

UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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NEUROLOGICAL DEVICES PANEL OF THE
MEDICAL DEVICES ADVISORY COMMITTEE

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TWELFTH MEETING

+ + + + +

THURSDAY,
SEPTEMBER 16, 1999

+ + + + +

The meeting was held in Room 20B of the Center for Devices and Radiological Health, 9200 Corporate Boulevard, Rockville, Maryland at 11:00 a.m., Dr. Alexa I. Canady, Panel Chairperson, presiding.

PRESENT:

- ALEXA I. CANADY, M.D., Panel Chairperson
- EVERTON A. EDMONDSON, M.D.
- CONSTANTINE A GATSONIS, Ph.D.
- GILBERT R. GONZALES, M.D.
- ROBERT W. HURST, M.D.
- ANDREW KU, M.D.
- SALLY L. MAHER, Esq.
- RICHARD D. PENN, M.D.
- PEDRO PICCARDO, M.D.
- CEDRIC F. WALKER, Ph.D., P.E.
- ANNE W. WOJNER, M.S.N.
- JANET L. SCUDIERO, M.S., Executive Secretary

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PRESENTERS:

STEPHEN RHODES
THEODORE MALININ, M.D.
P.J. PARDO
RUTH SOLOMON, M.D.
KEVIN DALY
KEITH FOX
LISA WEBB
KRISTEN A BOWSHER, Ph.D.
DREW JOHNSON
TRACY CAMERON
JOHN ERIKSON
BOB KLEPINSKI
RICHARD NORTH, M.D.

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Adjournment

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1 P-R-O-C-E-E-D-I-N-G-S

2 (11:05 a.m.)

3 MS. SCUDIERO: Hi. We'd like to begin.

4 My name is Jan Scudiero and I'm the Exec Secretary
5 of this Panel and I also am the Reclassification/
6 Classification Team Leader in the
7 Division. I'd like to remind you that if you
8 haven't already to please sign in at the sheets.
9 There's information about ordering transcripts and
10 other things about the meeting.

11 I commend you all for making it here in
12 the, this morning. I know it wasn't a great day to
13 travel. I'm supposed to read two statements that
14 are, into the record. And these are the Conflict
15 of Interest Statement for this meeting for today.
16 There will be another one for tomorrow. And then
17 there's the Deputization of Panel Members.

18 And first we have the Conflict of
19 Interest Statement. The following, oh, before
20 doing that I should mention to you we're having,
21 because of the rain we're having the Diversity
22 Picnic is coming indoors and it's going to be

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1 outside, just outside this area. And there's going
2 to be several presentations, food for \$4.00 that
3 you're welcome to participate in as much as you
4 like.

5 There will also, there's a Deli across,
6 just across in the next building, just across from
7 the lobby of our building. So there's two ways to
8 get lunch. We're having a longer lunch break than
9 scheduled and a little different time from noon
10 until 1:30. So that's what we'll be doing today.

11 Now for the Conflict of Interest
12 Statement.

13 The following announcement addresses
14 Conflict of Interest issues associated with this
15 meeting and is made part of the record to preclude
16 even the appearance of improprieties. The Conflict
17 of Interest Statutes prohibit special government
18 employees from participating in matters that could
19 affect their or their employer's financial
20 interest.

21 To determine if any conflict existed,
22 the Agency reviewed the submitted agenda and all

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1 financial interests reported by the Panel
2 Participants. The Agency has no conflicts to
3 report. In the even that the discussions involve
4 any other products or firms not already on the
5 agenda for which an FDA Participant has a financial
6 interest, the participant should excuse himself or
7 herself from such involvement and the exclusion
8 will be noted for the record

9 With respect to all other participants,
10 we ask, in the interest of fairness, that all
11 persons making statements or presentations disclose
12 any current or previous financial involvement with
13 any firm whose products they wish to comment on.

14 And now we have two Appointment to Temporary Voting
15 Statements.

16 The first one pertains to Consultants on
17 this Panel who are being deputized to Voting Member
18 status for the meeting. Pursuant to the authority
19 granted under the Medical Devices Advisory
20 Committee Charter, dated October 27th, 1990, and
21 amended August 18, 1999, I appoint the following as
22 Voting Members of the Neurological Devices Panel

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1 for the duration of this meeting on September 16th
2 and 17th, 1999. Constantine A. Gatsonis, Ph.D.,
3 for tomorrow.

4 Robert W. Hurst, M.D. for today and
5 tomorrow. Richard D. Penn on today and for the
6 morning of tomorrow for the discussion of the Draft
7 Guidance for Neurological Embolization Devices.
8 For the record these people are special government
9 employees and are Consultants to this Panel or
10 another Panel under the Medical Devices Advisory
11 Committee.

12 They have undergone the customary
13 conflict of interest review and have reviewed the
14 material to be considered at this meeting. And
15 this is signed by David W. Feigal, Jr., M.D.,
16 M.P.H., Director, Center for Devices and
17 Radiological Health on September 3rd, 1999. And
18 the second statement, pursuant to the authority
19 granted under the Medical Devices Advisory
20 Committee Charter of the Center for Devices and
21 Radiological Health, dated October 27th, 1990, and
22 amended August 18th, 1999, I appoint Pedro

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1 Piccardo, M.D., as a Voting Member of the
2 Neurological Devices Panel for the meeting on
3 September 16th.

4 For the record, Dr. Piccardo is a Voting
5 Member of the Transmissible Spongiform
6 Encephalopathies Advisory Committee and the Center
7 for Biologics Evaluation and Research. He has
8 undergone the customary Conflict of Interest Review
9 and has reviewed the material to be considered at
10 this meeting. And it's signed by Linda Suydam,
11 Senior Associate Commissioner on yesterday,
12 September 15th, thank you. And now I'll turn the
13 meeting over to Dr. Canady.

14 CHAIRPERSON CANADY: I'm Alexa Canady
15 and I'm Professor of Neurosurgery at Wayne State
16 University and Chair of Neurosurgery at the
17 Children's Hospital of Michigan. At this meeting
18 the Panel will make recommendations to the FDA on
19 four topics. Today we will deliberate on the first
20 two, which will be the Draft Guidance Document for
21 Dura Substitute Devices and the Classification of
22 Human Dura Mater.

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1 Tomorrow we'll deliberate on the Draft
2 Guidance Document for Neurological Embolization
3 Devices and the Classification Petition for Total
4 Implanted Spinal Cord Stimulators. I would like
5 for the record to note that Voting Members present
6 constitute a quorum as required by 21-CFR, Part 14.

7 I'd like with pleasure to take this time to have
8 the Panel introduce themselves. If we might start
9 right next to me with Dr. Penn.

10 DR. PENN: I'm Dr. Richard Penn from
11 Rush Medical School in Chicago.

12 DR. GONZALES: Gilbert Gonzales from
13 Memorial Sloan Kettering Cancer Center in New York
14 City.

15 CHAIRPERSON CANADY: If I could ask you
16 to also give your expertise, just for the Panel,
17 your specialty.

18 DR. GONZALES: I'm a Neurologist and
19 Neuro-Oncologist and Pain Specialist.

20 DR. PENN: And I'm a Neurosurgeon.

21 DR. PICCARDO: I'm Pedro Piccardo from
22 Indiana University, Neuropathology.

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1 DR. WITTEN: Celia Witten, Division
2 Director of DGRD in CDRH and FDA.

3 MS. MAHER: Sally Maher. I'm with, I'm
4 an Industry Rep. I'm with Westaim Biomedical in
5 New Hampshire.

6 DR. WALKER: Cedric Walker, I'm
7 Professor of Biomedical Engineering at Tulane
8 University with an interest in neuro-stimulation
9 and neurological devices.

10 DR. KU: Andrew Ku, Alleghany General
11 Hospital, Pittsburgh, Pennsylvania. I'm an
12 Interventional Neuro-Radiologist.

13 MS. WOJNER: Anne Wojner, I'm an
14 Assistant Professor of Clinical Nursing at
15 University of Texas, School of Nursing and a
16 Clinical Nurse Specialist in Nurse Research within
17 the Division of Stroke Neurology at UT Med School.

18 DR. EDMONDSON: I'm Everton Edmondson
19 and I'm a Neurologist/Neuro-Oncologist and Pain
20 Management Specialist in private practice at the
21 Methodist Hospital, Texas Medical Center in
22 Houston.

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1 DR. HURST: I'm Robert Hurst, University
2 of Pennsylvania, Interventional Neuro-Radiology.

3 CHAIRPERSON CANADY: Thank you very
4 much. Before we begin the first topic, Mr. Jim
5 Dillard, who is the Deputy Director of the Division
6 of General and Restorative Devices will give an
7 update on neurological devices activity since the
8 last meeting.

9 MR. DILLARD: Good morning. This, I
10 think it may be turned down but I've got a booming
11 enough voice, I don't think you need to worry about
12 it yet. Keep working on it back there.

13 My name is Jim Dillard. Thank you, Dr.
14 Canady. I'm the Deputy Director of the Division of
15 General and Restorative Devices and it's my honor
16 to welcome you all here today and have you here.
17 Thank you again also on my behalf for braving the
18 weather and coming and assisting us for the four
19 topics that Dr. Canady mentioned earlier.

20 I'd like to, which is also customary
21 from our standpoint, give you a little bit of an
22 update from the last Panel Meeting, tell you a

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1 little bit about what you deliberated on last time
2 that you met, which was June 12th, 1998, as well as
3 give one piece of information. You may have
4 noticed that the deputized Voting Members, the new
5 piece of paper that Jan mentioned was signed by Dr.
6 David Feigal, who is our new Center Director.

7 This time last year or 14 months ago,
8 when you were here last time, Dr. Bruce Burlington
9 was our Center Director and since that time Dr.
10 Burlington has taken a position in private industry
11 and gone back to drug development and international
12 regulatory affairs. Dr. David Feigal joined us a
13 few months ago, a little after Dr. Henney became
14 the new FDA Commissioner. And Dr. Feigal comes to
15 us with a lot of experience in both, from the
16 Center for Device, or Center for Drug Evaluation
17 and Research, excuse me, and the Center for
18 Biologics Evaluation and Research.

19 He spent about the last six or eight
20 years of his service, federal service at both of
21 those Centers, so he comes with a lot of very
22 diverse experience and is now our Center Director.

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1 At the last meeting you may recall we brought to
2 you a 515-I Reclassification Petition for
3 Embolization Devices. One of the recommendations
4 from you all as a Panel Member was that it be
5 reclassified from Class III to Class II. And you
6 had a number of suggestions for special controls
7 for us.

8 One of which was labeling controls as
9 well as bio-compatibility information. And one of
10 the things that's helpful and you will hear this
11 time and again from us, is that guidance documents
12 are one of the special controls that we use very
13 frequently for Class II devices. So tomorrow you
14 will be discussing the contents of that guidance
15 document, which includes not only some of the
16 things that you recommended to us, but some of the
17 things that we have been asking for in 510(k) Pre-
18 market Notifications.

19 And so we are looking very forward to
20 having your comments on that. And then I think
21 once we have some comments from you as well as the
22 public on that guidance document, we intend to move

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1 forward with the down classification of
2 embolization devices. That was the only thing at
3 the last meeting that we discussed and I think
4 that's really all I had to say here today. So
5 again welcome on behalf of the Division and on
6 behalf of the Office of Device Evaluation and thank
7 you, Dr. Canady, I'll turn it back over to you.

8 CHAIRPERSON CANADY: Thank you very
9 much. We would now proceed with the open public
10 hearing for the Panel discussion on the draft
11 document, Guidance Document for Dura Substitute
12 Devices. We have no scheduled speakers. Is there
13 anyone in the audience who would like to make
14 comments relative to this document?

15 (No response.)

16 CHAIRPERSON CANADY: If not, then we
17 could move on to the FDA comments that are going to
18 be delivered to us today.

19 DR. HUDSON: Good morning. It's my
20 pleasure to be able to address you today. My name
21 is Peter Hudson and I'm a Scientific Reviewer in
22 the Plastic and Reconstructive Surgery Branch of

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1 the Division of General and Restorative Devices at
2 the Center for Devices and Radiological Health. We
3 review dura mater substitute products in our branch
4 and evaluate them for safety and effectiveness.

5 We have drafted this guidance document
6 based upon our experience. I'm going to briefly
7 summarize the guidance document and then ask you
8 questions regarding the devices and the clinical
9 studies used to evaluate them for your comment.

10 The questions will be focused on issues regarding
11 device manufacturer, the timing and type of imaging
12 modalities used to assess device performance in
13 issues of clinical study design.

14 What is the purpose of the document and
15 what do we expect from you? The purpose of this
16 guidance document and guidance documents in general
17 is to assist manufacturers and FDA Review Staff in
18 focusing on issues that are important to consider
19 during the review of medical devices. They are
20 also intended to help level the playing field for
21 the device manufacturers.

22 In general, guidance documents provide

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1 assistance on issues associated with manufacturing
2 and testing of medical devices. The documents are
3 updated periodically to be consistent with current
4 scientific theory and practice. The documents can
5 represent the leading source of information
6 regarding the evaluation of medical devices.
7 Investigators evaluating novel medical devices may
8 be at the cutting edge of medical research. The
9 documents may be used in certain cases to serve as
10 special controls for Class II products.

11 We have identified in the guidance
12 documents what we believe is important information
13 that will assist in making regulatory
14 determinations. We would appreciate your thoughts
15 and comments as neurological device experts as to
16 whether the information provided in our guidance
17 documents is appropriate and adequate. The
18 definition of a dura substitute as defined in the
19 Code of Federal Regulations is a sheet or material
20 that is used to repair the dura mater.

21 On November 15th, 1978, FDA issued a
22 proposed rule recommending that dura substitutes be

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1 classified as Class II products. The proposed rule
2 for classification was based upon the
3 recommendations of the Neurological and Device
4 Classification Panel and FDA Advisory Panel. Class
5 II regulation indicates that special controls can
6 reasonably assure the safe and effective use of the
7 device.

8 On October 4th, 1979, the effective rule
9 classifying the devices went into affect. Dura
10 substitute products cleared for market distribution
11 include animal-derived tissues as well as synthetic
12 polymers. At this point, I would like to highlight
13 some important administrative, scientific elements
14 in the guidance. I will not discuss all of the
15 specific elements in the guidance but rather
16 highlight the format and content contained in the
17 guidance.

18 The guidance document outlines the
19 standard, administrative information to be
20 submitted in the pre-market notifications, such as
21 an introduction, a table of contents, a summary of
22 information regarding the safety and effectiveness

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1 of the device and a statement of the indications
2 for use of the device. And also a truthful and
3 accuracy statement.

4 Under the description of the device, the
5 guidance document suggests that the Sponsor
6 identify the materials and physical dimensions of
7 the device. Tables comparing the product to
8 predicate devices are recommended for the
9 assessment of equivalency. If the dura substitute
10 contains materials derived from animals, we ask the
11 manufacturer to indicate where and how the material
12 was obtained. Included in the recommended
13 information are details regarding the care and
14 health of the animal herd.

15 The guidance suggests that the
16 manufacturer provide a complete description of the
17 manufacturing processes and all reagents used
18 during the manufacture of the device. This
19 information is helpful when considering whether
20 potentially toxic residues of re-agents may be left
21 in the device. The guidance also recommends that
22 complete information regarding the sterilization

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1 methodology, the sterility level attained, be
2 provided to assure that the device is free from
3 bacterial, viral and fungal contamination.

4 The guidance suggests that viral and
5 activation validation studies be conducted with
6 tissue source material due to the potential for
7 disease transmission. Question one will ask you to
8 comment on validation procedures in general and if
9 you have any recommendations. In the guidance
10 document you will note that additional information
11 is necessary when the device is processed by
12 ethylene oxide gas sterilization.

13 Ethylene oxide has been demonstrated to
14 be neurotoxic and therefore it is reasonable to
15 request that dura substitutes contain minimal
16 levels of sterile residues. Product
17 characterization in final product specifications
18 describe the products structural, physical and
19 mechanical properties and bio-compatibility. For
20 dura substitute products that are under pre-market
21 review, the guidance document suggests
22 manufacturers conduct animal studies with their

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1 final product.

2 In these experiments, one can evaluate
3 whether the device may potentially leak or cause
4 adhesion formation in human clinical usage. In
5 addition, the issues of infection, hemorrhage,
6 device vascularization and foreign body reactions
7 can be examined. Animal studies are important for
8 assessing device performance prior to initiation of
9 human studies. The guidance also suggests that
10 manufacturers conduct prospectively defined,
11 concurrently controlled, randomized, multi-center
12 studies to evaluate their device's performance.

13 The patient follow up length is
14 suggested to be one year. In addition, the
15 guidance suggests that the sponsor evaluate the
16 patients with CT or MRI imaging analyses. You will
17 be asked to comment on these and other clinical
18 issues in response to questions two and three. Now
19 I'm going to go on to the Panel questions that we'd
20 like your comments on. I'm going to briefly
21 summarize each question and I will put each
22 question back up for your discussion afterwards.

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1 The first question concerns potential
2 disease transmission associated with tissue source
3 material. We would appreciate your discussion of
4 the appropriateness of validation measures in
5 general and would like to know if you believe long-
6 term safety information should be gathered on
7 tissue sourced dura substitute recipients. And
8 question two, question two discusses the measures
9 used to assess device performance in patients
10 receiving dura substitutes.

11 The draft guidance document recommends
12 that clinical trials follow patients for at least
13 one year, at which time patients are examined via
14 CT or MRI scanning to determine what changes might
15 have occurred at the implant site. Please discuss
16 the appropriateness of the time point of assessment
17 and the method of assessment. Question three
18 concerns clinical trial design. Currently, FDA
19 does not recommend that specific patient
20 populations or anatomic sites be studied.

21 We would like your input regarding the
22 following issues. Are there patient populations,

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1 in your opinion, that have specific, that have
2 special characteristics so that they should be
3 specifically identified in clinical trials? This
4 is in response to question 3-A. Question 3-B, do
5 you believe there are different anatomic sites or
6 sizes of dura substitute replacement which should
7 be specifically studied?

8 And finally, in response to question 3-
9 C, we'd like your comment on the recommendations of
10 the guidance document regarding how clinical
11 effectiveness of the device is assessed. And
12 please discuss the endpoints lists as potential
13 endpoints for assessing product effectiveness. I
14 will now turn the discussion over to you. Thank
15 you.

16 CHAIRPERSON CANADY: Before Dr. Hudson
17 leaves the platform, are there any questions for
18 him from the panelists?

19 (No response.)

20 CHAIRPERSON CANADY: Thank you, Dr.
21 Hudson.

22 DR. HUDSON: Thank you.

1 CHAIRPERSON CANADY: Is there anyone
2 from industry who would like to make comments
3 regarding the guidance document?

4 (No response.)

5 CHAIRPERSON CANADY: If not, then I
6 would propose that we begin an open discussion of
7 the Panel itself. We've been given, basically,
8 three questions they are interested in. We might
9 start with any general comments that the panelists
10 would like to make and then I think we could go
11 down the questions and begin a specific discussion.

12 Any general comments that somebody is burning to
13 make?

14 (No response.)

15 CHAIRPERSON CANADY: The first question,
16 as I understand it and correct me if I'm wrong, Dr.
17 Hudson, was the question of disease transmission,
18 both in terms of validation information and long-
19 term information. I suppose we could start,
20 perhaps, with Dr. Piccardo. If you would make some
21 comments regarding that?

22 DR. PICCARDO: I think my comments would

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1 be only related to the issue of dura graft coming
2 from cadavers. So the critical issue is that I
3 believe that most of the safety in a dura graft
4 coming from a cadaver would be the surveillance of
5 the donor. I mean it is critical to have clinical
6 records and to have a thorough neuropathology
7 examination of the donor. And the other thing is
8 that the dura should not be pooled. So that in
9 synthesis it is critical to have the complete
10 clinical history and to be able to trace that, to
11 have a complete neuropathologic examination and be
12 able to trace that back.

13 And of course to have the dura source
14 enable to, that it was not pooled so that
15 everything can be traced back for perspective.

16 CHAIRPERSON CANADY: Dr. Whitfield.

17 DR. WITTEN: Dr. Witten, yes. We're
18 going to have a more detailed discussion on
19 classification of dura allograft this afternoon.
20 This dura substitute specifically relates to, I
21 think, you know, substitutes other than allograft
22 which is the subject of another guidance document.

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1 So we'll certainly appreciate some more in depth
2 discussion when we get to that this afternoon.

3 CHAIRPERSON CANADY: Any other --

4 DR. PICCARDO: Sorry, that's why my
5 comment was related to when we talked about dura
6 coming from cadavers. That was my first thing.

7 CHAIRPERSON CANADY: Other comments the
8 panelists would like to make on this? Okay.

9 DR. GONZALES: Dr. Canady.

10 CHAIRPERSON CANADY: Yes, Dr. Gonzales.

11 DR. GONZALES: Just a question really,
12 rather than a comment. The question is, at the
13 present time are there any stipulation as to where
14 the animal collection takes place? That is to say,
15 are these, for instance, with bovine grafts or
16 bovine dura, is this at the present time purely in
17 the United States or is this also collected outside
18 of the United States. And could that influence
19 right now, in terms of the transmissibility of
20 diseases, is that an issue right now that we need
21 to be concerned about and discuss and is that a
22 factor in kind of the guidelines that we're

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1 discussing right now?

2 DR. HUDSON: Right, it's a good
3 question. Yes, we, we ask, the type of information
4 we want to know about the herd or the animal source
5 is where the animals were kept, what country. Was
6 it a BSE-free country. I don't believe there are
7 any specifications that it has to be in the United
8 States. At this level, I think we're concerned
9 whether it's a BSE-free country. And some of the
10 other information that we ask is whether or not a
11 veterinarian has checked the herd, the herd's
12 health.

13 How they have documented their records
14 for assessing that. Is the slaughter house under
15 some kind of regulation? In the United States it
16 would be USDA-type of regulation, for cleanliness
17 and sanitation and things like that. So, yes,
18 we're concerned about not only how the herd is
19 maintained, where it comes from and then additional
20 concerns on the processes that are used to, for the
21 manufacture of the device.

22 DR. GONZALES: So then dural grafts

1 could be received here in the United States from
2 herds outside of the United States. Here in the
3 U.S. with collection of organs and serum blood and
4 other products I understand that there are very
5 strict guidelines, veterinary guidelines, regarding
6 the care of herds, the slaughtering, the
7 collection, the preservation and then the analysis
8 after. Are those exact same guidelines followed
9 with herds that are outside of the United States?

10 DR. HUDSON: My understanding, you know,
11 they're not under the same USDA regulations that we
12 have. But, so they would be under whatever
13 countries' regulations they're governed by. And
14 they do, we do ask them how they are assessed,
15 whether or not they have a veterinarian checking
16 the records of the herd. And as far as tissue
17 biopsies for later analysis, I know that that's
18 come up in review and we've asked for that kind of
19 information.

20 Whether or not it's actually a
21 stipulation of part of a foreign country's
22 regulations, I'm not sure.

1 DR. GONZALES: So is it clear right now
2 that the products that are coming from outside of
3 the United States are exactly being followed or
4 better than the guidelines that we place on
5 collection of tissues from the U.S. That is to
6 say, the U.S. standards are being followed or
7 better for the collection of organs and dura
8 outside of the United States.

9 DR. HUDSON: I just heard over my
10 shoulder that they are, we can consider them
11 equivalent at this point. Whether they are
12 identical, I don't, we'd have to look at each case,
13 I think.

14 CHAIRPERSON CANADY: Go ahead, Dr.
15 Witten.

16 DR. WITTEN: Yes, if you have some
17 specific recommendations of course that would be
18 one of the purposes of this discussion. So we
19 would be interested in those recommendations.

20 DR. GONZALES: Well, I think it would
21 seem obvious that if there are regulations that
22 have been placed here in the United States

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1 regarding herds and collection of tissue,
2 specifically dura collection, that we're ensured
3 that the collection of dura from animals outside
4 the United States are exactly the same or better in
5 terms of standards for collection and standards of
6 testing animals and standards in terms of the
7 transmissibility or the prevention of
8 transmissibility of various prions versus viruses
9 and other transmissible organisms. Do we have that
10 in place at the present time? That was not clear
11 from the information that we obtained and that's
12 why I'm asking the question.

13 It was sort of assumed here but it was
14 never stated. And I just want a statement that in
15 fact those kinds of regulations for dura that's
16 collected outside of the United States follows the
17 standards for U.S.-type standards for the
18 collection of organs.

19 DR. DURFOR: Those are critical
20 questions. My name is Chuck Durfor, I'm also a
21 Reviewer in Plastics and Reconstructive Surgery.
22 I'd like to clarify, if I could, just to start

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1 because I think I understand a little bit of where
2 your question is coming from. At this point in
3 time, the products that we are seeing animal tissue
4 that would be used potentially as dura substitutes
5 are generally not neurological tissues.

6 We may see pericardium, we may see
7 something else, we may see collagen. I do not, at
8 this time, believe we have seen any animal dura
9 used as a human dural substitute. So that has
10 something to do in fact, in terms of if you were
11 concerned about prion transmission. Generally,
12 what we have done with these sort of products, and
13 it is, and most of the products, once again, we
14 have seen have been made within the United States.

15 In the rare instance where we have seen
16 something coming from overseas, we have requested
17 that the manufacturer take very good care to
18 investigate what the USDA requirements would be, or
19 many times in fact all of these manufacturers are
20 inspected by their own governments. And at that
21 point, we have the manufacturer come to us and say,
22 fine, we've been inspected by this government, how

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1 does that requirement of your government match up
2 to the USDA requirements for an abattoir?

3 DR. HUDSON: It's a very important
4 question and we look at it very critically. I
5 think what Chuck has mentioned is real important to
6 remember as well that the tissues that are commonly
7 used for dura substitutes and not coming from the
8 bovine brain dura or things like that. We haven't
9 seen something like that.

10 CHAIRPERSON CANADY: I think even more
11 so, if I could paraphrase it. You might be asking
12 that there be substantial equivalents in the
13 testing methods and that that be specifically
14 stated.

15 DR. GONZALES: Can you make that kind of
16 a statement right now?

17 DR. HUDSON: That the procedures that
18 would be used by foreign manufacturers would be
19 equivalent to what we would, what we have in place
20 here?

21 DR. GONZALES: Right.

22 DR. HUDSON: Yes, as a matter of, as a

1 kind of a course of review, we assess that and
2 evaluate whether or not they are equivalent.

3 DR. GONZALES: Okay.

4 CHAIRPERSON CANADY: Other comments? We
5 haven't addressed the issue of long-term
6 information which might be one, particularly since
7 he raised the BSE issue, that we might want to
8 address. Any comments?

9 (No response.)

10 CHAIRPERSON CANADY: The second question
11 that was of interest was measures used to assess in
12 terms of a clinical trial length, I believe, of one
13 year, as well as the examination of efficacy with
14 CT and MR. Comments from panelists?

15 MS. MAHER: This is Sally Maher. I have
16 one question. Is that what they're currently
17 looking at in the review of these 510(k)s?

18 DR. HUDSON: I'm sorry, could you repeat
19 your question?

20 MS. MAHER: I'm Sally Maher. Currently
21 510(k)s that are coming through for dura
22 substitutes, are you looking, having the one-year

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1 clinical studies and looking at these endpoints
2 also? Is this guidance document more putting down
3 in writing what your current requirements have been
4 or is this a new requirement of a year follow up?
5 And if so, is it based on some adverse events that
6 you've seen where these have not, there has been
7 problems?

8 DR. HUDSON: This is what we currently
9 recommend that manufacturers, how they conduct
10 their clinical trials. My impression is that a
11 year is the amount of time that we need to be able
12 to safely, you know, evaluate whether or not the
13 device is safe and effective. It's not, not the
14 case that we've noticed certain adverse events.

15 CHAIRPERSON CANADY: I guess I have some
16 concerns as I listen to CTs and MRs as one of the
17 means of evaluating and whether that's really an
18 accurate way to assess the effectiveness of the
19 graft itself or whether that's an assessment of the
20 technical more than the graft?

21 DR. HUDSON: Yes, that's encompassed,
22 yes. We'd like your comments on that.

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1 CHAIRPERSON CANADY: Dr. Penn.

2 DR. PENN: Can I have some help here?
3 Is there any dura substitute that meets any of the
4 guidelines that you've laid out currently? Does
5 anything meet these guidelines? I think the answer
6 is going to be no, right? Because no one has, that
7 I know, has done a systematic study of MR at one
8 year of these dura substitutes. And I don't know
9 whether all the animal data is in on each one of
10 these substitutes either. But is the answer then
11 no?

12 DR. WITTEN: I just want to clarify. I
13 assume you're asking specifically about the
14 clinical study part of the document, right, not the
15 pre-clinical information? Because --

16 DR. PENN: Well --

17 DR. WITTEN: -- is that right?

18 DR. PENN: Well, I'm asking about both,
19 really. Let's take it in two parts. Has anybody
20 gone through all the studies that you will be
21 asking for in this guidance for any of the dural
22 substitutes that are now available?

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1 DR. WITTEN: Let me just say that
2 usually we look at whether or not the sponsors
3 address the issues in the guidance. So if they
4 haven't done the identical studies, I think we
5 would feel, at least for most of the products and
6 correct me if I'm wrong, that we have the
7 information that relates to the pre-clinical
8 portion of the document. Although, it may be that
9 it addresses the issues, but it is not laid out the
10 way it is described here.

11 Now for the clinical studies, we don't
12 really require -- I hope this is -- you can feel
13 free to jump in. But we don't currently get
14 clinical studies on all the dura substitutes with
15 applications for market. But for the ones that
16 have specific questions, where we think that a
17 clinical study may be needed in order to address
18 whatever new questions come up in comparing that
19 product to a predicate, a predicate device.

20 And this is an attempt on our part to
21 outline the things that we think we would need to
22 see in a study. Although, I mean we do have a real

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1 question about the imaging studies which is why
2 we're bringing it up for discussion. That is what
3 is it really we should be looking at in evaluating
4 these dura substitutes.

5 DR. PENN: As you know the situation is
6 we have a hodgepodge of studies in the literature
7 that are not done anywhere like these studies that
8 are being suggested. And those materials are still
9 being used, as I understand it, correct?

10 DR. WITTEN: This will relate to new
11 products. This will relate, this guidance document
12 would relate to if a sponsor wanted to market their
13 product.

14 DR. PENN: So this will put at, in
15 essence, an enormous disadvantage anything new that
16 comes out because it will have to meet these
17 requirements, whereas nothing before has met these
18 requirements. So there isn't even a comparison
19 group for this.

20 DR. WITTEN: Guidance documents are
21 meant to assist the sponsor in addressing the issue
22 and going to market with a product. And as I

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1 mentioned, if there is, if there's a, let's say
2 there's a product that a sponsor wants to market.
3 If it's identical to a product that's on the
4 market, then they don't need, they wouldn't need to
5 do a clinical study. So it's for a product that
6 has new questions that need to be answered with a
7 clinical study that we would ask these questions.

8 DR. HUDSON: Chuck had just mentioned
9 that there are some dura substitutes that have
10 undergone this kind evaluation. And we focused the
11 question, umm, one of the more, newer aspects of
12 that question are whether or not the type of
13 imaging that's recommended in the guidance is
14 appropriate and that's really more of our focus
15 right now. There are some dura substitutes that
16 have not undergone the gamut as you --

17 DR. PENN: What will they know -- are
18 there any control studies where people have used
19 different dura substitutes in a random order and
20 assessed them in any blinded fashion? I mean
21 that's new knowledge to me if there is such studies
22 available, but I had the impression that the field

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1 was not like that.

2 DR. HUDSON: No, what you're referring
3 to is that a lot of the time that they use
4 historical controls. They look at some kind of
5 study cohort where they, you know, used a certain
6 type of dura substitute and compared that to
7 something they are testing now. And are they
8 concurrently controlled? Generally, not.

9 DR. PENN: Right and they're on
10 different types of patients and at different
11 historical times and so forth. And the guidelines
12 now will have nothing to compare with unless they
13 compare with current available dura substitutes
14 that have not undergone that type of testing, is
15 that correct?

16 DR. HUDSON: Right. I mean that would
17 be, yes. That doesn't mean that it wouldn't be a
18 good idea for them to be perspectivevely evaluated to
19 determine other, you know, efficacy endpoints.

20 CHAIRPERSON CANADY: One of the issues
21 of efficacy, from my perspective as you look at it,
22 is that since there's a highly technical component

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1 associated with failure of grafts, there are two
2 sides to that. Probably one is the ease of the
3 grafting and the second is the surgical component.

4 Can you even compare from surgeon to surgeon,
5 necessarily, the effectiveness of the grafting via
6 x-ray?

7 Again, I question whether x-ray is a
8 very effective method at all. And the real
9 standard, which we don't mention here, is failure,
10 is some kind of CSF leak that requires a second
11 intervention. Which would be a standard that I
12 don't see which would perhaps be --

13 DR. HUDSON: Right. Well that is
14 included in the guidance talk and that is something
15 that we want to, want to recommend to industry to
16 take a look at. But, you're right. I mean those
17 are different issues of clinical study design that
18 are really difficult to assess.

19 CHAIRPERSON CANADY: And most surgeons
20 make their decisions regarding effectiveness of
21 grafts by what they see at re-exploration, not be
22 radiographic imaging. So that if you see

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1 tremendous inflammation at re-exploration and you
2 see that the graft is falling apart at re-
3 exploration, that would be the guide that would
4 cause you to change your substitute.

5 I might ask if any of our radiographic
6 colleagues would give any comment regarding their
7 sense of the usefulness of CT or MR for this
8 question?

9 DR. HURST: Yes, I would agree that the
10 clinical evaluation is going to be the most
11 important thing. If you had to pick one of these,
12 I think that MR is going to be much more sensitive.

13 And I think that a year is probably a reasonable
14 time length. Certainly we know that arachnoiditis,
15 for example, from foreign substances can form ten
16 or 15 or 30 years down the road. I'm not sure that
17 that's really reasonable to request a hugely long-
18 term evaluation like that.

19 And I think a year is reasonable. MR
20 would probably be the most reasonable way to look
21 at that. Certainly if you suspect a CSF leak, and
22 again, the clinical manifestations of this are

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1 going to be what's most important, then MR is not
2 going to help you with that. But if you suspect a
3 CSF leak, you're going to do some arachnoid
4 contrast with a CT or some more specific
5 evaluation.

6 So that if you maybe said that an MR at
7 a year and certainly the clinical follow up would
8 go along at least for that period of time as well.

9 That would be maybe a reasonable way to look at
10 it.

11 CHAIRPERSON CANADY: Other comments?

12 MS. MAHER: Well, I'm wondering, from
13 what I'm hearing, is that you want to have the
14 sentence, I mean right now it almost reads that you
15 must do either an MR or a CT as well as examining
16 the patients clinically at the end of the year.
17 And from what I've heard, it sounds like the MR may
18 be useful in some cases, but the clinical is the
19 most important. And would it be better to say, if
20 you're going to have a year follow up, clinically
21 examine in a year and may use MR as well. And make
22 it a little more flexible to give the manufacturers

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1 some opportunity because again, the previous stuff
2 that they're comparing against has never been
3 examined by MR after a year consistently.

4 So nobody really knows what a pass/fail
5 look is going to look like. You know from a
6 clinical at least, I'm assuming, whether it's a
7 pass/fail. But you're not going to know what a
8 pass/fail on the MRI is going to look like.

9 CHAIRPERSON CANADY: Something else you
10 might want to add, although it would represent
11 probably some scheduling problems, is to get an MRI
12 at the time of failure, so that you have some sense
13 of what the failures look like.

14 DR. HUDSON: I just would want to remind
15 you that the clinical manifestation may be the most
16 important thing, but these maybe novel products,
17 novel materials. So that because we don't have,
18 you know, some background information, you know,
19 i.e., MR imaging on previous substitutes, I would
20 suggest that it doesn't mean that we shouldn't get
21 prospective stuff, prospective information about
22 how these new devices or new materials might act in

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1 the space.

2 One of the concerns of the 1978 Panel,
3 or two of the concerns was the tissue reaction to
4 the dura substitute as well as the CSF leak, the
5 two most important things.

6 CHAIRPERSON CANADY: Any other comments
7 or questions regarding this? Formulate your
8 thoughts, we're going to come back and get a formal
9 comment at the end from everyone regarding these
10 issues. Yes.

11 MS. WOJNER: I'll just make one quick
12 comment. I guess I would lean, from the Consumer's
13 perspective, in favor of the clinical judgement of
14 the neurosurgeon, simply because I'm assuming that
15 ultimately the person that's having to pay for this
16 is the consumer and it could be very unnecessary to
17 have this test performed, especially since what I'm
18 hearing is that we don't know how accurate and how
19 valid an indicator it's going to be to actually
20 look at this.

21 MS. MAHER: This is Sally Maher again.
22 I would also suggest, it sounds to me like, I'm not

1 sure whether these need to be randomized,
2 controlled studies at all times. Or whether there
3 maybe sometimes better if it was a non-random, or
4 better for industry and not harmful to patient care
5 and you also have it non-randomized to see how the
6 devices perform based on historical controls. I
7 know randomized control, there's a gold standard,
8 but a lot of times it's hard to enroll patients
9 into them if they want to try the newer or better
10 one.

11 And again, I think we need to be careful
12 as a Panel if we're looking at, you know, always
13 putting down the gold standard and expecting
14 manufacturers to try to comply to it. You may be
15 adding an unnecessary burden to the development
16 process.

17 DR. PENN: Aren't we getting to a
18 recommendation that what we really want to know is
19 when it fails and the surgeon takes a look at it,
20 what happens? Was there a hemorrhage, for example?

21 That happened with certain types of dura
22 substitutes. Do they get encapsulated badly? And

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1 the only person that can really report on that is
2 the surgeon at the time of an ex-plant or dealing
3 with a complication. Beyond that, we're putting a
4 number of speculative tests on with time limits
5 that we don't know are appropriate.

6 It might be that three or five years
7 down the line that it will be a problem. So the
8 most important thing from my standpoint as a
9 neurosurgeon, is proper reporting of complications
10 as they occur at any time afterwards. Because if
11 we found out that at three years time all of these
12 were encapsulated and they started hemorrhaging,
13 we'd know that there is a problem even though it
14 might have passed FDA recommendations that we're
15 suggesting here.

16 So I would like to see it written in a
17 much more simplified way that emphasizes the
18 primary look of the surgeon at the time of failure,
19 unless our Radiologists feel that there would be
20 enough information about, about the membrane
21 surface from MRI that that would be an overriding
22 consideration. And then we should do an MRI with

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1 infusion and without and maybe some other
2 specialized study.

3 DR. HURST: You know it might be
4 reasonable to look with an MR if you had clinical
5 evidence of failure. But I wouldn't think that it
6 would necessarily be reasonable to just get one on
7 someone who is doing very well. And you'd probably
8 do that anyway.

9 CHAIRPERSON CANADY: The question then
10 becomes though, perhaps it looks abnormal, but it
11 looks abnormal when there's no failure also.

12 DR. HURST: Right. And I guess the
13 question then, then becomes what sort of follow up
14 do you do in failure.

15 CHAIRPERSON CANADY: Right.

16 DR. HURST: I think if you're going to
17 go in and ex-plant the device you are going to have
18 some sort of radiologic evaluation prior to that.
19 But again, I think that the clinical manifestations
20 of failure are the things that you are going to
21 keep.

22 CHAIRPERSON CANADY: I think we also,

1 just from, as a surgeon I need to say I think when
2 these devices fail relative to certainly scarring
3 and adhesion, it's not clear that they're truly ex-
4 planted. Often what happens, for example, in the
5 spinal cord, is that you dissect free the dura and
6 put a new dura substitute. Probably not using the
7 same one, but that the ex-plantation, it's
8 certainly in the spinal canal of grafts that cause
9 exuberant reactivity is almost impossible.

10 You may piecemeal remove it, but usually
11 it's not removed in total as people conceive of ex-
12 planting. Any other general discussion on this.
13 Again, Dr. Walker?

14 DR. WALKER: Well inasmuch as there's no
15 good way to visualize a CSF leak without doing an
16 awful lot of handsprings right now, maybe we ought
17 not to require visualization now, but include some
18 phrase that if a cheap, economical and dependable
19 way of visualizing CSF leaks should be developed,
20 then manufacturers ought to consider that for a
21 routine one-year examination.

22 CHAIRPERSON CANADY: Other comments?

1 Dr. Witten?

2 DR. WITTEN: Yes, you, all of you have
3 spoken about the importance of looking at the
4 clinical manifestations of failure and the lack of
5 relative benefit of radiologic imaging studies.
6 And I wonder if you can just comment on the types
7 of things that we might want sponsors to assess in
8 terms of clinical assessment of graft failure.
9 That would be helpful. Yes, I'm sorry, and also
10 when those assessments should be performed?

11 CHAIRPERSON CANADY: I guess I'll start.
12 A resounding crowd. I think that at the time of
13 failure that you almost always get some component
14 of it. And so there should be a comment made, some
15 reporting device mechanism for re-exploration and
16 what it looks like at the time of re-exploration.
17 Cranially, sometimes for example it's used now in
18 decompressive craniotomy often.

19 And you are going to come back in six
20 months automatically or three to six months and put
21 in a cranioplasty so one can comment on the degree
22 of adhesiveness and the general appearance at that

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1 time. So I think at any time of re-exploration
2 there should be a comment made regarding the status
3 of the implant as well as at the time of failure,
4 graft failure, would be my recommendation. Other
5 comments?

6 DR. EDMONDSON: I think, too, if
7 clinically you have evidence of a CSF leak and
8 you're going to have postural headaches, dizziness,
9 a number of very sound clinical symptoms that
10 generally correlate well with CSF leak. I think at
11 that juncture it probably would be reasonable to
12 recommend intrathecal contrast CT to localize that.

13 CHAIRPERSON CANADY: I would hesitate to
14 recommend that over the clinical judgement of the
15 person who's taking care of the patient. Now I'm
16 not sure the industry can recommend that.

17 DR. HUDSON: I guess one of the problems
18 we've had is that, you know, we're trying to
19 standardize, I mean, some kind of common, you know,
20 pinpoints that we can use. So sometimes maybe, in
21 your opinion, a contrast CT might be indicated and
22 it may not be, well it may be less a dramatic

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1 difference. But specifically what kind of
2 manifestations would you think would necessarily,
3 would you know, say to that surgeon, yes, you
4 better go back in and do some kind of scan on that
5 person?

6 CHAIRPERSON CANADY: Well, I think
7 that's, I understand how you would perceive that.
8 On the other hand, if someone is leaking CSF out of
9 the wound, I don't feel the need to any of the
10 imaging studies if I know he has an implant. I
11 mean I think that I could do an imaging study for
12 somebody else, but my endpoint, which is whether he
13 needs an operation or not, has been answered.

14 DR. HUDSON: You're already there, yes.

15 CHAIRPERSON CANADY: Right.

16 DR. EDMONDSON: One query on that
17 regard. What if you have a CSF leak that's
18 contained by deep fascia, in which case it may be
19 contained indefinitely. Would it be helpful then
20 to do imaging to make sure that it hasn't extended
21 through the fascia?

22 CHAIRPERSON CANADY: I think there are

1 clearly times when the question comes up. That
2 symptoms present themselves that need to be
3 explained and then studies have value. I'm not
4 saying that the studies don't have value, but I
5 don't think that they always are necessary in any
6 circumstance. So that that's why it's difficult to
7 standardize, without adding additional testing. If
8 we could have -- any other comments, general
9 comments regarding question two?

10 (No response.)

11 CHAIRPERSON CANADY: If you could put
12 question 3 up from your Power Point. As I
13 summarized it there were three issues relative to
14 clinical trials we are being asked. One is are
15 there special patient populations that should be
16 considered and looked at? The site of the grafting
17 and again, how to assess, it's really a little bit
18 like Part 2.

19 DR. HUDSON: It's a repeat, right.

20 CHAIRPERSON CANADY: Right. Any
21 comments. Because I'd raise a question as to
22 whether anyone has used dura substitute anywhere

1 other than as a dura substitute and is that
2 acceptable or not acceptable. I think it's my
3 microphone.

4 DR. WITTEN: Yes, I'd just like to
5 clarify. This guidance is really just for looking
6 at these dura substitutes for that intended use.
7 So what we're really focusing on here is, let's
8 say, a sponsor ends up doing a trial or a case
9 series and looks at patients in a certain group of
10 surgeons' practices. Are there any patient
11 populations we need to make sure are either
12 represented in that study or studied separately
13 that might present different, you know, risks of
14 benefits with the use of these products?

15 For example, is the performance in
16 pediatric patients likely to be different or are
17 there special safety concerns with cancer patients
18 that need to be addressed?

19 CHAIRPERSON CANADY: Dr. Penn.

20 DR. PENN: Well, there's a real dilemma
21 here because it's the one of wanting to have
22 something for general use and having it, it's going

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1 to be studied in different types of populations and
2 can you get enough patients of each type to really
3 make a case for it. And I think we have to
4 recognize that it is a problem that a cancer
5 patient who may have a totally different criteria
6 for a dura substitute.

7 It might have to be much bigger than the
8 amount of dura substitute you'd use in a pediatric
9 patient. And the length of time it has to stay in.

10 And I think the best you can do in that situation
11 is not require that each group be done, but that
12 you have an accounting for what group it's being
13 done in. And that in your labeling you can say
14 that it has been tested in such and such situations
15 and maybe give even numbers to that.

16 But not require that it just be labeled
17 for pediatric use or for cancer use. Isn't, then
18 you'll have studies that have to be done on so many
19 different groups that we'll never get a new dura
20 substitute.

21 CHAIRPERSON CANADY: Other comments?

22 MS. MAHER: Yes, I would second that

1 comment. I think that the manufacturer should be
2 deciding in their, what studies, groups they are
3 going to go after and be able to explain why it's
4 relevant to the indication for use they want to put
5 on the product.

6 CHAIRPERSON CANADY: Other comments?

7 DR. KU: I have a question. Is there,
8 umm, we have these standard forms when a device
9 fails or when you have adverse drug reaction. Is
10 there a central computer where, you know, if a
11 certain number of incidents goes off in a certain
12 amount of time, you know, somebody takes notice?
13 Is there a central surveillance system that
14 operates all the time?

15 MR. DILLARD: Jim Dillard. The, I
16 believe you're asking at FDA is there a central
17 location, correct?

18 DR. KU: Correct.

19 MR. DILLARD: They, our --

20 DR. KU: I mean the manufacturers are
21 supposed to report to you guys.

22 MR. DILLARD: Right, right. The

1 manufacturers are supposed to report to us when
2 they've got an event that meets an MDR reportable
3 event by definition, serious adverse event, life
4 threatening, to that affect. We do have, through
5 that reporting system, we have a centralized
6 database that we gather those. We also, into that
7 database, get direct report from user facilities
8 also. Sometimes we'll get anonymous reports that
9 don't get to the manufacturer, but we'll get them.

10 And then there's other reports, of
11 course, that we don't get because they haven't been
12 reported to either, to the manufacturer or to FDA.

13 So for what our central database is worth, we do
14 have all of those reports. Those reports are
15 written reports. Sometimes we further investigate
16 the reports, sometimes they're comprehensive enough
17 for us to be able to enter them into the database.

18 And then we do periodic analyses,
19 trending analyses, both by manufacturer and by
20 product types. And we do those when they are
21 warranted. We also have a surveillance group that
22 looks at those and from time-to-time they will

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1 print out those trends and they'll look to see if
2 there's, you know, a higher trend or there's a
3 change in the trend, let's say in 1998, that might
4 warrant some further investigation.

5 So for what we have in the database, we
6 do that on a fairly regular basis. And then there
7 are a number of actions if something comes up that
8 we have kind of available to us to be able to
9 investigate those.

10 DR. KU: So this database presumably
11 will pick up significant adverse affects, but it
12 may not pick up device failure. Simply, like if
13 you have a device that has a 20 percent leak rate
14 versus something that has a five percent leak rate,
15 because the physician may just simply consider it a
16 technical failure rather than a device failure?

17 MR. DILLARD: Correct, it may not be
18 supported. Yes.

19 CHAIRPERSON CANADY: Dr. Witten.

20 DR. WITTEN: Yes, I would just like to
21 add tomorrow Dr. Kessler is going to be speaking
22 from that office that does the post market

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1 surveillance. But as Mr. Dillard said, it's
2 primarily not to look at rates of events. And I
3 think Dr. Kessler will make this point. It's more
4 to give an idea, for example, if something new
5 comes up or a new type of adverse event that we
6 haven't seen before. But it's not to, it's not a
7 database that's going to capture event rates.

8 I just would like to, before we leave 3-
9 A, question 3-A, I just would like to ask again,
10 though, what type of considerations might induce
11 you to or lead you to use one type of dura
12 substitute versus another in a specific patient
13 population? That is, you know, do different
14 things, you know, are different things important
15 aside from, it's already been mentioned by Dr. Penn
16 the length of time that the product is going to
17 stay in place.

18 Are there other types of considerations
19 involved when you, in your assessment of a dura
20 substitute and its appropriateness for one type of
21 patient versus another? I'm wondering if anybody
22 else has any comments on that?

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1 CHAIRPERSON CANADY: Immuno-suppression
2 would be an issue. Infection, whether the patient,
3 the site in which the graft is required is
4 infected. Those would be considerations.

5 DR. WITTEN: Okay.

6 DR. PENN: Size.

7 DR. WITTEN: Size, all right.

8 CHAIRPERSON CANADY: Any comments on
9 anatomic sites?

10 (No response.)

11 CHAIRPERSON CANADY: Umm, in the
12 clinical assessment, I think we kind of discussed
13 it.

14 DR. WITTEN: Well, before we leave 3-B,
15 I'd like to maybe clarify that question. Are
16 there, yes, are there different types of or
17 different sites of implantation that present a
18 particular challenge in terms of the performance of
19 these dura substitutes versus others? Or maybe
20 different types of surgical procedures? But
21 different anatomic locations, spinal cord, skull
22 base, you know, whatever.

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1 DR. PENN: Sure. There are areas where
2 you can suture it in place easily and there are
3 other areas where you can't. And it does make a
4 big difference in terms of the technical difficulty
5 of the procedure and how it's done. So those are
6 things that should definitely be recorded in any
7 study.

8 DR. HUDSON: Has anatomic site played a
9 role in the, like your choice of a different dura
10 substitute versus another?

11 DR. PENN: It would if there were good
12 choices available.

13 (Laughter.)

14 CHAIRPERSON CANADY: I think there's a
15 3-C. We've kind of discussed this one in
16 relationship to question 2, but is there some
17 additional clarification that you were seeking from
18 this one?

19 DR. HUDSON: Right, we'd like you to
20 comment on the, how we're basing our clinical
21 effectiveness evaluation currently, as based on the
22 adverse events and complications, re-operation, and

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1 currently have recommended one-year CT/MRI scan.
2 And then secondly to discuss potential other
3 endpoints. CSF leakage forces a, one of the
4 considered effectiveness endpoints for these
5 devices, but also ease of handling.

6 How the device might conform to the
7 tissue and the degree of adhesion formation and
8 knowing the shortcomings. Only that can be really
9 assessed in re-operation.

10 CHAIRPERSON CANADY: Comments,
11 panelists?

12 MS. WOJNER: Given the comments that we
13 made previously about the CT/MR, do we want to
14 remove that here?

15 DR. WITTEN: You don't need to reiterate
16 comments that you've already made. But I do want
17 to point out with this question, two things that
18 maybe at least some of the neurosurgeons could take
19 a shot at. And one is that we've already talked
20 about CSF leakage and what you look for clinically.

21 Which I think some commented mostly postural,
22 headache and dizziness.

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1 The other three things are things that
2 we've heard from neurosurgeons that are important
3 in considering, you know, a dura substitute and its
4 value. We really, I think, would appreciate some
5 advice on how to, what kind of assessment might
6 capture Numbers 2, 3 and 4, which we're really not
7 sure about. As well as we'd like to ask in general
8 if you have any suggestions for clinical endpoints
9 that would be good to assess in a study of dura
10 substitutes?

11 CHAIRPERSON CANADY: I think the degree
12 of adhesion formation would be answered, again if
13 comments are made at the time of re-exploration or
14 failure, at failure also, that would be
15 identifiable. The ease of handling is, might also
16 ask for people to report. I mean there is clear
17 favorite ease of handling between the available
18 dura substitutes now that I would think is
19 reasonably standard across the board. And also a
20 question you haven't really mentioned, which is one
21 of, that comes up I think. Is for example with
22 Goretex grafting, which would be included I think

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1 under this.

2 Although the material is wonderful, it
3 seems to have little adhesion and it's technically
4 difficult to get a good seal. So that that becomes
5 an ease of handling issue. And so it's used much
6 less often than you might like because of the
7 technical difficulties with securing a water-tight
8 closure. And again, that's something that's pretty
9 well understood and it's merely a matter of asking
10 for comment.

11 DR. PENN: It's certainly reasonable to
12 have a standard survey when you're doing this of
13 the surgeons to fill out on a new product about
14 ease of use in a number of categories. And you've
15 got, and related, maybe on a visual analog scale as
16 a zero to ten compared to normal dura. For
17 example, if you had a patient's normal dura to put
18 down, compare it to that as maybe the perfect thing
19 to use.

20 So did it deform correctly in the place
21 you were using it? And all those questions would
22 be answered by a good questionnaire. But it would

1 have to be done right after the surgery is done.
2 For other things, you can't find out until you get
3 to the complications stage, the CSF leaks and the
4 adhesion formation.

5 So that has to be a separate
6 questionnaire. But that has, that type of data has
7 to be insisted upon.

8 CHAIRPERSON CANADY: Other comments?
9 Dr. Edmondson.

10 DR. EDMONDSON: Yes, I was just
11 wondering, with regard to the degree of adhesion,
12 if you look at the spine perhaps there are clinical
13 clues that you are more likely to see. Pain,
14 particular symptoms for example, tethering, in
15 contrast to intracranial adhesion. So I was
16 wondering if any of that needs to be included in
17 terms of some, at least some comment about, you
18 know, clinical presentations.

19 CHAIRPERSON CANADY: I guess my sense is
20 that that's difficult because you're usually
21 exploring intraspinally for those kinds of
22 complaints. So that the need for the dura

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1 substitute comes up most often in the spine and
2 tethered cords which have already presented with
3 all those same symptoms. So it would be difficult
4 to sort out the pathology from the graft in that
5 regard. Other comments?

6 (No response.)

7 CHAIRPERSON CANADY: Just so people can
8 formulate their thinking, when we return from lunch
9 what we'll be doing is going around the room on
10 each question for comment. This is not an issue on
11 which we're going to vote. We're just going to ask
12 for your individual comments. So that as you eat,
13 if you might think about a succinct discussion of
14 your feelings about each question.

15 And we'll do them one at a time as we go
16 around. Now I think we'll break for lunch and
17 reassemble at 1:30 in this spot.

18 (Whereupon, the foregoing
19 matter went off the record at
20 12:11

21 p.m. and went back on the
22 record

1

at 1:34 p.m.)

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

2 (1:34 p.m.)

3 CHAIRPERSON CANADY: We're going to
4 resume our discussion of the Guidance Document for
5 Dura Mater Substitutes. As I mentioned before
6 lunch what we're going to do, this is not a voting
7 situation. We're going to make comments regarding
8 the questions and start with one, and Dr. Hudson so
9 kindly put it up for us. And I think we can start
10 with Dr. Hurst and just go around in sequence and
11 make whatever comments you'd like to provide
12 guidance for the FDA on this issue.

13 DR. HURST: Let me just find the right
14 page here. Just start with 1-A?

15 CHAIRPERSON CANADY: Yes. We're going
16 to just do Number 1 first and then Number 2 and
17 Number 3.

18 DR. HURST: Okay. I mean this is not my
19 area of expertise in terms of the validation
20 measures to ensure contaminants, but it certainly
21 does sound reasonable to be very careful about
22 donor surveillance. And I certainly agree with Dr.

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1 Penn's comment regarding making sure that the
2 source of these, sorry, Dr. Gonzales' comment
3 regarding the source of the dura when it comes from
4 another country to at least meet the standards that
5 we have here in the U.S. for that.

6 CHAIRPERSON CANADY: Dr. Edmondson. You
7 can make comments about all of Part 1, otherwise it
8 will become tedious, I think.

9 DR. HURST: Okay. In terms of long-term
10 safety information I think that we talked a little
11 bit about that in terms of the clinical monitoring
12 of these people. And that again is what I would
13 advocate. Clinical monitoring and then if that
14 indicates a problem, then whatever radiologic
15 studies are necessary to evaluate and deal with
16 that problem, with reporting on that as well.

17 In terms of the second question, again
18 kind of the same thing. I would, in most cases,
19 think that MR would be the better imaging modality
20 if you have a clinical problem. If you have
21 clinical evidence of failure, be it even onset
22 seizures, fever in addition to the things that

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1 might be more obvious like a CSF leak. Again, I
2 would lean more toward MR as the evaluation, based
3 on the clinical manifestations rather than
4 strictly, let's get an MR because it's one year
5 out.

6 In terms of the, let's see, the third
7 question, I would also agree that trying to do
8 these subsets, while it would be nice information
9 to know, would be very difficult to do. And I
10 think with very much delay getting things on the
11 market that might be very useful. I think that
12 that's one of the things that we have to keep in
13 mind that when we put something like that out on
14 the market, the people who use this are going to
15 make determinations as to what this is best used
16 for.

17 How it handles, how that affects whether
18 we use it in a pediatric spine or an adult head.
19 So I think that doing them in a fairly standard
20 fashion would be a better way to do it rather than
21 require subset research. And I think that pretty
22 much covers it.

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1 CHAIRPERSON CANADY: Dr. Edmondson.

2 DR. EDMONDSON: Okay, I'd have to say
3 largely ditto, but I have more questions than
4 comments really as far as validating measures to
5 ensure that contaminants are eliminated. And I'm
6 curious to hear from Dr. Piccardo, in particular,
7 regarding animal tissue that's used as a substitute
8 and how, what sort of solvents are really the most
9 appropriate ones to reduce the incidence of prion
10 infection. So that would be one concern.

11 And whatever the standard levels are for
12 residues and so on and so forth I guess is already
13 in place. In terms of long-term safety monitoring,
14 mainly ditto to what Dr. Hurst said.

15 CHAIRPERSON CANADY: Ms. Wojner?

16 MS. WOJNER: I'm going to basically say
17 that I agree with everything that Dr. Hurst has
18 stated. No further comment.

19 CHAIRPERSON CANADY: Dr. Ku.

20 DR. KU: The one, two comments. One, as
21 far as contaminants in dura and where the dura
22 originates from, I believe there are countries that

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1 are known to be BSE-free. It probably wouldn't be
2 a bad idea that the dura comes from those areas
3 and, you know, you would have less of a potential
4 problem statistically then if you were to obtain
5 dura from countries where it is known that it's an
6 endemic problem. The other thing is I did like the
7 study design where it recommended randomized
8 controlled studies for new products that are coming
9 on.

10 Because then it would give us the
11 opportunity to collect data as to what failure
12 rates are, both for conventional materials and the
13 new material that's being evaluated. I think that
14 the number of dura patches that an average surgeon
15 would perform over a year or two years is probably
16 fairly limited. And most of that experience as to
17 whether there's a failure in a particular patient
18 would be anecdotal.

19 So that if you have a large number of
20 cases that are performed you may see a trend. If
21 you have 500 cases, you know, where one type of
22 material you see a ten percent failure rate and

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1 another one you see a 20 percent and then you could
2 go back and retrospectively analyze, you know, if
3 there were a particular case population differences
4 to account for that, or if the cases, case mix was
5 fairly similar and it maybe an intrinsic property
6 of the graft material that you are using. Because
7 I, I did not get a good feeling that that has been,
8 that that information is available.

9 CHAIRPERSON CANADY: Dr. Walker.

10 DR. WALKER: Also I agree with Dr.
11 Hurst's comments.

12 CHAIRPERSON CANADY: If I could get you,
13 just for the purposes of clarification later,
14 everybody to address which comments are one, Number
15 2 or Number 3, since that format is one.

16 DR. WALKER: Number 1, I agree with Dr.
17 Hurst. Number 2, I agree with Dr. Hurst and would
18 add that since we don't have a good imaging
19 modality yet that shows CSF leaks, that to
20 mandatorily require a one-year post-imaging when we
21 can't really what, can't really see anything on the
22 image, probably is burdensome regulation. And

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1 Number 3, I agree with Dr. Hurst.

2 CHAIRPERSON CANADY: Ms. Maher.

3 MS. MAHER: I agree with Dr. Hurst most
4 of the way. I would urge the Agency to try and be
5 aware of the least burdensome and to not put
6 burdens on industry that would have them say, you
7 know, it's not worth it to pursue these. There
8 aren't enough dura patches to sell in the world to
9 make up for the clinical studies that we would have
10 to undergo to get them there.

11 And I think that's a serious concern in
12 that patient population is not that huge, at least
13 in any one Physician's site, to do a clinical study
14 with a one-year follow up without having a huge
15 number of sites. Which again, gets to be fairly
16 expensive. So it needs to be carefully decided how
17 to report. And a lot needs to be left up to the
18 manufacturer to justify how they have decided to
19 collect clinical data they may want to get and not
20 make this guidance document too prescriptive as to
21 what they need to do.

22 CHAIRPERSON CANADY: And again, if I

1 could get you to frame your comments in reference
2 to the questions asked.

3 MS. MAHER: Number 1, agree with Dr.
4 Hurst. Number 2, agree with Dr. Hurst. Number 3
5 is to deal with the least burdensome and to be
6 careful how the clinical studies are described so
7 that the manufacturers do not have a strict
8 guidance that they have to follow that may keep
9 them from doing what needs to be done.

10 CHAIRPERSON CANADY: Thank you. Dr.
11 Piccardo.

12 DR. PICCARDO: I agree with Dr. Hurst on
13 Number 1 and Dr. Gonzales. Regarding the source
14 of material, it is not clear to me the quality
15 control enforced on other countries that might
16 provide dura. And I think that's critical because
17 I called England before coming here and the
18 analysis of infectivity on dura, that was, it was
19 not done or finished, I am not sure, don't quote me
20 on this. But we don't have results on the
21 infectivity on dura on BSE in England.

22 And for that purpose I think it's very

1 critical, even material coming from other
2 countries. We know so little about these diseases
3 that I think the quality control here has to be
4 extreme. You can get areas of the brain that would
5 be negative. That does not mean that that cow did
6 not have BSE. Or, for that matter, infectivity.

7 So I think it's, we have to be very
8 tight in the quality control here. Regarding point
9 Number 2, surgical procedures and imaging studies,
10 that is not my area of expertise, therefore I will
11 make no comments. Regarding Number 3, I agree with
12 Dr. Penn. I think that the, I mean it's important
13 to have the, to study specifically a sub-population
14 of studies in which we can have long-term follow up
15 and data.

16 And that, again, falls back into this
17 TSE, transmission of TSEs. As you know, the
18 incubation times can be extremely long, so we are
19 talking many, many years. There are, there have
20 been cases as you well know of kuru that developed
21 the disease after 40 years, four, zero. So on
22 corneal transplants after 16 years. So follow up,

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1 I mean long-term follow up is critical I believe.

2 I leave it there.

3 CHAIRPERSON CANADY: Thank you. Dr.
4 Gonzales.

5 DR. GONZALES: Regarding question Number
6 1, I think that there has to be a standard set
7 that's both national and international regarding
8 quality assurance of dura substitutes. Regarding
9 dura substitutes that are, that are non-human, even
10 though there are statistics, at least with human
11 diseases, prion diseases such as Creutzfeldt-Jakob
12 Disease, where you have a worldwide incidence of
13 one per million population.

14 There are areas in the world, for
15 instance in Libyan Jews where the incidence is 30
16 per million. So I think that in endemic areas, hot
17 areas, these should be areas that are excluded from
18 non-human as well as human acquisition of these
19 products. I think what is needed is a systematic
20 search of, in the case of non-human dural or other
21 forms of tissue that's collected, that these
22 worldwide hot spots need to be identified.

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1 And that should be also taken into
2 consideration to spite what the outcome of the
3 studies that are being used to identify in that
4 tissue itself, whether the tissue is free of
5 disease or not. I think that we have to look at
6 this and put this as a factor into human tissue
7 acquisition for this purpose. Regarding the second
8 question, I think that clinical not imaging data is
9 needed for follow up.

10 That is to say patients can be
11 asymptomatic and you can have an MRI that will be
12 abnormal with a dural implant. What does that
13 abnormality necessary mean? The fact that it's
14 placed there will show most likely that the MRI
15 will show abnormalities. I think that the clinical
16 follow up is more important for whatever the
17 duration of time that patients are followed rather
18 than to count on the abnormalities seen on MRI.

19 And even if you have abnormalities on
20 MRI, what does that mean? What are you going to do
21 about that if the patient is asymptomatic. So I
22 think it's very important not to start looking for

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1 abnormalities that you really don't know what it
2 means when you're using foreign substances in the
3 body, when in fact you can expect that some
4 reaction will take place. That there will be
5 changes that will take place. That we won't
6 understand initially from a foreign substance that
7 has never been used in humans or studied long-term.

8 I think that has to be taken into
9 account. And I really think that clinical studies
10 are far, far more important in the situation than
11 looking at enhancement or other things that will
12 happen long-term. Regarding the third question, I
13 think that there are, especially 3-A, question 3-A,
14 I think that, you know, there are obvious
15 differences in patients. For instance, the cancer
16 patient that may have a dural implant, I mean we
17 know that cancer patients, for instance, taking
18 that as an example, are, you know, cancer is a
19 relative state of immunosuppression.

20 And cancer is a state of relative hyper-
21 coagulability. And although the numbers will be
22 small, it seems that the decision in terms of

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1 implanting patients is, should be strictly the
2 neurosurgeon's. And that when you collect data on
3 all of the patients, if you, over a period of time
4 can subcategorize them into cancer patients, into
5 pediatric patients or others, then you can start
6 looking at, you know, at the outcome.

7 But I think it's reverse to start first
8 looking at disease states or problem patients and
9 then say that you are going to study these people
10 over time when the numbers are going to be so
11 incredibly small. So I think that to designate
12 classes of patients that you feel need to be
13 studied, it can be done but I think it should not
14 inhibit the neurosurgeon's decision to implant any
15 and all patients that they feel, where it's
16 clinically indicated to do so.

17 And so I think it's great to start
18 categorizing them after the fact and I think that
19 that's important because of the small numbers that
20 are involved here. So I think that has to be taken
21 into account, rather than to start off with the
22 disease process and say we're going to look at this

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1 disease. When in fact when you identify disease
2 processes at the beginning, it states a concern
3 regarding those patients.

4 That in fact they are at higher risk and
5 therefore that the surgeon should take more
6 precautions because of that. That's my one concern
7 about categorizing early rather than later. So
8 that would be my only statement regarding 3-A. And
9 as far as the others, I have really nothing else to
10 say that hasn't already been said.

11 CHAIRPERSON CANADY: Dr. Penn.

12 DR. PENN: Okay, on Point 1, I think
13 that what should be emphasized is that the material
14 be safe. And those things can be done through the
15 animal studies and the proper investigation into
16 the source of the tissue. And I don't need to add
17 anything to what has been said here, but if I were
18 regulating it I would absolutely want to make sure
19 that everything were done to make, to be sure that
20 the material is safe, both in the studies using it
21 in animals and from the animals which it's
22 obtained.

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1 I certainly agree with what I said
2 before on Point 2 that we shouldn't use CT or MR,
3 except as an adjunct to a clinical-based diagnosis.

4 And the third, I view this as an extremely
5 difficult area to get good clinical information
6 about because we can't do randomized studies giving
7 different materials, telling the surgeon which
8 material to use because it just is not a practical
9 thing. There aren't enough patients to do that in
10 any one center.

11 And the surgeon probably has a good
12 sense of what material would be best for that
13 particular patient in the first place. And
14 shouldn't agree to doing that type of study. So
15 what I suggest the substitute for that should be is
16 very strict record keeping, certainly for a year
17 about any complications and the observations on
18 those. And maybe a questionnaire about the ability
19 to handle the material in various clinical
20 situations.

21 You have some idea how that goes. But
22 also surveillance after the particular dura

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1 substitute has been allowed to go forward into
2 general use. And as best as you can have mandatory
3 reporting of complications later on. And that
4 includes the one of, on encephalopathy because that
5 really has to go out as long as possible on these
6 patients.

7 So rather than trying to force
8 burdensome tests that companies can't meet in the
9 clinical arena, I would put my emphasis on pre-
10 clinical studies and the surveillance afterwards.

11 CHAIRPERSON CANADY: Thank you very
12 much. My opinions, I think, have already been
13 reflected on all three questions so I don't have
14 anything additional to add on that. Is that
15 helpful to you Dr. Hudson?

16 DR. HUDSON: That was great. Thank you
17 very much. I wish everybody here could be here all
18 the time when we're doing our reviews, but thanks
19 very much.

20 CHAIRPERSON CANADY: Thank you. We're
21 going to move on now to the second portion of the
22 meeting today. The topic of which is the

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1 Classification of Human Dura Mater. We're going to
2 begin with an open, public session. We have one
3 speaker who has asked to address the group, Dr.
4 Theodore Malinin, who is a Director, from the
5 Division of Tissue Banks, Department of
6 Orthopedics, University of Miami Medical School.

7 Is Dr. Malinin here? Are you expecting
8 him? Do we have any other participants who would
9 wish to address on the open session? Excuse us for
10 a minute. Anybody else who is here that would like
11 to speak at this time?

12 (No response.)

13 CHAIRPERSON CANADY: If not, then we'll
14 go on to the FDA presentation on this topic.
15 Actually, Dr. Piccardo is going to speak next,
16 right.

17 (Asides.)

18 DR. WITTEN: This is my initial --

19 CHAIRPERSON CANADY: Okay, Dr. Witten is
20 going to start.

21 DR. WITTEN: Pardon me?

22 CHAIRPERSON CANADY: You were going to

1 enlighten us.

2 DR. WITTEN: Yes, yes, this is my
3 initial foray into 20th Century technology on the
4 verge of the 21st Century, so hopefully I'll be
5 able to get this to work. Thank you. I'm going to
6 be giving the sort of background in terms of the
7 regulation of human dura mater allograft for dural
8 repair. And we're going to have two other FDA
9 presentations during this session. One is going to
10 be a presentation by Marjorie Shulman about
11 classification, which is what this panel is going
12 to be charged with.

13 But following my talk, Chuck Durfor will
14 be talking specifically about some classification
15 issues and classification questions we have on this
16 product. However, the reason I'm presenting a
17 broad background is because this product has been
18 looked at by two panels. One is this Neurological
19 Devices Advisory Panel in 1989 and 1990, and it's
20 also been considered by the TSE Advisory Panel
21 which is an HHS Panel administered by CBER.

22 So I want to explain the context of the

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1 discussion we're going to be having today.

2 CHAIRPERSON CANADY: If I could just,
3 I'm not sure what you did with those initials.

4 DR. WITTEN: I'm sorry. Did I say, what
5 are those -- TSE, Transmissible Spongiform
6 Encephalopathy Advisory Committee that's
7 administered by our sister center, the Center for
8 Biologics Evaluation and Research.

9 CHAIRPERSON CANADY: Thank you.

10 DR. WITTEN: Thanks for asking me to
11 clarify that, I kind of got lost in the acronyms, I
12 guess I've been at FDA too long. I want to first
13 just say a little bit about the fact these are, or
14 what kind of concerns these products raise since a
15 lot of, some products containing both animal or
16 human tissue are regulated as devices. And I have
17 a list here of just some examples and some of these
18 could be regulated as stand alone devices, like
19 dura mater for dura mater allograft repair or heart
20 valves. And some of these are examples of products
21 that could be devices for a particular indication
22 by themselves.

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1 Or might be a component of another, of a
2 combination device or possibly, we have also animal
3 products used during the manufacturing process of
4 some of the devices that we see. So all of these
5 can potentially present some risks in terms of
6 infection and transmission of disease. Not just
7 TSE as has been discussed this morning, but
8 potentially others as well.

9 The safety issue from implanted tissues
10 include such things as the sourcing, which is one
11 of the things that you all have discussed.
12 Manufacturing, which can include processing like
13 CJD disinfection, manufacturing controls such as
14 the use of batch processing or the use of
15 instruments, reuse of instruments, final product
16 sterilization, characterization and whether or not
17 the sponsor follows good manufacturing processes.
18 So all of these are safety issues that we look at
19 when we look at any medical device.

20 And in particular including medical
21 devices made out of animal and human tissue. The
22 regulatory status of human dura mater allograft is

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1 that it is currently regulated as an unclassified
2 medical device. And as you are aware we are going
3 to be having a discussion about classification of
4 this product later today. We are going to be
5 asking you to discuss, make the classification
6 recommendation.

7 However, I just want to mention, before
8 I give a little bit of the history of what we've
9 been doing in the product, in the regulation of
10 this product. I just want to mention that in
11 February of 1997, that is two years ago, FDA issued
12 a document called the Proposed Approach to the
13 Regulation of Cellular and Tissue-Based Products.
14 And this approach is an attempt by FDA to have a
15 unified approach to regulation of these kind of
16 products.

17 And in this proposed approach, it says
18 that FDA may in the future redesignate human dura
19 mater to regulation as a banked human tissue. So
20 that's just something to be aware of, but at the
21 present time it is regulated as a medical device
22 and that's why we need to fulfill our

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1 responsibility to regulate it responsibly. The
2 background of a product is as follows.

3 This product, like many human tissues
4 for transplant, was in commercial distribution
5 before 1976. And although FDA had the authority to
6 regulate this and other products, we didn't really
7 start regulating tissues as devices until the late
8 1980's on a case-by-case basis. And human dura
9 mater allograft was one of the first of these that
10 we began to regulate. In 1987, as probably most of
11 you know, CJD was reported by CDC and a recipient
12 of processed human dura mater.

13 And then subsequent to that, FDA had a
14 number of discussions with the, with our Advisory
15 Panel, that is this Advisory Committee, the
16 Neurologic Devices Advisory Committee, both in 1989
17 and 1990, and the Panel at that time made a
18 classification recommendation. And although we
19 didn't finalize a classification, we did put
20 forward a guide for 510(k) review that did
21 incorporate some of the concerns of the panel that
22 were voiced at that time.

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1 The reason that we're bringing this up
2 again for discussion is that nine years have
3 elapsed since this product was originally brought
4 up for discussion and there's been nine years of
5 additional information. So we want to bring it
6 back for this forum for further public discussion
7 for classification. Subsequent to the discussions
8 in 1990 and the publication of the guide, in 1996
9 there were 46 CJD cases associated with the use of
10 processed human dura mater identified in a Japanese
11 survey.

12 And shortly following that, the World
13 Health Organization recommended that processed
14 human dura mater no longer be used. Because there
15 were safeguards in place, the FDA did not ban the
16 use of human dura mater at that time, but instead
17 decided to take that product for discussion to the
18 TSE or Transmissible Spongiform Encephalopathy
19 Advisory Committee, which is the Committee I
20 mentioned earlier administered by our sister
21 center, the Center for Biologic Evaluation and
22 Research.

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1 This Committee has taken on a number of
2 topics for both medical products and food products
3 at which there is a risk, potentially, of disease
4 transmission. And because this is a broader issue
5 that doesn't affect human dura mater, this broader
6 committee that looks at risks of transmission in
7 the context of other products also was felt to be a
8 good forum for this discussion.

9 So I've listed here a couple of examples
10 of the topics that this Advisory Committee has
11 discussed in the past. We had several discussions
12 with this Committee. In 1997, this Committee was
13 asked to discuss potential safeguards for the use
14 of dura mater allograft for transplantation. And
15 actually the Advisory Committee was also asked
16 whether or not we should consider a similar ban to
17 what WHO had recommended.

18 The Advisory Committee did provide us
19 advice about safeguards. We worked to put those in
20 the form of a guidance document and we presented
21 the guidance document and an update in 1998, to the
22 Committee. The Committee made some additional

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1 recommendations and we presented our finalized or
2 almost finalized document to the Committee
3 subsequently. I just want to mention, before I
4 move on to talk about what's in that guidance
5 committee, what's in that guidance document, that
6 there is another FDA working group that looks just
7 at this issue.

8 And this working group has put together
9 two workshops, one of which just took place earlier
10 this week and is proposing a third one on TSE
11 diagnostics for next year. The dura guidance,
12 which I mentioned, was published on July 31st of
13 this year and I've put our web site there for
14 anyone in the audience who hasn't seen it and is
15 interested. The guidance document is really an
16 update of the 1990 document.

17 And I've just bulleted here the items
18 that are touched on in this guidance that are new
19 or revised from the 1990 document which touched on
20 donor selection to include both history and medical
21 record review, gross and histological exam of the
22 brain, archiving brain and dura mater tissue both

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1 fixed and frozen, PrP-RES testing, which the
2 guidance document does not currently recommend,
3 although it doesn't recommend against it, because
4 it's currently a research investigational use tool.

5 But when there is a test that's
6 validated for screening that's available, we will
7 recommend incorporating this testing into standard
8 operating procedures. The guidance document also
9 notes, suggests viral inactivation and CJD
10 disinfection. I'll just mention here that the TSE
11 Committee had recommend one normal sodium hydroxide
12 processing and made some recommendations about
13 processing against batch processing and makes
14 recommendations about record keeping and tissue
15 tracking, including the ability to track the tissue
16 both to the recipient and also back to the medical
17 records of the donor.

18 This guidance document was provided to
19 you in your panel pack and I'm not going to go into
20 anymore detail about what's in it. So I would just
21 like to mention, in closing, that we're taking this
22 product to you today for advice and classification

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1 and thank you for your participation in the
2 discussion.

3 And now, is Marjorie here? Okay. I'm
4 going to introduce Marjorie Shulman who is going to
5 just give you some general background about
6 classification and following that Chuck Durfor will
7 talk specifically about classification of this
8 product and give your questions related to device
9 classification.

10 (Asides.)

11 CHAIRPERSON CANADY: You have
12 skyrocketed into the 21st Century, Dr. Witten, you
13 did fine.

14 DR. WITTEN: Thank you, but I, however I
15 don't think I'm going to be able to leave the 20th
16 Century because we can't turn this off.

17 (Laughter.)

18 MS. SHULMAN: I think we might have to
19 just wait for the screen saver to kick in, sorry.

20 (Laughter and asides.)

21 MS. SHULMAN: Good afternoon, my name is
22 Marjorie Shulman and I'm just going to speak about

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1 device classification/reclassification procedures
2 and why reclassify, why reclassify and reclassify
3 devices. I know the panel heard all this morning,
4 this is much shorter. We'll start, the Act divided
5 the array of medical devices into two groups,
6 either pre-amendment devices or post-amendment
7 devices.

8 And this is, it all depends on when the
9 devices were introduced for commercial
10 distribution. The differentiation helps us
11 determine what procedures must be followed in order
12 to initially classify as well as reclassify such
13 devices. For classification of pre-amendment
14 devices, they are classified after FDA has received
15 a recommendation from a device classification
16 panel, published the panel's recommendation for
17 comment along with a proposed regulation
18 classifying the device and publishes a final
19 regulation classifying the device.

20 That's for those classified. For a
21 reclassification of a pre-amendment device, FDA may
22 reclassify a pre-amendment device in a proceeding

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1 that parallels the initial classification
2 proceeding, just as this is here, based upon new
3 information developed as a result of re-evaluation
4 of data before FDA originally classified or not
5 presented, available or developed at that time.

6 The classification of post-amendment
7 devices are automatically, -- post-amendment
8 devices are automatically classified in Class III,
9 and these devices remain in Class III and require
10 pre-market approval unless and until the device is
11 reclassified into Class I or Class II or FDA issues
12 a substantial equivalence decision.

13 Reclassification of post-amendment
14 devices may be initiated either by FDA or the
15 industry and FDA, for good cause shown, refer the
16 petition to a Device Classification Panel. The
17 Panel shall make a recommendation to the FDA
18 respecting the petition. The recommendation will
19 put it into one of three classes. And a device
20 shall be placed in the lowest class whose level of
21 control will provide reasonable assurance of safety
22 and effectiveness.

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1 The three classes or Class I, General
2 Controls, Class II, Special Controls and Class III,
3 Pre-market Approval. Class I devices are for which
4 any combination of the general controls are
5 sufficient to provide reasonable assurance of the
6 safety and effectiveness of the device. And
7 general controls include prohibition against
8 adulterated or misbranded devices, that includes
9 labeling, adequate directions for use, pre-market
10 notification if it is reserved.

11 Most class ones are exempt. Band
12 devices, GMPs, good manufacturing practices,
13 registration or manufacturing facilities, listing
14 them, listing of the device types, record keeping
15 and repair and placement and refund. Class II,
16 Special Controls, are devices which cannot be
17 classified into Class I because general controls by
18 themselves are insufficient to provide reasonable
19 assurance of the safety and effectiveness. But
20 there is sufficient information to establish
21 special controls to provide the assurance.

22 Special controls include performance

1 standards, discretionary, voluntary, national,
2 international standards or one recognized by rule
3 making. Close market surveillance either required
4 or discretionary. Patient registries, development
5 and dissemination of guidelines and guidances.
6 Design controls, recommendations and other
7 appropriate actions, that's a catch-all provision.

8 Tracking requirements and of course pre-
9 market notification, unless that's also going to be
10 exempt. Class III are devices for which
11 insufficient information exists to determine that
12 general, the Class I's and special Class II
13 controls are sufficient to provide reasonable
14 assurance of the safety and effectiveness of such
15 device and such devices are implants unless general
16 or special controls can mitigate the risks.

17 Life-sustaining and/or life-supporting
18 substantial importance in preventing impairment of
19 human health or present potential or unreasonable
20 risk of illness or injury. So those are the three
21 classes and that's what the Panel will vote on
22 today. Thank you.

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1 CHAIRPERSON CANADY: Mr. Durfor.

2 DR. DURFOR: Good afternoon to you all.
3 Unlike Dr. Witten, watching the lights dim, I'm
4 just hoping we'll stay in the 20th Century for the
5 rest of the afternoon. My name is Charles Durfor,
6 I'm a Reviewer in the Plastics and Reconstructive
7 Surgery Devices Branch, and I will be giving you
8 some information that will lead you to your
9 discussions this afternoon about classification of
10 human dura.

11 Some of the information I will provide
12 you overlaps with what Dr. Witten has already told
13 you. I will go through that very briefly and my
14 intent, once again, is just to help you move
15 towards your discussions. Okay, my presentation is
16 brief and it provides you both some regulatory
17 history, which is a little different than you've
18 heard, and then some information about the current
19 status of this product.

20 Once again, just as a point of
21 clarification, this morning we were talking about
22 dura substitutes which are Class II medical

1 devices. This afternoon and right now we are
2 talking about human dura, which is an unclassified
3 pre-amendments medical device. It is a pre-
4 amendments device because it was in commercial
5 distribution well before 1976.

6 February 2nd of 1990, this Committee,
7 Neurological Devices Advisory Committee, also
8 offered a classification recommendation. And as
9 stated by Dr. Witten, a significant amount of time
10 has past since those comments and are knowledge of
11 this field has also grown. And so we've come back
12 to you looking for advice. However, nonetheless,
13 to summarize what that Panel discussed, they did
14 recommend that it should be a Class II medical
15 device and in the process of evaluating this
16 product they listed the specific health hazards as
17 prion infection, infection by other agents as well,
18 concerns about CSF leakage and adverse tissue
19 reaction.

20 Other pieces of regulatory history that
21 are important. On December 14th of last year, FDA
22 enacted a tracking order for dura mater. This

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1 requires each provider of dura mater to design and
2 implement a system for tracking any product from
3 the time that it is sold, if you will, until either
4 ex-plantation or patient death. The other issue
5 already discussed by Dr. Witten is that we did in
6 deed, this summer, release an update of the 1990
7 guidance document on, for human dura.

8 And this document reflects considerable
9 deliberations by the TSE Advisory Committee.

10 Current status. If one goes into the FDA
11 databases, one will find that there are six
12 establishments who have registered with the FDA as
13 dura mater providers. Not all of them may be in
14 commercial distribution today, instead I'm just
15 giving you what is in the database.

16 So at some point in time we had six and
17 there may be less. If a new dura mater provider
18 were to come to the Agency at this time and look to
19 market their product, it would go through the pre-
20 market notification process known as 510(k), as
21 part of 510(k), part of the FDA law.

22 We have had two devices cleared through

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1 the 510(k) process. If one were to look at the
2 adverse event data reporting database, which
3 collects information back to 1984, there have been
4 four reports of infection and contamination, one
5 death, which was reported in 1990, and I have not
6 been able, at this point, to determine what the
7 cause of death was.

8 And there was also one adverse event
9 that talks about long-term ulceration related to
10 contact lens use. And it's not clear to me whether
11 that was off label use of dura mater or whether
12 that was just an adverse event that was put in the
13 wrong pro code and incorrectly filed. If one looks
14 at the indication for use for the two medical
15 devices that have been cleared, one is indicated
16 for neurological and/or neurosurgical repair of
17 dura mater.

18 The second is indicated for implantation
19 for use in neurosurgery. That brings me to the
20 questions that we hope you will discuss and provide
21 us guidance on. And let me just walk you through
22 what they are. The first one refers to the

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1 guidance document we did provide, which was
2 developed in consideration of the comments we
3 received from the TSE Advisory Committee. And what
4 we ask of you, given your knowledge and experience
5 in this area, is in addition to this guidance, what
6 other types of descriptive information should be
7 included in the classification identification for
8 human dura?

9 The second question also relies upon
10 your experience to give us information about what
11 other different uses or limitations might be
12 appropriate for human dura mater? Once again, what
13 would be a good indication? There also may be, and
14 we heard this morning with regards to discussion of
15 dura substitutes, we heard that there could be
16 differences in surgical technique. Whether
17 suturing or on lay graft and we would ask for your
18 advice on that in terms of if there are appropriate
19 limitations that should be reflected in the device
20 description?

21 Number 3 is also along this line and it
22 talks about whether it is appropriate to indicate

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1 this product for both cranial and spinal use.
2 Number 4, refers to the classification
3 questionnaire that you will be involved in
4 reviewing. And as you review that classification
5 questionnaire, we hope you pay some attention to
6 this issue. Once again, as we go back and we look
7 at the medical device report database, we have seen
8 that there are some clinical and technical problems
9 associated with the use of this product.

10 They would be device contamination,
11 death and infection and graft failure. With that
12 in mind, supplied on your experience, we question
13 whether have all the risks to health for dura mater
14 been adequately identified? And if not, what
15 additional risks would be recommend? And this is
16 related to question 3 of the questionnaire you will
17 be looking at shortly.

18 Secondly, have the appropriate methods
19 to control each risk, have they also been
20 adequately identified and there are some examples
21 and this is related to questions 5 through 7 of the
22 classification questionnaire. And finally, for

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1 this device when is it appropriate to obtain
2 additional clinical experience before pre-market
3 approval. And I thank you for your time and
4 attention.

5 CHAIRPERSON CANADY: Thank you very
6 much, Dr. Durfor. We're going to deviate a little
7 from the original protocol and go back to the open,
8 public hearing now. And Dr. Theodore Malinin from
9 the Division of Tissue Banks, Department of
10 Orthopedics, University of Miami Medical School is
11 going to make comments to us. Good afternoon, Dr.
12 Malinin.

13 DR. MALININ: Good afternoon, thank you
14 very much. My name is Theodore Malinin, I'm
15 Professor of Orthopedics at University of Miami
16 School of Medicine. I'm also Director of the
17 Tissue Bank which is part of the Department. For
18 better or for worse, I have been involved with dura
19 mater allografts since their inception at the Naval
20 Medical School, which dates back to 1960, 1958.
21 Since that time, and there have been number of
22 modifications applied to use and processing of this

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1 graft.

2 University of Miami is a non-profit
3 organization. We prepare dura mater allografts and
4 have been primarily because of the requests and
5 demands of our Neurosurgical Department. And as
6 you probably know Dr. Rosmoff, who was the pioneer
7 in use of this graft was our Chairman for a number
8 of years. Subsequently, our neurosurgeons still
9 request these grafts to be prepared and in our own
10 institution they are used frequently.

11 Since the beginning of the University of
12 Miami Tissue Banks' existence, which dates back to
13 1970, we have prepared some 50,000 dura mater
14 grafts and have distributed them for, to various
15 institutions throughout the country. We have not
16 sent any dura mater allografts abroad. The safety
17 precautions which are used in --

18 (Whereupon, the foregoing
19 matter went off the record at 2:23
20 p.m. due to a power outage.)

21

22

