FOOD AND DRUG ADMINISTRATION

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OBSTETRICS AND GYNECOLOGY DEVICES PANEL

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SEVENTY-FIRST MEETING

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OPEN SESSION

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Tuesday, March 28, 2006

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The Panel met at 9:00 a.m. in the Ballroom of the Gaithersburg Hilton, Gaithersburg, Maryland, Kenneth Noller, M.D., Chair, presiding.

PRESENT:

KENNETH NOLLER, M.D.	Chair
PAULA HILLARD, M.D.	Voting Member
HUGH MILLER, M.D.	Voting Member
JONATHAN WEEKS, M.D.	Voting Member
MARCELLE I. CEDARS, M.D.	Voting Member
HOWARD SHARP, M.D.	Voting Member
JOSEPH SANFILIPPO, M.D.	Voting Member
DIANA ROMERO, Ph.D.	Consumer Representative
ELISABETH GEORGE	Industry Representative
GERALD SHIRK, M.D.	Consultant
SCOTT EMERSON, M.D., Ph.D.	Consultant
NASSER CHEGINI, Ph.D.	Consultant
NANCY SHARTS-HOPKO, R.N., Ph.D.	Consultant
RUSSELL SNYDER, M.D.	Consultant
MICHAEL T. BAILEY, Ph.D.	Executive Secretary
NANCY C. BROGDON	Division Director

Call to Order

The Chairman called the open session to order at 9:02 a.m. and had the members introduce themselves. Dr. Bailey reviewed the remaining tentative Panel meeting dates for 2006. He read the conflict of interest statement into the record. No COI waivers have been issued for this meeting. Members were asked to recuse themselves if an issue arises in which they have a financial interest.

Introductory Remarks

Colin Pollard, Chief of the Obstetrics and Gynecology Devices Branch, started by announcing the FDA's Centennial year. There have been significant developments lately in condom labeling, the STAN fetal heart monitor, the OxiFirst fetal pulse oximeter, and the LUMA cervical imaging system. Last year, the Center issued a Notice of Proposed Rulemaking asking for more specific information on condom labeling about protection from STDs, highlighting that they work better against STDs like HIV/AIDS than those like herbes or HPV. The 90-day comment period ended last month.

In June, the Panel recommended approval of the STAN fetal heart monitor, and the PMA was approved in November. It is approved as an adjunct to conventional monitoring to determine whether intervention is warranted when there is increased risk of developing metabolic acidosis. It is intended to be used for patients with planned vaginal delivery, greater than 36 weeks completed gestation, singleton fetus, vertex presentation, and ruptured membranes. The Panel recommended post-approval studies, but the FDA did not make that a condition of approval. However, the device will be tracked through the MDR Adverse Event Reporting System and the MedSen Network.

The PMA for the OxiFirst fetal oxygen saturation monitoring system was approved in 2000, and two others were approved for manufacturers licensing the same technology. The PMAs required studies. The manufacturer completed the first study, and the NIH did a large study called the FOX trial, which failed to show an impact of the technology on Caesarian delivery rates for both the overall population as well as the indicated population of labors with a nonreassuring fetal heart rate. The manufacturer has voluntarily stopped marketing the monitor, although it will continue to provide technical support to customers still

using the monitor with remaining disposable centers at hand. The firm will also continue to fulfill other PMA requirements.

The LUMA Surgical Imaging System is indicated as an adjunct to colposcopy for the detection of cervical cancer precursors. Last May the Panel recommended that this PMA be disapproved, but the FDA approved the device. Analysis of the study results after the meeting led the Center to view the two endpoints as a ratio rather than independently. While LUMA results in four false positives for every true positive that colposcopy missed, that was considered acceptable due to the low risk associated with biopsies. Further analysis by MediSpectra showed that a high LUMA score has a direct relationship to the probability of a biopsy being positive. The decision was based on post hoc analyses not pre-specified in the study design and not available to the Panel when they made their decision.

The PMA requires that the labeling clearly and unequivocally, define use of the technology as a thorough colposcopy first with commitment to biopsy sites, followed by evaluation of the LUMA image and identification of any additional biopsy sites, without subtracting any committed to by colposcopy. MediSpectra has implemented new software that facilitates this device use sequence. The labeling also clearly indicates that use of the LUMA technology will inevitably lead to additional biopsies, and that it is unknown whether additional colposcopically-directed biopsies would yield comparable results. Training was implemented to underscore these aspects of the device use. One condition of approval is that the sponsor conduct a post-market study to answer some of the remaining questions about the technology.

FDA Presentation

Colin Pollard presented on symptomatic uterine fibroids. Symptomatic uterine fibroids lead to thousands of hysterectomies every year. A variety of technologies are emerging to treat them. The variety of size, location, and number of fibroids, along with the symptoms patients manifest makes the matter of determining what endpoints to use for a clinical trial tricky. Randomization is difficult because the patients must be offered something they would want done to them. Finally, some of the devices being made require a high degree of surgical skill. The Panel’s task was to look at symptomatic uterine fibroids, new treatment technologies, and clinical trial design.

In the past, the FDA has used many different endpoints: bleeding scores, quality of life instruments, contrast-enhanced MRI imaging, and whether or not the patient returned to surgery. In one ultrasound trial, firms used a nonrandomized control group with hysterectomies, though the Panel questioned the value of a nonrandomized arm.

The Panel is charged to consider the papers provided, listen to the speakers, and discuss what kind of studies are needed to answer the important questions, using the discussion questions as a framework. There is no application before the Panel, so there will be no vote.

Open Public Hearing

The Chairman started the open public hearing, reminding the speakers to disclose any financial relationships at the beginning of the statement.

Dr. Nadir Alikacem of InSightec North America presented on ExAblate 2000, an MR-guided focused ultrasound device. The device has already approved. It offers an outpatient procedure as an alternative to surgery for certain patients. The procedure offers a next-day return to normal life, management of symptom relief, and realtime visualization and control.

MR-guided focused ultrasound uses high intensity focused ultrasound to ablate tissue such as a fibroid, using heat, and MR imaging to monitor the treatment with three-dimensional anatomic information. The MR also visualizes the ultrasound beam, and MR. thermometry can be achieved during the treatment itself. When the treatment is finished, the MR can give a realtime outcome.

In clinical trials, a study endpoint must take into account management of patient symptoms as well as management of patient lifestyle. The study must also take into account the lifetime of the device as well as its continuous R&D innovation.

Dr. Fred Burbank of Vascular Control Systems presented on the Flotstat System, a device that allows obstetricians and gynecologists to identify and control the uterine arteries transvaginally, without surgery. The system has three parts, each of which has passed a 510(k): a transceiver ultrasound box that does not generate energy or heat; a guiding tenaculum, and a vascular clamp. The tenaculum attaches to the cervix to guide the vascular clamp to the area of the uterine arteries in the three o'clock and nine

o'clock position. When advanced along the guiding tenaculum, the clamp can fold the urinary arteries posterially and superially and, when closed, can occlude the urinary arteries for a brief period of time.

Women with fibroids tend to have menorrhagia as well as bulk symptoms measured by quality of life instruments or uterine imaging. A woman seeking Flotstat therapy seeks to continue to have menstrual cycles, have reduced menstrual blood flow, and have improvement in quality of life related to the treatment. Therefore, the metrics used are the Ruta scale and quality of life metrics

The pilot shows that of women treated with the system, 100 percent returned to continued menstrual cycles. Of those who had a menstrual cycle, 81 percent had a 50 percent or greater reduction in their menorrhagia score on the Ruta scale. Of that 81 percent, 80 percent experienced improvement in quality of life on the SF-12 questionnaire.

John Greenbaum, an independent consultant for Biocompatibles, UK Ltd. And their distributor, Terumo Interventional Systems, spoke on the embolization agents GelSpheres, BeadBlock, LC Bead, and Precision Beads. These microspheres are 100 to 1000 microns in size and, in uterine fibroid embolization, are put into the uterine artery. There is thrombus formation, and the fibroid infarcts or shrinks down.

GelSpheres and BeadBlock have been cleared for embolization of hypervascular tumors and arteriovenous malformations. They were originally cleared as Class III devices before FDA put out the special controls guidance on embolization devices that reclassified the devices as Class II special controls. The company is concerned because the guidance document states that the health risks of vascular embolization are the same as the risks of neurovascular embolization. As a result, the companies are trying to obtain a 510 (k) approval when they have already obtained a five percent clearance based solely on preclinical and laboratory data with no clinical study for much higher risk procedures in neurological embolization.

Dr. Phyllis J. Gee of the North Texas Uterine Fibroid Institute, who performs MR guided focused ultrasound and is a principle investigator for InSightec, presented on the device. It operates like a magnifying glass to focus the ultrasound only on the specific point to be destroyed or ablated. The MRI is used in planning and for imaging and temperature feedback during the treatment.

Patients want procedures that give good symptom relief, are minimally invasive, have a low incidence of adverse events, do not require follow-up, allow a rapid recovery, and are less disruptive to their way of life. Physicians want low risk, efficacy, prompt improvement of symptoms, real time feedback, minimal invasiveness, and for the procedure to not preclude other options in the future. The trials for ExAblate 2000 followed symptoms and quality of life.

Dr. Jessica Grossman is the CEO of Gynesonics, a company developing a minimally invasive device for the treatment of fibroid tumors, a single needle RF electrode probe that is inserted transvaginally, transcervically, or laparoscopically. Using ultrasound for imaging and guidance, the device would deliver radiofrequency (RF) energy to the target area to ablate or desiccate the tissue. A thermocouple at the tip of the electrode does realtime temperature monitoring.

There are predicate devices already cleared, such as VersaPoint, which was cleared by 510(k) and required no clinical trial data. Substantial equivalence can be demonstrated by bench testing, and because the mechanism of action is well-known and of extremely low risk to the patient, clinical trials should not be required for all technologies for treatment of fibroids. Least burdensome principles apply.

Dr. Sew-Wah Tay presented for American Medical Systems. AMS is in the early stages of exploring different approaches to fibroid treatment. The objective is to develop a tool to aid gynecologists in treating fibroids via minimally invasive surgery and allow patients to retain their uteruses. The device will be used as a first line of treatment with hysterectomy as a backup if it doesn't work. They are looking into using cryomolysis.

In considering what the study should look like, they have considered what the endpoints should be. Because most fibroids are benign, the study endpoints should be symptom relief and quality of life improvement. The best option seems to be the Symptom Severity Score (SSS), which is a subscore for the UFS Quality of Life. AMS will consider an improvement of more than 10 points six months after treatment to be a success.

Developing a control population will be difficult. Hysterectomy is the most common treatment, but that is invasive and SSS will not apply to patients without a uterus. UAEs could be used, but they are not the standard of care and

they are not done by gynecologists. Sham surgery is not an option because it is unethical. The most feasible study will be a single arm study using the patient as her own control and using the UFS Quality of Life vehicle.

Dr. Bryan Cowan of the University of Mississippi is developing a clinical protocol for pivotal studies on the treatment of cryoblation in uterine fibroids. He is an investigator for Galile and Wyeth and is on the Speaker's Bureau for Wyeth. Cryoblation is in wide use and has been cleared by the FDA for multiple indications.

He is developing a research protocol to assess safety and efficacy of percutaneously laparoscopically assisted cryomyolysis (PLC) for treatment of symptomatic uterine fibroids. The protocol has two endpoints: efficacy and safety. The efficacy endpoint is Symptom Severity Subscale of the Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire, the SSF-UFS QoL published in 2002. The safety endpoint is treatment-related major operative and post-operative complications.

There will be two control groups. For efficacy, the patient is her own control because there is no other appropriate control group. For safety the study population will be compared to the laparoscopic supercervical hysterectomy population, since the patients report with the same symptoms and both procedures use laparoscopy. This control cannot be randomized.

The inclusion demographics of this study would be premenopausal women who have completed childbearing. Three types of fibroids would be treated: intramural, sub-serosal, and sub-mucosal type II. The patient would have to be symptomatic but have a QoL score greater than 40 points.

For a patient, success would be defined as a ten-point improvement of SSS-UFS-QOL at six months. The study will be a success if 50 percent of the patients demonstrate success.

Dr. Anthony C. Venbrux of George Washington University had no conflicts of interest to report. Often, women who undergo myomectomy for symptomatic fibroids require another procedure, usually a hysterectomy. Transcatheter embolotherapy has long been used to reduce pelvic arterial bleeding. The procedure uses existing and inexpensive materials such as Gelfoam or embolization coils. Embolizing a tumor, leaving it in the body, and having it involuted reduces blood loss. Pain is scaled by having the patient mark the degree of pain on a scale.

The procedure is not for every woman with fibroids. About 1 in 50,000 women have a contrast reaction. Non-target embolization is a danger, and there is a 4 percent risk of ovarian failure and premature menopause in 35-year-old women. In 45-year-old women, the risk jumps to 14 percent. As the doctor began to describe how to perform the technique, he ran out of time.

Dr. Seth Stabinsky is a shareholder in Albion, Incorporated, and Scineras Medical, which has a license to perform cryotherapy in women's health but is not currently working on anything in the fibroid area. He has no conflicts of interest. He worked on the VersaPoint at Stanford. When RF is used under direct visualization in a hysteroscopic manner, it is safe. It can be directed visually. It does not have the same kind of visualization as cryo, so one protocol may not fit all devices. He also added that it makes sense to follow patients out to six months after an ablation treatment, but it is also important to watch for regrowth in fibroids further down the line.

Mr. Pollard responded to the open session, thanking the speakers for their input. To the comments about embolic products and the related guidance document, he clarified that the document accompanied a reclassification of the general category of certain kinds of embolic products from Class 3 to Class 2, and uterine artery embolization was included. That was done to recognize that the FDA had cleared two 510(k)s for embolic particles, but the policy on treating fibroids and the clinical trials had not changed. The FDA may later develop a guidance document specifically for UAE. No clinical data was needed for neurologic and other peripheral vascular applications because the risk profile is different.

Panel Discussion

The Chairman opened the Panel Discussion.

Question 1: The primary symptom of problematic fibroids is bleeding. Other symptoms include pain, urinary problems, infertility, bulk symptoms, etc. Please discuss what you believe to be the most appropriate parameter to use in the evaluation of device effectiveness (e.g., bleeding score self-report, measurement of fibroid size (or perfusion) after surgery, quality-of-life instruments, other).

The Chairman said that the Panel recognizes that this is a difficult area. Most women with fibroids do not have

symptoms. Those who have symptoms don't have the same symptoms. He disagreed with the statement that the primary symptom of problematic fibroids is bleeding, since there are so many different symptoms.

Dr. Shirk compared the matter to establishing the criteria for endometrial ablation. The technique was intended to treat abnormal uterine bleeding in women. Those women were not going to reproduce. Bleeding was the only issue, so it was graded with a PBLAC score, a scoring system that uses specialized tampons and pads. The patient had to have 150 ml of blood loss to qualify the study, and an endpoint of 75 ml of blood loss was considered a success. With fibroids, there are more issues. There are other symptoms. Some patients have other uterine pathology. Many of the patients are approaching menopause. Fibroids can be cured with a hysterectomy. Patients looking for other treatments are trying to avoid hysterectomies, so the issue is one of quality of life rather than achieving an objective goal. If an objective goal is needed, bleeding scores or fibroid size reduction could be used.

Dr. Sanfilippo suggested looking at the literature. A study published in Fertility and Sterlility comparing uterine artery embolization and laparoscopic myomectomy used quality of life as the endpoint. Dr. Snyder said that the important endpoint is how many patients eventually need a hysterectomy. Dr. Sharp pointed out that there are objective and subjective outcomes. The problem with subjective outcomes is that patients in studies often want to please the investigator. It would be worthwhile to have objective data, such as how the devices affect the tumor.

Dr. Cedars said that the primary indication is the symptoms, and that has to be the endpoint, since there is no medical reason to remove a fibroid. The Chairman pointed out that the placebo effect would affect quality of life scores. Dr. Cedars agreed but added that the placebo effect wears off and won't affect results later on.

Dr. Emerson said that if fibroids were the cause of the symptoms, then there should be an objective measure of fibroids. He also added that repeat treatments are not bad if the treatment is minimally invasive and didn't cause adverse events. Addressing placebo affect, he said there are three things called by that name: one is the true placebo effect, second is the natural progression of the disease having nothing to do with the treatment, the third is the fact that a woman who has symptoms that get better and worse is likely to go to the doctor when the symptoms are at their worst. This is called regression to the mean, and it is part

of why a study cannot use a patient as her own control because what you are actually measuring is change in the patient. Perhaps different symptoms would require different trials.

Dr. Chegini said that patients being treated for infertility have to be treated differently, since hysterectomy is not an option. Because African Americans are having more symptomatic fibroids than Caucasians, the studies populations should be representative. Another issue is the necrotic cells left in a patient can cause problems, and the studies should look at that. Dr. Shirk agreed that the safety issue was a concern; with uterine embolization, fibroids can slough out or get infected. This is important when discussing necrosing technologies. There is no data on these technologies as far as reproduction and incidence of uterine rupture. If women are using the technologies to maintain reproductive status, this will be important to know. Dr. Sanfilippo said that the inclusion criteria should include the question of whether or not the patient is interested in future fertility and treat the women as two separate populations, then the study should also monitor inadvertent conceptions in those who were not interested in fertility. Dr. Hillard said that background reproductive function and menstrual function associated with age is important to consider as well.

Dr. Sanfilippo said that there must also be criteria for rapid growth of mass that turns out to be malignant.

Ms. George commented that all of this stratification of data and analysis will delay getting products out. It might be better to restrict the usage indications, use very specific populations, and get the products out. Indications could be expanded later, as more is learned either through post-market studies or in separate submissions. Dr. Shirk emphasized that no matter what the FDA recommends, nothing prevents a physician from using devices off label.

Dr. Chengini emphasized the substantial biological difference, not only between normal tissue and tumors but also between African American and Caucasian. With the differences between patients, there have to be hard objective numbers. Otherwise, a statistical analysis has little meaning. He also pointed out that some of the smaller fibroids are problematic, but the technology cannot detect or treat those. This has to be considered in the criteria of a study.

The Chairman proposed using a bleeding tool for bleeding, a quality of life tool, and an objective measure of mass. That would give a mixture of objective and subjective

scores. Dr. Snyder agreed, but he pointed out that size doesn't correlate with change in symptoms, and reperfusion probably doesn't either. Dr. Sharts-Hopko said that compliance may be difficult with self-assessment bleeding tools unless the process is simplified. Dr. Romero argued that when multiple endpoints, some endpoints won't apply to some patients. Instead, he would prefer to see a study design that matches the endpoints to the presentation by the patient. He also said that many racial disparities are due to psychosocial issues and don't really apply to a scientific study. Dr. Snyder pointed out that as study groups are divided into subgroups, the groups will have to get larger to facilitate that.

Dr. Shirk asked, when setting a bleeding endpoint, whether it is to look for a percentage of reduction or to set a ceiling on the amount of bleeding.

Dr. Miller said that the invasiveness of the procedure is a quality of life issue and should be considered.

Dr. Emerson wanted the study to look at the safety concerns of leaving necrotic tissue in the body and the risk of embolizing the wrong blood vessels. He also raised the distinction between efficacy (removing fibroids) and effectiveness (treating symptoms).

Question 2: Based on your response to the previous question, please comment on any specific inclusion and/or exclusion criteria that should be made part of the eligibility criteria for subject enrollment, including minimum or appropriate baseline scores, measurements or symptom level.

The Chairman said that the women should be between 18 and 40. Dr. Cedars said that patients who want future fertility and those who do not are separate groups that should be studied separately. However, there are more women who do not want to preserve fertility, so the industry may not make a device for the smaller group. Also, in many perimenopausal women the fibroids are unrelated to the bleeding, so they should be screened out. Dr. Hillard agreed that failure of other therapies, including hormonal therapy, should be a criterion. Dr. Emerson asked whether that exclusion would be to eliminate people for whom the therapy would not work or for whom it would not be safe. Safety is the larger issue, since irrelevant data points can be dealt with statistically. Dr. Snyder said that it is important to treat what is causing the problem. Otherwise, there is the safety issue of overlooking another reason for the bleeding, such as endometrial or cervical cancer.

Dr. Weeks said that if not seeking future fertility is an inclusion criterion, then hysterectomy can be used as a control. He suggested a subgroup of women who do want future childbearing and have symptoms, but not symptoms severe enough to seek a hysterectomy or myomectomy.

Dr. Romero said that if fibroids were not the cause of the symptoms, the patient should not be included in a study to prevent fibroids. Dr. Shirk pointed out that the location of the fibroid affects its symptoms. Submucosal fibroids are more likely to cause bleeding, but they are also more likely to slough off after an embolization.

Mr. Pollard commented that there was a lack of women desiring future fertility coming in the studies. He asked the Panel whether those women should be included and whether they should be tracked for pregnancy. Dr. Snyder said that unless future trials looked at pregnancy, there will be no way to counsel patients who conceive in the future. Dr. Cedars said that those who want to retain fertility and those who do not are two separate populations with different views of success. Perhaps a future study in patients who wanted to maintain fertility could use myomectomy as a control. Dr. Miller said that the size of the population and the risk of liability is going to be a disincentive to companies' including women who want to remain reproductively active. Dr. Weeks said that the way to look at future fertility is to look at patients who have had pregnancy losses due to fibroids. Dr. Shirk said that rupture is an issue in pregnancy, but the main question is whether or not a pregnancy can be achieved.

The Chairman opened the floor for input from the audience. Dr. Keith Isaacson, who was not a consultant in today's discussion, commented on objective measurements. Fibroid size is not an effective measurement because embolization data shows that fibroids can reduce in volume by 15 or 40 percent and still have the same effect on symptomology. In fact, smaller fibroids can cause more bleeding than larger ones. Because there is no hormonal treatment for fibroids, failure of hormonal therapy can't be a criterion.

Dr. Greenbaum of Biocompatibles said that patients go to the doctor because they want symptoms treated. The patient is not interested in the fibroids. The endpoints should reflect the symptoms for which the patient sought treatment. He urged that time be put into comprehensive bench and laboratory preclinical testing. UFS QoL is a validated fibroid-specific tool for bleeding. PBLAC use can harm compliance.

Dr. Seth Stabinsky said that no company would want to work with the pregnancy issue, even if it is important to know about pregnancy. NIH should address that issue and do studies on that.

Dr. Tay from AMS said that the UFS QoL is a composite fibroid symptom questionarre that covers most of the issues the Panel has discussed.

Dr. Alikacem from Insightec pointed out that there is a difference between fertility and making pregnancy safe. The Chairman moved to question 4, feeling that question 3 had been addressed in the previous discussion.

Question 4: Selection of an appropriate control arm for surgical procedures can be challenging. In the past, the Panel has criticized a non-randomized control group of hysterectomy patients. For some procedures, a sham control is not possible. Discuss other possible control options, e.g., myomectomy vs. no control (i.e., patient serving as her own control). What is the role of randomization?

Dr. Sharp said that uterine artery embolization would be a reasonable control. It could be randomized, but not blind. A hysterectomy is not a reasonable comparator to a minimally invasive technique. Dr. Cedars said that the problem with uterine artery embolization is that it has not been used in people who want to preserve fertility and is not the gold standard. Hysterectomies and myomectomies are; myomectomies should be the control. Dr. Shirk said that women looking into necrosing procedures do so to avoid surgery, so a surgical arm to the study would not be acceptable and uterine artery embolization is a better choice.

The Chairman raised the issue of having no control. Dr. Emerson said that this approach is being taken with cancer, and it is proving unsuccessful. Dr. Miller agreed, saying that uterine artery embolization is a reasonable control group. Dr. Snyder said the Panel would have to accept that there is no perfect study, and they would have to rely on symptomatology. There will ultimately have to be a randomized, controlled trial, as occurred with uterine endometrial ablation. Dr. Sharts-Hopko supported the randomization but felt that a second level of consent would be needed if hysterectomies are involved. Dr. Shirk pointed out that there never was a trial comparing endometrial ablation to hysterectomy. Dr. Sharp said that the importance of randomization is to mitigate the heterogeneity of fibroids.

The Chairman pointed out that the indication the sponsor is seeking determines the type of trial. Dr. Cedars said that if the trial is not really about answering a question, the patients would not want to be randomized. They will want the better treatment. Uterine artery embolization has never been compared to myomectomy, so there is no basis for making it a standard of comparison.

Dr. Weeks said that in patients not seeking to maintain fertility, hysterectomy is still the gold standard, so maybe the best way to track these women is to see how many, after any noninvasive technique, still end up having a hysterectomy.

Mr. Pollard asked the Panel, if bleeding were the indication being pursued, then what would be the control and the role of randomization? He wanted to know the Panel's consensus on whether or not there can be an outcome measure in a single arm study on bleeding. The Chairman said that single arm studies would be appropriate in some cases, but the results would have to be pretty strong. Dr. Emerson said that randomizing is good for quality of life, but control groups against the standard of care will be needed in some cases. Dr. Cedars reiterated the perimenopausal connection and the need to treat patients with hormones first. After that, there has to be randomization, and the duration of the study depends on the comparator and the endpoints. Dr. Shirk said that a double arm study makes it possible to get data on overall success as well as complications of the procedures. Dr. Snyder said that it is possible to have a randomized controlled trial on abnormal bleeding or menorrhagia. If the trial is not randomized and controlled, the criteria will have to be very stringent. Dr. Miller felt that in any trial the variability would have to be monitored because a disproportion of patients could easily throw the results off.

Because Question 5 had already been addressed in the discussion, the Chairman moved to the last question.

Question 6: FDA has typically asked manufacturers to provide premarket evidence of treatment success at the 6-month point after surgery, with the understanding that study subjects will be followed for a minimum of three years. Please discuss the appropriateness of this pre-market/post-market balance. Does it depend on the outcome measure itself?

The Chairman pointed out that no sponsor wants to wait three years after the last patient before seeking approval. However, it is important to know how many patients need hysterectomies within three years. The three years may be part of a post-approval study. Dr. Emerson said that many

studies last three years and have 1,000 patients with other diseases. Dr. Snyder said that safety and some efficacy can be studied quickly, but the real measure of efficacy is long term and is the question of whether another procedure is needed before menopause.

Ms. George pointed out that lengthy trials are preventing products from being approved in the US, while they are being approved more quickly in other countries. There is a risk to keeping products off the market.

The Chairman commented that procedural risks are over in two days, but the risk of another procedure is a long-term risk. Dr. Cedars said that six months of data is nearly inconsequential, but three years of data is onerous; she suggested a minimum of a year with a requirement for post-market follow-up. Dr. Shirk said that the long term follow-up and failure has not been established even for myomectomy. It may not be appropriate to hold these devices to a higher standard than the standard of care surgical procedures. Many of the newer technologies are coming out of small companies that cannot afford long-term studies. Dr. Miller agreed that no one would argue for mediocre clinical trials, but if the trials are too big to be done, the patients don't get the benefit of the devices. The point is to get the most benefit with the least risk.

Dr. Emerson pointed out that delaying a hysterectomy for two years may be all the patient wants in some cases. Dr. Snyder commented that different patients had different measures of success, but the literature shows that the incremental increase in failure after one year is very small.

Mr. Pollard clarified that the three-year period mentioned in the question is post-market. The six months was pre-market. The Panel consensus, though, was a one-year pre-market follow-up. These tumors grow slowly, and it would take that long to know if the tumors are regrowing. Ms. George asked about the different devices and how they would be treated in the process, whether these time periods would apply to all device submissions. Dr. Cedars said that the devices would be dealt with in terms of their safety and efficacy, but an indication of bleeding fibroids would require the same duration. The Chairman added that the trial will depend on the indications being sought.

Mr. Hillard said that NIH spearheaded a symposium last year on fibroids. They symposium looked at clinical trial design for drugs to control fibroid-related bleeding and addressed the issue of validating a more modern tampon or pad for PBLAC. The two endpoints were reduction in bleeding by

the PBLAC score and the need for surgery at some point. The drug study had a placebo group.

Dr. Shirk had questions about safety: whether interrupting the surface of the uterus, laparoscopically, thermally, or with lasers may lead to internal adhesions; whether necrotic tumors cause infection; and whether compressing the uterine arteries will result in ureteral injuries. There can be short-terms complications, but there may be long-term complications as well. Dr. Cedars said that most adverse events would manifest within three months. At a year, most adverse events would have occurred.

Dr. Snyder expressed concerns about the reproducibility of pictoral-based assessments of bleeding. Dr. Sharts-Hopko said that women are not going to weigh or save their pads. The best you can expect these days is a pad count and estimate of saturation. Dr. Cedars said it would be very difficult to get an objective idea of the amount of bleeding. Dr. Romero pointed out that objective and subjective measures are a matter of degree. Measurement of change in symptom by a patient as a quality of life measure is a symptom measure. If the patient believes that less bleeding is taking place, then the complaint has been addressed. Dr. Sharp suggested looking into literature on PBLAC, Ruta, and UFS scoring systems to see what is most appropriate.

Mr. Pollard said that FDA has a good track record with PBLAC scores. He also asked for more comment on question 5.

Question 5: For the various study design possibilities, please discuss the definition of study success, i.e., how good is good enough. Please specifically comment on what would be the minimally accepted percentage of treated patients who meet the individual patient success criteria discussed previously, to define the study as an overall success. In the case of a controlled study, comment on whether there is a minimum difference between the percentage of successful patients in each arm that would be needed for the study to be called a success.

Dr. Sharts-Hopko said that the patient defines success. There are many things to monitor, but if the patient feels cured, she will not seek further treatment. Dr. Shirk commented that the question can only be answered if there is a defined study and a statistical way to look at things. Dr. Emerson said that the answer to Question 5 is a matter of cost (in terms of risks and invasiveness) versus benefit (clinical endpoint).

Dr. Chegini commented that many of these devices are being used by specialists in other fields, and obstetricians

and gynecologists are going to have to bridge the disciplines to take care of the patients.

Dr. Carey Corrado commented that the studies will need to produce data that can be put on a label.

Adjourn

The Chairman thanked the Panel and the FDA for his time as chairman and adjourned the meeting at 2:18 p.m.

I certify that I attended this meeting of the Obstetrics and Gynecology Devices Panel on March 28, 2006, and that these minutes accurately reflect what transpired.

Michael Bailey, Ph.D.
Executive Secretary

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

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Kenneth Noller, M.D.
Panel Chair

Summary prepared by
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