

SUMMARY MINUTES

MEETING OF THE OBSTETRICS AND GYNECOLOGY DEVICES

ADVISORY PANEL

OPEN SESSION

June 10, 2003

**Gaithersburg Hilton
Gaithersburg, MD**

**Obstetrics and Gynecology Devices Advisory Panel Meeting
Open Session June 10, 2003**

Attendees

Chairperson

Mary Jo O'Sullivan, M.D.
University of Miami/Jackson Memorial
Hospital

Executive Secretary

Joyce M. Whang, Ph.D.
Division of Reproductive, Abdominal, and
Radiological Devices

Voting Members

~~Evelyn R. Hayes, Ph.D.
College of Health and Nursing Sciences
University of Delaware~~

~~Hugh Miller, M.D.
Department of Obstetrics and Gynecology
Arizona Health Science Center~~

~~Jonathan W. Weeks, M.D.
Suburban Hospital, Maternal-Fetal Medical
Center
Louisville, KY~~

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University of Illinois at Chicago

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Denver Health Medical Center

Michael P. Diamond, M.D.
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Evelyn R. Hayes, Ph.D.
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University of Delaware

Kinley Larntz, Ph.D.
School of Statistics, University of Minnesota

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Michael Neuman, M.D., Ph.D.
Joint Program of Biomedical Engineering
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Nancy C. Sharts-Hopko, Ph.D.
College of Nursing, Villanova University

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Consumer Representative

Kleia R. Luckner, J.D., M.S.N.
The Toledo Hospital

Industry Representative

Mary Lou Mooney, R.A.C.
SenoRx, Inc.

FDA Participants

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Abdominal, and Radiological Devices

Colin Pollard
Chief, Obstetrics and Gynecology Devices
Branch

Veronica Price

Obstetrics and Gynecology Devices Branch

Julia Corrado, M.D.
Obstetrics and Gynecology Devices Branch

IsaacA. Chang, Ph.D.
Division of Physical Sciences,
Office of Science and Technology

CALL TO ORDER

Panel Chair Mary Jo O’Sullivan, M.D., called the meeting to order at 8:31 a.m. and asked the panel members to introduce themselves. **Panel Executive Secretary Joyce M. Whang, Ph.D.**, noted that upcoming panel meetings have been tentatively scheduled for September 8 and 9 and November 3 and 4, 2003. She also stated that three new voting members were present: Evelyn R. Hayes, Ph.D., Hugh Miller, M.D., and Jonathan W. Weeks, M.D. In addition, Andrew I. Brill, M.D., and Charles C. Coddington, III, are new panel consultants. Dr. Whang read the appointment to temporary voting status, which stated that Drs. Brill and Coddington as well as Michael P. Diamond, M.D., Kinley Lartz, Ph.D., Michael Neuman, M.D., Ph.D., and Nancy C. Sharts-Hopko, Ph.D., had been granted temporary voted status for the duration of the meeting. She then read the conflict of interest statement. Full waivers had been granted to Drs. Brill and Lartz for their interests in firms that could be affected by the panel’s recommendations. The Agency took into consideration certain matters regarding Drs. Brill, Miller, Neuman, and Sharts-Hopko, who reported current and/or past interests in firms at issue but in matters not related to the day’s agenda; they could participate fully.

Colin Pollard, Chief, Obstetrics and Gynecology Devices Branch, welcomed the panel and introduced several new branch employees. He read a letter of thanks from Linda Skladany, associate commissioner of external affairs, thanking Dr. Sharts-Hopko for her service over the past 4 years. Finally, he emphasized the importance of the panel’s input in FDA’s review of the Microsulis device.

OPEN PUBLIC HEARING

No comments were made.

MICROSULIS PRESENTATION: P020031

Marc Finch, executive vice president, Microsulis Americas, Inc., said that the company specializes in understanding the effects of microwave-induced dielectric heating of human tissue. The Microwave Endometrial Ablation (MEA) System is a thermal ablation device intended to ablate the endometrial lining of the uterus in premenopausal women with menorrhagia due to benign causes for whom child bearing is complete. The technology for the proposed use has been in development since 1992. Clinical validations include the treatment of 655 subjects by 23 investigators in 11 investigational sites between 1994 and 2001.

Ted Anderson, M.D., Ph.D., FACOG, co-lead investigator, U.S. pivotal trial, listed treatment objectives for excessive uterine bleeding, then described the MEA System. The device consists of a microwave generator, an applicator 8 mm in diameter, and a treatment feedback display. After presenting a video that illustrated MEA treatment, Dr. Anderson described the treatment process, which takes ~~about 3~~an average of 3½ -minutes.

The microwaves have a frequency of 9.2 GHz and penetrate to 3 mm; tissue heating typically occurs up to 6 mm from the tip. A thermocouple at the applicator tip measures the temperature of adjacent tissue. The temperature should stay in the 70 to 80°C degree range. If the temperature reaches 85°C, an alarm sounds; if it reaches 90°C, the device shuts off. If the temperature rise during the first 5 seconds is abnormal, the system pauses, and a screen prompt appears.

Ian Feldberg, senior executive vice president of technology, Microsulis, provided an overview of thermal penetration. Heating occurs to a depth of 5 to 6 mm through thermal conduction. Temperatures during the MEA procedure achieve coagulation but are not sufficient to physically remove tissue. The objective is to coagulate 5 to 6 mm of tissue.

In analyzing maximum thermal penetration, the most extreme conditions were assumed.

Bench testing in unperfused porcine liver was conducted. A computer model was then developed and validated using the results of testing in liver, and bench testing was performed with unperfused porcine liver. With a maximum applicator temperature of 90°C at the tip and a maximum time of 12 minutes, the depth of thermal penetration was 9 mm. This penetration depth cannot be exceeded in living tissue due to the presence of blood cooling. In addition to preliminary bench testing, the sponsor conducted a number of in vivo tests in patients undergoing hysterectomy. The device resulted in tissue necrosis of uniform depth following treatment.

The computer model predicts that maximum thermal penetration will vary from 6.4 mm to 7.2 mm for the maximum allowable period of 12 minutes using a blood perfusion rate of 15.8 mm per 100g per minute. Assuming a ~~With~~ blood perfusion rate that is of 20% of this value at least 50 percent of normal, the, penetration depth reaches ~~up to~~ 8.1 mm. There is ~~no no~~ fundamental difference between the sponsor's and FDA's methodology in determining depth of penetration. The difference between the values presented by the sponsor and FDA is based on the fact that the sponsor's analysis is made with respect to time. ~~understanding perfusion effects.~~

Ted Anderson The mathematical model represents thermal penetration to 8.1 mm in the case of putting the probe in a single spot and leaving it there for 12 minutes at 90°C; that would not happen clinically. Bench testing is theoretical, however; it is important keep a clinical perspective.

MEA treatment is effective, has minimal risks, and carries limited patient restrictions. It completely destroys the basal layer, has repeatable and predictable results, and results in high patient satisfaction. In addition, it can treat irregular cavities and cavities of many sizes and does not exclude fibroid uteri. It requires ~~no~~ no general anesthesia or operative hysteroscopy.

Claude Fortin, M.D., FACOG, co-lead investigator, presented the pivotal study results. The study took place at eight sites and involved 324 premenopausal women age 30 or older with PBLAC scores of at least 185. Two patients were excluded because the site withdrew from the study. The 107 patients in the control group received rollerball endometrial ablation (REA); the 215 patients in the experimental group received MEA. Follow-up took place at 2 weeks and at 3, 6, and 12 months. Dr. Fortin listed the inclusion and exclusion criteria. He emphasized that patients with myometrial wall thickness of less than 8 mm, as determined by transvaginal ultrasound, were excluded. Patients received 3.75 mg Lupron 3 to 5 weeks before treatment; immediately prior to treatment, hysteroscopy was performed to document normal cavity landmarks and intracavitary pathology. Hysteroscopy has great value as an adverse event mitigator. Five subjects were excluded from treatment following hysteroscopy (2 patients) and ultrasound (3 patients).

The primary efficacy endpoint was a reduction in menstrual bleeding to a PBLAC score of 75 or less at 12 months. The intent-to-treat population was used in reporting all primary endpoint outcomes. Eighty-seven percent of MEA patients and 83.2 percent of REA patients were considered treatment successes. Subjects with lost or missing data were counted as failures. Secondary endpoints were amenorrhea at 12 months, patient satisfaction, duration of treatments in terms of anesthesia and procedure time, and anesthesia use. The MEA group had significantly

shorter procedure and anesthesia time than the REA group. Patients in both groups were comparable in their levels of satisfaction.

Investigator training emphasized the importance of protocol adherence, completion of case report forms, use of the foam simulation unit for multiple practice sessions, and preceptorship of initial cases.

No device-related complications were reported. Procedural complications included four cases of cervical laceration (~~12~~ MEA and ~~24~~ REA), one case of cervical stenosis (MEA), and two cases of uterine perforation during dilation prior to treatment (MEA). The most commonly reported adverse events in the 24 hours postprocedure were nausea, vomiting, and uterine cramping; the MEA group was more likely to experience those effects than the REA group. Adverse events reported between 24 hours and 1 year included endometritis (5 MEA and 1 REA), bacteremia (1 MEA), and pregnancy (1 REA).

The results of the pivotal trial demonstrate that MEA is safe and effective for its intended use. It can treat normal uterine cavities between 6 and 14 mm and cavities with fibroids smaller than 3 cm.

Ted Anderson, M.D., Ph.D., FACOG, co-chair, Microsulis Clinical Advisory Panel, described the commercial experience with the device outside the United States and the sponsor's response to the reported adverse events. Commercial experience consists of 15,129 treatments as of the end of the first quarter 2003. A total of 12 perforation- and 13 non-perforation-related adverse events, resulting in 23 cases of bowel injury, were reported. In an additional two cases, investigators were unable to determine whether perforation had occurred. The sponsor has significantly reduced adverse events despite continued increase in the number of treatments and users.

With many adverse events, Microsulis' internal review found deviations from the protocol. Corrective actions included requirement of Microsulis-certified preceptors in training. In addition, the company made modifications to the instructions for use. Recommendations for mitigation include diagnostic hysteroscopy in all patients prior to insertion of the MEA applicator, strict adherence to contraindications, and ultrasound evaluation of the uterine wall prior to MEA for all patients. After implementing the changes, adverse events immediately diminished, and none have been reported since November 2002. Because the applicator is returned to the company after its useful life, communication between company and users is ongoing; underreporting is unlikely.

Dr. Anderson then summarized the evidence for mitigation of adverse events from controlled clinical trials, including the U.S. pivotal study. In more than 3,600 treatments since November 2002 performed in accordance with the proposed instructions for use and incorporating preceptorship, no device-related adverse events have been reported.

Marc Finch, senior executive vice president, Microsulis, described the physician training used in conducting the clinical trial. The training includes printed materials and preceptorship, which involves use of a foam uterus simulation unit as well as observation and mentoring of initial cases. The current instructions for use are similar to the document used in the clinical trial; they clearly define the role of ultrasound screening and call attention to the need for hysteroscopy. The patient assessment form is important because it documents completion of the ultrasound ~~and~~ measurements. The sponsor is proposing preceptorship for all U.S. users.

Mr. Finch concluded by emphasizing that when used in patients evaluated, screened, and treated in accordance with the proposed instructions for use, the MEA device is safe and effective for its intended use.

FDA PRESENTATION

Veronica Price, Lead FDA Reviewer, listed the members of the review team and summarized the history of the PMA review. The agency used a modular approach to the review. Only Module 1 (general information, device design, and description) is closed and accepted; review of other modules is ongoing. A major deficiency letter was sent to the sponsor in December 2002; FDA received a major amendment in March 2003.

Ms. Price briefly reviewed the MEA System's key performance and design attributes. She noted that after 30 uses, a chip inhibits use of the applicator; the applicatorshaft is then returned to Microsulis. Ms. Price also reviewed key safety specifications of the device.

Julia A. Corrado, M.D., summarized the FDA clinical review. The proposed indication is essentially the same indication as for recently approved global endometrial ablation devices (GEA). The device is in commercial use in Canada, Australia, and the United Kingdom. Although the pivotal trial was designed to be similar to other trials of global endometrial ablation devices, it had some exceptional characteristics: All women received pretreatment ultrasound to locate the thinnest portion of the uterine wall and measure thickness, and they also received CO₂ hysteroscopy after cervical dilation but prior to MEA. Uterine length up to 14 cm was allowed, longer than in other trials. In the U.S. trial, ultrasound was done prior to GnRH (Lupron) administration. In addition, the temperature rise gate (TRG) a software modification was introduced midway during pivotal trial; it detects atypical temperature rise during the first 5 seconds of treatment.

The hypothesis was that there would be a statistical difference of less than 15 percent in patient success rates between MEA and REA groups. Dr. Corrado reviewed the primary and

secondary endpoints. No statistically significant differences in success rates were found in the two groups. However, efficacy dropped for women with fibroids in both arms of the study.

The clinical trial met the primary success criterion, and no unanticipated serious adverse events occurred.

~~Bowel injury following perforation has occurred with other devices. However, T~~the FDA analysis of adverse events from non-U.S. commercial use found a total of 27 serious adverse events. At least 11 of these adverse events involved bowel injury resulting from MEA treatment in the presence of a uterine perforation. FDA has seen similar adverse event reports for other devices following uterine perforation.

There was no uterine perforation in 14 of ~~those the~~ 27 cases. In 11 of these 14 cases, the patient requiredeases, no evidence demonstrated that the uterus was perforated bowel resection. FDA felt that this was unusual. , yet 11 subjects required bowel resection. These injuries appeared to have been caused by transmural thermal injury to the uterine wall and thermal injury to overlying bowel in the absence of uterine perforation.

Dr. Corrado reviewed the etiology of uterine perforation injuries and the sponsor's plan for detecting uterine perforation. She also reviewed the sponsor's plan to reduce the risk of transmural thermal injuries. She noted that mandatory ultrasound is a key part of the mitigation plan. The primary hypothesis is that transmural thermal injuries occurred in patients with evidence of wall thinning. The sponsor is proposing a minimum wall thickness of 10 mm in women who are potential candidates for MEA treatment.

FDA reviewed issues related to safe minimum wall thickness and focused on three considerations. First, thermal damage is related to the temperature at which cell damage occurs and to tissue perfusion. Second, no serious adverse events were reported in the U.S. clinical

study. Third is the ultrasound procedure itself—how should such an important ultrasound be performed? Considerations for performance of ultrasound prior to MEA include the need for standardization of the procedure, inter- and intraobserver variability, and qualifications of the examiner.

Isaac A. Chang, Ph.D., Division of Physical Sciences, Office of Science and Technology, discussed efforts to model the thermal penetration of device. The goals of computational modeling are to describe the worst-case scenario and develop a scientific basis for determining minimum wall thickness. He described the methodology underlying the modeling process. The ~~validated computer~~ model was validated by testing conducted in used polyacrylamide gel and excised liver tissues; perfusion rate is an uncertain parameter. The model suggests a thermal penetration depth~~minimum wall thickness~~ of 7.5 to 11 mm.

Panel members asked Dr. Chang for clarification on different details of the model. He answered their questions and noted that with regard to the nature of the tissue, the model assumes homogenous tissue. Fibroids ~~and so forth~~ can potentially change the thermal distribution pattern, but that is hard to model. Microwave effects are related to density, perfusion, and other tissue properties. When tissue is coagulated, as through microwave, electrical conductivity tends to increase, causing penetration depth to increase. The energy is likely to penetrate more deeply as coagulation occurs.

OPEN COMMITTEE DISCUSSION

Panel members asked the sponsor a variety of questions related to what would happen if the operator's motion of the probe is interrupted, whether the endometrium is included in the measurement of uterine thickness, how bowel damage could occur without associated uterine damage, what the company does when it receives an applicator after 30 uses, whether the

company analyzed the data to see at what point in the applicator's 30 uses the adverse events occurred, how often the temperature warning sounded during the trial, why frank curettage was removed from the scheme, why the MEA patients had greater vomiting and cramping, and what the level of provider training and experience was. They also asked the sponsor to provide a sample of the foam uterus used in training.

Jay Cooper, M.D., FACOG, Microsulis (via videoconference) and other sponsor representatives answered the panel's questions. If the operator discontinued or interrupted operation and the applicator remained in the same place, the reflected temperature would rise to 85°C and an audible alarm would sound. If the applicator did not move after that, the temperature would rise to 90°C, then shut off. In only 6 percent of cases did that happen; only 2.5 percent of cases rose above 85°C.

The sponsor is aware of the issues regarding incorporation of nonhomogeneous tissues into the model. Twenty percent of the patients had fibroids, and 25 percent had had prior uterine surgery; those patients had wall thickness ranging from 9 to 26 mm. Only 1 patient had treatment that lasted longer than 8 min. Concern over the effects of prolonged treatment is not in line with the clinical reality.

None of the sponsor's calculations include endometrial buffer. The effects of Lupron on the endometrium can be dramatic, but it is rare to see it endometrial thinning by ~~more~~-less than 1 or 2 mm. The sponsor did not consider the endometrium when considering a 10 mm recommendation, but it adds a margin of safety.

The only possible answer as to why damage occurs to bowel in the absence of perforation is by having the applicator and the source of microwave generation within 6 mm of bowel, which could only occur with a thin uterine wall. In the clinical trial, 3 patients had myometrial thickness

of less than 8 mm—about 1 percent. Extrapolating to the number of patients treated worldwide thus far, one could expect about 150 patients to have myometrium thickness of less than 8 mm. Establishment of minimal wall thickness is critical.

Nausea, vomiting, and cramping were the only adverse events that achieved statistical significance. Many of the cases were at a single site that does not routinely use nonsteroidal anti-inflammatory drugs (NSAIDs), so patients had increased cramping posttreatment. Some MEA patients who did not get NSAIDs were prescribed Demerol, which contributes to nausea and vomiting. Of the five patients with endometritis, three were from same site; one had prophylactic antibiotics, and one had a positive culture for strep. Everything resolved with antibiotics.

Finally, all applicators, regardless of when they are returned (after 30 uses or after adverse events), are tested for the same parameters as when they come off the production line. All were operating normally when returned. Pre-treatment cCurettage was contraindicated in accordance with a recommendation from the clinical trial advisory panel. Concerning training and preceptorship, it was not until mid-2001 that the sponsor began mandating preceptors, so the level of expertise is difficult to assess.

PANEL QUESTIONS

1. Does the panel agree that the results [of the pivotal study] demonstrate the clinical effectiveness of the MEA system?

The panel concurred that clinical effectiveness had been demonstrated. Dr. Larntz pointed out that the study is a noninferiority study, ~~;~~ however and, p values are not appropriate for tests of noninferiority. The sponsor needs to provide confidence intervals in the labeling. The study easily met the requirement for success. Confidence intervals also need to be reported for the adverse events; there were significant differences in long-term vomiting and cramping in the MEA and REA groups.

2. Does the panel agree that **among the 27 serious adverse events that occurred in (non-U.S.) commercial use**, the cases without evidence of uterine perforation were primarily the result of relative thinning of the uterine wall, inappropriate pre-treatment, and failure to follow the instructions for use?

The panel ~~had some concern that cases without evidence of perforation were due to thermal penetration~~ expressed uncertainty as to the causes of the events. They also discussed the ~~possibility that~~ the nausea and vomiting in the MEA group may be associated with ~~undetected~~ transient bowel or peritoneal injury. Panel members were concerned that the origin of the bowel injury is not understood or is due to ~~unidentified~~ unrecognized thinning of the uterus.

3. Does the panel believe that the measures taken by the sponsor to improve the training and labeling will sufficiently reduce or eliminate the risks associated with the MEA system? In particular, will these changes minimize the risk of transmural thermal injury?

The panel concurred that the measures will minimize the risk of transmural injury. The panel suggested contraindicating both mechanical and suction preparation and ensuring that physicians, not company representatives, serve as preceptors. Strict adherence to the protocol is critical to safe treatment.

4. ~~W~~**The sponsor is currently proposing a minimum wall thickness of 10 mm as measured by ultrasound.** ~~W~~**hat does the panel consider to be a reasonable minimal uterine wall thickness to prevent transmural thermal injury?**

The panel agreed that 10 mm is a reasonable minimal uterine wall thickness; ~~however, current ultrasound devices can have 2 to 3 mm of uncertainty in their measurements.~~

5. Does the panel agree with the instructions provided in the labeling for an ultrasound evaluation in 3-views?

The panel concurred that the instructions are adequate. Some panel members expressed concern that the ultrasound measurements were taken prior to administration of Lupron and that the hormone could ~~shrink the~~ reduce the wall thickness. ~~Most panel members thought any shrinkage~~

~~would be insignificant~~ The panel agreed that as long as 10 mm referred only to myometrium, and excluded endometrium, then the ultrasound could be performed prior to GnRH administration.

6. Are the [safety measures] sufficient for identifying a uterine perforation prior to treatment?

The panel members agreed that the safety measures are sufficient.

7. Does the panel have any comments on the labeling provided by the sponsor?

Panel members suggested that the instructions should clarify what to do if the physician discovers an anomaly—e.g., a septate or bicornuate uterus—and ~~where to take measurements of the uterine wall~~ that measurements of uterine wall thickness should include the cornua. Panel members suggested that the procedure should be contraindicated for patients with the Essure and other metal devices because of the effects of microwave energy on metal. Confidence intervals should be added to the data in the labeling. The panel questioned why treatment should be allowed for uteri up to 14 cm, given that the pivotal clinical trial only included patients with sounds of up to 12 cm. Also, the labeling should emphasize that the operator must sterilize the applicator before use.

8. Does the panel have any comments or additional recommendations regarding the appropriate level of training and/or qualifications necessary for physicians who use the MEA system?

The panel concurred that physicians must be ~~experienced with pelvic ultrasounds and be able to~~ conduct skilled at performing diagnostic hysteroscopy.

9. If the panel votes to recommend approval of the MEA system, is there a need for additional postapproval studies or other postmarket measures? If so, what is the purpose of such studies and what are the key elements of the study design?

The panel suggested continued evaluation of injuries to the bowel, including pathology and recommended that resected tissue undergo full pathological evaluation to document the extent and nature of the injury.

OPEN PUBLIC HEARING

Cindy Domecus, executive vice president, government affairs, Conceptus, the maker of the Essure device, stated that the device is not contraindicated for microwave. In Essure's labeling, it states that no data are available regarding endometrial ablation devices that operate at microwave frequency; use of microwave with metallic implants has been shown to cause injury and should therefore be avoided.

Mr. Pollard reminded the panel that the PMA is still under review. Many details, such as ~~the labeling and~~ the issue of minimal uterine thickness, specifics on how ultrasound should be performed to evaluate myometrial thickness, and the labeling, have not yet been decided ~~remain to be worked out~~.

A representative of the sponsor thanked the panel for its comments.

VOTE

Panel Executive Secretary Whang read the voting options. The panel voted unanimously to recommend approval of the device with the following conditions:

1. The sponsor should correct the statistical analysis for noninferiority and provide confidence intervals based on the true intent-to-treat population.
2. Only experienced physicians should be preceptors; no mechanical preparation of the uterus will be done in conjunction with the procedure; and operators should perform hysteroscopy on all patients after dilation to confirm that uterus is intact.
3. Myometrium thickness, as-which, ideally would be measured by transvaginal ultrasound, should be at least 10 mm; measurement should exclude the endometrium and include the cornua.

4. Operators must be ~~experienced~~ able to perform with diagnostic hysteroscopy.
5. The labeling must be changed in accordance with the above conditions.

When asked to explain the rationale for their votes, panel members stated that the sponsor has taken a responsible approach to ensuring safety. Members expressed concerns about possible bowel injuries, but felt that the company is diligent in working to ensure safety. The data for effectiveness are strong. Panel members suggested that as the device is put into practice, careful scrutiny is needed to determine whether there are continued adverse events, including nausea and vomiting. Less severe bowel injury may be occurring.

Mary Lou Mooney, R.A.C., Industry Representative, commended the manufacturer for improving the quality of life of premenopausal women. Tightening the training requirements and ensuring strict adherence to the instructions for use and indications should ensure safety.

ADJOURNMENT

Dr. O'Sullivan thanked the participants and adjourned the meeting at 4:00 p.m.

I certify that I attended this meeting of the
Obstetrics and Gynecology Devices
Advisory Panel Meeting on June 10, 2003,
and that these minutes accurately reflect
what transpired.

Joyce M. Whang, Ph.D.
Executive Secretary

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

Mary Jo O'Sullivan, M.D.
Chairperson

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