR. CANADY: I think if we can separate it
2 from this product does not clearly prevent clinical
3 CSF leaks, then that's what we're going to get sued
4 on. So if we say there's no clear data to show you
5 that this is effective for that, then you've separated
6 the two and protected the surgeon.

7 CHAIRPERSON BECKER: So it sounds like
8 maybe rewording the condition that you had to reflect
9 that would be appropriate.

10 DR. GERMANO: I think what Dr. Canady
11 worded is perfect, that this product is approved or
12 has been shown to be effective to stop intraoperative
13 CSF leak and no clear benefit for postoperative CSF
14 leak has been demonstrated yet.

15 MS. SCUDIERO: What about just withdrawing
16 Dr. Loftus or voting his motion down and starting over
17 with the clear --

18 DR. GERMANO: Yes.

19 MS. SCUDIERO: I think that one is good.

20 DR. GERMANO: And also this, going back to
21 using Dr. Canady's wording before, this is a nice
22 incentive to do those postoperative, post labeling

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1 study because the sponsor can reapply and say now we
2 have demonstrated that this clearly decreases the
3 postoperative CSF leak, and so it's a good incentive
4 for the sponsor to show that data to the agency.

5 CHAIRPERSON BECKER: So everybody in favor
6 of withdrawing the previous condition set forth by Dr.
7 Loftus, may I see your hands?

8 (Show of hands.)

9 CHAIRPERSON BECKER: So that's Dr.
10 Germano, Dr. Jayam-Trouth, Dr. Haines, Dr.
11 MacLaughlin, Dr. Canady, Dr. Jensen, Dr. Egnor, Dr.
12 Loftus, yourself.

13 So then there's been a motion to reword or
14 change the condition essentially to state that this
15 device has been used to effectively stop
16 interoperative CSF leaks, and that the clinical
17 significance of this is unknown. Is that reasonable?

18 Is there a second for that motion?

19 DR. JAYAM-TROUTH: Second.

20 CHAIRPERSON BECKER: Okay. So everybody
21 in favor of that condition, may I see your hands?

22 DR. MacLAUGHLIN: Wait. Could I have a

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1 little discussion?

2 CHAIRPERSON BECKER: Sure.

3 DR. MacLAUGHLIN: Just I have a technical
4 question. Not having read a lot of these labels, can
5 you qualify? Do you see other qualified statements
6 like that for a product? You know, this efficacy
7 hasn't been proven yet. It implies lots of things.
8 Has that ever been seen before?

9 CHAIRPERSON BECKER: I could actually give
10 you an example from the recent concentric device
11 approval stating that it was used to remove clots from
12 the CNS vasculature, but not for the treatment of
13 stroke, right? So --

14 DR. MacLAUGHLIN: No, I can understand
15 that qualification. I'm talking about, you know, it's
16 a clear demonstration that it stops leaks
17 interoperatively, but the other phrase after that I
18 didn't know. Can you be that qualified?

19 CHAIRPERSON BECKER: Can you, Dr. Witten?

20 DR. WITTEN: Well, I don't think we say
21 what things don't do. You know, we would say what
22 it's for, not what it's not for. We would describe

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1 the study and what the study -- for any product, this
2 one or any other product. In the study description in
3 the label we would describe what the product had or
4 hadn't been shown to do, but we don't put in the label
5 it does this, but it doesn't do that.

6 I'm not sure exactly what you're quoting
7 from, you know, because when we put out -- well, that
8 example wasn't a PMA, but I think we might have had a
9 press release, but in this we'd have a safety and
10 effectiveness that would say something.

11 But we wouldn't say, for example, it
12 doesn't -- I mean, if you're voting to approve it,
13 you're voting that there is reasonable assurance that
14 it will provide clinically significant results. So
15 we're not going to say it works, but it doesn't work.

16 I mean we could say in the indications this is what
17 it's intended for and in the study this is exactly
18 what was shown and what wasn't shown.

19 But I can't imagine us saying it works and
20 it doesn't work.

21 DR. MacLAUGHLIN: I guess I was trying to
22 be real sensitive to the clinicians who need to be,

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1 you know, protected from someone reading it and
2 saying, "Oh, gee, you didn't do this. So you've been
3 negligent," and you know, making other conclusions. I
4 don't know. It just sounded --

5 DR. CANADY: We'll just subpoena Dr.
6 Witten and she'll come and testify that we couldn't do
7 what we wanted to do.

8 DR. WITTEN: Yes. So maybe somebody will
9 have to read more than just the first sentence in the
10 label of the SS&E. I mean that's also a possibility.

11 CHAIRPERSON BECKER: So, Dr. Jensen, did
12 you have a point you wanted to make?

13 DR. JENSEN: I guess just looking at the
14 indication all it says is that it's for use in
15 watertight closure and that's it. It doesn't say
16 anything else about "and to prevent this," or
17 whatever.

18 Now, I know you probably want it to say
19 that in more glaring language, but that can be said --
20 correct me if I'm wrong, Dr. Witten -- over in the
21 clinical experience aspect of it?

22 DR. WITTEN: Well, yes. When we put a

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1 label and we describe a study, we typically describe
2 the study, the study population and the important
3 endpoints that were assessed in the study, both the
4 primary endpoint and some of the other things.

5 Clearly, this is one that we put in that
6 would be the clinical CSF leak experience.

7 DR. ELLENBERG: Let me -- oh, I'm sorry.

8 CHAIRPERSON BECKER: Actually, we'll let
9 Dr. Haines make his point and then.

10 DR. HAINES: In the label under warnings,
11 it starts and says the "safety and performance of
12 DuraSeal hydrogel has not been established," colon, in
13 Section 2, the first part of the label. Would it be
14 acceptable --

15 DR. WITTEN: I need to see what you're
16 talking about here.

17 DR. HAINES: Okay. The first column right
18 down at the bottom, warnings. "Safety and performance
19 of DuraSeal hydrogel has not been established," colon.
20 Would it be acceptable to add another bullet that
21 says "for the prevention of clinically significant CSF
22 leaks"?

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1 DR. WITTEN: A warning or these
2 contraindications and warnings are, you know,
3 circumstances in which, I mean, I'm not sure exactly
4 whether we agree with precisely how they have these in
5 here, but they are to indicate situations in which you
6 wouldn't want to use it either because there's a
7 safety issue for the patient -- well, that's pretty
8 much -- a contraindication is when there's a known
9 safety issue, and a warning is when there's a
10 potential safety issue with how you might use it.

11 So we wouldn't do what you just said
12 because that doesn't fit in with the warning.

13 DR. HAINES: Well, how about precautions,
14 the last bullet, safety and performance has not been
15 established in persons younger than 18 years of age
16 and procedures involving petris bone drilling and add
17 a third bullet for the prevention of clinically
18 significant postoperative CSF leaks.

19 DR. WITTEN: Well, that precaution is --
20 I'm not sure where you're reading from, but a
21 precaution is something that you need to take into
22 account, you know, during the actual process of use.

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1 It's not to say something about where it doesn't work.

2 So, again, I have to go back to, you know,
3 there's a definition of reasonable assurance of safety
4 and effectiveness, and if we're approving it for a
5 specific indication, then we're saying there's a
6 reasonable assurance of safety and effectiveness for
7 that indication. And if there are some limitations
8 about what it doesn't do, those aren't described as it
9 doesn't do that. During the study description, that's
10 under the -- I see. It's called the clinical
11 experience section of the label. That's where it
12 would be described, what happened, what didn't happen,
13 you know, what we didn't see, what we did see. That's
14 where that would go.

15 DR. HAINES: Maybe that's a good solution,
16 you know, is to have -- I'm really, like I said, I'm
17 very concerned that people feel protected in this kind
18 of setting, and I don't know how -- I'm not at risk.
19 So maybe we're just trying to decide where to put that
20 kind of information, you know, defining where it's
21 really working.

22 CHAIRPERSON BECKER: To kind of summarize,

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1 the indication, I think, is pretty clearly stated that
2 the dural sealant system is intended for use as an
3 adjunct to sutured dural repair during cranial surgery
4 to provide watertight closure, and then the issue
5 really comes up about warning that this may not have
6 the long-term effectiveness of preventing CSF leaks.

7 And I guess the question is: can we put
8 that in the clinical description? Is that sufficient?

9 Does someone want to make a motion about
10 that or how should we proceed?

11 DR. WITTEN: Well, you don't need a motion
12 for it to go in the clinical experience section
13 because that's something we would decide whether that
14 was important, which in this case it clearly is and we
15 would put it in there.

16 And I'm not sure whether there's anywhere
17 else that it could logically go. So you know, like I
18 say, unless there's an underlying concern about
19 reasonable assurance of safety and effectiveness.

20 DR. JENSEN: What about in the clinical
21 experience where they say the incidence of
22 postoperative CSF leaks in the study was low? But

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1 then can you put after that "but no different than
2 other" --

3 DR. WITTEN: I mean, we will have to work
4 on the label, but we usually stay away -- I'm just
5 saying in general we usually stay away from describing
6 things as low or high, but we just put in a number
7 saying this is what we saw and not say --

8 DR. JENSEN: Okay.

9 DR. WITTEN: -- you know, it was high, it
10 was low, it was good, it was bad. It's just usually
11 pure statements of material fact go in here like what
12 it was.

13 CHAIRPERSON BECKER: So it sounds like if
14 we want to include some kind of labeling that states
15 that this was of short term benefit or it's effective
16 in the short term, but the long-term benefits are
17 unclear, then that would almost be a vote for
18 nonapproval is what you're saying.

19 DR. WITTEN: Yes, yes. Either you think
20 it has reasonable assurance of safety and
21 effectiveness, and then we describe the experience
22 under clinical experience, or you don't.

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1 CHAIRPERSON BECKER: Dr. Jayam-Trouth, did
2 you have something to say?

3 DR. JAYAM-TROUTH: It was different from
4 the present discussion, and that was maybe in the
5 warning there was another bullet we might try to put
6 in and that is that we don't have studies on what it
7 does at CSF and CSF inflammatory responses because
8 that hasn't been studied.

9 CHAIRPERSON BECKER: Dr. Loftus.

10 DR. LOFTUS: I don't want to belabor this,
11 but are you basically saying, Dr. Witten, that we
12 shouldn't tinker with this wording in this document?
13 Because I'm going to suggest one more tinkering if you
14 don't say that.

15 DR. WITTEN: No, I'm not suggesting that
16 you not tinker with the wording. In fact, quite the
17 opposite, but I'm just pointing out that the specific
18 tinkering that's under discussion about saying it
19 works and then warning that it doesn't work is just
20 not something that, you know, I could understand.

21 DR. ELLENBERG: It works in the indicated
22 usage in the patient population that was studied.

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1 DR. WITTEN: Yes.

2 DR. ELLENBERG: If we don't put in the
3 patient population that was studied in here, we're
4 giving carte blanche. So just put it into the
5 clinical experience --

6 DR. WITTEN: Yes.

7 DR. ELLENBERG: -- it seems to me, and in
8 the clinical experience to describe the patient --

9 DR. WITTEN: No, sorry. I'm sorry if I've
10 been misunderstood. If you want to put something in
11 about the patient population and the indication like
12 only use it in patients with two millimeter, you know,
13 or patients who don't have it near the bone or only
14 use it in patients who are, you know, a certain age
15 range, you know, you could suggest that. I mean, you
16 certainly could suggest that for the indications.

17 I was merely commenting on the specific
18 business of putting a warning in saying that, you
19 know, it doesn't work long term and where that would
20 go.

21 DR. ELLENBERG: Well, my sense would be
22 the warning for the long term would be a statement

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1 either in clinical experience that simply says there
2 is no evidence concerning long term. That's not
3 denying or abrogating the concept of safe and
4 effective for what it was studied.

5 DR. WITTEN: Yes, something describing
6 what happened in the study, what was or wasn't
7 discussed or reviewed in the clinical experience, it
8 would go in the clinical experience section, or
9 responding to the suggestion that it be put in as a
10 warning about the product.

11 CHAIRPERSON BECKER: Dr. Loftus.

12 DR. LOFTUS: Yes. Thank you.

13 May I suggest that we consider this
14 possibility? Under indication, the DuraSeal Dural
15 Sealant System is intended for use as an adjunct to
16 sutured dura repair during cranial surgery where
17 watertight dural closure or primary watertight dural
18 closure cannot be either achieved or assured.

19 CHAIRPERSON BECKER: So you're making a
20 motion for that change in labeling?

21 DR. LOFTUS: Yes, ma'am.

22 CHAIRPERSON BECKER: Someone second that

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1 motion.

2 DR. EGNOR: Second.

3 CHAIRPERSON BECKER: Dr. Egnor.

4 So can we take a vote on that? And could
5 you read it one more time so that I don't get around?

6 DR. LOFTUS: I was hoping somebody else
7 would do it. The DuraSeal Dural Sealant System is
8 intended for use as an adjunct to sutured dural repair
9 during cranial surgery where primary watertight dural
10 closer cannot be assured.

11 DR. CANADY: Why don't you just say
12 "obtained"? Because "assured" over --

13 DR. LOFTUS: Obtained, achieved, assured,
14 I'm happy to consider amendments.

15 DR. GERMANO: But then you have to say it
16 has to be only two millimeters and away from the bone
17 because that's what they studied. So you don't know
18 if it works if it's three millimeters and next to the
19 bone.

20 CHAIRPERSON BECKER: And in many ways
21 that's reflecting the condition three that we had laid
22 out as an adjunct, right? To primary dural closure.

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1 So it's almost a repeat of that.

2 DR. LOFTUS: Well, you can certainly have
3 the opportunity to vote my motion down.

4 CHAIRPERSON BECKER: So let's take a vote
5 on that motion, that the indication be changed as Dr.
6 Loftus had just read. Everybody in favor of making
7 that change.

8 (Show of hands.)

9 CHAIRPERSON BECKER: Dr. Jayam-Trouth,
10 MacLaughlin, Haines, Egnor and Loftus.

11 Everybody opposed to that change?

12 (No response.)

13 CHAIRPERSON BECKER: And everybody
14 abstaining from voting?

15 (Show of hands.)

16 CHAIRPERSON BECKER: Drs. Ellenberg,
17 Jensen, Canady, and Germano.

18 DR. ELLENBERG: I think you have to vote.

19 CHAIRPERSON BECKER: Was it four to four?

20 So everybody in favor of that change,
21 please, again raise their hands.

22 (Show of hands.)

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1 CHAIRPERSON BECKER: Jayam-Trouth,
2 MacLaughlin, Haines --

3 DR. ELLENBERG: I miscounted.

4 CHAIRPERSON BECKER: Yeah. -- Egnor and
5 Loftus. Five to four. Okay.

6 Any other motions?

7 DR. JAYAM-TROUTH: As I said before, we
8 have to somewhere indicate that the CSF inflammatory
9 process has not been studies.

10 CHAIRPERSON BECKER: Is there a second for
11 that motion?

12 DR. JENSEN: Second.

13 CHAIRPERSON BECKER: Dr. Jensen.

14 So that would be potentially a warning?

15 DR. JAYAM-TROUTH: A warning.

16 CHAIRPERSON BECKER: A bullet for warning.

17 So everybody in favor of adding a warning that states
18 that the CSF inflammatory response has not been
19 studied in these patients?

20 DR. GERMANO: Could we have discussion for
21 that?

22 CHAIRPERSON BECKER: Sure.

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1 DR. GERMANO: How good or bad does it look
2 that we approve something without knowing what it
3 does?

4 DR. ELLENBERG: That's what we've done.

5 CHAIRPERSON BECKER: Yeah.

6 (Laughter.)

7 DR. EGNOR: Well, you never know
8 everything. I mean, there's no way you can know
9 everything. We're just pointing out things.

10 DR. GERMANO: Something like CSF is so
11 simple to do.

12 DR. MacLAUGHLIN: I don't know. I think
13 we kind of have to deal with the cards we're dealt at
14 the moment. You know, the claim is that it stops the
15 leak in the CSF in the operating room. I think these
16 kinds of discussions always bring up lots of other
17 studies to do and lots of other things to do, but I'm
18 always trying to weigh one thing, you know, the safety
19 issue against what other stuff we'd like to know. Do
20 you know what I mean?

21 I'm just thinking of the sort of motion in
22 front of us about whether this seals and whether we

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1 think it's safe, I guess, not what hasn't been done.

2 DR. GERMANO: Well, wouldn't it make it a
3 stronger label if some of those "ifs" were removed and
4 this application is reviewed when the CSF data is
5 available, the radiographic data is shared?

6 I mean, maybe we cannot answer all of the
7 questions, but we can answer some and make a very
8 strong label with less questions.

9 CHAIRPERSON BECKER: I think that's, sure,
10 the label would be improved, and I think that's what
11 we're being asked to vote on, is how strongly do we
12 want to prove this now and how strongly would we like
13 the sponsor to come up with information first.

14 Since we have had a motion and a second
15 for changing the labeling about the CSF issue,
16 reflecting the fact that there is no information about
17 the effect of the DuraSeal system on CSF inflammatory
18 response, how many people are in favor of changing the
19 labeling to indicate that? Let me see your hands.

20 (Show of hands.)

21 CHAIRPERSON BECKER: Drs. Jensen and
22 Jayam-Trouth.

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1 Everybody opposed to that labeling change.

2 (Show of hands.)

3 CHAIRPERSON BECKER: Dr. Canady, Dr.
4 Haines.

5 Everybody abstaining.

6 (Show of hands.)

7 CHAIRPERSON BECKER: Drs. Loftus, Egnor,
8 Ellenberg, MacLaughlin, and Germano.

9 So it's a vote of two to two for the
10 labeling change, and I'll vote in favor of it. We'll
11 put that warning in.

12 So any motions for other conditions at
13 this point? Dr. Ellenberg.

14 DR. ELLENBERG: I would like to make a
15 motion that the characterization of the population
16 studied be included in the clinical experience, first
17 paragraph, as a condition of approval.

18 CHAIRPERSON BECKER: We don't necessarily
19 need to make a motion about things included in the
20 clinical experience?

21 DR. WITTEN: Well, you certainly can if
22 you want to. We typically would put it in, but if you

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1 feel strongly enough, you can suggest that, and like I
2 say, that's the kind of thing you could also suggest
3 for the indication. I didn't mean to say you couldn't
4 put things somewhere else. It was just the one
5 specific suggestion I was commenting on.

6 DR. ELLENBERG: I would like to accept a
7 friendly amendment to put that in the indication with
8 the wording that FDA will determine.

9 CHAIRPERSON BECKER: Is there a second to
10 that motion about stipulating that this device is
11 effective in the patient population studied?

12 DR. EGNOR: Second.

13 CHAIRPERSON BECKER: Second, Dr. Egnor.

14 Any discussion on that issue?

15 (No response.)

16 CHAIRPERSON BECKER: So everybody in favor
17 of stipulating that the DuraSeal Sealant System is
18 effective in the patient population studied, as laid
19 out in the study design, may I see your hands?

20 (Show of hands.)

21 CHAIRPERSON BECKER: Drs. Loftus, Egnor,
22 Jensen, Canady, MacLaughlin.

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1 DR. WITTEN: Actually, can I ask for some
2 specific clarification for that condition? Because I
3 know in advance that one thing will come up, which is
4 the age. You know, if we look at the population, if
5 we look at all of the inclusion criteria and all of
6 the exclusion criteria, then one we will end up having
7 some discussions about later is that the age for this
8 study was 18 to something.

9 So is that part of this recommendation as
10 far as the indications?

11 CHAIRPERSON BECKER: Let's open it up for
12 panel discussion. Is age going to limit the use of
13 this product?

14 DR. EGNOR: There certainly is nothing
15 about what we've seen about the product that would
16 make one think or make me think that there would be a
17 differential outcome regarding age. How would this be
18 dealt with with other devices by the FDA?

19 DR. WITTEN: Well, it's the kind of
20 question we'd ask the panel for their advice on, and
21 the panel could either tell --

22 (Laughter.)

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1 DR. WITTEN: No, seriously, could either
2 tell us that they think that it should be limited in
3 the indication also in terms of age. They could
4 recommend that they think that there's no reason to
5 expect that it would be different in the pediatric
6 population, and recommend that the age not be limited
7 in the indication or, you know, some third option not
8 specified. I don't know what that would be.

9 DR. HAINES: There's already a statement
10 in the precautions about age. I think it would be
11 redundant to put that in the indications, and I think
12 we're beginning to actually increase the risk of the
13 things that Dr. Loftus is concerned about by making
14 things way too specific and creating opportunities.

15 There are certain social problems we can't
16 solve in the label in this device.

17 DR. ELLENBERG: Well, the final statement
18 in the current label says the safe and effective use
19 of this DuraSeal sealant for its intended use is
20 supported by the findings of this study, and if we
21 don't indicate the nature of the cohort in the study,
22 it seems to me that's giving a general license to use

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1 for all patients.

2 DR. CANADY: But won't it be listed in
3 your summary of the study?

4 DR. WITTEN: Yes.

5 DR. ELLENBERG: I think that's a much
6 lesser --

7 DR. CANADY: Do you think this label is
8 going to limit how people are going to use it at all?

9 DR. ELLENBERG: No. I thought you argued
10 that you read labels.

11 DR. CANADY: I read them, but that doesn't
12 mean I don't just do --

13 (Laughter.)

14 DR. CANADY: I think we're over
15 engineering.

16 CHAIRPERSON BECKER: So the motion that we
17 had just voted on, actually, Dr. Jayam-Trouth, I
18 didn't see whether you had voted for or against
19 stipulations about the device being effective in a
20 patient population studied for the indications.

21 DR. JAYAM-TROUTH: I put against because I
22 think it was random.

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1 CHAIRPERSON BECKER: So who else is
2 opposed to making that change in the indications?

3 DR. CANADY: I am because I think it's
4 just as good in young people as it is in old.

5 CHAIRPERSON BECKER: And who is abstaining
6 from voting there?

7 (Show of hands.)

8 DR. ELLENBERG: Has it passed?

9 CHAIRPERSON BECKER: Okay. Motions for
10 other conditions.

11 DR. ELLENBERG: Has that passed or failed?

12 CHAIRPERSON BECKER: It's passed. Four to
13 three is my count.

14 DR. GERMANO: Four abstained?

15 CHAIRPERSON BECKER: Now. Four for, two
16 against, three abstained.

17 DR. GERMANO: Four abstained.

18 CHAIRPERSON BECKER: Can I see hands
19 again? Everybody who abstained from voting on that
20 change?

21 (Show of hands.)

22 CHAIRPERSON BECKER: So four. Okay.

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1 Everybody opposed to that change indication?

2 (Show of hands.)

3 CHAIRPERSON BECKER: Two.

4 DR. JAYAM-TROUTH: Three.

5 CHAIRPERSON BECKER: Ah. Everybody for
6 that change in indication?

7 (Show of hands.)

8 CHAIRPERSON BECKER: Two. Okay. I'm
9 sorry. That one does not get approved.

10 DR. ELLENBERG: I would like to make a
11 motion that the nature of the patient population be
12 specifically stated in the first paragraph of clinical
13 experience.

14 CHAIRPERSON BECKER: So it's a change in
15 the motion from moving the stipulations about the
16 patient population from the indications to the
17 clinical experience part of the labeling indication.

18 Is there a second for that motion?

19 (No response.)

20 CHAIRPERSON BECKER: No second?

21 DR. JAYAM-TROUTH: Second.

22 CHAIRPERSON BECKER: So there is a second.

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1 So any discussions on this point?

2 It's essentially just moving what we just
3 talked about to a different part of the label.

4 DR. ELLENBERG: Can I speak on this?

5 CHAIRPERSON BECKER: Sure.

6 DR. ELLENBERG: It seems to me that this
7 is the crux of what we've been discussing all day and
8 not to highlight it in the clinical experience to me
9 does not make much sense because it seems to me that
10 it would allow that this could be used for any cohort
11 of patients regardless of whether or not this
12 particular data set given to us today justified it.

13 CHAIRPERSON BECKER: Okay. Dr. Loftus.

14 DR. LOFTUS: There is to my mind a
15 tangible risk in over engineering this as Dr. Canady
16 had said. I sought to protect the surgeon against an
17 error of omission. This potentially exposes the
18 surgeon to an error of commission if they were to use
19 this in a trauma patient and it was defined that the
20 study had not -- or in a pediatric patient -- who were
21 not included in this very limited study. And I find
22 that troublesome.

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1 DR. JENSEN: But the FDA is not saying
2 that it's disapproved for those uses. It would be an
3 off label use of the device, correct?

4 DR. WITTEN: No, if it's not in the
5 indication, if the indication stays as it is and the
6 contraindications warnings and precautions stay as
7 they are, that's a pretty general indication, and it
8 wouldn't be off label for these various populations.
9 We would typically put in the clinical experience
10 section the study so that the physician reading the
11 label, of which hopefully there would be some, would
12 have some understanding of the basis for the use and
13 the instructions for use and what to expect in terms
14 of the results.

15 DR. JENSEN: All right. So outlining the
16 patient population up front in the clinical experience
17 doesn't --

18 DR. WITTEN: Doesn't limit the
19 indication, and frankly, we do that. We will expect
20 to do that in any case. I mean, that is what we do
21 when we describe the study, is who was studied, but
22 you don't expect -- I mean, just in general for a lot

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1 of our products the study doesn't study the entire
2 universe of patients in whom our product might be
3 used, and we don't go, you know, specifically -- you
4 know, there are some cases where we might feel that
5 the study was a model for one particular group, and
6 then we would label it in the indications for that
7 group and put that in the clinical experience.

8 But then there's other cases where the
9 study, you know, perhaps supports a broad indication
10 even though those weren't specifically who was
11 studied. It would still go in the clinical experience
12 section as statements of fact about the study but
13 wouldn't make it into the indication.

14 CHAIRPERSON BECKER: So I think that we
15 had made a motion and a second regarding making sure
16 that information got into the clinical experience.
17 Can we take a vote on that? Everybody in favor of
18 making sure that gets into the clinical experience?

19 (Show of hands.)

20 CHAIRPERSON BECKER: Dr. Jayam-Trouth, Dr.
21 Haines, Dr. Jensen, and Dr. MacLaughlin.

22 Everybody against putting that in the

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1 clinical experience?

2 (Show of hands.)

3 CHAIRPERSON BECKER: Drs. Canady,
4 Loftus --

5 DR. CANADY: That's just a routine place
6 where you would put it? No, I'm for that.

7 CHAIRPERSON BECKER: Okay. Dr. Loftus,
8 you were against or for?

9 DR. LOFTUS: I'm going to abstain.

10 CHAIRPERSON BECKER: Anybody against
11 putting that information?

12 (No response.)

13 CHAIRPERSON BECKER: Anybody abstaining
14 from putting that information in?

15 (Show of hands.)

16 CHAIRPERSON BECKER: So that's Dr. Loftus,
17 Egnor, Ellenberg, and Germano. Five to four.

18 Any motions for other conditions?

19 So I think that now we have to go back
20 through and read all of the conditions again since it
21 has been so long since we've done that and hopefully
22 get them right.

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1 So this is a vote for approval of the
2 DuraSeal Sealant System with the following conditions.

3 Firstly, that there be post approval surveillance for
4 infections;

5 Secondly, that there be explicit warnings
6 for the risk of an infection in the labeling and that
7 the labeling be changed to reflect all of the
8 infections as a single entity as opposed to separated
9 out into type of infections.

10 Thirdly, that we make sure that the
11 indications are for using this device as an adjunct to
12 primary dural closure.

13 Fourthly, that there be information in the
14 labeling warning the clinicians that there are CT and
15 MR changes associated with use of the device.

16 Fifthly, that the company get some
17 information for us about the nature of these changes
18 and the duration of the changes after device
19 implantation.

20 Next, that there be warnings in the
21 labeling that there is no information about the CSF
22 inflammatory response with -- actually, I'm going to

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1 take that one out. I think we voted against that.
2 No, we didn't. I'm sorry. So that one is in.

3 So CSF inflammatory response is unknown
4 after device implantation.

5 Next, that the patient population studied
6 in the dural sealant system pivotal study the
7 explicitly outlined in the clinical experience
8 section.

9 And then someone may be actually able to
10 help me because I have another condition here that's
11 very similar to one that is already mentioned, and
12 that is that in the indications we mentioned that the
13 DuraSeal Sealant System is intended for use as an
14 adjunct to sutured dural repair during cranial surgery
15 to provide watertight closure where it can't otherwise
16 be obtained, yeah, otherwise can't be obtained.

17 DR. GERMANO: I think we voted against
18 that one because it was redundant.

19 CHAIRPERSON BECKER: Yeah, I thought so,
20 too.

21 DR. GERMANO: Yeah, in the precaution they
22 already say do not use it if it's more than two

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1 millimeters and do not use if it's three millimeter
2 next to the bone.

3 CHAIRPERSON BECKER: So that last one
4 falls off then.

5 DR. LOFTUS: I'm sorry. I thought we
6 voted in favor of the change of the indication to say
7 that or to provide a watertight closure where it could
8 not be obtained, where primary watertight closure
9 could not be obtained. Did we not vote in favor of
10 that motion?

11 CHAIRPERSON BECKER: I think we voted for
12 it, yeah, although it seems very similar to the
13 wording that this only be used as an adjunct. It
14 seems very similar to me.

15 DR. CANADY: Why don't we put them
16 together and let them work out the specifics?

17 CHAIRPERSON BECKER: Is that fair that we
18 put those two conditions together and let the FDA work
19 out the wording?

20 So with those conditions as outlined, can
21 we have a final vote then on the approvability of this
22 premarket approval for the DuraSeal Sealant System?

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1 Everybody in favor of approval, may I see
2 your hands?

3 (Show of hands.)

4 CHAIRPERSON BECKER: Drs. Jayam-Trouth,
5 MacLaughlin, Haines --

6 DR. CANADY: Point of order. Are we
7 voting for the approval with limitations?

8 CHAIRPERSON BECKER: We're voting for the
9 approval of all the conditions as outlined.

10 Canady, Jensen, Egnor, and Loftus.

11 Everybody against approval, may I see your
12 hands?

13 (Show of hands.)

14 CHAIRPERSON BECKER: Dr. Ellenberg and Dr.
15 Germano.

16 And anybody abstaining from voting at this
17 point?

18 (No response.)

19 CHAIRPERSON BECKER: So it looks like the
20 panel has voted in favor of approval with conditions,
21 seven people voting for the approval, two people
22 abstaining from voting.

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1 DR. CANADY: No, they didn't abstain.
2 They opposed.

3 CHAIRPERSON BECKER: Opposed. I'm sorry.
4 They abstained at all the other points. Two opposed
5 to voting.

6 And I think at this point it's usually
7 customary for everybody to go around and give some
8 closing remarks on their thoughts about its
9 approvability. So why don't we start with Mr. Balo?

10 MR. BALO: I mean, what can you say after
11 everything has been said all day today? Let me tell
12 you, but this is sort of my last panel meeting, and
13 I'd sure like to take the time to really thank Dr.
14 Witten and the panel members and really the sponsors
15 for the hard work that they do to bring this to the
16 panel.

17 It takes a lot of hard work to get here,
18 and I think the panel does a great job to really try
19 and sort out the facts, look for the public benefit.
20 I think as we said through the questions that the FDA
21 asked, I think we all agree that it was effective as
22 the study was designed, and I think we sort of had

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1 questions about safety, but we put some conditions on
2 that will sort of sort that out.

3 So I'd just like to applaud the panel for
4 their work today.

5 Thank you.

6 CHAIRPERSON BECKER: Dr. Loftus.

7 DR. LOFTUS: Yeah, if I may just
8 summarize, you know, the decision making, the facts
9 that entered into my decision making, first, the type
10 of agent is clearly in common use. This is a fact of
11 life. As Dr. van Loveren finally alluded to the
12 thing, I thought they would have said first thing this
13 morning that the current product has a very distinct
14 advantage, no lineage from human material, which
15 cannot be overstressed.

16 The study has some artificial attributes
17 regarding eligibility and interoperative testing.
18 It's a pity the data is not available for the 23
19 patients, et cetera. I do believe the product works
20 as intended.

21 And finally, if approved, when approved,
22 now approved, right or wrong, I believe the product is

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1 going to be used off label for spinal CSF egress
2 repair probably as much or more than cranial repair.

3 CHAIRPERSON BECKER: Dr. Egnor.

4 DR. EGNOR: Regarding the safety of the
5 product, it's very good that it involves off-shelf
6 components, and there's no major toxicological issue.
7 The dog studies were well done, and while the
8 clinical studies, I believe, need to be done further,
9 there's no compelling evidence in my view that this is
10 unsafe, and I believe that the benefit outweighs the
11 risk overall.

12 As far as effectiveness, again, the dog
13 studies were well done. Clinical studies should be
14 continued. However, it seems to be as best one can
15 see at least as effective as what is routinely used
16 for this, and it's better studied than most things
17 that we routinely use.

18 CHAIRPERSON BECKER: Dr. Ellenberg.

19 DR. ELLENBERG: I voted no only because of
20 the issue of lack of control in assessing the safety
21 of this product and, therefore, I am not able to judge
22 the risk-benefit ratio, which is a requirement for

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1 voting for approval.

2 CHAIRPERSON BECKER: Dr. Jensen.

3 DR. JENSEN: I think the data supports the
4 safety and efficacy for immediate closure to obtain a
5 watertight seal. I strongly encourage the sponsors to
6 get the postmarket data to the FDA as soon as it's
7 reasonably available, and otherwise I would just like
8 to thank Dr. Becker for doing a great job.

9 CHAIRPERSON BECKER: Thank you.

10 DR. JENSEN: And wish her well.

11 DR. CANADY: I'd just like to say I think
12 the entire discussion today has been certainly an
13 interesting one. I think it highlights the need to
14 really assess from a clinical perspective the issue of
15 CSF leaks and identify those factors that are related
16 and in a much more scientific way than has been done
17 in the past.

18 CHAIRPERSON BECKER: I wasn't asked to
19 vote. I think the sponsor did a great job in doing
20 what the FDA asked them to do. I think we still find
21 ourselves in this place where we don't know what the
22 long-term clinical benefit of this m is, and I am

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1 hoping that at some point in time we can actually get
2 that data, and I think that we really can't say that
3 this device does work to prevent CSF leaks long term,
4 but we don't know that it doesn't either.

5 So I think we're just kind of left in a
6 quandary.

7 Dr. Haines.

8 DR. HAINES: I believe that the reasonably
9 thorough nonclinical evaluation of safety was a very
10 important part of my decision. This is clearly an
11 application for which we need a good product.

12 I think the clinical evaluation was more
13 burdensome than it needed to be, and I think that with
14 a small investment of a little bit more effort in a
15 more appropriate clinical evaluation we could have had
16 a much, much easier time in arriving at this
17 conclusion.

18 CHAIRPERSON BECKER: Dr. MacLaughlin.

19 DR. MacLAUGHLIN: Yes, I voted in favor
20 because I think if you look at the sort of mandate of
21 what we were asked to evaluate, which was the closure,
22 the interoperative time, I think that was well met. I

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1 think the materials taken by themselves are not, you
2 know, toxic or dangerous. I think the future though
3 will show us what the long-range efficacy is, and I
4 think you have to start somewhere in a study like
5 this.

6 You know, we couldn't agree -- I think all
7 of us -- what the good control would be for these
8 patients, and maybe as more experience is there and
9 more data is accumulated we'll begin to learn, you
10 know, how this begins to compare to other modes of
11 treatment, but I think I didn't see anything to stop
12 me from moving ahead.

13 CHAIRPERSON BECKER: Dr. Jayam-Trouth.

14 DR. JAYAM-TROUTH: Well, I guess I also go
15 with the crowd, and I voted yes because there's
16 definitely a need for some material to, you know,
17 close CSF leaks, and I think the clinicians are
18 struggling with that, and they put all types of
19 autologous materials in there for which we don't have
20 any data at all.

21 Certainly this is safe. You know, it is
22 effective under the circumstances that are shown, and

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1 I think there's definitely need, you know, for more
2 trials and especially in difficult circumstances. You
3 know, I think those are the circumstances where
4 surgeons really need something.

5 And to me, I mean, to show it and the
6 regular case with just spontaneous leaks doesn't make
7 as much sense as to show it in difficult cases where
8 there is nothing else that would work.

9 CHAIRPERSON BECKER: Dr. Germano.

10 DR. GERMANO: I voted no, and I think that
11 this was a study that had struggled putting together
12 the sponsors with the FDA view, and I think this is
13 why we had so much struggle today with the vote.

14 And it seems that some of the issues that
15 were raised today perhaps should have been dealt with
16 and raised up front when the study was being created.

17 In any event, my vote against was based on
18 the lack of being able to establish safety and
19 efficacy on the data that was presented, and I believe
20 that some of the data is available and that the
21 sponsor does have some of the information that this
22 panel wanted to see, some of it fairly simple like CSF

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1 and radiographic, and probably by investing in a
2 little extra time looking at cases where CSF leak is
3 really known to be a problem, such as posterior fossa,
4 and I would have hoped that by having that data the
5 label would have been crystal clear and much
6 friendlier than what was suggested today.

7 CHAIRPERSON BECKER: And Dr. Witten, do
8 you have any comments?

9 DR. WITTEN: No. I'd just like to thank
10 the panel for their work today, as well as the FDA
11 review team and the sponsor, too.

12 CHAIRPERSON BECKER: So I guess this then
13 concludes the 18th meeting of the Neurological Devices
14 Panel.

15 Thank you very much.

16 (Whereupon, at 4:42 p.m., the panel
17 meeting was concluded.)
18
19
20
21

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