DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

SUMMARY MINUTES
Fourth Meeting
NEUROLOGICAL DEVICES PANEL

February 2, 1990

Room 100
Piccard Building

1390 Piccard Drive
Rockville, Maryland

PANEL MEMBERS PRESENT

Harold Stevens, M.D., Ph.D., Chair
Howard H. Kaufman, M.D.
Mary K. Gumerlock, M.D.
Raj K. Narayan, M.D.
Roger W. Kula, M.D.
Wilbert Fordyce, Ph.D.
Joel B. Myklebust, Ph.D.
Edith I. Jones, M.D. (Consumer Representative)
Marvin L. Sussman, Ph.D. (Industry Representative)

PANEL CONSULTANTS

Norman D. Anderson, M.D. (Chair, GPS Devices Panel)
Glenn D. Warden, M.D. (Consultant, GPS Devices Panel)

FDA REPRESENTATIVES

George C. Murray, Ph.D., Director, Division of Anesthesiology, Neurology and Radiology Devices (DANRD), Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH)
Robert F. Munzner, Ph.D., Executive Secretary, Neurological Devices Panel, DANRD, ODE, CDRH
Levering Keely, R.N., DANRD, ODE, CDRH
John Dawson, DANRD, ODE, CDRH

AUDIENCE

Theodore Malinin, M.D., South-Eastern Organ Procurement Foundation
John R. Kateley, Ph.D., American Association of Tissue Banks
Jeanne C. Mowe, American Association of Tissue Banks
Angela Hefferman, "The Gray Sheet"
Joel S. Faden, Advanced Bioresearch Associates
Robin Bush, Aesculap
Eberhard F. Mammen, Wayne State University
L. Philip Carter, University of Arizona Med. Center
Madeleini Kindeffy, Datascope Corporation
Paul Schneider, Datascope Corporation
John Casale, Datascope Corporation
Jacqueline Kelly, Applied Logic Associates
Joan H. C. Voormolen, AZ Leiden-Holland
Richard T. Skalski, Johnson and Johnson
Sophia Pesotchinsky, Vitaphore Corporation
Evan Dick, E. G. Dick and Associates
Judith E. O'Grady, Colla-Tec, Inc.
Linda S. Alexander, Medtronic, Inc.
Kate Beardsley, Weil Gotshal
Dennis F. Heinrichs, Florida Regional Bone & Tissue Bank
Jerri Perkins, M.D., Perkins and Perkins, Inc.
Claudia Gaffey, M.D., FDA, CDRH, Office of Health Affairs (OHA)
Gordon Johnson, M.D., FDA, CDRH, OHA
Greg Alexander, M.D., FDA, CDRH, OHA
Jim Weixel, FDA, OHA
Ken Palmer, FDA, CDRH, ODE, DSRD
Nirmal K. Mishra, FDA, CDRH, ODE, DSRD
Bernard H. Berne, FDA, CDRH, ODE, DSRD
Gopal Bhatnagar, FDA, CDRH, ODE, DSRD
Edappallath Radha, FDA, CDRH, ODE, DCLD
Jim Lucas, FDA, CDRH, OCS
Don Watchko, FDA, CDRH, OCS
Gail C. Provencher, R.N., M.S.N,, FDA, OCS, DPS
Lily Ng, FDA, CDRH, OCS, DPS
Lillian Gill, FDA, CDRH, OST
Mel Seidman, FDA, CDRH, OST
Pat Trisler, FDA, CDRH, ODE
Doyle Gantt, FDA, CDRH, ODE, DANRD
Steve Hinckley, FDA, CDRH, ODE, DANRD
Mike Gluck, FDA, CDRH, ODE, DANRD
Casper Uldriks, FDA
Lynne Edwards, FDA
Brenda Hayden, FDA
Elaine Frost, FDA
Arnold Alpert, FDA
Barry Sands, FDA
Judith Kuhin, FDA

OPEN PANEL DISCUSSION

FDA staff told the panel that the Agency is considering processed human dura mater as a product that meets the definition of a medical device and which require classification as a preamendment device. FDA staff briefly described the requirements for medical device classification as defined by the Food, Drug and Cosmetic Act. The panel was provided with reference copies of the documents listed in Attachment A.

The panel heard extensive testimony from Dr. John Kately, President of the American Association of Tissue Banks (AATB) and Dr. Theodore Malinin of of the South-Eastern Organ Procurement Foundation (SEOPF) describing the methods used by the tissue banks to assure the safety of the grafts they distribute.

OPEN PUBLIC HEARING

HEMOPAD™ Hemostatic Agent (Datascope Corp.)

The panel was asked to make recommendations regarding a supplemental premarket approval application for the neurosurgical use of the hemostatic agent HEMOPAD™, which is manufactured by Datascope, Inc., and which is currently being marketed for use in other surgical applications.

The panel heard extensive testimony from Datascope concerning the data provided in their PMA supplement. The firm was cautioned that the introduction of new data (data not present in the application) might require amendment of the PMA and another review by the panel.

The firm's presentation was followed by a review of the data in the application by FDA staff. Staff members indicated FDA had the following concerns with regard to the adequacy of the animal studies and the clinical study conducted by the firm to support the PMA supplement:

1. The number of patients in whom the product was used in contact with neural tissue or central nervous system fluids was not sufficient to make a scientific assessment of the risks and benefits. No concurrent control subjects were enrolled.

2. Complication rates of 50% and failure rates of greater than 18% with implanted patient population were observed. Complications included rebleeding, hydrocephalus, neurological deficits, meningitis, infection, infarction and cerebral spinal fluid leaks. HEMOPAD™ could not be excluded as a possible cause of these complications.

3. Deaths occurred in 13% of the neurological patients having HEMOPAD™ in situ. In a significant number of these deaths, the possibility that the cause of death might have been related to HEMOPAD™ use could not be ruled out.

4. Among several institutions participating in the study there was a wide diversity among the patient populations studied.

5. Follow-up data was obtained for only 52% of the study subjects at 20 weeks.

6. There were no stated selection criteria for admission of surgical patients into the study, thereby making comparison with any historical data difficult.

7. The applicant's data analysis did not take into consideration the variability in the several patient populations studied.

8. In animal studies that were intended to show that the presence of HEMOPAD™ in the cerebral spinal fluid (CSF) circulation does not induce hydrocephalus, measurements showed elevated CSF pressure which was not explained.

9. In animal studies intended to show that the use HEMOPAD™ does cause surgical complications, approximately 9% of the animals exhibited post-surgical complications, and the cause of these complications remained unexplained.

Dr. Gumerlock, the primary panel reviewer, summarized her observations and indicated that her concerns about the adequacy of the clinical data with regard to safety were the same as those expressed by the FDA staff.

CLOSED SESSION

It was not necessary to meet in closed session.

OPEN PANEL DISCUSSION -- RECOMMENDATIONS

HEMOPAD™

The panel voted to recommend that the application be considered not approvable (6 in favor of the motion; one opposed). Some panel members suggested that the application might be approvable if the use in neurosurgery use was limited to extradural use (ie, not in contact with CSF or neural tissue). The panel also concurred with the FDA's suggestions regarding data needed for approval and recommended that the PMA supplement by amended as follows:

1. New studies should be performed to demonstrate the use of this product as indicated. The patient population should be representative of the anticipated neurosurgical population and should include: (a) use within the brain or other deep intracranial structures (gray or white matter) and to control bleeding in intracranial tumor beds; (b) use in proximity of the spinal cord to control bleeding.

2. If the product is intended for implantation to control bleeding, future studies should demonstrate safety by performing studies that include implantation in deep intracranial structures, intracranial tumor beds or in the spinal cord.

3. The number of subjects in the study should be sufficient to statistically demonstrate that the product is safe and effective for all intended uses.

4. As part of the demonstration of safety, all subjects should should have well documented follow-up examinations at appropriate times with long term follow-up performed by examiners who are "blinded".

5. Additional study of adverse affects is needed using a population that is relatively free of complications. Design of these studies should consider the inherent risks associated with the surgical procedures and should be designed to measure the incidence of identified possible complications such as failure to obtain hemostasis, re-bleeding, possible hydrocephalus, seizures, etc.

6. Detailed documentation of each subject's status should be required prior to the operation, immediately following the operation, and at follow-up. The documentation should include the use of established neurological measurement criteria such as trauma scores, coma scores and other established measures. Autopsy data should be obtained whenever possible.

7. Selection criteria for the entry of subjects into the study need to be clearly identified.

Processed Human Dura Mater

The panel voted to recommend that the processed dura mater be classified in class II (See Attachments B and C). In addition, the panel recommended that FDA use the guidelines developed by AATB and SEOPF to the greatest extent possible in determining the equivalence of products offered by new manufacturers and that these guidelines be used in developing standards. The panel recommended that the priority status for a performance standard be "high".

I approve the minutes of the meeting as recorded in this summary.

Harold Stevens, Ph.D., M.D., (date) 3/31/93
Chair

I certify that I attended this meeting of the Neurological Devices Panel on February 2, 1990, and that these minutes accurately reflect what transpired.

Robert F. Munzner, Ph.D. (date) 3/29
Executive Secretary, Neurological Devices Panel

Attachment A

REFERENCES

1. American Association of Tissue Banks, "Standards for Tissue Banking", Arlington, Virginia, AATB, Copyright 1984, Revised September 1985.

2. American Association of Tissue Banks, "Technical Manual for Tissue Banking", AATB, Arlington, Virginia, Copyright 1987.

3. Department of Health and Human Services, "FDA Safety Alert: Possibly Contaminated Dura Mater", open letter dated April 28, 1987 signed by John C. Villforth, Rockville, Maryland.

4. Health and Welfare Canada, "ALERT Medical Devices", open letter dated May 28, 1987 signed by A. J. Liston, Ph.D., Ottawa, Ontario.

5. Tri-Hawk International, "Lyodura™", product labeling (undated), Montreal, Quebec.

6. South-Eastern Organ Procurement Foundation, "Guidelines and Standards for Excision, Preparation, Storage, and Distribution of Human Cadaver Tissues for Implantation", Richmond, Virginia, SEOPF, undated.

7. CDRH Memorandum from John Villforth concerning Regulation of Human Tissue Products, to The Commissioner, dated November 29, 1989.

8. Sec. 513 of Food, Drug, and Cosmetic Act (Amended 1976), "Device Classes".

9. Classification interpretation with questionnaire form and Supplementary Data Sheet.

CLASSIFICATION QUESTIONNAIRE FORM

Medical Device Classification System

Panel Member: Harold Stevens, M.D., Ph.D. Date: Feb. 2, 1990

Device: Processed Human Dura Mater

Use Categories: ☐ Diagnostic ☐ Monitoring ☐ Prosthetic ☑ Surgical ☑ Therapeutic ☐ Other

Regulatory Level: I. General Controls (II.) Performance Standards III. Premarket Approval

Specific device problems: (Yes) No

Classification System	Yes	No	Do Not Know	Regulatory Level	Question Scheme
1. Custom Made?		✓			Yes--2 No--3
2. Custom Made: Standard?					Yes / No 17
3. Life-sustaining?	✓				Yes--5 No--4
4. Potentially hazardous to life, good health	✓				Yes / DNK } 5 No--7
5. (a) Can standards be developed now; and (b) would standard be adequate?	✓				Yes--7 No / DNK--6
6. Marketed in U.S.?	✓				Yes / No } 7
7. Remote from body?		✓			Yes--14 No / DNK } 8
8. Powered?		✓			Yes--9 No--13
9. Failure of power: hazardous to patient?					Yes / DNK / No } 10
10. Introduce energy into body?					Yes--11 No--13
11. Acceptable energy levels?					Yes / No } 12
12. Safe energy levels if malfunction?					Yes / No / DNK } 13
13. Material regarded as safe without standard:		✓			Yes / No / DNK } 14
14. Prescriptions needed? limitation, hazards, difficulties, problems	✓				Yes / No } 15
15. Labeling, instructions or precautions on measurement function?				N/A	Yes / No } 16
16. Performance Standards?	✓				Yes / No } 17
17. Special safety systems considerations?	✓				Yes / No / DNK } 18
18. Potentially hazardous to fetus and/or gonads		✓			Yes / DNK } To Ob-Gyn Panel
Low Density Coding Form					

Supplementary Data Sheet
Summary of Reasons for Classification

1. Device Name: Processed Human Dura Mater

2. Classification Panel: Neurological Devices Panel

3. Is device an implant? YES

4. Indications for use prescribed, recommended, or suggested in the device's labeling that were considered by the panel: can be used to surgically repair dural defects to present loss of CSF.

5. Identification of any risks to health presented by device

General: can transmit micro-organisms from host and can fail to function allowing leakage of CSF.

Specific Hazards to Health		Characteristic or Feature of Device Associated with Hazard	
a.	"prion" infection	a.	donor selection criteria
b.	infection, general	b.	sterilization process
c.	CSF leakage	c.	material strength, integrity
d.	adverse tissue reaction	d.	processing affect on biocompatibility

6. Recommended panel classification and priority

Classification	Priority (Class II or III Only)
II	High

7. If device is an implant, or is life-sustaining or life-supporting, and has been classified in a category other than Class III, explain fully reasons for the lower classification with supporting documentation and data

Data and publications provided by Dr. John Kately and Dr. Theodore Mali in support the use of current AATB and SEOPF processing standards as being adequate to assure safety and effectiveness.

8. Summary of data including clinical experience or judgment upon which classification recommendation is based

References listed in Attachment A of Summary Minutes; presentations by Dr. Malinin and Dr. Kately to the panel on July 14, 1989.

9. Identification of any needed restrictions on the use of the device

10. If device is in Class I, recommend whether FDA should exempt it from:

Not applicable

	Justification/COMMENTS
a. Registration	a.
b. Records and Reports	b.
c. Good Manufacturing Practice	c.

11. Existing standards applicable to the device, device subassemblies (components), or device materials (parts and accessories)

Standards published by the American Associates of Tissue Banks and the South-Eastern Organ Procurement Foundation (see Refs. 1, 2, and 6)

Distribution for Summary Minutes

Harold Stevens, M.D., Ph.D., Chair
Joel B. Myklebust, Ph.D.
Howard H. Kaufman, M.D.
Raj K. Narayan, M.D.
Mary K. Gumerlock, M.D.
Wilbert Fordyce, Ph.D.
Edith Irby Jones, M.D.
Marvin L. Sussman, Ph.D.
Ruth B. Loewenson, Ph.d.

HFZ-1 Director, CDRH
HFZ-2 Deputy Director, CDRH
HFZ-20 DMcKenna, KLevin
HFZ-40
HFZ-70 Health Affairs
HFZ-80 Standards & Regulations
HFZ-210 Small Manufacturers Assistance
HFZ-300 Office of Compliance
HFZ-323 JLucas
HFZ-323 DWatchco
HFZ-400 Director, ODE
HFZ-400 Panel Coordinator
HFZ-402 POS Staff
HFZ-450 DCRND
HFZ-456 RFMunzner(Chron)
HFA-224
HFA-305 Dockets Management Branch
HFA-306 Committee Management Officer