SUMMARY MINUTES

OF THE

OBSTETRICS AND GYNECOLOGY DEVICES

ADVISORY PANEL MEETING

SIXTY-FIRST MEETING

OPEN SESSION

October 4, 1999

Parklawn Building
Conference Rooms G and H
Rockville, MD

Obstetrics and Gynecology Devices Panel
October 4, 1999

Panel Chairperson
Jorge Blanco, M.D.

Executive Secretary
Elisa Harvey, D.V.M., Ph.D.

Voting Members
Grace Janik, M.D.
David Katz, Ph.D.
Johanna Perlmutter, M.D.
Subir Roy, M.D.
Nancy Sharts-Hopko, Ph.D.
Elizabeth Connell, M.D.*
Michael Diamond, M.D.*
Barbara Levy, M.D.*
Michael Pentecost, M.D.*+
Anne Roberts, M.D.*+
Gerald Shirk, M.D.*

***Temporary Member**
+Afternoon Session only

Consumer Representative
Diony Young

Industry Representative
Cindy Domecus

FDA
Daniel Schultz, M.D.

OPEN SESSION—OCTOBER 4, 1999

Panel Chair Jorge Blanco called the Open Session to order at 9:05 a.m., asking panel members to introduce themselves and state their areas of expertise. **Panel Executive Secretary Dr. Elisa Harvey** read the appointment to temporary voting status for Drs. Diamond, Connell, Levy, Shirk, Roberts, and Pentecost. Dr. Harvey read the conflict of interest statement, noting that the FDA had considered matters involving Drs. Diamond and Levy and had granted waivers allowing both to participate fully. Matters concerning Drs. Diamond, Katz, Janik, Roy, Sharts-Hopko, and Perlmutter had been considered and their full participation allowed. She disclosed matters pertaining to guest speaker Dr. James Trussell of the Office of Population Research, Princeton University. Tentative dates for upcoming panel meetings were announced as January 24-25, April 10-11, July 24-25, and October 9-10, 2000.

Colin Pollard, chief of the Obstetrics and Gynecology Devices Branch, gave a general update on division activities. He noted that draft guidance documents are available on assisted reproductive devices and electro-optical sensors, as well as one accompanying reclassification of home uterine activity monitors. Draft guidances on barrier devices and labeling of fetal vacuum extractors will be available soon.

VAGINAL BARRIER CONTRACEPTIVE DEVICES

Mr. Pollard gave an overview of the panel's agenda for the morning, which was to consider FDA's evaluation of vaginal barrier contraceptive devices. After a brief review of the regulatory history of premarket evaluation of these devices, he noted that their features require unique considerations and a unique approach. While the percentage of

contraceptive users using vaginal barrier contraceptives is quite small, the FDA is considering whether these are an underused contraceptive option and whether having more options available and accessible will make a difference in the number of unintended pregnancies. Mr. Pollard reviewed different devices such as the diaphragm, the Prentif cervical cap, the Reality female condom, and the Lea contraceptive and discussed the evolution of clinical study requirements such as number of subjects and length of follow-up. Other pertinent issues included ease of access through over-the-counter versus prescription availability and contraceptive effectiveness. Mr. Pollard reviewed FDA's role in ensuring safety and effectiveness and accurate labeling, as well as postmarket activities such as education, surveillance, and follow-up studies. Other public health groups are also being consulted, and their input as well as that of the panel would be considered in any upcoming draft guidance document.

James Trussell, PhD., Office of Population Research, Princeton University, presented results from the 1995 National Survey of Family Growth on the discontinuation and resumption of contraceptive use. Stressing that the small numbers given for many methods limited the data, he noted that the risk of pregnancy during typical use is not rare (9% within one year) and that high pregnancy rates reflect imperfect use rather than lack of efficacy. He also observed that discontinuation for a method-related reason is very common and that the high rates of discontinuation almost surely reflect dissatisfaction with current methods. The vast majority resume use of contraception shortly after becoming exposed to the risk of pregnancy.

Cindy Pearson, Executive Director of the National Women's Health Network, discussed approval of vaginal barrier contraceptives, a topic she said is very important to

women consumers. She stated that women want more contraceptive choices, especially alternatives to hormonal contraception, because they are constantly balancing the importance of safety, effectiveness, convenience, disease prevention, and impact on health. Noting that the approval of new vaginal barrier contraceptives has all but ceased, Ms. Pearson said that the Network believes that the safety and efficacy requirements for barrier contraceptives should be different from those for hormonal methods and those that are provider-dependent. She stated that women do not have the same long-term safety concerns with vaginal barrier contraceptives and can make their own decision to stop using the method if desired. Regarding efficacy, women want enough information to compare barrier devices to other similar methods. Thus, she recommended that new devices require data from a single-arm clinical trial that follows 200 couples for six months; variations on existing products could produce less data. Ms. Pearson stated that women want the FDA to help get new vaginal barrier contraceptives on the market by developing clear and consistent guidelines to allow more contraceptive choice.

OPEN PUBLIC HEARING

Heather Boonstra of the Alan Guttmacher Institute stated that the Institute's view is that the regulatory process should be streamlined and standardized, keeping in mind that there is a need in the United States for additional contraceptive methods. She noted that much of the groundbreaking research is being performed by small private or government-funded firms, which must target their limited resources required for costly clinical trials to obtaining the information most relevant to FDA review and approval. The Institute's analysis of contraceptive use-failure rates, based on the 1995 National Survey of Family Growth, indicates that six-month failure rates for barrier contraceptives are

substantial, more than half the 12-month failure rates, and that other analyses of that data find that a quarter to a half of women using barrier contraceptives do so for no more than six months. Thus, an appropriate regulatory standard for expediting approval of new barrier contraceptive devices is critical, while ensuing that the rigor of the FDA approval process is not diluted.

Rosalie Dominik of Family Health International stated that guidelines for clinical development of new barrier contraceptives should be driven by the need to collect information relevant to the label. Contraceptive labeling should accurately reflect the limits of our current knowledge about method effectiveness. She proposed three recommendations to the FDA: that current contraceptive labeling should be redesigned to more accurately reflect current knowledge about effectiveness; that the clinical development process for new products should focus on collecting information that reflects the new labeling paradigm; and that the paradigm should be central to guidance documents related to all contraceptive methods.

Erica Gollub, Ph.D. of the University of Pennsylvania Health System presented data from recent intervention studies among women. She stated that there is a public health emergency with the lack of male condom use by men and that the vast majority of her women clients show great interest in trying female barrier methods. She added that women will use most effectively those methods they like and thus it pays to have maximal choice in methods. She concluded by stating that FDA has a moral responsibility to fast-track women's barrier methods and to ensure that the regulatory process for women's barrier methods is in line with their low level of inherent risk.

Dennis Martin of Janesway discussed the Janesway Condom, which is undergoing trials in California. He stated that the company would embrace clearer guidelines for female condoms and that the lack of fast-track approval had hindered Phase I of the trials for his company's device.

Christine Mauck, M.D. of the Contraceptive Research and Development Program (CONRAD) stated that CONRAD supports the concept of getting more contraceptive devices to market without extensive, costly clinical trails that are marred by the impact of participant noncompliance. Once safety and proof of concept have been established, determination of efficacy estimates could be shifted to post-approval requirements without harming consumers and in fact thus giving them more choices. Premarket testing could evaluate safety and a proxy of efficacy such as postcoital testing, dislodgment studies, and limited efficacy studies. Postmarket efficacy testing in the real world could also evaluate acceptability and patterns of use. She suggested that results could be standardized against an accepted population used for standardization of all studies.

Amy Allina of the National Women's health Network, speaking on behalf of the Boston Women's Health Book Collective and the National Black Women's Health Project, stated that women want better contraceptive options, particularly safe and effective alternatives to long-acting hormonal contraceptives. Despite lower rates of effectiveness for the average user, she observed that vaginal barrier contraceptive devices offer important advantages for some women in terms of safety and unique health benefits. She added that by approving vaginal barrier contraceptive methods whose efficacy has been established along with a reasonable amount of safety data, the FDA would better

serve women's needs. She urged the FDA to do what is needed to get more barrier contraceptive methods on the market.

FDA PRESENTATION

Dr. Diane Mitchell of the Office of Device Evaluation presented statistics on unintended pregnancies in the United States and suggested that consumers, industry, other governmental agencies, and nonprofit organizations have been asked to reevaluate the premarket review process for barrier contraceptives. The Advisory Panel was asked to provide input on appropriate clinical studies, particularly considering aspects of safety, effectiveness, and labeling. Safety issues include tissue trauma, as evidenced through gross examination and colposcopy, and likelihood of increased vaginal infection or susceptibility to sexually transmitted infections. Effectiveness questions include whether there is a range of effectiveness within which all barrier contraceptives fall, whether the number of patients needed in the study can be reduced, and whether the length of premarket follow-up for these studies can be reduced. Questions on postmarket follow-up involve the type of the study, the results it is intended to show, and the number and type of participants. Labeling issues include the need to describe effectiveness in an easily comprehensible and accurate manner.

PANEL DELIBERATIONS

The panel thought that gross examination for possible tissue trauma definitely provided appropriate data for safety evaluation, but they were less unanimous about the need for colposcopic exam. The majority of the panel members thought it unnecessary, especially for devices that are similar to those already available, although there was some disagreement. All agreed that documenting symptoms and comparing vaginal microflora

with and without device use were appropriate, as was a vaginal pH test. The majority of the panel also thought that the evaluation criteria for over-the-counter (OTC) availability were generally the same as for prescription use, although they noted the need to evaluate efficacy, trauma, and fit for each device. Information on removing the device must be carefully described in all labeling, with better instruction sheets.

The panel was unable to reach consensus about the appropriate design for an efficacy study, with some members suggesting a control arm composed of those not using any contraceptive. Other members suggested a three-arm trial of a known device, a new device, and no method of contraception. The panel was divided on whether the study should compare a device to no contraception or to another contraceptive method, with some debate on which conclusions were more useful to prospective users. The majority of the panel thought six months sufficient for a new device, with a three-month trial possible for devices presenting no new issues for evaluation. On OTC versus prescription use, the panel again stressed ease of use and instructional material as key issues.

There was little specific resolution on the appropriate balance between premarket and postmarket studies. The need for specific health questions to be addressed in any postmarket study was emphasized, as was the expense of a good postmarket study.

One member of the panel suggested a minimum level of efficacy that vaginal barrier contraceptives should meet before FDA approval, but others argued that the consumer should simply be informed of the risks and allowed to decide as long as the device is safe and has some level of effectiveness, which was not absolutely specified. All agreed that presentation of information is crucial, with the labeling understandable to a wide range of consumers.

Key points that should be conveyed in the labeling included that the method is woman-controlled and that efficacy results will differ in perfect use versus imperfect use conditions. Advice on insertion, removal, possibility of dislodgment, and length of time for use should be covered in simple, straightforward language at the fourth or fifth grade reading level. OTC and prescription handouts should be the same, and some minimal testing of patient instructions should be done. Video instructions were also suggested. Some disclaimer about lack of prevention of STDs should be included, as should some emergency contraceptive advice such as, "If the barrier is dislodged, seek medical attention for possible pregnancy prevention within 24 hours."

FDA PRESENTATION ON UTERINE FIBROID TREATMENT

Dr. Diane Mitchell introduced the topic of non-extirpative methods of uterine fibroid treatment with an assessment of fibroid surgery, including how much is done, what types of surgery exist, and what the risks are. She discussed the prevalence, causes, symptomatology, and presentation of fibroids, as well as the indications for treatment. Treatment can be medical (hormonal), myolysis (lasers, bipolar electrodes, or cryomyolysis), or uterine embolization. Dr. Mitchell asked the panel to provide guidance on the various technologies of treating fibroids concerning topics such as appropriate control, study objective, inclusion and exclusion criteria, and study duration.

OPEN PUBLIC HEARING

Patricia Cole, M.D., Ph.D., of the Society of Cardiovascular and Interventional Radiology (SCVIR) listed SCVIR activities on uterine artery embolization, which include research initiatives, education, standards development, and

public information. She noted that their policy statement and more information on each of their activities are available on their web page.

Jay Cooper, M.D., of Women's Health Research (on behalf of BioSphere Medical)

discussed uterine fibroids and the need for alternatives to hysterectomy such as myomectomy, myolysis, and operative hysteroscopy. He stated that uterine artery embolization (UAE), although not without potential risks or failure, could fill a void among therapeutic options for women with fibroids. As an alternative to a prolonged and perhaps infeasible randomized clinical trial, he recommended a prospectively designed premarket study with short-term results of six months to one year. FDA clearance would be conditional on participation in and submission of results from a post-market surveillance study or patient registry. The premarket study would be a multi-center, nonrandomized study with either one common control group of surgical patients from several clinical sites, either prospectively or retrospectively, or historical data on at least 100 patients for each type of embolization agent, with specific key inclusion criteria and endpoints. The postmarket study would provide long-term follow-up results of three to five years from a postmarket surveillance study.

Fannie Fonseca-Becker, a patient from Baltimore, Maryland, and Elizabeth Pedicini, a patient from Laurel, Maryland, both described their successful experiences with UAE procedures after painful fibroids.

Robert Rosen, M.D., of the Society of Cardiovascular and Interventional Radiology gave a statement on uterine artery embolization in which he described the history, indications, and risks of the procedure. He discussed training issues involved for

physicians and described it as a first-line option of treatment with a low rate of adverse events.

Dr. Tony Shiley of Georgetown University spoke on behalf of **Boston Scientific,** saying that he was very impressed with the effectiveness of UAE. He suggested that hysterectomy not be considered the gold standard of treatment for fibroids because it is not a safe or reliable treatment. He suggested the need for safety and effectiveness criteria for UAE but not based on a comparison to hysterectomy.

Cindy Pearson of the National Women's Health Network noted that fibroids are a big issue for women and the need for a reliable and safe treatment is real. Women need to know how long the procedure will take, the risks and pain involved, how effective it will be in the short and medium term, and how likely they are to get the desired results. She stressed the need for a questionnaire on quality of life.

Written materials from Endocare Incorporated and Cook Incorporated were provided to the panel but not discussed.

GUEST SPEAKER

Dr. Robert Vogelzang of Northwestern University and SCVIR discussed the history of interventional radiology and its applications in obstetrics and gynecology. He listed the current indications for pelvic embolization, noting that the procedure has extremely high reported success rates with few complications. Dr. Vogelzang described the anatomy of the uterine artery and gave statistics on uterine leiomyoma, as well as embolization for treatment of uterine myomata. He listed the clinical and technical skills required for UAE and outlined both the technique and the post-procedure management, as well as complications of pelvic embolization. He summarized the literature available on

UAE and stated that all published reports show similar results on control of pain and bleeding, reduction in uterine volume, bulk-related symptoms, and safety. What is unknown, he added, is the effect of UAE on future fertility, long-term durability, fibroid recurrence rate, and other complications. Dr. Vogelzang showed a video of cryomyolysis.

PANEL DELIBERATIONS

Dr. Dan Schultz of the FDA explained that the panel was asked to provide input because companies have asked FDA to allow the addition of UAE to their device labeling.

Dr. Michael Diamond led the panel discussion on five FDA questions. On appropriate study design, the majority of the panel agreed that a randomized control trial would be impractical, although Dr. Diamond thought it might be possible. Possible suggestions included a prospective multicenter trial, a registry, or a similarly matched cohort study. Prospective matched cohort studies would not require randomization but could collect matched data on various efficacy comparisons. A registry of long-term data in large numbers with standard models and case reports could answer very specific safety questions such as incidence of sepsis, possibility of future pregnancy, ovarian function, and endometrial necrosis. Other endpoints could include adhesion, necrosis, quality of life, bleeding, and sepsis. The low rate of complications might also make the registry option preferable to a randomized controlled trial, as would the difficulty in selecting a suitable control. Several panel members stressed the importance of a validated quality of life assessment. Other health issues to be answered for women include the efficacy of the procedure, the long-term complication rate, the implications for future fertility and future cancer, and the long-term recurrence of symptoms. Major unanswered issues include

sepsis, premature ovarian failure, and reproductive capability. Information on optimal particle size would also be useful.

On clinical endpoints, the panel agreed that clinical indications such as bleeding and pain should be measured; surrogate endpoints cannot substitute. They could be evaluated in various creative ways. Fibroid size is an extremely important surrogate measurement that should be performed and correlated with other factors, but it cannot be a substitute for clinical endpoints. Magnetic resonance imaging (MRI) studies should be done as a marker before Lupron is given or any other intervention performed. Other important criteria include pre and post FSH levels, pre and post procedure endometrial thickness, and patient satisfaction. A six-month to one-year study should be done to answer at least the early questions on short-term outcome. Longer-term outcomes can be studied through a postmarket evaluation.

Postmarket surveillance should focus on the need for any future interventions and long-term sequelae such as endometrial cancer and adverse pregnancy outcomes, which could be reported through a registry.

In terms of inclusion criteria, the panel though the most important factor was for the cohorts to match in size and numbers. It was recommended that postmenopausal women be excluded. Those with prior adenomyosis were not excluded. Adenomyosis was thought difficult to diagnosis. Biopsy for leiomyosarcoma was not thought necessary. Pretreatment with GnRH agonist should be noted, as should the size before and after use. It was noted that women with multiple fibroids rather than single ones are the rule, and that multiple fibroid patients may have more adhesions.

The panel agreed that there should be warnings on the labeling to women of childbearing age, as well as information about the uncertainties of the device use regarding future childbearing. A double-blinded myomectomy/procedure study was suggested for patients who want pregnancy, although there was disagreement over this. Labeling was stressed for both patient and medical provider; and the patient insert should list the risks of the procedure.

A three to five year postmarketing follow-up period was recommended. Possible topics for a cohort study would include data on narcotic use, discharge time, return to work, febrility, and antibiotic use.

Panel Chair Dr. Blanco thanked the panel and presenters, as did Dr. Schultz. The meeting was adjourned for the day at 4:55 p.m.

I certify that I attended the Open Session of the Obstetrics and Gynecology Devices Advisory Panel Meeting on October 4, 1999 and that this summary accurately reflects what transpired.

Elisa Harvey, D.V.M., Ph.D.
Panel Executive Secretary

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

Jorge Blanco, M.D.
Panel Chair

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