SUMMARY MINUTES

OF THE

OBSTETRICS AND GYNECOLOGY DEVICES

ADVISORY PANEL MEETING

SIXTY-FOURTH MEETING

OPEN SESSION

May 21-22, 2001

Gaithersburg Holiday Inn
Gaithersburg, Maryland

Obstetrics and Gynecology Devices Panel
May 21-22, 2001

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OPEN SESSION—MAY 21, 2001

Panel Chair Jorge D. Blanco called the Open Session to order at 1:05 p.m., asking panel members to introduce themselves and state their areas of expertise. **Panel Executive Secretary Joyce Whang, Ph.D.**, noted that the July 2001 panel meeting had been cancelled and listed a tentative future panel meeting date of October 15-16, 2001. Dr. Whang read appointments to temporary voting status for Machelle Allen, M.D., Ralph B. D'Agostino, Ph.D., Gary S. Eglinton, M.D., Jay D. Iams, M.D., and Michael Neuman, M.D., Ph.D. Dr. Whang also read the conflict of interest statement. She noted that the FDA had considered declarations by Michael Neuman, M.D., Ph.D., about his interest in a firm at issue in matters unrelated to the day's agenda and by Gary S. Eglinton, M.D., about an imputed interest through his employers, and had allowed their full participation.

Introductory Remarks

Colin Pollard, Chief of the Obstetrics and Gynecology Devices Branch, reviewed Branch activities since January 2001. He stated that three PMAs had been approved: the Corometrics Fetal Monitor, BEI's HydroTherm Ablator, and CyroGen's HerOption cryosurgical ablation device, of which only the last had been brought to panel. The Agency has also reclassified home uterine monitoring devices from Class III to Class II with special controls, has issued a guidance document, and is looking at a device registry.

MALLINCKRODT OXIFIRST FETAL OXYGEN SATURATION MONITORING SYSTEM MODEL N-400 (P990053/S1)

Mr. Pollard introduced the first item on the panel's agenda, consideration of a supplement to a premarket approval application (PMA) for Mallinckrodt's OxiFirst Fetal

Oxygen Saturation Monitoring System (P990053/S1). He reviewed the history of the PMA, noting FDA concerns during its initial review about investigator bias, device accuracy and safety, and the clinical significance of its results. At the January 2000 meeting, the panel recommended device approval subject to changes in the indications and labeling, and to postapproval studies. Those proposed studies include a human factors study, a general use study, and information acquired through FDA outreach to other public health and professional groups such as the National Institutes of Health (NIH) and the American College of Obstetricians and Gynecologists (ACOG). The panel was asked to look at what sponsors are proposing as a revised postapproval study plan. The proposed alternative general use study would include a patient registry, a dystocia study, and a three-arm randomized controlled trial of 10,000 patients, including a sham control. With thanks to panel member Jay D. Iams, M.D., for his help, Mr. Pollard then read the FDA questions for panel discussion.

Open Public Hearing

George Macones, Ph.D., University of Pennsylvania, spoke on behalf of the **American College of Obstetricians and Gynecologists (ACOG).** He stated that ACOG is following results on the fetal pulse oximeter with excitement, but is not ready to embrace or endorse the device for routine use. Before any such endorsement, ACOG would need to see more well-designed clinical studies to look at the reason for the puzzling study results on dystocia-related increase in cesarean sections and on whether the device has a significant rate of false negative findings.

Barry Schifrin, M.D. of Glendale, California, discussed pitfalls in fetal heart rate monitoring. He stated that part of the problem in discussion of fetal monitoring lay in the

presupposition that monitoring can be used to analyze the need for acute rescue. The need for rescue, he said, is driven by analysis of overall patterns rather than a single value. He analyzed a study of fetal heart rate tracings, suggesting what could and could not be extrapolated from fetal monitoring and stating that what is most dangerous and must be prevented is a series of variable decelerations in heart rates. Dr. Shifrin was also concerned that the implication of the monitor's goal is the need to decrease the C-section rate rather than to improve fetal outcome, stating that the goal of fetal monitoring should be to decrease perinatal mortality, not just to decrease the C-section rate. Dr. Shifrin warned that an absolute focus on decreasing the C-section rate would mean an increase in the length of labor, in duration of second stage labor, in birth weight, and in the need for skilled medical care during labor.

Presentation by Mallinckrodt of PMA Supplement P990053/S1

Simon Thomas, Nellcor Business Unit of Tyco Healthcare's Respirator Division, presented the conclusions of the pivotal randomized controlled trial on which the PMA was initially approved. He noted particularly findings that addition of fetal oxygen saturation monitoring improves accuracy of fetal assessment and reduces cesareans performed for fetal distress but increases cesareans for dystocia. After listing four possible explanations for the puzzling dystocia findings, he listed five unanswered questions remaining from the pivotal trial that led sponsors to conclude additional studies were needed and six issues the FDA wanted sponsors to address in the three proposed postapproval studies.

Mr. Thomas stated that sponsors intended to use data from a general use study, a dystocia study, and an NIH study to answer the FDA's six issues. He said that the general use study is more than a registry, and he explained variables, definitions, enrollment criteria,

management protocols, inclusion and exclusion criteria, training, study size, duration, and analysis plan for the study.

Richard Porreco, M.D., principal investigator, discussed the proposed dystocia study. As background, he summarized findings of the pivotal randomized controlled trial on dystocia and gave potential explanations for the increase in cesareans for dystocia. He presented the conclusions of the trial investigators that inclusion criteria selected patients who were at increased risk for dystocia and that improved fetal assessment with the fetal oxygen monitoring device allows safe continuation of labor that might otherwise be prematurely interrupted by a cesarean for nonreassuring fetal heart rate syndrome.

Dr. Porreco synopsized the proposed nonrandomized prospective cohort observational study at five sites to evaluate the incidence and management of dystocia in 500 patients with nonreassuring fetal heart rate patterns by fetal heart rate and oxygen saturation monitoring. He listed variables of interest, purpose, primary objective, secondary objectives, design, inclusion and exclusion criteria, definitions, variables, independent review, and analysis plan for the study.

Questions from the panel concerned use of concurrent versus historical controls and debate over whether the 30 % oxygen saturation cut-off point had been sufficiently validated. Concerns were also noted over a possible broadening of the conditions for use and whether use of this device itself will increase the rate of dystocia.

Presentation by NIH

Cathy Spong, M.D., Chief of the Pregnancy and Perinatology Branch of the National Institutes of Health, presented information on the NICHD Maternal Fetal Medicine Units (MFMU) Network's randomized trial of fetal oximetry (the FOX trial), which plans to

measure the impact of fetal oximetry as an adjunct to conventional electronic FHR monitoring on the overall cesarean delivery rate. Dr. Spong explained the three-arm design and randomization procedures, inclusion and exclusion criteria, intrapartum management plans, primary and secondary outcomes, feasibility, sample size and data management, and oversight. She discussed whether the FOX trial will provide useful data on the currently approved indication, noting that of the 10,000 women studied, at least 2000 will have abnormal fetal heart rate tracings. She added that the masked arm of more than 3000 women (with electronic fetal monitoring and blinded oxygen saturation monitoring) will give significant data on the natural history of fetal oxygen saturation values and information on the prognostic significance of the 30% cutoff. Dr. Spong stated that the labor management protocol in the FOX trial will allow for meaningful interpretation with respect to the management protocol in the device labeling in that physicians will be instructed to use the device according to labeling and a computer archive will allow for measurement of compliance.

Panel questions to Dr. Spong involved the timing of the study and whether safety data would be available in time to help supplement PMA data.

Panel Discussion

Study A—NIH Study

1. Will the proposed NIH study provide useful data, per the panel's earlier recommendation, on the currently approved indication? If not, are there patient subsets that can be analyzed?

The sense of the panel was that the NIH study will not provide results within a timeframe to address the current indication, nor will it address the concerns expressed by the panel at

conditional approval. It was noted that one useful aspect in the NIH study will be whether use of the device increases the dystocia rate.

2. Will the sham arm of the NIH study provide information toward further understanding of the validity of the 30% FSPO2 cutoff value?

Again, the panel thought the timing of the NIH study would not provide timely information on this topic. There was disagreement over whether the 30% cutoff had been sufficiently validated, but there was concern still that the cutoff has not been tied to clinical meaning. One member of the panel stated that it is a disservice to create instrumentation that makes physicians rely on a single number, although he thought that is what sponsors are doing, based on previously reached agreements and understandings with the FDA.

3. Will the labor management protocol employed in the NIH study allow for meaningful interpretation with respect to the management protocol in the approved labeling?

The panel agreed that the NIH study will provide such interpretation, but that it will take time.

Study B—General Use Study

4. Considering the nature of the clinical centers in the NIH study and dystocia study, should the General Use Study target different types of hospital settings to optimize the overall information gained?

The panel recommended looking at hospitals with a high C-section rate and approaching centers formerly in the NIH network with recent data on C-sections. It was also recommended that sponsors collect data on those patients who refuse the device.

5. What would be the appropriate overall timeframe for the conduct of this study? Is there a need for longer-term tracking?

The panel thought that data should be collected for at least one year or longer.

6. Are there any other improvements that can be made in the clinical protocol?

The panel mentioned a concern about collecting the period of time a baby remains below the 30% cutoff and the correlation between how long that period is and the effect. A concern was also noted about whether broader use of the device under conditions not intended by the labeling would lead to inappropriate device use.

Study C—Dystocia Study

7. Will this study help elucidate the findings from the pivotal PMA study that showed more cesarean deliveries for dystocia in the OxiFirst arm?

The panel had nothing further to add. They encouraged the NIH study to follow patients as long as possible, although Dr. Spong stated that restricted funded would only allow follow-up through discharge. The panel added that the evidence to date did not provide the basis for a change in their recommendations.

Open Public Hearing

Dr. Shifrin stated that a preliminary study is underway to look at the relationship between heart rate and oxygen saturation below the 30% cutoff. He asked if device use might prove to be unnecessary if study results show that certain heart rate patterns are related to low oxygen saturation and to the need for intervention.

FDA Comments

Mr. Pollard observed that the FDA does not typically bring supplements to the panel and asked if the panel would like to see more of this kind of issue in the future. Panel members responded they would if the FDA and sponsors thought the day's discussion was of benefit to

them and that the discussion underscored the need for careful panel consideration of postapproval study requirements when approval is granted.

Sponsor Comments

Simon Thomas stated that sponsors had no knowledge of a current study on heart rates and had found no link between heart rate patterns and oxygen saturation in post-hoc analysis. He emphasized that the studies will be performed only on patients meeting the approved indication for use and that there had been no association shown between length of time the oxygen saturation remains below 30% and damage to the baby.

Panel Vote

It was clarified that there was no need to vote on this topic and that the panel had given a sufficient sense of its thinking on the proposed studies. **Panel Chair Dr. Blanco** thanked all presenters, panel members, and FDA staff for their participation.

NOVATRIX LABOR ASSISTER DEVICE: DISCUSSION OF REGULATORY PROCESS ISSUES

Introductory Remarks

Colin Pollard, Chief of the Obstetrics and Gynecology Devices Branch, explained that the next topic on the agenda, the Novatrix Labor Assister, was a device that had not developed as sponsors hoped. He and **Panel Chair Dr. Blanco** thanked the sponsors for offering to brief the panel on the regulatory issues involved.

Evelyn Lopez of Novatrix briefly explained the regulatory process and the protocol. She stated that the company's interaction with the FDA had gone well.

Howard L. Golub, M.D. of CareStat, defined the clinical problem the device was intended to address: to help shorten the second stage of labor for nulliparous women who have elected epidural analgesia. He described the device, which consisted of a belt designed to detect contracts and inflate, causing additional external pressure. Dr. Golub explained the device function, development and testing of the contraction detection algorithm, and the feasibility study. Possible safety issues, which included complications from increased intra-uterine or intra-abdominal pressure, were assessed during the pre-pivotal trial ascertainment of safety, and methods to address them were found.

Dr. Golub stated that the study was a prospective, multicenter, randomized clinical trial of active versus sham device with randomization at the onset of second stage labor. The study hypothesis was that nulliparous women with uncomplicated pregnancies who elect epidural analgesia who use the device during the second stage of labor would have a reduction in the proportion of deliveries that require an operative delivery, in comparison to the sham group. After explaining study definitions and study size of 451 patients per group, Dr. Golub explained clinical management techniques, operation of the device, randomization procedures, eligibility and exclusion criteria, and screening.

Results of the clinical trial showed no safety concerns, but overall results found no statistically significant difference between groups in operative delivery rate in all sites for all subjects. Trends were positive in three sites and negative in three sites, and positive in some subpopulations and negative in others. After examining various hypotheses, Dr. Golub stated that differences between the sites in management of the two groups may explain differences in effect size, but it is not possible to implement a study protocol that would control these

management decision. The subpopulations where the device group had a lower operative delivery rate than the sham group have some biologic plausibility, but effect size was only clinically meaningful among patients with high device use. Therefore, although there is a suggestion that the device may be effective in certain subpopulations (if tolerated), it would be impractical to mount a successful PMA study limited to these subpopulations.

Dr. Golub summarized that there is an important clinical problem for which the device was a plausible potential solution. The device functioned as designed and there were no substantial prestudy safety concerns that should have prevented the study. The protocol was sufficient to adequately evaluate the safety and effectiveness of the device. However, the results of the study indicated that while safe, the device was not effective in the prospectively defined patient population. In answer to a question from the panel, sponsors added that there were follow-up studies done on patient satisfaction and device placement.

Dr. Blanco thanked the presenters and commended the company for a well-designed study.

Mr. Pollard noted that the 1997 FDA Modernization Act called for an early collaborative mechanism between the Agency and industry, which this company had used to mutual advantage. He noted that more sponsors will continue to do so, and that panel members may have additional "homework" assignments evaluating such products.

Dr. Blanco thanked the panel and all presenters and adjourned the Open Session for the day at 4:55 p.m.

OPEN SESSION—MAY 22, 2001

Panel Chair Dr. Jorge Blanco called the Open Session to order at 10:08 a.m.

Executive Secretary Joyce Whang introduced three new panel members: Nancy C. Brogdon, Director of the Division of Reproductive, Abdominal, and Radiological Devices, Rebecca Schroeder, M.D., of the Department of Anesthesia at Bethesda Naval Medical Center, and Mary Lou Mooney, of SenoRx, who is the panel's Industry Representative. She thanked Acting Consumer Representative Stanley Reynolds, who customarily serves as Consumer Representative to the Microbiology Devices Panel. After the remaining members of the panel had introduced themselves and stated their areas of expertise, Dr. Whang reminded the panel of the tentative upcoming panel session on October 15-16, 2001, and read the conflict of interest statement. Waivers had been granted to Nancy C. Sharts-Hopko, Ph.D., Barbara Levy, M.D., and Michael Diamond, M.D., for their interests in firms at issue that could potentially be affected by the panel's deliberations. Matters concerning Ralph B. D'Agostino, Ph.D., Anne C. Roberts, M.D., Subir Roy, M.D., Nancy Sharts-Hopko, Ph.D., had been considered and deemed unrelated, as had past interests of Barbara Levy, M.D., and Anne C. Roberts, M.D. The full participation of all these members was permitted.

Introductory Remarks

Colin Pollard, Chief of the Obstetrics and Gynecology Devices Branch, introduced the first topic, a discussion of room air and gas emboli during hysteroscopy. He stated that after reports of eight episodes involving emboli during hysteroscopy, Ethicon had voluntarily withdrawn its Versapoint device last fall and had returned it to the market in late January only after making changes to the labeling. The panel charge was to discuss this issue to help FDA focus on important aspects of the problem. Mr. Pollard listed several caveats: that the

problem involved issues of terminology, that the focus of the discussion was on operative rather than diagnostic hysteroscopy, that multiple device systems were involved, and that FDA's Mandatory Device Reporting System has limitations that must be understood.

Presentation by Ethicon

Richard Isenberg, M.D., Director of Medical Affairs at Ethicon, described the sequence of events, noting that Ethicon was the sole distributor for the Gynecare Versapoint Bipolar Electrosurgery System, which had been on the market since 1996. The device is a hysteroscopic surgical technology that operates in normal saline distention medium and enables diagnosis and treatment of benign intrauterine pathology. It was voluntarily withdrawn in September 2000 after Gynecare received seven reports of suspected air/gas embolism during operative hysteroscopy using the Versapoint device. No patients died or suffered permanent sequelae.

Dr. Isenberg listed the actions Gynecare took after withdrawal to investigate, including a meeting of international scientists and advisors to evaluate the cases. This panel concluded that four cases were most likely caused by air embolization and three may have resulted from embolization of electrosurgically created gases. The panel of experts agreed that the true incidence of embolism is unknown, that it is inappropriate to conclude that the incidence of gas embolism is higher with the Versapoint than with any other hysteroscopic electrosurgical device, and that monopolar and bipolar devices likely have similar risks of embolism. Various risk factors associated with air embolism were listed, and the international panel recommended that the rate and composition of the gases generated during both monopolar and bipolar electrosurgery should be investigated and warnings incorporated into instructions for use.

Dr. Isenberg described a gas production study that demonstrated that rates of gas production by Versapoint electrodes are comparable to those of commonly employed monopolar devices and that there is no significant difference between the volume of gas produced by monopolar and bipolar technologies. As a result of theses investigations, no changes were made to the Versapoint device components, but warnings were added to the instructions for use before the device was returned to the market.

Malcolm G. Munro, M.D., of the UCLA School of Medicine, presented recommendations of the scientific panel regarding hysteroscopy. He explained the various types of hysteroscopic electrosurgical systems and listed the recommendations of the panel regarding patient selection, patient preparation, facility preparation, physician preparation (both surgeon and anesthesiologist), team preparation, and intraoperative considerations and precautions. Dr. Munro summarized the conclusions of the panel that hysteroscopy remains a safe procedure, that air embolism is rare, potentially catastrophic, and associated with any procedure involving the endometrial cavity, that gas embolism arising from the products of electrosurgical vaporization occurs with unknown frequency but seems rarely if ever associated with permanent sequelae, and that in vitro evidence suggests there are no clinically significant differences between unipolar and bipolar systems in the volume or composition of electrosurgically generated gases.

Presentation by FDA

Julia Corrado, M.D., Medical Officer in the Obstetrics and Gynecology Devices Branch, summarized the FDA staff response to the reported instances of room air and gas embolization. After hearing of the problem in early November 2000, the Agency

convened a working group that reviewed the company reports and the recommendations of their expert advisory panel. The FDA looked at the company's bench testing results and worked with the company to make more prominent the risks of room air emboli in the product labeling. Dr. Corrado recognized in particular panel member Rebecca A. Schroeder, M.D., and the role of anesthesiologists in addressing this issue, and she thanked Jay Houser of Karl Storz for offering to make a presentation and Isaac Chang of the FDA Office of Science and Technology for his cooperation.

Dr. Corrado discussed physiologic, iatrogenic, and equipment-related risk factors for pulmonary embolism. She listed signs of intraoperative pulmonary embolism and techniques for intraoperative management techniques. Dr. Corrado also reviewed the recommendations of the expert scientific panel regarding considerations and precautions prior to and after commencing operative hysteroscopy and the panel's conclusions. She discussed unipolar, bipolar, and hybrid systems and their methods of vaporization and distension media. After briefly reviewing the eight embolic events involving the Versapoint system, she listed labeling revisions the company had made.

Dr. Corrado stated that the FDA's role is to assess the risk of room air and gas embolism during unipolar and bipolar hysteroscopy, to respond commensurate with risk, and to decrease that risk through research, labeling, and clinician awareness, as well as to improve event reporting and analysis.

Sharon Dillard, M.S., of the FDA Office of Surveillance and Biometrics, gave an overview of FDA's Medical Device Reporting Program and reports associated with embolytic events during operative hysteroscopy. Mandatory adverse event reporting for manufacturers

involves cases of death, serious injuries, and malfunctions; user facilities must report deaths and serious injuries. There is also a voluntary reporting program available to healthcare professionals and consumers called "MedWatch." Ms. Dillard discussed strengths and limitations of the FDA's adverse event reporting system, emphasizing that it cannot be used to reliably determine incidence or prevalence of a given product problem or to differentiate between good or bad firms or products.

Ms. Dillard stated that an MDR search from 1996 to the present found no MDR reports associated with unipolar electrode use. One report was received in association with the hybrid device, since withdrawn. Eight reports were submitted in association with the Versapoint device from July 1999 to April 2001. She looked at questions raised by the reporting pattern and asked whether FDA needs to do more at this time, given the company's response. In conclusion, Ms. Dillard listed postmarket initiatives available to the FDA in addition to MDR.

OPEN PUBLIC HEARING

Jay Houser, of Karl Storz Endoscopy, discussed electrocautery procedures of the uterus, listing possible complications of operative hysteroscopy. He compared monopolar and bipolar energy resectoscopes and their method of operation. Mr. Houser reviewed the history of uterine surgery and the findings of the MGH pilot study in 1999. He concluded that there is a need to understand the difference in the reported incidence of gas/air embolism between monopolar and bipolar systems, including the incidence and significance of the formation of bubbles and the risk that might be associated with each under varying intrauterine pressures. He also asked whether the study should be extended to urology resectoscopes.

Andrew Brill, of the University of Illinois and a Gynecare consultant, observed that there are various factors affecting the development of air/gas emboli. He stated that bubble formation is an observational event but one that has no clinical sequelae. He thought this problem an amalgam of clinical issues and observational concerns.

Panel Discussion of FDA Questions

1. What are the underlying conditions that lead to the formation of room air and gas emboli during operative hysteroscopy with RF unipolar and/or bipolar electrosurgery?

--How common are room air and/or gas emboli during operative hysteroscopy using RF ablation techniques?

--Are the risks essentially the same, whether using bipolar or monopolar modes?

--Are there other studies that should be done to understand this risk?

The panel stated their impression that clinically significant events of this sort in operative hysteroscopy are very common, although impossible to quantify precisely. The sense of the panel was that there is always some amount of air embolism in hysteroscopy, and that there is no easy way to quantify gas embolism except to note when it is happening. Serious problems arise when the amount is significant enough for a pulmonary obstruction or atrial/ventricular defect to shunt the gas within the heart or an embolus to the brain. Fortunately these are rare, but almost all patients undergoing these procedures have some amount of gas going into their systems.

The panel could not answer whether the risks are essentially the same for unipolar and bipolar systems, saying that this will take ongoing MDR and MedWatch surveillance.

The panel advised that studies should be done using transesophageal echocardiograms, esophageal Doppler, and end tidal CO 2 and nitrogen monitoring. Patients with ASD/VSD and intracardiac shunts should be excluded from the studies. A marketing issue for companies should be to study how much gas is produced and goes into the patient. The focus of studies should be on keeping the patient safe, not design.

The panel recommended that the FDA should send out an alert to stress labeling improvements such as the risk of sucking air into the venous system in certain positions and the need to exercise care in the procedure, to educate all members of the operating team, and to report MDRs.

2. How can we improve our communication of risk, as well as recommended practices for reducing risk?

Again, the panel stressed the importance of issuing an FDA alert and the need for better education on reporting of adverse events.

3. How can we improve reporting of events such as air/gas emboli? Are there additional communication means that would facilitate MDR reporting?

The panel suggested that relevant professional societies should develop and post a website with a template for the information to be collected. They stressed that this is a human factors rather than a technical problem and urged training for residents and other medical professionals.

4. Are there additional measures that can be taken by FDA, NIH, and relevant professional societies that will add to the understanding of the risks of air and gas emboli during operative hysteroscopy?

The panel stated that basic research is up to NIH. Endoscopic laboratories should be used to educate residents and clinicians. Cases of intraoperative emboli should be published so others can learn from them. Also, information on the reporting process should be included as part of the alert for physicians.

Comments from the Public

There were no additional requests to address the panel.

Comments from the FDA

Mr. Pollard thanked the panel and suggested a possible homework assignment for some members on the reporting template. **Dr. Blanco** thanked all presenters and panel members.

UTERINE FIBROID EMBOLIZATION (UFE)

Panel Executive Secretary Joyce Whang introduced arriving panel member **Anne C. Roberts, M.D.**

Introductory Remarks

Colin Pollard, Chief, Obstetrics and Gynecology Devices Branch, gave an overview of the regulatory status of uterine fibroid embolization (UFE), which was reviewed at the October 4, 1999 panel meeting. At that meeting, the panel heard a presentation from the Society for Cardiovascular and Interventional Radiology (SCVIR) that updated the panel on their establishment of a patient registry, on standards for reporting data, and on UFE in the United States. As UFE has continued to grow in use, there have been more study proposals and more published literature. The polyvinyl alcohol particles used in UFE are a Class III device on track for reclassification to Class II. There are currently two FDA approved clinical trials

underway to study artificial agents for UFE, and an FDA guidance document is under development to look at what is needed in clinical studies and 510(k) submissions. The FDA discussion questions were designed to elicit panel feedback on the contents of that guidance.

Presentation by Society for Cardiovascular and Interventional Radiology

James Spies, M.D., of Georgetown University, gave an overview of uterine artery embolization (UAE) for leiomyomata, providing background, technique and slides from case histories. He presented findings from nine peer-reviewed published series that showed promising improvements in symptoms at follow-up ranging from five to 29 months. He also presented findings from a Georgetown study on 200 patients with a minimum follow-up of 12 months that showed an improvement in most symptoms. He summarized periprocedural complications and stated that results of a regression analysis found very few predictors of success.

Dr. Spies also gave SCVIR's response to the FDA's discussion questions. On inclusion and exclusion criteria, Dr. Spies looked at the difficult issues involved in studying women on hormone therapy and concluded that eliminating patients on hormones may prevent complete assessment of safety of UAE, in particular thrombotic complications. The FDA could ask for statistical comparison of users versus nonusers as a part of the submission. Simple hyperplasia patients should be excluded until treated and cured; those with endometrial polyps should be eliminated. On design, he suggested that patients should represent their own controls and each study should set an appropriate level of symptom change measured by validated means. Randomization is not feasible for most studies, so a parallel prospective cohort design of UAE versus other therapy could be used. On follow-up, he recommended six months for premarket

surveillance and two years for postmarket surveillance, which could be done through the FIBROID Registry. Retreatments should be considered failures. Labeling should focus on future fertility, and each patient should be assessed to determine which therapy is most likely to preserve the uterus in a functional state. UAE should not be used as an infertility treatment. He concluded that the comparative studies currently approved by the FDA are a major step forward in assessment of this therapy. Other efforts such as the FIBROID Registry and the adoption of uniform validated measures for assessing outcome are critical, as are physician education and training standards.

Malcolm Munro, M.D., University of North Carolina, discussed the FIBROID Registry and SCVIR standards activities. He presented UAE survey results and looked at growth of UAE in the United States. SCVIR activities on UAE have included activities on training standards, research initiatives, physician education, public information, and payment advocacy. Training standards for physicians, radiation safety, and reporting have been developed. Research initiatives include a RAND health multidisciplinary expert panel meeting and five research grants. The FIBROID registry is an ongoing effort, and Dr. Munro described its organization, goals, design, study procedures, inclusion criteria, data, follow-up, and outcomes. He concluded that the registry will provide long-term data on the use of UAE for treatment of fibroids with a 24-month follow-up for 450 patients and 12-month follow-up for 1350 patients. Dr. Munro stated that it is difficult to conduct randomized controlled trials comparing surgical to nonsurgical treatment, but the registry will provide answers to key questions.

Open Public Hearing

Vicky Hufnagel, of No More UAE spoke against uterine artery embolization, stating that the general destruction of normal uterine tissue as a result of UAE has not been given significant status in the evaluation of this procedure. She also stated that women are not being fully informed about the procedure, its risks, its results, and alternative treatments. Ms. Hufnagel expressed her concerns about radiation exposure to the female for a non-life threatening condition and the long-term affects of radiation on the ovaries, as well as toxic exposure from polyvinyl particles. She stated that there has been lack of adequate disclosure of complications and lack of follow-up care.

Nora Coffey, of HERS, stated that UAE is now performed in those lacking a risk to life and those lacking symptoms. The numbers of adverse events have increased, although the reports of adverse effects have not yet been published in journals. She asked the FDA to exercise its authority to require vendors and physicians to curb advertising and publicity that suggests the results are in and are positive, saying the sequelae will be learned on women's bodies. She asked for full written disclosure in clinical trials, with an opportunity to ask questions in writing and receive a written response. Adverse events should be reported in triplicate to the doctor, to the FDA, and to the patient. Women should also be told of all alternative treatments.

Susan Booker spoke as an individual and a health advocate, saying that this surgery will be known as barbaric in 20 years. She asked for complete follow-up on UAEs immediately.

Panel Discussion

1. *Are the inclusion and exclusion criteria appropriate? Should hormone therapy (hormonal contraception) be an exclusion criterion for UAE studies? If patients on hormone therapy are included, should their data be pooled with data from patients not on any hormones, or should they be a subset? Should simple endometrial hyperplasia be considered a premalignant condition?*

The panel discussed extensively whether hormonal contraception should be an exclusion criterion, with the majority urging that patients on hormonal contraception be included. These data should be not pooled but stratified and should be stratified not only for those on or off hormonal contraception, but also for those on standard birth control versus high- dose birth control for bleeding. The majority of the panel agreed that pregnancy should be an exclusion criterion until more information is available and that women should not be required to have regular menstrual cycles to be included. Patients on dialysis should not be excluded, although those with borderline renal function should be. Uncorrectable coagulopathy and allergy to IV contrast media should be exclusion criteria. Simple endometrial hyperplasia should be considered a premalignant condition and excluded.

2. As the primary study endpoint, FDA-approved studies currently use either a quality of life (QOL) instrument validated for uterine fibroids or a validated uterine bleeding scoring instrument coupled with a QOL instrument. Secondary endpoints include adverse events, fibroid and uterine size, time to return to normal activities, and comparisons to controls. Patients are serving as their own controls, with secondary comparisons to patients in nonrandomized arms. Please comment on the interpretation of these studies.

The panel thought the primary and secondary endpoints appropriate. They urged that quality of life questionnaires be done early in the studies and that concurrent controls be used rather than historical controls. The panel also stated that radiation exposure estimation should be done in a subgroup of patients, with accounts kept of radiation time and the number of images because of concerns about radiation exposure to the ovaries in young women—whether this would generate cancer, premature menopause, or damage the ovaries. Sponsors should stratify the data to see if the procedure fails more often in uteri over a certain size because this would be important information for patient awareness.

3. *FDA currently asks for a six-month follow-up (premarket) with an additional six-month follow-up (postmarket) for a total of a one-year follow-up. Is this an appropriate follow-up regime?*

The panel thought this an appropriate regime, although they suggested continuing the registry for five years. While they thought six months sufficient for safety, they also suggested giving sponsors an option of a six-month or 12-month follow-up to provide a bigger delta.

4. *Should there be specific study requirements regarding retreatment? How should the clinical study design account for this? Should these subjects be handled as primary treatment failures? Can these data provide additional information on the success of UFE retreatment?*

The panel consensus was that retreatments are failures and should be counted as such, although retreatment should be given. Data should be collected and followed for data on demographics, size, location, and so forth. Those with large ovarian arteries should be warned about the possibility of retreatment in the informed consent.

4. *What are the key elements that should be covered in the professional labeling of embolyzing agents that are cleared for UFE? How should labeling handle the issue of women who desire a future pregnancy? Should bleeding results be stratified by use and nonuse of hormonal contraception?*

The panel agreed that pregnancy and recurrence rate must both be discussed in the labeling, but it must be clearly stated that there is a lack of data and that results are unknown. The informed consent document needs to present clearly the possibility of increased morbidity. Panel members agreed with public presenters about the need for a well-crafted, written informed consent document that would list possible alternative treatments and all data obtained on results to date.

Panel Chair Dr. Blanco thanked the panel and all presenters.

Public Remarks

Dr. Vicky Hufnagel stated that she resented the dismissal of negative comments and legitimate concerns about UAE other than to ridicule them. She thought the panel did not listen and respond in an appropriate way to her concerns.

FDA Remarks

Nancy C. Brogdon, Director of the Division of Reproductive, Abdominal, and radiological Devices, thanked the panel on behalf of FDA for their preparation and input.

Panel Chair Dr. Blanco adjourned the Open Session at 4:46 p.m.

I certify that I attended the Open Session of the Obstetrics and Gynecology Devices Advisory Panel Meeting on May 21-22, 2001, and that this summary accurately reflects what transpired.

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Joyce Whang, Ph.D.
Panel Executive Secretary

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

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Jorge D. Blanco, M.D.
Panel Chair

Summary minutes prepared by
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