

1 DR. CAMPBELL: And the test has been --
2 since we established the correlation, we validated it
3 by repeating the test with similar lots at 37 and at
4 higher temperature --

5 DR. MacLAUGHLIN: Understood.

6 DR. CAMPBELL: -- to show that that
7 correlation held true across multiple lots.

8 DR. MacLAUGHLIN: Get it.

9 DR. CAMPBELL: Now, if I get it right, the
10 next question you raised had to do with an update on
11 our current stability studies following the radiation.

12 DR. MacLAUGHLIN: Yes. I don't think that
13 was complete, was it? It looked --

14 DR. CAMPBELL: No, it's ongoing. We have
15 multiple lots of product which have been put onto room
16 temperature and higher temperature, accelerated aging,
17 following irradiation.

18 We have recently completed one year of
19 shelf life testing at room temperature, and we will be
20 sharing that data with the agency soon.

21 We also are working on accelerated aging
22 data and establishing or determining that correlation,

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1 the erraneous (phonetic) for accelerated aging.

2 DR. MacLAUGHLIN: Okay.

3 DR. CAMPBELL: And we have that
4 information also.

5 DR. SAWHNEY: And those studies, it's an
6 ongoing process. Our hope is to demonstrate two year
7 stability, but you know, you don't have that
8 information until you actually complete that length of
9 time. The company is a young company, and we don't
10 see any obstacles to achieving that. It's just it
11 takes time.

12 DR. MacLAUGHLIN: Right. I don't need it.
13 I just wanted to see where you were.

14 DR. CAMPBELL: Okay. You also raised a
15 question about the reproductive toxicology.

16 DR. MacLAUGHLIN: Just a comment. I don't
17 think you should do anything differently. It's just
18 maybe an interpretation issue because you're not
19 talking about the earliest stages. That's all.

20 DR. CAMPBELL: Okay. If I recall, the
21 last question you raised had to do with the in vitro
22 cell line test, where we evaluated four different

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1 human cancer cell lines. We looked at galea blastoma,
2 lung cancer, ovary cancer, and colon cancer, I
3 believe, cell lines. We evaluated them at four days
4 in the presence of the product. It was just an
5 initial screening test. It was not meant to be a
6 definitive test to replace potential in vivo studies,
7 but yet as you mentioned, there's nothing in the raw
8 materials to suggest there's a carcinogenicity
9 problem. It's just a screening test to gather initial
10 information on those four cell lines.

11 DR. SAWHNEY: Let me provide some
12 extrapolation. As we start, as the product is
13 launched internationally, and clinicians begin using
14 it, somebody may have a concern question of what does
15 this do to seeding of cancer cells.

16 The short answer is nothing, but what data
17 do we have? So this was an attempt to try to see if
18 we changed the growth rate of a few different cancer
19 cell lines in the presence of the material. Were we
20 having any kind of nutritional supplement effect where
21 we enabling the cells to adhere and proliferate?

22 The answer we found it's an inert

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1 substance. it really doesn't do anything. Whether or
2 not these studies are the most appropriately designed,
3 I don't think these are standard studies. So they are
4 somewhat speculative, and the conclusions one can draw
5 from these are somewhat limited.

6 I would submit to you that I don't think
7 this is the most robust way to look at it, but it was
8 work that we've done, and we thought in the interest
9 of completeness and the spirit of openness and sharing
10 that we would share that information.

11 DR. MacLAUGHLIN: I appreciate that. With
12 all due respect, I don't think the way you're going
13 about it is the way to answer those questions, but
14 that's a matter for another day. I think it just
15 doesn't tell me anything.

16 DR. SAWHNEY: I t wasn't required of us to
17 do those.

18 DR. MacLAUGHLIN: No, I understand. I
19 thought I'd respond to it when I saw it.

20 Thank you.

21 PARTICIPANTS: Thank you.

22 CHAIRPERSON BECKER: The next lead panel

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1 reviewer is Dr. Canady.

2 DR. CANADY: It is clear from the
3 conversation that's already taken place that my fellow
4 clinicians need not much help in sorting out the
5 issues here. I think that the elephant in the room is
6 really the change from a non-evidence based approach
7 to medicine to an evidence approach where we have a
8 practice that is not really validated. So trying to
9 assess new experimental methods on top of that
10 practice is extremely difficult.

11 I mean, it's interesting to me as you go
12 through the report how often the comment is the
13 clinicians will be uncomfortable, not that there's
14 data to say that you can't do this, but that the
15 clinicians will be uncomfortable, and I think that's
16 the crux of the issue here.

17 Yes, I believe that's true. The
18 clinicians will be uncomfortable, but as Dr. Germano
19 brought up earlier, is that a valid basis for that
20 discomfort or just the training practices that we've
21 gone through through the years?

22 Plus in the absence of historical controls

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1 and the range for infection is zero to 20, the range
2 for CSF leak is zero to 20, you can pick any number
3 and any study that will be comfortable.

4 So I think there is a daunting task faced
5 by this PMA in the ability to compare itself to
6 current practices and to compare itself to the
7 literature.

8 The second issue, I think, is the use of a
9 clinical endpoint rather than an interoperative
10 endpoint. If we accept that the standard of leakage
11 is comparable to other studies, then we have to
12 question whether the 100 percent or essentially 100
13 percent -- and I'll give you the ten to 13 Valsalva
14 patients, interoperatively is not a useful standard.

15 If we end up with the same kind of CSF leak that
16 other people end up with, then that standard has no
17 validity, and I think that that's an issue, although,
18 again, we end up at a five to six percent leak rate
19 which is comparable in general to other studies,
20 although two of the prospective studies showed
21 significantly less leaking rate at two percent.

22 Also, I think when you evaluate the

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1 clinical risk of leaking, you have to include the
2 excluded patients, which would include those that
3 would be most apt to leak, which would be all of the
4 patients with chemotherapy, radiotherapy, infection,
5 and all trauma patients were excluded from this study.

6 So we have a highly selective population
7 that ends up with substantially equivalent statistics,
8 and I think we have to struggle today with what that
9 means.

10 Similarly, on wound infection, all of the
11 same issues apply. We don't have a comparable
12 comparative group, and I've been trying all morning to
13 tease out the DuraGen control, which seems to be the
14 closest to a real control group, and I'm still not
15 sure what that group constitutes, and also the numbers
16 are low, but on a regular basis, that number of
17 patients, the infection rate was lower.

18 When you look at all of the studies -- I
19 won't say "all" -- the majority of the studies that
20 have other kinds of materials implanted, their
21 infection rates were higher than without them as well,
22 which raises the question as to whether or not there

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1 may be some acceptable increased risk with another
2 kind of implant, which I don't think I can tease the
3 answer to, but I think is a real question.

4 The final question is the easy one, which
5 is I think that as we saw on the MR today, this has an
6 MR appearance. So I think that with the labeling
7 issues and education issues, we need to make sure
8 people don't get operated because of the appearance of
9 the materials, and we need to make sure that in the
10 labeling and somehow in the education materials that
11 the radiologist in particular who may not be talking
12 to the neurosurgeons and they may not be aware don't
13 read those out in such a way that these people end up
14 with operations that they don't need.

15 CHAIRPERSON BECKER: Thank you, Dr.
16 Canady.

17 Does anybody have any questions for Dr.
18 Canady?

19 (No response.)

20 CHAIRPERSON BECKER: I guess I should also
21 open it up for any general questions for the sponsor
22 or the FDA from the panel.

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1 Dr. Jensen.

2 DR. JENSEN: A question to Dr. Campbell.
3 I'll ask the same question I asked to Dr. Hudson.
4 Since this material is applied in such a fashion that
5 it's in contact with CSF, why did you choose not to
6 study CSF parameters in the animal studies?

7 And I bring this up because, number one,
8 it just makes sense to me that you should examine the
9 CSF. You've gone to all of the trouble to inject the
10 material into the ventricle and you do all of these
11 other studies, but you don't do a CSF examination, and
12 number two, some of your complications you had in your
13 patients included hydrocephalus and aseptic
14 meningitis, and there have actually been some
15 anecdotal cases of those similar complications, quote,
16 unquote, in patients that had hydrogel implanted into
17 aneurysms.

18 So it does sort of bring up the question:
19 is hydrogel actually as -- and it's a different type
20 of hydrogel. I'll give you that, because it does not
21 degrade and it's intravascular. However, yours is
22 directly applied to the CSF or is adjacent to the CSF

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1 in some cases, and it also degrades.

2 So it just seems intuitive to me that you
3 would have studied the CSF, and I'm curious as to why
4 you did not and whether or not that should be done.

5 DR. CAMPBELL: As you mentioned, we
6 performed the neurotoxicity study where an extract of
7 the gel was injected directly into the lateral
8 ventricle or cisterna magna of rats. As you're all
9 familiar with, we performed the canine study where
10 the durotomy was performed. So the material was
11 applied. Certainly extracts of the gel that was
12 implanted was certainly in contact with the subdural
13 space.

14 And in that study we performed
15 neurological examinations of the animals, looked at
16 nine different neurological indices. There was no
17 neurological deficits, but you are correct. We did
18 not do specific analysis of the CSF of animals that
19 had DuraSeal applied.

20 DR. SAWHNEY: However, we did look at the
21 ventricle enlargement. What we were most interested
22 in, it's a question of what are you looking for. What

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1 we were most interested in is are the extracts of the
2 materials since it will be placed on the dura and can
3 be in contact with CSF, is any material being
4 extracted out which can impede the resorption or the
5 production of CSF and deaths contribute to ventricle
6 enlargement, hydrocephalus, things of that nature?
7 Are we somehow clogging up the system?

8 And for that we actually did histology on
9 the animals after they were sacrificed to look at
10 ventricles and did not see any ventricle enlargement.

11 We looked for inflammation, which would
12 have been a sign of aseptic meningitis. We did not
13 see any of that.

14 The hydrogel that you allude to, which is
15 on the hydrogel quartered coils, it's a very different
16 substance, and I would immediately like to very
17 clearly establish it's a different material. It's a
18 nonabsorbable polyacrylamide gel that you allude to.
19 Acrylamide is a known neurotoxin and PEG is not.

20 So I would really say that that's pretty
21 different, and we did look at all of the reasonable
22 things that we felt were important with indwelling

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1 catheters where in the extract materials are directly
2 administered inside, direct intracortical
3 implantation. There's not much else that we could do.

4 We did comparator studies with other
5 materials that were implanted to kind of look at
6 controls. So we studied it as best as we could, and
7 we were picking up any signs of inflammation.

8 We should have seen that either in the
9 blood values of the animals or in the histological
10 sections of the brain that were done and
11 microscopically examined.

12 DR. JENSEN: So you think that if you had
13 elevated proteins and elevated white cells in a CSF,
14 that that would have adequately been reflected in the
15 peripheral system? Because, I mean, you went to the
16 trouble of --

17 DR. SAWHNEY: No, you would see irritation
18 of the meninges.

19 DR. JENSEN: Right, but I mean, you have
20 examined a focal area of the meninges, right? I mean
21 there are other things that we have --

22 MR. SAWHNEY: No, we did a whole brain

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1 section, and we looked at the meninges, the
2 ventricles, the parenchyma. All of those were
3 examined by the pathologist.

4 DR. JENSEN: Okay.

5 CHAIRPERSON BECKER: Dr. Egnor.

6 DR. EGNOR: This is a question for the
7 FDA, perhaps Dr. Witten.

8 It's a philosophical question. If we find
9 that the safety and the effectiveness of DuraSeal is
10 commensurate with the safety and the effectiveness of
11 standard practice, but we don't know if standard
12 practice is safe or effective by FDA definition, what
13 do you do?

14 DR. WITTEN: Well, I guess I'll give you a
15 philosophical answer. Well, I'll give you two
16 answers. One is that you're going to be read the
17 statutory definition of safety and effectiveness. You
18 should go by that.

19 But I suppose to answer your question more
20 directly, it would probably depend on what you are --
21 you know, if you think this is safe and effective as
22 some other practice that you believe is safe and

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1 effective, then that would help you make your answer.

2 If you think there's a question, that would give you
3 another answer.

4 CHAIRPERSON BECKER: Any other questions?

5 (No response.)

6 CHAIRPERSON BECKER: Perhaps we'll just
7 get some general comments no and we'll go around the
8 table. Mr. Balo, do you have any comments you'd like
9 to make?

10 MR. BALO: Yeah, I guess we sort of talked
11 a lot from a sponsor perspective, and I am the
12 industry rep., and it's pretty difficult. In this
13 study design, I agree with Dr. Cosgrove and with what
14 Dr. Schlosser said relative to trying to compare a
15 study to an unapproved device.

16 I mean, I'm in the industry, and usually
17 when you get into a situation like that you will talk
18 to the FDA. You'll ask for guidance from the FDA, and
19 if the FDA gives guidance to the sponsor that says,
20 "Well, we don't think this is really going to be a
21 good control arm," from their perspective, usually the
22 sponsor will listen to that. Most good sponsors will

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1 listen to that.

2 And they'll say, "Okay. The FDA is sort
3 of guiding us in this direction," and I think this
4 heterogeneous type of control will cause statistical
5 issues. It will cause evaluation issues, and from
6 this perspective, let's just come up with a different
7 type of study arm.

8 And in addition to that, the sponsor went
9 to outside help and consultants, to other
10 neurosurgeons and asked them for their advice. So I
11 think from my perspective, the sponsor went to the
12 avenues that they had accessible to them relative to
13 helping design the study.

14 Secondly, a literature search is a very
15 difficult thing to do. Being on the other side of the
16 fence and having to do literature searches in the
17 past, it's always difficult to get up common
18 definitions. I think we talked about that this
19 morning.

20 But it's hard when a company is trying to
21 find something in the literature to make a comparison
22 when they run a single arm study, and I think the

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1 panel should take that into consideration for what the
2 sponsor did because I think they did a good job, as
3 Dr. Schlosser did relative to trying to come up with
4 some comparable with the standard of care.

5 I'm not saying that they couldn't have
6 used the standard of care. I'm just saying I think
7 that the sponsor did the guidance from the FDA and
8 tried to put it all into perspective in the design of
9 this study.

10 CHAIRPERSON BECKER: Dr. Loftus.

11 DR. LOFTUS: Yes, thank you.

12 I assume that we'll have time to review
13 these questions and give a summary later. This is not
14 the appropriate time, but the one comment I would make
15 that just keeps recurring in my mind, and I want to
16 learn from this; I don't know the answer, but that is
17 that I've been involved in a number of NIH trials, and
18 every time the patient goes through the informed
19 consent process in such a trial and is entered, they
20 are followed to the same endpoints and with tracking
21 of all the same criteria as the patients who actually
22 undergo the intervention.

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1 And I guess from what I heard this morning
2 this data is not available, but you know, all of our
3 or a lot of our questions here could be solved if we
4 have the data on the 23 operated patients who were
5 then excluded, if we knew what their infection rate
6 was and what their CSF leakage rate was.

7 In an NIH trial, we would have that
8 information, and I guess we don't have it here, and my
9 understanding is for my questions that it's not
10 requisite, but it would certainly be interesting to
11 know.

12 CHAIRPERSON BECKER: Dr. Egnor.

13 DR. EGNOR: I agree with Dr. Loftus. I
14 think that I can understand from the standpoint of the
15 sponsor and the standpoint of the FDA that the use of
16 these controls would not be probative in ultimately
17 making this decision, but it sure would add
18 information, but I understand that that's not a fault.

19 The dog studies are fairly convincing and
20 I think are fairly well done, and I think it just
21 comes down to the notion that is the way that we
22 manage this problem in general safe and effective,

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1 because it seems to me that there's reasonable
2 evidence that the safety and effectiveness of DuraSeal
3 is commensurate with other ways of managing this.

4 CHAIRPERSON BECKER: Dr. Ellenberg.

5 DR. ELLENBERG: Let me raise a new
6 question with regard to the issue of the lack of a
7 concurrent randomized control situation. The
8 standard, the gold standard perhaps, for testing
9 efficacy and safety is to have a control population,
10 but in addition to that, a sophisticated protocol will
11 make sure that the definitions used in both groups are
12 the same, which has just been pointed out, and that
13 sparked my new point here.

14 The definitions are the same, but also
15 everything about a protocol is done up from. It's
16 prescribed in a protocol that then goes out to the
17 sites and you do a prospective study.

18 On reflecting on the evidence that's being
19 presented as a surrogate control group, it's not clear
20 that in the beginning in the protocol the comparison
21 group was defined. The comparison group being perhaps
22 the 2,800-plus study and the subgroup within that

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1 study was not as I understand it put into the protocol
2 as the group that was going to be compared to the
3 safety and the efficacy results of DuraSeal.

4 And even that very previous standard that
5 is used in every single comparative trial was not met
6 here. I'm not saying that my view on the use of the
7 literature as a control to test both the efficacy and
8 safety might be dramatically different, but it would
9 be somewhat different.

10 My sense is we're picking this control
11 group after the fact, after the study has been
12 completed, and that is simply not good science in my
13 view.

14 CHAIRPERSON BECKER: Dr. Jensen.

15 DR. JENSEN: Well, Dr. Loftus made the
16 point I was going to make. So I have nothing further
17 to add.

18 CHAIRPERSON BECKER: Dr. Canady.

19 DR. CANADY: I don't have anything further
20 to add.

21 CHAIRPERSON BECKER: I don't think I have
22 anything further to add either.

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1 Dr. Haines.

2 DR. HAINES: Yeah, I would just make a
3 couple of points. The primary purpose stated for this
4 device is a very limited technical one, which is that
5 at the time after dural closure that the sealant is
6 applied and you do a Valsalva maneuver, you don't see
7 spinal fluid coming out.

8 That's what we've been asked to look at in
9 terms of efficacy, but it's just important to
10 understand that we have absolutely nothing to tell us
11 that meeting that standard leads to a reduction in
12 clinical CSF leaks.

13 Secondly, to beat the horse that
14 apparently isn't dead --

15 (Laughter.)

16 DR. HAINES: -- having no information
17 about the leak and infection rates of the surgeons
18 involved in this study, given that there is no agreed
19 standard in the literature for those rates fails in my
20 opinion to meet any minuscule standard of valid
21 scientific evidence.

22 And while that approach may be least

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1 burdensome to the sponsor, it is most burdensome to
2 the panel and it really is creating a lot more
3 difficulty, I think, for the panel than really needs
4 to be.

5 And while I'm sympathetic to the sponsors
6 who act on the guidance from the agency, very
7 sympathetic, our responsibility ultimately is to the
8 public and not to the sponsor, and we have to deal
9 with the lack of information that we have.

10 CHAIRPERSON BECKER: Dr. MacLaughlin.

11 DR. MacLAUGHLIN: Thank you.

12 I think I conflict a little bit. I'm not
13 a clinician, but I see the Catch-22 that we're up
14 against with respect to what a good design is and what
15 could be done.

16 The only thing that occurs to me is while
17 it would be very interesting to see that other
18 information, what are the other surgeons doing? What
19 is the leak rate? What's the infection rate in these
20 other nonapproved things, nonapproved approaches?

21 It would kind of give some special weight
22 to those, I think, in our deliberation when it

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1 probably doesn't deserve it.

2 I understand the scratching for the
3 information, but I'm not sure how much weight you
4 could put on it at the end of the day because you
5 don't have -- that's not controlled, you know. That
6 work is not controlled. They're doing what they feel
7 is right, but there isn't a protocol that they're
8 following. You don't have the same trail of
9 information that you would have in a well controlled
10 study.

11 So that's my problem, is I see or
12 recognize what really had to be done and with advice
13 and so on from the FDA, but I'm not sure how much
14 weight I would have paid. Again, I'm a little bit
15 outside the loop. I'm more interested in the material
16 side of things, but how much that would influence me
17 because it isn't controlled either.

18 So it's out there. You know, like you
19 say, it's this giant, you know, elephant in the room.

20 You want to see what everybody else is doing, and
21 what's the infection rate in any institution taking
22 care of patients like this? You know, some sort of

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1 denominator you can compare it to.

2 The trouble is what in the heck is the
3 right denominator. That's what I'm struggling with.

4 Thank you.

5 DR. JENSEN: Dr. Jayam-Trouth.

6 DR. JAYAM-TROUTH: I think many have
7 voiced the problems of a clinician. Dr. Canady just
8 put it all together there, and I'm struggling with the
9 same thing. I have no question that this is, you
10 know, a good product. It's safe; it's efficacious.
11 It stops all leaks. I mean it looks like the product
12 is good, but I'm not going to use it.

13 Why am I going to use it? Is this any
14 better than anything else on the market? I mean, do I
15 have to use it?

16 You know, if you have to do a Valsalva and
17 show me a leak and even in spite of showing with the
18 Valsalva there's no leak, I'm getting a six out of 111
19 leak; that means something went wrong somewhere.

20 You know, and is it really necessity? And
21 we don't have that background there, and we don't have
22 that information, and that is really what is the

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1 problem that I see.

2 CHAIRPERSON BECKER: Dr. Germano.

3 DR. GERMANO: What I find fascinating
4 about the study is that there is an incidence of leak
5 in the hands of reputable neurosurgeons of 100
6 percent, and that has never been reported before.

7 (Laughter.)

8 DR. GERMANO: So the question is: can
9 this data be reproduced either or the other question
10 is does an interoperative CSF leak really result in a
11 clinical leak, and although some derogatory comments
12 were made about an ethnicity, there are reputable
13 neurosurgeons in this country that were born and
14 raised in the United States and trained in the United
15 States, and some of those are panel members of this
16 panel that do not close the dura, and their data is
17 available at the hospital or state Q&A showing that
18 the incidence of CSF leak is virtually close to zero.

19 And so the question really is: do we
20 really need to close the door?

21 Now, with that said, each of us, including
22 myself, struggled with complications from CSF leaks.

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1 So I don't want to try to seem cavalier about the fact
2 that CSF leaks can and do pose a very challenging
3 management in patients.

4 But usually those patients are patients
5 that are operated in the posterior fossa, that have
6 had multiple surgeries, that had radiation and
7 chemotherapy, and trauma. In none of those
8 categories, except for the 19 patients of the
9 acoustics, none of those other categories are
10 represented in the study.

11 So I don't think we have enough answers to
12 the clinically relevant questions.

13 CHAIRPERSON BECKER: Dr. Witten, do you
14 have anything to say?

15 DR. WITTEN: No.

16 CHAIRPERSON BECKER: So I think at this
17 point we can focus on the FDA questions. What I'll do
18 is I'll go ahead and read each question, and after the
19 question we'll allow the panel members to make a
20 statement regarding that question, and we'll provide a
21 summation to Dr. Witten.

22 So while they're setting up the questions,

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1 let's just start. The first question has to do with
2 infection.

3 The safety evaluation included adverse
4 events collected to three months after surgery. The
5 overall rate of surgical wound infection in the
6 DuraSeal clinical study was nine out of 111 patients,
7 or 8.1 percent, with a 7.2 percent rate of deep
8 surgical infection, all requiring repeat surgery.

9 Please discuss whether this infection rate
10 raises concern.

11 And, Dr. Germano, we'll start with you and
12 go around the table in the opposite direction.

13 DR. GERMANO: Yes, it does raise a
14 concern. I think that the infection rate is high.
15 Again, if you pull the articles from the literature,
16 you can go from an infection rate of zero to 20
17 percent. So it's hard really to find a denominator.

18 And I think that what Dr. Haines pointed
19 out should be stressed, and that is that if we had a
20 denominator for each of the surgeons that participated
21 in this study, it would be a little bit easier to
22 understand if for their practice this is falling

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1 within the norm or out of the norm.

2 CHAIRPERSON BECKER: Dr. Jayam-Trouth.

3 DR. JAYAM-TROUTH: I think, again, there
4 is no good comparison. So it kind of stands by
5 itself, but if these were selected patients and these
6 were clean patients and they were done under the best
7 cares selectively, electively, I mean, I would have
8 then expected that the infection rate should have been
9 lower.

10 CHAIRPERSON BECKER: Dr. MacLaughlin.

11 DR. MacLAUGHLIN: I think as a biochemist
12 I'll have to abstain from commenting on how bad these
13 infections are.

14 CHAIRPERSON BECKER: Dr. Haines.

15 DR. HAINES: Well, I think this is the
16 biggest concern on the safety issue. I agree. I
17 think the infection rate is higher than I would expect
18 from this group of surgeons for this group of
19 patients.

20 I think that the attempt to find a
21 comparison in the literature is completely
22 unconvincing, and not useful. I will even quote

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1 myself. In the published review comments on the
2 Narotam article where it says, "The absolute infection
3 rates reported by the authors, therefore, should not
4 be used as a standard for comparison unless their
5 liberal definition of wound infection is also used."

6 So I just don't think that we have any
7 valid comparison and, therefore, we have to fall back
8 on our assessment that this looks like a high
9 infection rate and that this probably is an issue for
10 this device.

11 CHAIRPERSON BECKER: I would have to
12 concur, and I think the infection rate is high, and
13 these weren't infections that were simply treated with
14 antibiotics. These patients all had re-surgery. So I
15 think that is a big issue, and again, without an
16 adequate comparison group, it's just hard to know what
17 to do with it.

18 DR. CANADY: I concur.

19 CHAIRPERSON BECKER: Dr. Jensen?

20 DR. JENSEN: I concur.

21 CHAIRPERSON BECKER: Dr. Ellenberg?

22 DR. ELLENBERG: I concur.

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1 DR. EGNOR: I just raise one issue. These
2 are not clean cases or many of them were not clean
3 cases. I thought that Dr. van Loveren did a nice job
4 in showing that when one looks at clean-contaminated
5 cases in neurosurgery that these infection rates are
6 not high. When one considers the breakdown of the
7 kinds of cases, most of the clean-contaminated cases
8 came from the duration of the operation. Some of
9 these were major procedures.

10 So I do agree. Looking at the rates, it
11 seems awfully high for craniotomies, but for major
12 procedures I do think there is some literature support
13 for the notion that these are infection rates that are
14 consistent with that.

15 CHAIRPERSON BECKER: Dr. Loftus, before
16 you make your point, Dr. Haines would like to respond.

17 DR. HAINES: Well, let's remember that in
18 the study protocol, the CDC definition of wound
19 classification was proposed, and then when the results
20 were called into question a different classification
21 was sought, and that, number one, is a real violation
22 of any kind of sensible study design and analysis.

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1 Secondly, the classification by Narotam
2 has not been validated by anybody else. It was first
3 published in a nursing journal. The data supporting
4 the inclusion of cases lasting longer than two hours
5 as clean-contaminated is not solid, and it is not an
6 established part of our understanding of surgical
7 wound infection.

8 So it's one paper. It was found post hoc,
9 and I don't think that it's a valid way of looking at
10 it.

11 CHAIRPERSON BECKER: Dr. Loftus.

12 DR. LOFTUS: Yeah, it's a thorny issue. I
13 mean, in and of itself we could certainly justify
14 either position on this panel among the surgeons in
15 this room that based on the co-morbidities, this is an
16 acceptable infection rate or it's not.

17 But I don't think that's the fundamental
18 question. To me the fundamental question is: is
19 there a linkage between the use of the product and the
20 infection rate as stated?

21 And unfortunately, to my mind we have not
22 been able yet to come up with a credible answer to

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1 that question, but this remains, you know, a sort of
2 nagging doubt.

3 DR. CANADY: The only question was in the
4 initial univariate analysis the amount of material
5 used was associated, although it fell out on the
6 multi-variate.

7 CHAIRPERSON BECKER: Mr. Balo.

8 MR. BALO: Yeah, I can't comment on it.

9 CHAIRPERSON BECKER: So, Dr. Witten, I
10 think that overall the panel has some concerns about
11 the infection rate in this study, but probably the
12 bigger concern is that we have no comparison to know
13 how significant this infection concern really is.

14 DR. WITTEN: Thank you.

15 CHAIRPERSON BECKER: The second question
16 has to do with postoperative CSF leaks. The primary
17 efficacy endpoint of the study was the number of
18 patients with continued CSF leak interop. after
19 DuraSeal application. The study design specified a
20 greater than 80 percent study success criteria. The
21 sponsor achieved a success rate of 98.2 percent.

22 The purpose of establishing a watertight

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1 closure of the dura is to limit the postoperative CSF
2 leak rate and associated morbidity. There are five
3 cases, 4.5 percent of the population of the protocol
4 defined postoperative CSF leaks observed in this
5 study. Three patients had a pseudomeningocele seal
6 and the two other had incisional CSF leaks. There's
7 one additional case of a CSF leak during reoperation
8 for a deep wound infection. Including this event, the
9 rate is six out of 111 patients, or 5.4 percent.

10 Please discuss the observed postoperative
11 CSF leak rate.

12 And we're going to start with Mr. Balo's
13 end of the table on this question.

14 MR. BALO: Again, like Dr. MacLaughlin,
15 not being a physician, I'm not going to comment on
16 this.

17 CHAIRPERSON BECKER: Dr. Loftus.

18 DR. LOFTUS: I'll just keep this brief. I
19 believe that this product is effective in obliterating
20 CSF leaks at the time of surgery in the fashion that
21 was described, considering somewhat of the artificial
22 nature of the testing parameters.

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1 The linkages between that and the clinical
2 CSF leak related problems, as Dr. Germano has
3 iterated, is a little bit more unclear.

4 CHAIRPERSON BECKER: Dr. Egnor.

5 DR. EGNOR: I think it's generally
6 accepted by neurosurgeons that the absence of a CSF
7 leak interoperatively by whatever technique one uses
8 to achieve that is the goal. In that sense DuraSeal
9 helps achieve that goal, and it makes that particular
10 operation equivalent from that respect to a good
11 mechanical closure of the dura.

12 The question then is what influence does
13 that have ultimately on how the patient does regarding
14 clinically significant CSF leaks. We don't know that
15 answer at all, but at least intraoperatively the
16 DuraSeal seems to accomplish what we all try to
17 accomplish surgically, which is to not see CSF when
18 you do a Valsalva.

19 CHAIRPERSON BECKER: Dr. Ellenberg.

20 DR. ELLENBERG: I think the response to
21 this question from a non-clinician will come back to
22 the issue of compared to what.

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1 In addition, as was raised during the
2 discussion in the morning, the endpoint defined could
3 have been focused on CSF leaks. It could have been
4 focused on long-term infection rates, but instead it
5 was focused on whether the leak was stopped.

6 So this question is going on to perhaps an
7 unfair level in the sense that you're going beyond
8 what the sponsor was tasked with doing and what they
9 proposed to do, which was simply to measure whether or
10 not this device stopped the leaks.

11 CHAIRPERSON BECKER: Dr. Jensen.

12 DR. JENSEN: I think the sponsor has shown
13 that it stops intraoperative leaks. I agree with Dr.
14 Ellenberg. I'm not sure what to compare it to in
15 terms of preventing further leaks. I would say that I
16 don't know if the last case should actually be
17 included because it sounded like that at surgery the
18 dura was not leaking until after the material was
19 removed. So I think that one is kind of not fair to
20 include.

21 CHAIRPERSON BECKER: Dr. Canady.

22 DR. CANADY: I would agree that it clearly

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1 stops interoperative leaks. The significance of that,
2 however, is unclear.

3 CHAIRPERSON BECKER: Yeah, I would fully
4 agree. I mean, there's no question that it seems to
5 stop interoperative leaks, but the question is what
6 does that really mean for the patient.

7 Dr. Haines.

8 DR. HAINES: Yeah, as a tool, for a
9 neurosurgeon who wants to stop a leak, at the time of
10 surgery it seems to be incredibly effective, and
11 that's a tool, I think, most neurosurgeons would like
12 to have at their disposal.

13 CHAIRPERSON BECKER: Dr. MacLaughlin.

14 DR. MacLAUGHLIN: Yes. I agree completely
15 that it's a great way of stopping leaks in the
16 operating room, but I really can't comment on -- and I
17 agree, too, with Dr. Ellenberg. That was one of the
18 goals of their study, and I can't comment on the
19 clinical ramifications.

20 CHAIRPERSON BECKER: Dr. Jayam-Trouth.

21 DR. JAYAM-TROUTH: Concur.

22 CHAIRPERSON BECKER: And Dr. Germano.

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1 DR. GERMANO: No additional comments.

2 CHAIRPERSON BECKER: So, Dr. Witten, I
3 think that with regards to CSF leaks, I think the
4 panel in general agrees that this product is very
5 effective at stopping interoperative leaks. The
6 bigger question remains as to what that means long
7 term for the patient and whether or not perhaps the
8 way they look for leaks actually has been used in
9 other studies. So is this product really better than
10 other products that have been used?

11 The third question: to be included for
12 treatment, patients were assessed for CSF leaks after
13 sutured dural closure. If CSF was observed leaking
14 from the standard incision, either spontaneously or
15 during an induced Valsalva maneuver to 20 centimeters
16 of water, the patient was included for treatment with
17 DuraSeal. The selection process was intended to
18 include a subset of patients at risk for postoperative
19 CSF leak. However, all of the patients tested leaked.

20

21 The proposed instructions for use for all
22 patients was sutured dural closure. So the first part

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1 of this question is: do you believe that the results
2 of this study support an adequate risk-benefit ratio
3 in spontaneous leakers?

4 The second part is: do you believe the
5 results of this study support an adequate risk-benefit
6 ratio in all patients with sutured dural closure as
7 described in the proposed indication for this study?

8 So I'll allow you to make comments
9 regarding both parts of the question, and we'll start
10 with Dr. Germano.

11 DR. GERMANO: I don't think we have the
12 answer for Question 3(a) because all patients were
13 include -- sorry -- because all 111 patients were
14 included. So we don't know whether or not this
15 product is good for spontaneous CSF leak because the
16 sponsor did not test for this hypothesis.

17 CHAIRPERSON BECKER: If I can point out
18 that 60 percent of their patients had a spontaneous
19 leak at the time of surgery; isn't that right?

20 PARTICIPANT: That's correct.

21 DR. CANADY: No, 40 percent spontaneous.

22 CHAIRPERSON BECKER: Forty percent and 60

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1 percent Valsalva, right.

2 Sixty percent spontaneous, 40 percent
3 Valsalva.

4 DR. GERMANO: So I would rather comment
5 there was a percentage of patients that had a
6 spontaneous CSF leak, and so then what we have to do,
7 and I don't remember the data, is to go back and see
8 how many of those that leaked spontaneously had a CSF
9 leak after the surgery.

10 DR. CANADY: There wasn't good overlap. I
11 think I looked at that. There wasn't an overlap
12 between the patients.

13 DR. GERMANO: So on page 9 of the document
14 it shows that spontaneous leaks intraoperatively was
15 5.9 percent and leak induced by Valsalva was 4.5. So
16 that does not seem to be statistically different.

17 CHAIRPERSON BECKER: Correct.

18 DR. GERMANO: But then again the question
19 here is risk-benefits. So I think I stated previously
20 that there are some concerns about the product, and
21 there are some concerns about the benefits.

22 I guess my answer is that there are

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1 concerned.

2 Question 3(b) is the same for all
3 patients, and so then I guess the label if this
4 product were to be approved, the label should say that
5 it is approved for all patients after the dura has
6 been closed because the authors show that there is
7 leakage in 100 percent of the patients.

8 So I still have an issue with this.

9 CHAIRPERSON BECKER: Dr. Jayam-Trouth.

10 DR. JAYAM-TROUTH: I guess the answer to
11 Question 3(a) is yes. I mean, it seems as if it does
12 work, you know. It does stop the leaks and
13 spontaneous CSF leakage. Now, what I am not really
14 sure about is, you know, do you really need to do the
15 Valsalva maneuver to show that the Valsalva increasing
16 the pressure to 20 centimeters produces a leak or
17 induces a leak?

18 You know, which means then that if those
19 people do not do the maneuver, you know, then in all
20 cases they have to then opt to put in this as a dural
21 sealant, and that is where I have a problem because, I
22 mean, most surgeons don't do the Valsalva. I mean,

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1 correct me if I'm wrong. Many surgeons probably don't
2 do the Valsalva every time there's a general closure
3 that they're doing.

4 If they see a spontaneous leak, you put
5 the sealant; it works. But for 3(b), I mean, should
6 you put it in every case? Now, I don't think so.

7 CHAIRPERSON BECKER: Dr. MacLaughlin.

8 DR. MacLAUGHLIN: Yeah, again, I'm in a
9 little bit of this gray area for me. I think it shows
10 clearly that you get the closure, and there seems to
11 be no significant difference at least for 3(a), I
12 guess, between the group. So I agree that, you know,
13 it has some early effect and early benefit, but again,
14 for the same reason of not being a clinician, I want
15 to comment on my thoughts on the other areas.

16 CHAIRPERSON BECKER: Dr. Haines.

17 DR. HAINES: I don't see a way to
18 distinguish between (a) and (b), and I think that all
19 of the next three questions address the risk-benefit
20 ratio. I'm not sure when to answer that.

21 CHAIRPERSON BECKER: I agree. Go ahead.

22 DR. HAINES: Well, I think that

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1 effectiveness for the limited purpose that's stated
2 has been well demonstrated that there are no major
3 safety issues, that there is a significant concern
4 about the possibility of a clinically important but
5 relatively small increase in deep wound infection
6 rates, and that with some -- and I'll put my card on
7 the table -- with some adjustment in labeling, that
8 the risk-benefit ratio is achieved.

9 CHAIRPERSON BECKER: I guess for my part
10 I'm not exactly sure what the benefit is. I think
11 it's effective for closing the dura. I don't know
12 what benefit that has led to in this study. We
13 certainly know what the risks are.

14 Dr. Canady.

15 DR. CANADY: I think it turns on the risk-
16 benefit ratio. Clearly, it's effective in the short
17 term for both groups.

18 CHAIRPERSON BECKER: Could you use the
19 microphone, please?

20 DR. CANADY: Clearly, it's effective for
21 both groups in the early stages, and the question
22 becomes what is the relative, if any, change in

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1 infection rate and whether or not the patients in whom
2 -- which of the patients and what is the criteria by
3 which patients go on to clinical leaking, and those
4 are questions for which we don't have answers.

5 Do I think it's terribly unsafe? No.

6 CHAIRPERSON BECKER: Dr. Jensen.

7 DR. JENSEN: Again, I think that you've
8 demonstrated that the material closes interoperative
9 leaks, and again the question comes down to the risk-
10 benefit ratio.

11 In terms of benefit of stopping
12 postoperative pseudomeningoceles and leaks, I mean,
13 you still have them and they're still five to six
14 percent, which is what we see in other studies using
15 other materials. So it's hard without, again, a
16 control group to figure out whether or not you're
17 improving things there.

18 And I still have a problem with the
19 potential infection rate.

20 CHAIRPERSON BECKER: Dr. Ellenberg.

21 DR. ELLENBERG: On a technical point, we
22 have not seen, I believe, the confidence intervals for

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1 the CSF leak rate stratified by the spontaneous versus
2 Valsalva maneuver. So I'm not sure we can comment on
3 whether we feel comfortable with the simple
4 proportions given on the slide on the lower left of
5 page 9.

6 So I would be very cautious about
7 splitting these questions into (a) and (b) at this
8 point without further data, and with regard to the
9 risk-benefit ratio, I agree with all of the comments
10 that have been made to date that we have to look at
11 this with a safety profile that we understand compared
12 to what else.

13 CHAIRPERSON BECKER: Dr. Egnor.

14 DR. EGNOR: Regarding the risk-benefit
15 ratio, we certainly can't say anything coherent about
16 the risk-benefit ratio as regards the ultimate outcome
17 of clinically significant CSF leaks. It seems that
18 the evidence interoperative CSF leaks are preventive
19 by DuraSeal is quite strong, and that risk-benefit
20 ratio we can say something about in the sense that as
21 neurosurgeons, we typically will spend whatever time
22 is necessary, particularly in the posterior fossa, to

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1 get an anatomically watertight dural closure even if
2 it adds quite a bit of time to the operative
3 procedure.

4 I sometimes will spend an hour trying to
5 make sure the dura is really watertight. So clearly,
6 in the everyday surgical decision making of risk-
7 benefit, I'm willing to risk the extra hour of
8 anesthesia time for the benefit of a watertight dural
9 closure. Therefore, it would seem that the risk-
10 benefit ratio of achieving that watertight closure
11 using DuraSeal is sensible. That does seem to make
12 sense.

13 The long-term risk-benefit ratio we don't
14 have a clue about. The science is woefully inadequate
15 there.d The infection stuff is of concern. I wonder
16 if we could request that that be studied in time.

17 CHAIRPERSON BECKER: Dr. Loftus.

18 DR. LOFTUS: You know, it's a puzzle, and
19 so my answer will be cryptic, but let me give you the
20 positive and the negative.

21 I mean, the positive is, as I see it, -- I
22 mean, we shouldn't deny this -- this is a common

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1 surgical practice. Now, supratentorial patients, at
2 least in my practice, don't customarily undergo the
3 Valsalva maneuver.

4 For those of you who are not surgeons, you
5 should understand that in the spinal dura and in the
6 posterior fossa dura, this is a common paradigm, and I
7 think I would say that most surgeons do that.

8 Therefore, that being said, it would be
9 nice and ideal, and the public would be well served,
10 to have an on label product that was FDA vetted,
11 validated and approved, to subserve this function.

12 The negative is these are serious
13 infections in these patients, and basically ten
14 percent of these patients, serious, morbid infections,
15 and if there is a linkage -- and I don't know whether
16 there is or not -- it is troublesome.

17 CHAIRPERSON BECKER: Mr. Balo.

18 MR. BALO: Yeah, I really can't comment
19 about the infection rate, but you know, just like Dr.
20 Loftus says, I don't know if it's basically correlated
21 with a DuraSeal or not, but I do think that the
22 company has demonstrated DuraSeal does seal and

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1 provides a watertight when it is applied, and also I
2 think a benefit of it would be to reduce surgical time
3 and anesthesia time to provide that watertight seal.

4 CHAIRPERSON BECKER: Okay. So in summary
5 for Question 3, Dr. Witten, it seems that the panel
6 doesn't believe that you can artificially separate out
7 the spontaneous leakers from the Valsalva induced
8 leakers, and that while the DuraSeal is very effective
9 for closing the dura, the risk-benefit ratio, I think,
10 still is a question that cannot be adequately answered
11 based on the data we have.

12 So Question 4, and as Dr. Haines already
13 alluded to, the next couple of questions are really on
14 the same theme, but Question 4 states that 21 CFR
15 860.7(d)(1) states that there's a reasonable assurance
16 that a device is safe when it can be determined that
17 the probable benefits to health from use of the device
18 for its intended uses, when accompanied by adequate
19 instructions for use and warnings against unsafe use
20 outweigh any probable risks. Please discuss whether
21 the data in the PMA provided to us today, provided
22 reasonable assurance of safety.

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1 And, Mr. Balo, we'll start with your end.

2 MR. BALO: Well, just starting where Dr.
3 Loftus left off with the previous question, you sort
4 of left that open in here relative to we have no way
5 to correlate if the dura is still material, basically
6 correlate some of the infections that were produced.
7 So for my end of it, I still think that the device
8 does as it's intended to do, and from my little
9 experience, I think it would be safe.

10 CHAIRPERSON BECKER: Dr. Loftus.

11 DR. LOFTUS: Yeah, it's really hard for me
12 to know the answer to this, but I'm going to take a
13 stab at it, and once again, it's based on pragmatic
14 information from my own practice. That is, I use all
15 the time off-label material to subserve this exact
16 function for which I don't have data whether or not
17 infections are present or not.

18 And so I would say my answer to this
19 question is since at least this product has been
20 scrutinized in a more rigorous way, although the
21 answers are imperfect, I have to say that the safety
22 profile is at least commensurate with what I'm doing

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1 in my off-label uses of devices in my daily practice.

2 CHAIRPERSON BECKER: Dr. Egnor.

3 DR. EGNOR: Yeah, I agree with Dr. Loftus.

4 This product has been studied, I believe, more
5 carefully certainly with regard to infection and so on
6 than the stuff I use every day, and it would seem to
7 me that the risk-benefit ratio would be acceptable in
8 light of that.

9 CHAIRPERSON BECKER: Dr. Ellenberg.

10 DR. ELLENBERG: The nature of Question 4
11 is, of course, the question that's asked of this panel
12 at every meeting. Well, we need to look at the
13 standards for both efficacy and risk.

14 In terms of the standards for efficacy for
15 the primary endpoint as stated in the application, I
16 think that has been adequately proven, and in terms of
17 the measurement of risks, my sense is that we do not
18 have an adequate comparison group even in the protocol
19 defined endpoint of three months, let alone long-term
20 follow-up.

21 So I find it difficult to make an
22 objective statement just based on data presented to

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1 this panel that the benefits outweigh the risks.

2 CHAIRPERSON BECKER: Dr. Jensen.

3 DR. JENSEN: Well, unfortunately, not
4 being a surgeon, or maybe fortunately -- I'm not
5 sure --

6 DR. CANADY: We would consider it
7 unfortunate.

8 DR. JENSEN: -- I don't have a practice to
9 base infection rate upon. All I really have is what
10 has been presented in the package, and again, I
11 believe that the material can be used safely. I still
12 have an issue with whether or not the infection rate
13 is substantially greater than a group that you see,
14 Dr. Loftus, you know.

15 So the infection rate is not substantially
16 higher than what's been reported in the literature,
17 but again, like Dr. Ellenberg said, there's no good
18 control.

19 So I personally have difficulty since I
20 don't have the clinical experience that you have in
21 saying definitely it's safe.

22 CHAIRPERSON BECKER: Dr. Canady.

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1 DR. CANADY: I think it turns on your
2 perception of the material, and I guess if I classify
3 this material as an implant like my shunts and say
4 that, given that it's an implant, there's an
5 additional infection risk associated with the implant,
6 which is essentially what's been done in the
7 comparison to DuraGen, DuraSis, Bio; then you can say,
8 yes, this material is safe, but it's an implant, and
9 with an implant you have an additional risk of
10 infection every time you implant something, and that
11 has to be factored into your decision to use this
12 product.

13 I think that then it sounds reasonable to
14 me. I think that's not what's going to clinically
15 happen. I mean, people aren't going to read it and
16 make that kind of decision, but I think that given the
17 information that we have today of an infection rate of
18 11 percent, which is comparable to other implants,
19 that I would be comfortable with that decision tree,
20 with the knowledge that this is an implant and not
21 just a material that's there.

22 CHAIRPERSON BECKER: I have to say that I

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1 think the infection rate isn't out of line with the
2 other infection rates reported in the literature,
3 although they're imperfect comparisons. I guess still
4 the issue I have is it's not clear to me what the
5 benefits to the patient are long term compared to
6 doing nothing or doing nothing different than has been
7 done.

8 Dr. Haines.

9 DR. HAINES: Well, I'd have to say after
10 Dr. Loftus and Dr. Egnor's comments, since I don't
11 routinely use off-label stuff to reinforce my dural
12 incisions --

13 (Laughter.)

14 DR. HAINES: -- and think that I have the
15 same CSF leak rate that they do, I'm actually a little
16 more concerned that if there is actually an increased
17 serious infection rate associated with the use of this
18 material and it is that widely used, that we might
19 actually have a concern.

20 I mean if this doubles the infection rate,
21 the deep wound infection rate, and it's used in 70 or
22 80 percent of the craniotomies done in this country,

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1 and we approve it, we have done a bad thing.

2 CHAIRPERSON BECKER: Dr. Loftus?

3 DR. LOFTUS: Dr. Egnor was first.

4 DR. EGNOR: Go ahead.

5 DR. LOFTUS: You know, Alexa brought up a
6 very interesting point, but I disagree. I mean, this
7 is no more of an implant than a dissolving suture is
8 an implant. I mean, this is a temporary expedient
9 meant to disappear, and I think we do need to --

10 DR. CANADY: But does it hold bacteria in
11 place?

12 DR. LOFTUS: -- evaluate it in that term.

13 DR. CANADY: Does it hold bacteria in
14 place the time that it's there? I mean, I don't think
15 we know the answer to that, but I think, you know,
16 that that's a very real possibility.

17 DR. EGNOR: To comment on Steve's point,
18 there's, I think, quite a difference in the extent to
19 which neurosurgeons place materials with a specific
20 intent of preventing CSF leaks. I think that
21 practically every craniotomy wound that's closed is
22 closed at least with gelfoam in the upper dural space,

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1 certainly with some suture material, deep and
2 superficial sutures, and often with plates and things.

3 So while there may not be routine for
4 everyone placement of material to prevent CSF leaks,
5 there's a lot of material that everybody puts in every
6 craniotomy.

7 CHAIRPERSON BECKER: Dr. MacLaughlin.

8 DR. MacLAUGHLIN: These discussions
9 actually point out the trouble of designing a study
10 like this, you know, with the varied approaches by
11 different institutions and different world class
12 surgeons.

13 I think I'd prefer to answer this question
14 with a time line. It seems to me hearing the surgeons
15 talk about how -- and I know actually from my own
16 experience it's better, you know, to be put to sleep
17 for less time than more time -- if you have a
18 procedure and there's some interoperative benefit, (a)
19 no leak, (b) let's say shorter time under anesthesia,
20 that feels like a real benefit to me.

21 The longer term issues, you know,
22 infection rate, that as I say I can't comment on

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1 because I don't have any personal experience -- I'm
2 really a noncombatant in this issue -- but I don't
3 think we have enough data to support that. So I
4 compartmentalize this thing saying, yeah, it stops
5 leaks. that's a good thing in the operating room. It
6 may be a good thing overall. It may not be any
7 significantly different, let's say, than the other
8 devices that are used. Maybe it's easier to use. Who
9 knows?

10 But we don't have that, you know, to look
11 at. So I guess overall I think it does have a
12 benefit, and I just can't assess, you know, how real
13 the risk is. It doesn't seem worse than other
14 studies, but I know that those are flawed.

15 CHAIRPERSON BECKER: Dr. Jayam-Trouth.

16 DR. JAYAM-TROUTH: Kind of listening to my
17 neurosurgical colleagues again, and from what I can
18 see then, you know, the problem or the time, the area
19 where it might be most applicable will be in those
20 that are prolonged surgery, those that are in the
21 posterior fossa, maybe those in the spine which they
22 are not asking for approval, you know. So perhaps we

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1 may have to look at it and say in those situations
2 where it's complicated and where you need excess time
3 and anesthesia and stuff, that is where perhaps, you
4 know, we take that additional risk and use the
5 material.

6 But in those that are regular, normal
7 craniotomies with clean wounds, you know, I don't see,
8 you know where the potential or where the extra
9 benefit is in using the material.

10 CHAIRPERSON BECKER: Dr. Germano.

11 DR. GERMANO: I don't have enough data
12 presented to be able to deliberate on the safety of
13 this product.

14 CHAIRPERSON BECKER: So, Dr. Witten, I
15 think there's a lot of mixed feelings and controversy
16 with regards to Question 4. I think that the panel
17 doesn't really seem to have a consensus on whether
18 this product is both safe and effective, whether the
19 benefits outweigh the risks. I think that's unclear.

20 DR. WITTEN: Thank you.

21 CHAIRPERSON BECKER: So Question 5, 21 CFR
22 860.7(e)(1) states that there's reasonable assurance

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1 that a device is effective when it can be determined,
2 based upon valid scientific evidence, that in a
3 significant portion of the target population use of
4 the device for its intended uses and conditions of
5 use, when accompanied by adequate directions for use
6 and warnings against unsafe use, will provide
7 clinically significant results.

8 Please discuss whether the data in the PMA
9 provide a reasonable assurance of effectiveness.

10 And we'll start with Dr. Germano and come
11 around the other way.

12 DR. GERMANO: So, again, the question is
13 does the interoperative CSF leak result in clinical
14 leak, and the results presented on page 40 of the
15 company presentation, for the infratentorial
16 craniectomy, 19 patents, and acoustic neuroma, six
17 patients, with a total of five percent leak are very,
18 very promising. I would like to see those numbers
19 with a zero after each and then we consider the
20 product.

21 CHAIRPERSON BECKER: Dr. Jayam-Trouth.

22 DR. JAYAM-TROUTH: Well, as worded, you

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1 know --

2 DR. GERMANO: I'm sorry. Zero meaning to
3 go through 190 and 60 for the denominator, not zero
4 incidence of CSF leaks. So have the same study done
5 with 190 infratentorial craniectomy and at least 60
6 acoustic neuroma with the CSF leak remaining five
7 percent and then we consider the product.

8 CHAIRPERSON BECKER: Okay.

9 DR. JAYAM-TROUTH: I guess when you look
10 at the wording of the question and it says, you know,
11 when the device is used for its intended use and
12 conditions of use, you know, is it safe, yes, it's
13 safe. It does seal. It does do a job, but then is
14 there enough valid evidence that we need to use the
15 device? That is where I have my problems, and I guess
16 that, you know, depending on how you answer this
17 question, I'd say that, yes, it is safe to use and it
18 does produce a good sealant.

19 But is there enough scientific evidence
20 that it needs to be used? And I think the answer to
21 that, I'm not convinced that it is.

22 CHAIRPERSON BECKER: Dr. MacLaughlin.

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1 DR. MacLAUGHLIN: Yeah, I think I agree
2 with a lot of what you just said. It definitely
3 closes, and in that interoperative space, it certainly
4 seems safe.

5 I think whether one uses it or not is up
6 to the surgeon, among other choices. So I'm not tying
7 so much weight on that aspect of things. I just
8 think, you know, if it's out there, it's out there.

9 CHAIRPERSON BECKER: Dr. Haines.

10 DR. HAINES: For the limited purposes for
11 which the product is evaluated, it is effective.

12 CHAIRPERSON BECKER: For me, I think the
13 important part of this question has to do with whether
14 or not the product will provide clinically significant
15 results, and to me that's not clear.

16 Dr. Canady.

17 DR. CANADY: I concur.

18 CHAIRPERSON BECKER: Dr. Jensen.

19 DR. JENSEN: It seems to do no worse in
20 terms of clinical outcomes. So it's clearly effective
21 interoperatively. It's not worse than --

22 CHAIRPERSON BECKER: Doing nothing.

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1 DR. JENSEN: -- than doing nothing, but I
2 will say that one of the things that is appealing is
3 the fact that it does appear to markedly diminish the
4 amount of interoperative time, which I think is a
5 benefit.

6 CHAIRPERSON BECKER: Dr. Ellenberg.

7 DR. ELLENBERG: Let's see. I think I may
8 be mincing words here, but in terms of how Dr. Haines
9 responded, it seems to me that the effectiveness has
10 been shown as defined explicitly by the submission.
11 Introducing the clinically significant phrase is an
12 interesting turn of words at this late stage.

13 From what we've heard from the surgeons
14 this afternoon, as was just said, just cutting the
15 anesthesia short by an hour seems to me as a layperson
16 to be a clinically significant result.

17 But that's not what we've been tasked to
18 assess in our review of the materials or in the
19 discussion today. So I think it meets its limited
20 standard as submitted.

21 However, the one comment that I would like
22 to make now is if this device were to be approved, it

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1 would be approved based on perhaps a high risk group
2 of subjects, but that high risk group of subjects is
3 by no means, as was mentioned throughout the day, the
4 totality of subjects for which this device would be
5 used.

6 So while I have limited belief in a
7 restriction in labeling for certain types of cases
8 being an effective stopping of a surgeon using this
9 off label, if this were to be approved, I think we
10 have to realize that it would be used based on no
11 patients that were not covered, and if it were
12 approved, if it were to be considered for approval, I
13 think as a condition for approval even though it might
14 not be efficacious one might consider limiting its use
15 to the patients studied in this cohort or some
16 definition like that rather than essentially saying
17 its use for stopping leaks is the intended use.

18 CHAIRPERSON BECKER: Dr. Egnor.

19 DR. EGNOR: I certainly think that were it
20 to be approved, that it could only be approved for the
21 limited indications in this clinical trial. There's
22 absolutely no evidence that it's of any value in any

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1 other indication, except these patients and for the
2 purpose of intraoperatively stopping CSF leaks.

3 However, we do exert a great deal of
4 effort during surgery to accomplish that, and by
5 diminishing anesthesia time, one could certainly say
6 that it would seem that the benefits might outweigh
7 the risks.

8 DR. GERMANO: We have not seen any data
9 showing that there was a decreased anesthesia time in
10 any of the material that was submitted to us.

11 DR. EGNOR: Right, right.

12 DR. GERMANO: So we are basically now all
13 speculating on one sentence --

14 DR. EGNOR: Absolutely.

15 DR. GERMANO: -- that Dr. Loftus
16 interjected ten minutes ago, a beautiful sentence.

17 DR. EGNOR: Yes, but I get the sense that
18 what we're doing here is our focus isn't really to
19 evaluate the science. The science here is woefully
20 inadequate. It's a terrible study.

21 What we're evaluating is the product, and
22 if we demand utterly perfect science, I don't know

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1 that any product will come to market. So the --

2 DR. GERMANO: No, but now if you're saying
3 that what is striking to you is the decreased
4 operative time, then I would like to see that data,
5 and if the data is not available, it has to be
6 produced.

7 DR. EGNOR: Well, it's not striking, but
8 it's sort of intuitive.

9 DR. HAINES: But no. I mean, the surgeons
10 were instructed to do everything they normally could
11 do to reconstruct the dura first and then take another
12 five minutes to apply the stuff.

13 So, in fact, although it's not
14 significant, the time has increased.

15 DR. EGNOR: Well, we don't know in fact.
16 I mean, we don't know in fact that it was increased.

17 DR. HAINES: Well, it can't be decreased
18 because they had to do everything they had to do
19 before applying the sealant.

20 DR. EGNOR: I mean, in the real world one
21 could certainly imagine spending more time if you
22 don't have some adjuvant to help you.

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1 DR. HAINES: Well, again, there's another
2 danger that we're looking at the possibility that this
3 will be -- the overwhelming likelihood that this will
4 be used in place of closing the dura.

5 DR. EGNOR: Right, right, and that's
6 another perfectly valid concern, a very valid concern.

7 CHAIRPERSON BECKER: Dr. Loftus.

8 DR. LOFTUS: You know, this is
9 sufficiently muddy and sufficiently gray that I want
10 to focus exactly on the question. So what do I know
11 with reasonable assurance?

12 I know basically one thing, and that is
13 that in the study that this stuff, this product, will
14 close the dura very effectively within the population
15 which was studied, which consists of the patients who
16 are by far the easiest to close anyway, but that all
17 of the difficult cases where dural closure is too
18 problematic were eliminated from consideration.

19 And that's okay, but that's what I know
20 and anything beyond that is an extrapolation, and that
21 may be acceptable, but that's what it is.

22 CHAIRPERSON BECKER: Mr. Balo.

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1 MR. BALO: It's kind of hard to follow all
2 of these comments since I don't practice medicine, but
3 I do think from the data that was presented, from what
4 I read, the limited amount, I agree with what the
5 panel has said, that the device does seal when it is
6 applied, you know, but relative to infection, relative
7 to the safety question we discussed, I think that just
8 has to be discussed among the clinicians.

9 CHAIRPERSON BECKER: So with regards to
10 efficacy, Dr. Witten, I think that everybody is in
11 agreement that this device works interoperatively to
12 close the dura. I think that the data is not really
13 adequate to judge it against anything else, to know
14 whether it's of clinical significance in the long term
15 regarding CSF leaks.

16 So then the final question, Question 6,
17 which is really kind of the meat of the matter, is
18 that reasonable assurance of safety and effectiveness,
19 as defined in Questions 5 and 6, must be demonstrated
20 for device approval. If you believe this has been
21 demonstrated but think there are specific focus
22 questions regarding this device that still remain and

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1 can be addressed in a post approval study, please
2 identify those questions.

3 So, Dr. Germano, we'll start with you.

4 DR. GERMANO: Well, my conclusion with the
5 data that I have today is that reasonable assurance of
6 safety and effectiveness is not demonstrated.

7 CHAIRPERSON BECKER: And do you think
8 there's anything the sponsor could do to address it in
9 a post approval study?

10 DR. GERMANO: Yes. As I said, I would
11 like to see those cases that have a tendency for CSF
12 leak that is of clinical significance, and that is to
13 prolong the length of stay and/or result in additional
14 surgery.

15 So I would like for that patient
16 population to be expanded, and I used before the
17 number 190 instead of 19 and 60 instead of six, and I
18 would definitely defer the correct n to Dr. Ellenberg
19 because I don't know if what I stated would be
20 statistically meaningful. It might be that it's less
21 or more. So I would defer that to Dr. Ellenberg.

22 DR. ELLENBERG: One hundred and thirty-

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1 two.

2 DR. GERMANO: Thank you.

3 (Laughter.)

4 DR. GERMANO: In addition to that, I would
5 like to have, as the panel already recommended, some
6 information on the infection rate of the surgeons that
7 participated in the study and see whether or not the
8 infection rate that we have here is comparable or not
9 to what the standard of those surgeons are.

10 And then I think the panel already
11 addressed other concerns with the possibility of
12 having a controlled arm and so on and so forth.

13 CHAIRPERSON BECKER: Dr. Jayam-Trouth.

14 DR. JAYAM-TROUTH: I concur with Dr.
15 Germano, and I want to add one more thing. I think
16 where the device really needs to be studied is in the
17 complicated cases. You know, in those cases that are
18 difficult, in those cases that are posterior fossa, in
19 those cases that are three millimeters close to the
20 suture lines, in those cases where there's jagged, you
21 know, kind of a dural tear. You know, I think that is
22 where they really need to try and see.

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1 If you're going to put an implant without
2 strong evidence that it does any better, you know, we
3 cannot say that just because it is just as bad as
4 everything else it is better. You know, so,
5 therefore, to me where it would be really effective or
6 where it could be better is if it were shown that in
7 the complicated case it makes a difference.

8 CHAIRPERSON BECKER: Dr. MacLaughlin.

9 DR. MacLAUGHLIN: I agree with the first
10 comments of my previous two panel members here, and I
11 feel like I can't really well define a post approval
12 study that would shed the most light on the problem
13 that you surgeons are seeing.

14 Thank you.

15 CHAIRPERSON BECKER: Dr. Haines.

16 DR. HAINES: I believe that for the
17 specific proposed indication that effectiveness has
18 been demonstrated, that the overall safety of the
19 product has been demonstrated, and that if an
20 effective post approval study of the actual clinical
21 CSF rates and infection rates could be done, that that
22 would be a very adequate solution to our dilemma.

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1 CHAIRPERSON BECKER: I agree. I think if
2 this device were to be approved that we'd definitely
3 need some way of following patients to look for
4 infection rates as well as clinically significant CSF
5 leak rates so that we know whether or not in the long
6 run this device is effective or whether it's actually
7 safe.

8 DR. CANADY: The big question here is
9 really whether closure of the dura watertight is
10 useful or not, and that's really not an appropriate
11 question for the sponsor to answer, but maybe Steve,
12 sine you like those kind of studies.

13 It's clearly, just in the conversation
14 here, something that needs to be established because
15 the expense that's going to come with this kind of a
16 thing being approved is significant because it's going
17 to be used, you know. Neurosurgeons are still belt
18 and suspender people, and even if you think you have a
19 good closure, people are going to throw it out.

20 I think it is effective in sealing the
21 dura in the short term, clearly.

22 The third point would be that I could be

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1 comfortable with this device labeling it as an implant
2 with the possible risk of increased infection with any
3 added device.

4 And I would strongly support additional
5 collection of data regarding infection, although if we
6 just collected data, we're going to have the same
7 problem at the end. You don't have a comparison
8 group.

9 CHAIRPERSON BECKER: Dr. Jensen.

10 DR. JENSEN: I agree that for the
11 interoperative use it's safe and effective. I still
12 struggle with the clinical follow-up.

13 I have a question for Dr. Ellenberg.

14 Is there a way to get some statistically
15 significant data by retrospectively reviewing the 23
16 patients that were excluded based upon interoperative
17 criteria if the company were able to do so, to help us
18 get some sort of control group?

19 DR. ELLENBERG: It seems to me that the 23
20 excluded patients might represent an extraordinarily
21 heterogeneous cohort of subjects that were excluded
22 for a whole slew of reasons. So I'm not sure that

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1 this could add to our knowledge base.

2 But if the data were available, it could.

3 But I would probably say that there's no selection
4 bias operating in why they were excluded and probably
5 not very beneficial.

6 I don't find that I can agree with the
7 premise of the start of the second sentence and,
8 therefore, will not comment on the latter part of the
9 second sentence.

10 CHAIRPERSON BECKER: Dr. Egnor.

11 DR. EGNOR: I certainly think that the
12 only scenario in which I could vote for approval would
13 be if it were specifically for the cases that were, in
14 fact, studied by the sponsor.

15 I also believe that post approval studies
16 would be imperative, and the two post approval
17 studies, I think, that would be critically important,
18 first of all, would be to track infections with case
19 controls. You really have to know. If a high
20 infection rate is associated with this product, and
21 that can be clearly shown, then the product shouldn't
22 be used.

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1 But I don't know that we right now have
2 reason to think that, but that should be studied
3 carefully with concurrent controls.

4 The second thing is it probably ought to
5 be studied with patients who are difficult patients to
6 stop from leaking instead of easy patients to stop
7 from leaking, and that could be of great value to the
8 patients if it, in fact, demonstrated some benefit
9 there.

10 CHAIRPERSON BECKER: Dr. Loftus.

11 DR. LOFTUS: I turn this over minute by
12 minute as we sit here and talk, as we all do, but let
13 me tell you what I believe in my heart. I mean, I
14 believe in my heart that this manufacturer has made a
15 credible and sincere effort to work with the FDA to
16 design a trial that would answer these questions, and
17 in many respects, you know, it hasn't worked out.

18 Nonetheless -- and I would temper those
19 comments only if it became clear, and I don't think it
20 is clear, that the data which I continue to seek on
21 the 23 patients had been withheld or suppressed in
22 some duplicitous way, and I don't think that's the

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1 case, but obviously that would change my opinion.

2 And I think that couched in that framework
3 then, when I consider the alternatives that are
4 available to me, as I said before, which is off-label
5 use of things that haven't been tested and might have
6 an infection rate even higher, even though I don't
7 think in my hands they do, that this is a credible
8 application that has met my standard.

9 But I do think, as Dr. van Loveren was
10 talking, I sketched out what I thought would be the
11 ideal study, and that is, say what you like, best
12 surgical practice to seal the dura with or without
13 DuraSeal and study the infection rates, and I really
14 think that ultimately that would be very, very useful.

15 CHAIRPERSON BECKER: And Mr. Balo.

16 MR. BALO: Again, I do concur from the
17 information I heard today and from what I've read that
18 DuraSeal did show its effectiveness in the population
19 that they had selected and that they used it on.

20 Safety, again, I've heard a whole spectrum
21 of analysis from the different panel members, and I
22 just heed up to their expertise on that.

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1 CHAIRPERSON BECKER: So with regard to
2 Question 6, I think that the panel believes that if
3 this product were to be approved there are some
4 studies that would need to be done post approval
5 specifically to address the infection rate, as well as
6 to address high risk patients and clinical outcomes in
7 those patients.

8 So I think at this time we'll take a
9 break. Let's say to three o'clock or five after
10 three. Five after three, and at that point we'll
11 resume and have the rebuttals by the sponsor and have
12 more questions.

13 Thank you.

14 (Whereupon, the foregoing matter went off
15 the record at 2:49 p.m. and went back on
16 the record at 3:06 p.m.)

17 CHAIRPERSON BECKER: It's now five after
18 three, and before we move on Dr. Egnor has asked for
19 the opportunity to clarify a point that was made in
20 the discussions prior to the break.

21 DR. EGNOR: If I may ask a question of Dr.
22 van Loveren, please.

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1 Dr. van Loveren, Dr. Haines had mentioned
2 earlier in the sessions that the higher infection rate
3 in the longer operations is not necessarily widely
4 accepted as being the normal situation, and you had
5 quoted a study. You had shown us a study in which
6 that assumption was made.

7 Do you know the basis that the people who
8 wrote that study used to make that assumption that the
9 Class II operations have a higher or that the longer
10 operations have a higher infection rate?

11 And what is the basis for that assumption?

12 Because the fact that the infection rate is a bit
13 high for our sense of what clean craniotomies would
14 normally have, I'm willing to accept that if there's
15 clear evidence that the longer cases are intrinsically
16 associated with higher infection rates, but Dr. Haines
17 implies that that may not necessarily be the case.

18 DR. VAN LOVEREN: Well, I think there are
19 two responses. It comes at two levels. One is that
20 the finding that longer cases have a higher infection
21 rate is simply a statistical monitored finding when
22 you analyze and divide cases.

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1 The second component is searching for
2 mechanisms or explanations for why the longer cases
3 have a higher infection rate, and then you get into
4 hypotheses about wound exposure, the progressive
5 vascularity of the wound, the progressive bacteria
6 load on the wound, and the association of longer cases
7 with multiple surgeons, multiple episodes of
8 contamination, and the use of additional equipment.

9 Some studies have said any operation with
10 a microscope, a plastic drape and a surgeon with his
11 mouth against the drapes and on the handles is a
12 contaminated case. So as the case grows longer, there
13 are multiple reasons for infection rate to increase
14 both to do with the physiology of the patient and the
15 nature of the case and how it's being done.

16 DR. EGNOR: I certainly understand those
17 considerations, but are there other neurosurgical
18 studies of infection rates for otherwise clean
19 neurosurgical cases that clearly show this increase in
20 infection rate with operative times that are
21 commensurate with what is seen in your study?

22 DR. VAN LOVEREN: Yes. I mean, the only

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1 reason I hesitate is because I don't know if they
2 would meet Dr. Haines' need for statistical relevance
3 at the highest degree, but there are several studies
4 even in the packet that we present where there is
5 stratification of cases with demonstrable increased
6 infection rates.

7 But as we showed, especially, for
8 instance, in the Narotam study, greater than two hours
9 was a statistical increase in infection rate. The
10 greater than four hours looked like a twofold
11 increase, but was not statistically relevant because
12 of low numbers.

13 So I don't know with which of each data
14 points would reach statistical relevance.

15 CHAIRPERSON BECKER: Dr. Haines.

16 DR. HAINES: May I?

17 As usual, Dr. van Loveren says it very
18 well, and, yes, in univariate analysis the duration of
19 surgery is associated with increasing infection rates,
20 but it all of the factors that Dr. van Loveren
21 mentions that create the question, and when you do
22 apply good clinical science to the question, you find

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1 out that you have a great deal of difficulty blaming
2 the duration of the operation, focusing on that as the
3 cause of the increased infection rate.

4 So that to take duration of operation and
5 turn that into a reason to classify a case as clean-
6 contaminated is a novel idea that Narotam did, but we
7 can't compare it to the other studies because the
8 other studies don't do that.

9 DR. VAN LOVEREN: But wouldn't one
10 anticipate that the other factors would also be
11 present in the DuraSeal cases? I mean, one agrees
12 that --

13 DR. HAINES: One would like to know. One
14 would like to know.

15 DR. VAN LOVEREN: And yet it's probably
16 true. I mean longer cases have a higher infection
17 rate, and, yes, the duration of surgery may be a
18 surrogate for other physiologic and technical factors,
19 but there does seem to be an association between very
20 long operations and higher infection rates.

21 CHAIRPERSON BECKER: Thank you.

22 Okay. So now that the panel has responded

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1 to the FDA questions, we'll have the second open
2 public hearing of this meeting. Is there anybody in
3 the audience who would like to address the panel at
4 this point?

5 (No response.)

6 CHAIRPERSON BECKER: No. Okay.

7 So does anybody on the panel have any
8 further questions for the FDA? Would the FDA like to
9 make any further comments or clarifications?

10 (No response.)

11 CHAIRPERSON BECKER: So at this point
12 we'll all the sponsor to make further comments and
13 clarifications.

14 MR. ANKERUD: Thank you, Dr. Becker.

15 Eric Ankerud from Confluent Surgical.

16 We do have some closing remarks, and I
17 would like to just briefly comment on labeling as that
18 was a discussion point in the afternoon session here.

19 Dr. van Loveren and Dr. Cosgrove will also make some
20 closing remarks.

21 As you know, we proposed an indication for
22 use for the DuraSeal system and conducted a pivotal

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1 study against which we were measuring performance to
2 that stated indication. Our intent as a company
3 should this product be approved is to commercialize
4 the product and label it in a way that matches the
5 patient population that was studied. We do not have
6 an intent to commercialize this product in any other
7 way.

8 The study measured interoperative sealing
9 efficacy, and we are seeking an indication that
10 indicates the product for sealing interoperatively for
11 watertight dural closure, and I can assure you that is
12 the intent of our company should this product gain
13 commercial approval.

14 At this time I'd like to invite Dr. van
15 Loveren to the podium.

16 Thank you.

17 DR. VAN LOVEREN: Thank you.

18 It's not one of my closing remarks, but
19 the Coranet (phonetic) study also looked at infection
20 rates and found significant statistical increase with
21 duration past four hours, but you'd have to look at it
22 statistically.

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1 As for closing remarks, I agree with
2 everyone in the room that this is a very difficult
3 study design and would have benefitted from a
4 reasonable control arm. The problem, of course, is
5 that none existed and now we are contemplating
6 alluding to the redesign of the study to a methodology
7 that long ago in discussions with the FDA panel we
8 were warned against.

9 So there is, as people have said, an
10 elephant in the room, but I think it goes beyond the
11 absence of a control arm. It goes to the very heart
12 of the absence of an FDA approved substance or device
13 for this purpose, and I do believe that there is a
14 time, there comes a time to move forward and be first,
15 and there is a need for there to be a first product on
16 market approved, first device approved for this
17 purpose so that this burden cannot be placed again on
18 other people coming to trial to be told that there is
19 no suitable FDA approved control, which would thwart
20 studies and thwart innovation.

21 I think we have shown that this device is
22 reasonable first step to come onto market. It has

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1 done what it was supposed to do. It seals CSF leaks.

2 It seals the dura interoperatively.

3 When you look at the overall study, in 111
4 patients we had two CSF incisional leaks. This is an
5 incredibly robust number that could have been put up
6 against any device or sealant studied in the
7 literature and would have come out equivalent or
8 better.

9 That's not to say that it is equivalent or
10 better. That's to say that no matter what you have
11 designed this to be studied against, it would have
12 succeeded.

13 There is an incredible need for this
14 product. I think the characterization that we looked
15 at the easiest cases is not really correct. The cases
16 that were enrolled in this study, the cases I
17 enrolled, are on the ridiculous end of complicated
18 neurosurgery. These are seven to ten hour cases with
19 20 centimeter durotomies, almost 50 percent
20 infratentorial, and a third of those craniectomies
21 without replacement of bone. There's no neurosurgeon
22 that would consider that set easy, and there's no

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1 neurosurgeon that would think that closing the dura at
2 six in the evening for a case that started at 7:30
3 isn't a hazardous high risk case.

4 As a skull base complex cranial
5 neurosurgeon, you know, I am pursuing the study of
6 dural sealants not because I'm interested in the
7 company. I'm interested in my patients stopping
8 leaks, closing dura. This stuff actually works, and I
9 think a number of us will be disappointed if a month
10 from now we find ourselves in the posterior fossa
11 honestly trying to close a dura that won't close and
12 because of this technical absence of control, this
13 product is not able to come off the shelf, and it's a
14 remarkably easy product to use when you compare it to
15 what's available in the market because it's an off-
16 the-shelf product. It's not fibrin glue which has
17 dubious results to begin with, which you have to order
18 ahead of time, which takes 20 to 30 minutes to arrive
19 in the OR, which has some small concern of transfusion
20 effects.

21 So I think this is an incredible unmet
22 need. I think this is a good first product to set

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1 that standard so that second generation studies can
2 begin.

3 DR. COSGROVE: Dr. Rees Cosgrove.

4 First of all, I would like to thank all of
5 the panel members for spending so much time and effort
6 in reviewing this information, and it's probably only
7 slightly less than the time we put into getting this
8 product in front of you.

9 I think that I agree with many thing that
10 the panel members have said, that we clearly in terms
11 of the design of the study, we clearly have satisfied
12 the objective that we set out to satisfy, which was to
13 get watertight dural sealing at the time of closure.

14 But as Dr. Haines pointed out, we have
15 satisfied a limited objective, and all of the
16 clinicians in the room are saying, "Well, that's
17 great." And I think the neurosurgeons are saying,
18 "That is great. I mean that is an important thing to
19 do because in our gut we say we've got to do this."

20 And as we're all operating to closing up a
21 posterior fossa, and there would be nothing better
22 than to do it quickly, but we actually get our

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1 pericranial tissue. We spend an extra 45 minutes to
2 an hour sewing it in. We check it. We do it again
3 because we know the consequences of a CSF leak, and
4 it's far better to put in an extra 45 minutes to an
5 hour at that point, get it right, than dealing with
6 the complication five, ten, 15 days down the road and
7 reoperating in all of the issues that are involved
8 there.

9 So as neurosurgeons we have this inherent
10 acceptance in some ways of a watertight sealing.
11 However, we also have this very great discomfort
12 about, well, yeah, but does it have clinical efficacy
13 down the road, and I think everybody, myself included,
14 all physicians on the SAB have the same feeling. Does
15 it really then translate into clinical efficacy?

16 And I think that's that big question, and
17 this study doesn't answer that. However, in a
18 surrogate way, you can look at some of the numbers
19 and say it's in our comfort zone in terms of it did
20 extremely well on the overt CSF leaks because nearly
21 half of our patients, and these are the ones as
22 pediatric neurosurgeons, you know, doing a lot of

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1 posterior fossa work and some of us doing a lot of
2 posterior fossa work, these are the ones that we
3 really take the extra efforts.

4 I agree with some of the supratentorials.

5 It's less of a problem because there's no dependency
6 there, but certainly these are the ones we take extra
7 care of, and we have nearly half of the patients. So
8 I probably wouldn't agree that this was an easy
9 population to do. There's not many neurosurgeons or
10 not many neurosurgical series that are about half
11 posterior fossa procedures.

12 So we all have this sort of general
13 discomfort, and I have it, too, because I'd like to
14 know that it really is effective, but I don't think we
15 can say that on the basis of this study, although I do
16 think that it's in, again, our comfort zone for
17 certainly safety, and there's still some issues, and I
18 understand your issues about some of the infection and
19 efficacy.

20 But we're in the zone although it's not
21 statistically significant and it wasn't a well
22 designed trial. It wasn't designed to answer that

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1 question. We all know that.

2 And I do understand the panel's
3 responsibility to the public, but as a neurosurgeon, I
4 have a responsibility to my patient, and as Harry
5 said, there is nothing out there that does this,
6 nothing. We use inferior, off label, non-FDA approved
7 devices, and we use them because there's no
8 alternative, and we know that -- I know personally
9 that, you know, you can't test it in the operating
10 room to see if you really got everything covered with
11 fibrin glue, which is the one that we use the most,
12 especially in the posterior fossa.

13 And I'm not going to do a Valsal. but to
14 test and see it because you can do a Valsalva and then
15 it flips off and then where are you at? You have to
16 do it again and scrape it off and do it again. And so
17 you won't test it.

18 And we continue to have complications.
19 CSF leak related complications have not gone away with
20 our off-label use of fibrin glue. They have not gone
21 away, and I mean, the pediatric neurosurgeons and any
22 posterior fossa neurosurgeon knows this.

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1 So we have a very pressing need, and
2 having used this product, it's a remarkable product,
3 and, yes, I am a consultant for the company, but I
4 like this product, and there's nothing out there,
5 nothing out there for us at the moment.

6 So I would ask you to give very careful
7 consideration to the things that we have set as
8 clinicians and listened to the neurosurgeons on the
9 board who we all have a discomfort with the study
10 design. I accept that, but listen to honest
11 practitioners and see what they have to say because
12 it's not a perfect world.

13 Thank you.

14 CHAIRPERSON BECKER: Thank you.

15 So Ms. Scudiero will now read the panel
16 recommendation options for premarket approval
17 applications.

18 Ms. Scudiero.

19 MS. SCUDIERO: These are the three panel
20 recommendation options for premarket approval
21 applications.

22 The medical device amendments to the

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1 Federal Food, Drug, and Cosmetic Act, as amended by
2 the Safe Medical Devices Act of 1990, allows the Food
3 and Drug Administration to obtain a recommendation
4 from an expert advisory panel on designated medical
5 device premarket approval applications, or PMAs, that
6 are filed with the agency. The PMA must stand on its
7 own merits, and your recommendation must be supported
8 by the safety and effectiveness data in the
9 application or by applicable publicly available
10 information.

11 Safety is defined in the Act as reasonable
12 assurance based on valid scientific evidence that the
13 probable benefits to health under the conditions of
14 intended use outweigh any probable risks.

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

20 Your recommendation options for the PMA
21 vote are as follows:

22 One, approval if there are no conditions

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1 attached;

2 Two, approvable with conditions. The
3 panel may recommend that the PMA be found approvable
4 subject to specified conditions, such as physician or
5 patient education, labeling changes or a further
6 analysis of existing data.

7 Prior to voting, all of the conditions
8 should be discussed by the panel.

9 Three, not approvable. The panel may
10 recommend that the PMA is not approvable if the data
11 do not provide a reasonable assurance that the device
12 is safe or if a reasonable assurance has not been
13 given that the device is effective under the
14 conditions of use prescribed, recommended or suggested
15 in the proposed labeling.

16 Following the voting, the Chair will ask
17 each panel member to present a brief statement
18 outlining the reasons for his or her vote.

19 CHAIRPERSON BECKER: Thank you.

20 Are there any questions from the panel
21 about the voting options before we begin?

22 So is there a main motion for

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1 approvability, approval with conditions, or
2 disapproval from the panel? Dr. Canady.

3 DR. CANADY: I move approval with
4 conditions.

5 CHAIRPERSON BECKER: So is there a second
6 for the motion?

7 DR. EGNOR: I second.

8 CHAIRPERSON BECKER: Dr. Egnor.

9 So everybody in favor of a vote for
10 approval with conditions, please raise your hand.

11 (Show of hands.)

12 CHAIRPERSON BECKER: Okay. So that's Dr.
13 Jayam-Trouth, Dr. MacLaughlin, Dr. Haines, Dr. Canady,
14 Dr. Jensen, Dr. Egnor, and Dr. Loftus.

15 Okay. Well, I think that's the majority
16 of people voting for approval with conditions.

17 DR. WITTEN: But you have to vote on the
18 conditions first before you vote on the whole motion.

19 CHAIRPERSON BECKER: Right. I guess we
20 need to start now with laying out what those
21 conditions are, and since Dr. Canady made the main
22 motion, why don't you tell us your conditions?

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1 DR. CANADY: Post market surveillance of
2 infection and labeling for possible infection risk
3 increased.

4 DR. MacLAUGHLIN: Excuse me. Could you
5 expand upon what you mean by the labeling change? I
6 understand the post approval monitoring of the
7 patients.

8 DR. CANADY: Who's talking to me?

9 DR. MacLAUGHLIN: I am. I'm over here.

10 DR. CANADY: Oh.

11 (Laughter.)

12 DR. CANADY: By labeling I would label
13 that there's a possible increased risk of infection
14 with this device.

15 DR. MacLAUGHLIN: All right. Thank you.

16 DR. ELLENBERG: Madam Chair, point of
17 order. Can you record the abstentions?

18 CHAIRPERSON BECKER: Sure. Before we talk
19 about the motions or the conditions for approval --

20 MS. SCUDIERO: I think we got a little bit
21 out of order. We voted. We had a main motion and
22 second for this, and then the next point of order is

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1 any discussion on the motion, and then we go into
2 identifying the specific conditions.

3 A vote wasn't required at that point. So
4 we would go into what the conditions are since we have
5 a -- is there a condition? There was one seconded.
6 Was it seconded?

7 CHAIRPERSON BECKER: Yes.

8 MS. SCUDIERO: And then we discuss that
9 condition and vote upon it, and then we go through if
10 there are other conditions. Then we will vote on the
11 whole package with all of the conditions.

12 Should the conditions be voted down, then
13 we will start over with a new main motion.

14 CHAIRPERSON BECKER: Okay. So as I see
15 it, the first condition that has been brought forth is
16 that there be some requirement for a post market
17 surveillance of patients who receive the DuraSeal
18 device. So I guess we shall vote on that condition
19 initially.

20 Any discussion on that particular motion?

21 Dr. Loftus.

22 DR. LOFTUS: You know, I'm not familiar

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1 with this process. What's the mechanism for that post
2 approval? Is there a periodic reporting function to
3 the FDA?

4 CHAIRPERSON BECKER: That's a great
5 question that maybe Dr. Witten could answer.

6 DR. WITTEN: If we ask the sponsor to do a
7 post approval study, we would typically agree on the
8 outlines of the study prior to approval. The sponsor
9 would then after approval submit the study in a
10 supplement for us to approve, and then they are
11 required to report on their progress during the study,
12 and then at the end of the study we would typically
13 add it to the label for the product.

14 I'm going to answer the following question
15 because I know it comes up, which is whether or not we
16 have any actual hammer if the sponsor doesn't perform
17 the study, and the fact is we try very hard to work
18 with the sponsors to get the studies done, and I would
19 say we have a fair amount of success, but there's not
20 some specific action that we have taken when sponsors
21 don't do this, and so I guess that answers that
22 question, although it wasn't asked. I'm assuming

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1 somebody will ask me that. So I thought I'd answer it
2 first.

3 DR. LOFTUS: Well, my question would be
4 somewhat different. What happens if the data comes
5 back and it's unfavorable?

6 DR. WITTEN: Certainly what we've done is
7 we will put any additional information on the label,
8 but if you're asking whether or not it would come back
9 to the panel and possibly a product would get pooled,
10 the answer is no. So the expectation is that if the
11 panel is recommending that a product get approved that
12 the panel believes that reasonable assurance of safety
13 and effectiveness has already been demonstrated.

14 DR. LOFTUS: Thank you.

15 CHAIRPERSON BECKER: Dr. Haines, did you
16 have a question?

17 DR. HAINES: A further follow-on is simply
18 to ask if there really are the resources to supervise
19 such a post marketing study and be sure that it
20 actually gets done and the results are disseminated.

21 DR. WITTEN: Well, I really don't know
22 what I can add to what I have already said. We

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1 certainly have resources to work with the sponsor as
2 we would engage our Office of Surveillance and
3 Biometrics that does, you know, look at post approval
4 issues, and we certainly have the resources to work
5 with the sponsor and make sure that there's something
6 that we agree on as a study after approval that would
7 take place.

8 But in terms of our ability to insure that
9 those studies actually occur, we have had a fair
10 amount of success in working with sponsors and getting
11 studies to happen, but we haven't -- you know, our
12 options are limited if the studies don't take place.

13 DR. JAYAM-TROUTH: Can I ask another
14 question?

15 DR. WITTEN: Sure.

16 DR. JAYAM-TROUTH: How expensive is this
17 product?

18 DR. SAWHNEY: The same as fibrobryl.

19 CHAIRPERSON BECKER: So the question is
20 how expensive is the product?

21 DR. JAYAM-TROUTH: How expensive is this
22 product?

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1 DR. SAWHNEY: Again, Amar Sawhney,
2 president of Confluent.

3 It's --

4 CHAIRPERSON BECKER: Excuse me. Before
5 you answer that question, can I just ask a question of
6 the FDA?

7 Is this supposed to be something we
8 consider?

9 DR. WITTEN: No.

10 CHAIRPERSON BECKER: Okay. So never mind.

11 DR. GERMANO: Just for the record, am I
12 correct in saying that the panel has not voted yet
13 because the motion was put on the floor, was seconded;
14 there was no discussion and there were no conditions?

15 CHAIRPERSON BECKER: So what's happened is
16 that there was a motion for approvability with
17 conditions. There was a second for that motion. So
18 now we're going to list out the conditions, vote on
19 each separately, and then we'll vote on the
20 approvability of conditions as an entire package at
21 the end, after we've laid out all of the conditions.

22 DR. GERMANO: So we have not voted yet.

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1 CHAIRPERSON BECKER: Correct.

2 DR. JAYAM-TROUTH: We're still discussing
3 conditions.

4 CHAIRPERSON BECKER: We're still
5 discussing conditions, and we'll vote on each
6 condition after discussion.

7 DR. EGNOR: I'm a little bit concerned
8 that the approval can't be pulled if danger is seen,
9 that is, if we do a study of the infection rate and
10 find a year from now that the infection rate is much
11 higher than the infection rate one would typically
12 encounter in cases like this, we couldn't do anything
13 except add something to the label?

14 DR. WITTEN: Well, let's say that we
15 haven't done anything of that nature and so the
16 expectation is that if it's approved that there's
17 reasonable assurance of safety and effectiveness.

18 I will say that I think if some adverse
19 information became available that a product -- and
20 became public, you know, the hope would be that the
21 user community would adjust their expectations of the
22 appropriate setting for the use of that product.

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1 However, the answer to your question is no
2 or yes. I've forgotten how you phrased it.

3 CHAIRPERSON BECKER: Any other questions
4 or comments regarding the first condition of
5 approvability?

6 (No response.)

7 CHAIRPERSON BECKER: So then I think that
8 we should vote on the first condition of
9 approvability, which would be that the sponsor conduct
10 some sort of post approval surveillance for infections
11 in the patients treated with the DuraSeal device.

12 So everybody in favor of this condition.
13 So everybody in favor of this condition, please raise
14 your hands.

15 (Show of hands.)

16 CHAIRPERSON BECKER: So in favor is Dr.
17 Jayam-Trouth, Dr. MacLaughlin, Dr. Haines, Dr. Canady,
18 Dr. Jensen, Dr. Egnor, and Dr. Loftus.

19 Everybody opposed to this condition raise
20 your hand.

21 (No response.)

22 CHAIRPERSON BECKER: Everybody abstaining

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1 from voting.

2 (Show of hands.)

3 CHAIRPERSON BECKER: Dr. Ellenberg and Dr.
4 Germano.

5 Thank you.

6 The second condition that was brought
7 forth was that there be some change in the labeling of
8 the device to reflect that there may be an increase in
9 infection related with this device. So would people
10 have any comments or questions regarding this
11 condition?

12 DR. HAINES: Yes.

13 CHAIRPERSON BECKER: Dr. Haines.

14 DR. HAINES: I would have two specific
15 recommendations about the labeling. The first is that
16 in the table of adverse effects, that the infection
17 complications be brought together and listed together
18 under a title "infection," rather than being separated
19 and alphabetically listed in ways that make them hard
20 to find, and that the total infection rate we listed
21 as well as the subsection infection rates.

22 That was done for neurologic symptoms, but

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1 it should be done for infection as well.

2 And secondly, I think that there should be
3 an explicit warning in the warning section that says
4 the use of the DuraSeal Sealant System may increase
5 the risk of deep surgical site infection.

6 CHAIRPERSON BECKER: Any further comments?

7 Dr. Jayam-Trouth.

8 DR. JAYAM-TROUTH: And I think it should
9 also state that it should not be used in lieu of
10 closing up the dura. You know, the dura should be
11 closed, and this is, you know, in addition to closing
12 up the dura.

13 CHAIRPERSON BECKER: Any other comments,
14 thoughts?

15 DR. ELLENBERG: That sounds like a
16 separate condition.

17 CHAIRPERSON BECKER: Yeah, I think that's
18 going to be the third condition.

19 What you bring up is a third condition,
20 not the second condition. So the second condition
21 that we'll deal with is that the labeling won't be
22 changed to reflect the fact that there may be an

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