FOOD AND DRUG ADMINISTRATION

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OBSTETRICS AND GYNECOLOGY DEVICES PANEL

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SEVENTY-FIRST MEETING

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Monday, March 27, 2006

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The meeting came to order at 10:00 a.m. in the Gaithersburg Hilton, Gaithersburg, MD. Kenneth Noller, M.D., Panel Chair, presiding.

PRESENT:

Kenneth Noller, MD	Panel 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
Diana Romero, Ph.D.	Consumer Representative
Elisabeth George	Industry Representative
Scott Emerson, M.D., Ph.D.	Consultant
Nasser Chegini, Ph.D.	Consultant
Keith Isaacson, M.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 meeting to order at 10:05 a.m. and recognized the presence of a quorum. The Panel members present introduced themselves by name, expertise, position, and affiliation.

The Executive Secretary, Dr. Bailey, gave the tentative dates for the remaining 2006 meetings: June 5th and 6th, August 28th and 29th, and November 13th and 14th. He then read the deputization statement, signed March 14, 2006, by Daniel Schultz, for the temporary voting members: Russell Snyder, Nancy Sharts-Hopko, Keith Issacson, and Nassar Chegini. A second statement, signed by Jason Brodsky on March 14, appointed Scott Emerson as a temporary voting member.

He read the conflict of interest statement into the record and noted that no COI waivers had been issued for this meeting. Elisabeth George, the non-voting industry representative, is employed by Phillips Medical Systems. He asked all members to recuse themselves from discussions involving products or firms they have a financial interest in and requested that all participants state their financial interests.

Introductory Remarks

Colin Pollard, Chief of the Obstetrics and Gynecology Devices Branch, noted that Dr. Noller will be leaving the Panel to become the President of the American College of Obstetricians and Gynecologists.

He then turned to the PMA from Innovata for its Adept Adhesion Reduction Solution. The Center has approved three PMAs for adhesion barrier products with a gynecological indication: Interceed in 1988, Seprafilm in 1996, and Intergel in 2001. None of these were approved for laparoscopic use and only Interceed and Seprafilm remain on the market. Gynecare removed its product from the market due to adverse event reports.

In January of 2000, the Panel discussed several key study design issues for adhesion barrier products. These discussions led to FDA's issuance of a guidance document on the type of studies FDA expects to see for adhesion barrier products. One key point in the discussion was that, although each patient gets pelvic surgery for a specific clinical reason, it should be sufficient for a pre-market primary outcome measure to look at and properly evaluate the presence of adhesions at second laparoscopy, since this could be a clinically meaningful outcome. The Panel recognized the

value of downstream clinical outcome measures such as pain, infertility, and small bowel obstructions, but it did not believe that those must be the pre-market outcome measures.

In a closed session in May of 2001, the Panel considered the study design for Innovata's product. This discussion led to the protocol employed for the pivotal study. The Panel liked the size of the study, the blind randomization, and the entry criteria, but it commented that counting adhesions without considering severity would be insufficient. The panel also did not like the shift table analysis and commented there must be a significant reduction in adhesions.

The members emphasized the importance of independent video scorers, recommended looking at the AFS score, and recommended data to collect, including age and the kind of infertility. The market claim should be specific to what the study showed.

Working with the Panel and the FDA, the sponsors set a stringent definition of patient success at the individual level. FDA set a mark for the minimum difference between the study and control arms and the proportion of patients achieving success. That was Primary Endpoint One. Primary Endpoint Two reflects a change at the subject level in the overall number of adhesion sites. Primary Endpoint Three is a change in the number of patients with dense adhesions.

In this study, many patients met the definition for individual success in Endpoint One but did not pass the five percent confidence interval and were not counted. The study succeeded for Endpoint Two. In Endpoint Three, there was no difference between the experimental and control arms. For the study to succeed, it had to succeed on three separate hypotheses. The Panel must decide, after taking into account how the study fared biostatistically on the three hypotheses, whether the clinical findings from this study are of sufficient merit. The decision must be based on valid scientific evidence, demonstrated safety, and demonstrated effectiveness.

Open Public Hearing

The Chairman opened the floor for public comment. Seeing none, he moved to the sponsor presentations.

Sponsor Presentations

Lorna Clisby introduced her presentation team. The sponsor is seeking approval for the Adept Adhesion Reduction Solution as an adjunct to adhesiolysis in gynecological

laparoscopic surgery.

Dr. Colin Brown, Medical Director of Innovata, described Adept as a non-viscous, clear fluid made of a four percent icodextrin glucose polymer solution buffered in an electrolyte solution. It is isotonic to blood. The icodextrin glucose polymer is linked at the 1,4 position so that it is metabolized by amylase to maltose, then to glucose, unlike a dextran glucose polymer, which is linked at 1,6. Because there is no amylase in the peritoneal cavity and due to the size of the molecule, icodextrin remains in the peritoneal cavity for a prolonged duration and is not metabolized until it is absorbed into the vascular system by way of the lymphatics. As a result, the solution remains in the peritoneal cavity for a prolonged duration.

Icodextrin solution was originally developed as Extraneal, a 7.5 percent solution used for continuous peritoneal dialysis. It is used in a higher concentration and frequency than Adept in about the same volume. Extraneal is approved in the US, UK, and Japan, and there is a large history of safe experience with this product in patients with renal failure. Although patients requiring dialysis often develop infections due to the indwelling of the peritoneal catheter, there is no evidence of icodextrin increasing infections. Despite the complications of renal failure, diabetes, and the destruction of the mesothelial layer, these patients do not experience adhesion-related problems. That was the inspiration for using the solution to prevent adhesions.

In a study of patients undergoing intra-peritoneal chemotherapy, the subjects were infused with either two liters of saline solution or of 4 percent icodextrin solution. After four days, only half the solution was absorbed, compared to saline solution, which was three-quarters absorbed in one day. This is important because the first three days are the critical adhesion formation time.

Adept was approved in Europe in 1999 for all abdominal surgery, laparotomy or laparoscopy, gynecological and general surgery, and 125,000 patients have received Adept to date. The ARIEL registry was established, which showed 2069 gynecological laparoscopies and 813 gynecological laparotomies for those patients. The registry showed that adverse event rates among those using Adept reflected the expected rates in gynecological surgery.

Adhesions can cause pain, infertility, and small bowel obstructions. Other consequences include readmission of patients and re-operations. It is with this in mind that the sponsor began the Adept Pivotal Study.

Dr. Elizabeth Peers, director of Clinical Development at Innovata, reported on the trial. The Adept program has been running since 1997. It is the largest study in adhesion reduction and the only one that has been double-blind. The study was set up to determine the safety and efficacy of Adept in the reduction of adhesions after gynecological laparoscopic surgery that included adhesiolysis. The device is used as an intra-operative irrigate of at least 100 ml every 30 minutes and as a one liter instillate left in after closure.

The control device was Lactated Ringer's Solution (LRS), which looks the same as Adept. The study was held in 16 centers in the US. The study consisted of four patient visits. The first was a screening visit, at which consent and eligibility were taken. Second was the first surgery, the laparoscopic procedure for which the patient was undertaking surgery. The intra-operative eligibility criteria were taken and the patients randomized at this point. The surgical procedure was recorded on video, and the adhesion assessments and scoring all took place. One to three weeks later, visit three occurred, a safety visit to follow up on any events that happened for patients since the surgical procedure. Visit four was a second laparoscopy four to eight weeks after the initial procedure. Again, a patient assessment and scoring was conducted and recorded on video.

The primary eligibility criteria considered in the first visit were that the patient be undergoing laparoscopic peritoneal surgery for a gynecological procedure which included adhesiolysis and that the patient agreed to a second-look laparoscopy four to eight weeks later. The most important four exclusion criteria were that the patients must have at least three adhesions lysed at the time, must not have an anatomical site removed, and all the sites must be visible; this was determined in the operating room.

Of 777 women who consented to take part in the trial, 449 were eligible. Adept was used in 227 patients and LRS in 222, and this set of patients was studied for the first endpoint. The second endpoint was studied in 402 patients, 203 with Adept and 199 with LRS, because 29 patients, 14 LRS and 15 Adept, withdrew and 18 were excluded. The primary reasons for the surgery were well balanced between the two arms of the study.

When the safety assessment was completed, the number of adverse events and types of adverse events were very similar between the LRS and Adept arms for the top ten AEs: post-procedural pain, headache, nausea, leakage at port-site,

dysmenorrheal, constipation, pelvic pain, arthralgia, flatulence, and vomiting. In many cases where one device caused an AE more often, the results were not statistically significant. Even in cases such as dysuria or pyrexia, which were more common in Adept patients, the investigator found that most of the events were unrelated to the device, so the result was still statistically insignificant. Vaginal bleeding is more common among Adept patients to a degree approaching statistical significance, but was also found to be mild and unrelated. Vaginal, vulvar, and labial swelling was statistically greater in Adept users, but it occurred immediately after surgery and went away with no intervention within a few days. There were no deaths in the study. The Adept group had 8 serious adverse events. The LRS group had 11. Only bladder and bowel perforation and bleeding from a nicked vessel were not close on both sides, and those events are not related to the device. Abdominal pain, pelvic pain, and urinary retention are considered adverse events related to Adept, though they occur nearly as frequently with LRS.

The laboratory values at visits 1, 3, and 4 found that there was no mean difference between the two groups, most patients remained within reference ranges, and there was no difference in blood or urine glucose levels.

The safety data shows that the adverse events and serious adverse events were largely related to the procedure or underlying condition, not the device. Adept was well tolerated, though labial swelling was observed in around six percent of the patients. That may need to be included in the product labeling. The study is consistent with the experience in Europe and the ARIEL registry.

Dr. Peers then moved to the primary efficacy results. In the adhesion assessments, each of the 23 anatomical sites were assessed and videoed by a trained investigator at the 1st and 2nd surgery for the incidence, extent, and severity of adhesion. The consistency of the scoring was audited by a blinded video reviewer, and he reported good consistency both among reviewers and for individual reviewers throughout the study.

Efficacy was judged by three primary endpoints. First, the study should show a difference between Adept and LRS patients' successes, success being defined as a decrease in adhesions of at least three sites or 30 percent of sites lysed, whichever is greater. Second, Adept-treated patients should not have more sites with adhesions at the 2nd surgery than at the 1st. The third primary endpoint is the difference between Adept and LRS in the percentage of patients having fewer sites with dense adhesions at the

second surgery than at the first.

For the first primary endpoint, the confidence interval showed a 95.2 percent likelihood that the difference between Adept and LRS would be between 0.7 percent and 18.9 percent. Indeed, the LRS group showed 35 percent success and Adept showed 45 percent, which is a statistically significant difference and falls near the middle of the confidence interval. For the second primary endpoint, there was a 95.2 percent confidence that the result would lie between -2.83 and -1.62 for the difference between the first and second surgeries. The data showed that the endpoint was met. Adept showed a 23 percent reduction in the mean number of sites with adhesions at the second surgery. That's a mean reduction of 2.4 sites. For the third primary endpoint, 50 percent of Adept patients had fewer dense adhesions at the second surgery, but so did 49 percent of the LRS group. That is no real difference. Dense adhesions are especially challenging, and both devices showed a meaningful result. In sum, the first primary endpoint did not meet the lower bounds of the confidence interval but had a statistically significant result. In the second, there was a statistically significant result that met the confidence interval requirement. In the third, there was not a statistically significant result, but half the patients had fewer dense adhesions.

Dr. Gere diZerga commented that the surprising part of the study was not how well Adept worked but how well LRS worked. He summarized the available literature on placing liquid in the pelvis to separate organs and prevent adhesions. The literature contains first and second-look laparoscopies and are measured by an AFS score, which is a measure of adnexal adhesions. The literature shows a significant reduction in adhesions as LRS instillate is increased. Though when both solutions are used at 1 liter, Adept users have fewer adhesions.

The device has two components. The first is frequent irrigation during surgery to remove the progenitors of adhesion formation: fibrin, fibrinogen, and blood clots. Adept and LRS had equal benefit in that situation. In the post-surgery instillate function, Adept shows fewer adhesions due to its longer interperitoneal residence. Adhesion formation begins in the first 36 hours after surgery. A liter of LRS is absorbed in 20 to 30 hours, so it prevents adhesions through a portion of that time. Adept protects through the entire time.

The secondary endpoints were measured at the second-

look laparoscopy. An odds ratio display shows Adept is more likely to help a patient for all of the secondary endpoints but “free of reformed adhesions.” Over 50 percent of Adept patients were free of de novo adhesions, compared to just over 40 percent of LRS patients.

The AFS score, developed by the American Fertility Society, measures adnexal adhesions to the tube and ovary and the extent of the adhesion, describing it as dense or filmy and giving a score for the adhesion’s severity, 0-32. Patients with moderate to severe scores, 11-32, are unlikely to conceive. Adept patients had a mean reduction in AFS score of 35 percent while LRS patients had a mean reduction of 15 percent. On the second look, 26 more Adept patients were classified with minimal or mild AFS scores than on the first look, over twice as many as in the control. This is important because a classification of minimal or mild makes a woman much more likely to conceive.

Of patients who presented to the study with infertility, Over 50 percent of Adept patients showed a reduction in AFS score, compared to 30 percent in LRS patients, a difference of 23 percent. Adept infertility patients showed a 34 percent mean reduction in AFS score, compared to 12 percent in LRS patients. Just over 35 Adept infertility patients had moderate or severe AFS scores on the first look. On the second look, it was just over 20, a reduction of 16. LRS patients, starting with 35, showed a reduction of 5.

On the first primary Endpoint, fifty percent of Adept patients were successful, compared to 30 percent of LRS patients.

Over two thirds of the patients in the study had endometriosis. Looking at the number of sites with treated endometriosis, the rates of success were high, and the advantage of using Adept becomes more pronounced as the number of sites increases.

Among patients undergoing adhesiolysis, Adept does not show an advantage over LRS when the adhesion burden is low. However, Adept shows significantly greater effectiveness than LRS as the adhesion burden increases.

Although it was difficult to meet some of the primary endpoints, the endpoints were unique to this trial, and LRS did better than the sponsor had expected. However, compared to LRS, Adept has a greater success rate, showing greater adhesion reduction, reduction in visceral sites with adhesions, reduction in AFS score for infertility patients. Adept use results in more patients free of de novo adhesions

and more patients with a reduction in AFS score.

Adept offers many benefits: a significant reduction in adhesions compared to baseline, significant reduction in dense adhesions compared to baseline, a reduction in sites with dense adhesions in 50 percent of patients, and an efficacy that is maintained with an increasing burden of adhesions and adhesiolysis for all patients. Adept shows the ability to preserve and improve fertility potential. In endometriosis patients, it significantly reduces adhesions compared to baseline and maintains efficacy with increasing disease. It reduced pelvic pain in 80 percent of patients with pelvic pain. It has an extensive safety record, so it has a high benefit/risk ratio.

FDA Presentation

Michael Kuchinski, the lead reviewer on this application, started the FDA's presentation and introduced the review team and the other presenters. The IDE Pilot trials began in 1999 under the Classics and Rapids protocols. The IDE for the pivotal trial was submitted and approved April 2001.

The sponsor is seeking an indication that will allow it to be used as an adjunct to good surgical technique for adhesion reductions and for use during gynecological laparoscopy, as an irrigate during surgery and as a post-surgical instillate.

Adept is essentially identical to Extraneal, but with a lower concentration of icodextrin, 4% versus 7.5%, respectively. Extraneal is used in a different population, is considered a drug, and was reviewed by CDER. Adept is a device because of its principle mode of action: temporarily separating peritoneal tissue surfaces. Adept acts as a colloid, and draws fluid from the surrounding tissue, retaining the fluid reservoir for up to 96 hours.

The sponsor submitted validation and verification testing on the device sterility and proposed a shelf life of, two years, that the FDA found acceptable. Material safety testing was conducted to include biocompatibility pursuant to ISO 10993 Biological evaluation of medical devices. The Animal testing generally focused on key testing for device safety including: Testing for delay of/or prevention of healing, Infectivity testing, Reproductive toxicity testing, Carcinogenesis/metastasis effects (justification) and Pharmacokinetics studies. Our manufacturing review looks at compliance with design controls and this aspect of the PMA has been determined acceptable and has been closed.

Baxter Healthcare voluntarily recalled selected lots

of Extraneal due to cloudy dialysate in peritoneal dialysis patients in Europe. These episodes of aseptic peritonitis were attributed to certain batches of Extraneal that had been contaminated with peptidoglycans. The source of the contamination was not used **to** manufacture Adept, and the contamination issue has been resolved by the company's institution of vigorous cleaning and monitoring processes.—

Dr. Julia Carey-Corrado presented on the clinical review issues. She pointed to Extraneal's safety record and added that skin rashes are the most common side effect. In the case of the recall, the patients were asymptomatic.

She discussed the two pilot studies. The first was the CLASSIC study, a prospective, randomized open label, multi-center controlled study. The procedure was laparoscopic gynecological surgery, and a liter of fluid was used, Adept in 34 patients, LRS in 28. LRS was used as the control device because it has an off-label use for adhesion prevention and is visually identical to Adept. However, LRS is not FDA-approved for adhesion prevention, has not demonstrated effectiveness, and is rapidly resorbed. Adept patients had an observed reduction in adhesion number, extent and severity, and there were two adverse events of labial or vulvar edema. This study was too small to be conclusive.

The sponsor also conducted a RAPIDS study, which was similar to the CLASSIC except that there were 25 Adept patients to 12 LRS and there was a larger volume of test solutions used, since the solution was used as an irrigant and not removed before the instillate was added. In Adept patients, there was one case of dyspnea associated with abdominal distension and one case of vulvar edema. There were also complaints of bloating, distension, and oozing from the incision. There was an observed reduction in the number, extent and severity in the Adept subjects, but there weren't any huge differences in the two groups.

There was a closed Panel discussion in 2001, at which the Panel weighed in on the Primary Endpoints for the study. The Panel said that it was acceptable to look at fertility post-market, depending on how the pivotal trial worked out. Any labeling claims would have to be tied to the pivotal trial data.

She reviewed the primary and secondary endpoints for the pivotal trial and stated that the patients were well balanced for baseline adhesion assessment, primary diagnosis, and demographics. .

Dr. Xuefeng Li gave a statistical review of PMA for Adept. The study was randomized, double-blind, and had a randomization ratio of one to one, 227 patients each for

Adept and LRS. The overall study would be successful in terms of effectiveness if all co-primary hypotheses were met.

There were three primary endpoints with corresponding statistical hypotheses. The first primary endpoint, success rate, was defined as a decrease at the second-look laparoscopy of at least three sites if 10 or fewer sites with adhesions present at the first look, or decreased by at least 30 percent if more than 10 sites with adhesions were realized at the first look. The study hypothesis was that the success rate of the Adept group would be larger than that of the control group by at least five percent. In statistical terms, this endpoint is deemed successful if the lower limit of the confidence interval for the difference in success rates between the Adept and control groups is greater than five percent.

The second primary endpoint was the number of sites with adhesions. The corresponding study hypothesis was that the Adept patients have fewer sites with adhesions at the second look compared to the first look. This endpoint is deemed successful if the confidence interval on the difference between the number of adhesions at the second look from the number at the first look in the Adept group had an upper limit of less than zero.

The third primary endpoint was the percentage of patients with fewer sites with dense adhesions at the second look. The study hypothesis for this endpoint is that the percentage of patients with fewer sites with dense adhesions in the Adept group is greater than in the control group. The confidence interval for the difference between Adept and control groups would have to have a lower limit greater than zero.

The sample size calculation for this superiority trial was based on the first primary endpoint. The expected success rates were 40 percent for the Adept group and 25 percent for the control group. An acceptable clinical difference of five percent was specified in the protocol. The resulting sample size was 410, and assuming a loss or fallout rate of 10 percent, the total approved study sample size was 450. For the pivotal trial, 777 patients were screened. Of the 449 patients who passed the screening test, 227 were randomized to the Adept and 222 were randomized to the control. Twenty-nine patients withdrew after treatment and 18 patients were excluded due to protocol deviations, so the protocol population consisted of 203 Adept and 199 control patients. The two groups had very similar demographic and prognostic characteristics.

For the first primary endpoint, the Adept group had a

success rate of 45.4 percent and the control group had a success rate of 35.6 percent. The difference between groups is 9.8 percent, and the confidence interval ranges from .7 percent to 18.9 percent. The confidence interval is above zero, which means that the Adept group had a statistically higher success rate than the control group. However, the lower limit of this interval is not greater than five percent; therefore, the first primary endpoint did not meet the success criterion.

For the second primary endpoint, the Adept group had an average decrease of 2.22 sites with adhesions. The confidence interval is below zero, so the second primary endpoint matched the success criterion. The control group also had a statistically significant reduction in the number of sites with adhesions, but the Adept group had a slightly larger reduction than the control group. Although 158 Adept patients had fewer sites with adhesions on the second look, 69 had the same or more. This is compared to 78 in the control.

For the third primary endpoint, there was about a 50 percent reduction in the number of patients with dense adhesions for both groups. The difference between the two groups is 1.12 percent, and the P value is .73, which is not statistically significant; hence, the third primary endpoint did not meet the success criterion.

As a principle of statistics, generally, if the primary endpoints fail, the secondary endpoints should not be used to show effectiveness. If it is necessary to evaluate secondary endpoints, there should be a pre-specified plan to adjust for the multiple endpoints before any statistical conclusions can be reached.

Although the study failed, on the success criteria for the primary endpoints, the results are consistent with the analysis of the primary endpoints. The Adept group showed an improvement over the control group in most of the secondary endpoints, though some P values were less than .05. After adjustment for multiplicity, only the endpoint “percentage of patients with reduction in AFS” might be significant.

Ultimately, the study met one of the three primary endpoints. For the first, the difference in success rates was not shown to be greater than five percent. In the second, there was a significant decrease in the number of sites with adhesions over baseline in the Adept group. In the third, there was no significant difference in the percentage of patients with fewer sites with dense adhesions. No firm statistical conclusion can be drawn from analysis of the secondary endpoints.

Dr. Carey-Corrado gave a clinical review. She presented adverse event data. Within seven days of the first laparoscopy, the most common adverse events were headache, abdominal pain, disurea, vaginal bleeding, vulvar edema, vomiting, diarrhea, and fever. LRS and Adept have similar rates, except with vulvar edema, which is 5.7 percent for Adept and .5 percent for LRS.

There were two readmissions for Adept-related serious adverse events, labial swelling and pelvic pain. Two LRS patients were also readmitted for LRS-related serious adverse events, abdominal pain and decreased urinary output.

She read the proposed indication and the first three discussion questions to the Panel so they could consider them. The primary endpoints and hypotheses were challenging, and LRS performed better than anticipated, but there have been no serious Adept-related safety issues.

Dr. Baoguang Wang reported on the experiences outside the US and postmarket expectations. ARIEL (Adept Registry for Clinical Evaluation) has data on 4,620 patients on whom Adept has been used in Europe. The registry was established in the UK in 2000 to gather surgeons' experiences with the device and to monitor adverse events. The registry is voluntary and includes 253 centers (150 gynecological) in six countries. The population of the registry represents eight percent of the 55,802 patients treated with Adept during the life of the registry. Of the 4,620, less than half underwent laparoscopic surgery for a gynecology procedure.

Data collection was done with a five-page physician data collection form that collected patient demographics, medical history, surgical procedures, use of Adept, and surgeon's inspection with handling Adept and their clinical observations as well as complications and adverse events during and after surgery. Adverse events data were also collected post-discharge, but the post-discharge adverse events were collected on the basis of spontaneous patient self-reporting.

There were 755 adverse events reported, a 16 percent adverse event rate. The lowest AE rate was found in the gynecologic laparoscopic patients, where the AE rate was 5.5 percent, and the top five events were abdominal pain, pyrexia, leakage, abdominal distension, and urinary retention. The highest AE rate was found in general surgery laparotomy patients, where there were ten deaths, six peritonitis cases, and an overall adverse event rate of 28.4 percent. This may serve as a warning against off-label use in the US. ARIEL provides assurance of safety in the indicated use for Adept and indicates no negative long-term

impacts.

Although the registry data show that the AE ratio is relatively low in gynecologic laparoscopic patients, providing some assurance of safety, the data was collected on a voluntary basis, and that should be taken into account, as well as the fact that post-discharge adverse events are self-reported. The registry also does not have race or ethnicity data.

Post-approval studies are mentioned in panel questions 4 and 6. The objective of a post-approval study is to evaluate device performance and problems in a broader patient population and over a longer period of time after a determination of reasonable safety and effectiveness. They are not intended to evaluate unresolved issues of safety and effectiveness from the pre-market phase. Post-approval studies can gather post-market information on community performance, study the effectiveness of training programs, find rare adverse events, and monitor performance in subgroups not represented in the trial.

Questions and Answers

Dr. Cedars asked the sponsors whether there was any difference due the the surgeons' judging the primary endpoint and whether there was any difference in viscosity intra-abdominally or in the interaction between the substance and blood. Dr. Anthony Luciano, one of the principle investigators, said that in over 50 patients he could not tell the difference.

Dr. Miller asked the FDA about the five percent lower boundary for the confidence interval and why that boundary was chosen. He asked the sponsor for any speculation about why one cohort had more adhesion formation. He asked both about interpreting the safety of Extraneal relative to Adept. Dr. Carey-Corrado addressed the first question. Five percent was chosen because lower bars have been set in the past and FDA wanted to change that practice. The number was chosen because it seemed achievable. Dr. Steven Piantadosi addressed the question for the sponsor. He commented that having a 95 percent confidence interval along a five percent tolerance is equivalent to having a 99.9 percent confidence interval above zero. The operational consequence of a five percent rule is to restrict the Type 1 error for the primary comparison to 0.1 percent rather than to the usual 2.5 percent that would be expected from a two-sided five percent rule. The five percent boundary has skewed the results. Dr. diZerega answered the question about the bad cohort. There is nothing linking the population who responds poorly except that they

are women who tend to form adhesions, and this has been a problem since the first laparoscopic study in 1979. There are predisposing factors relating to alternations in plasma and activator activity that predisposes a small population to form more adhesions than the general population.

Ms. Clisby addressed Dr. Hillard's request to hear more about ARIEL. The registry ran between September 2000 and December 2003 and was a voluntary program. All the data was collected while the patients were in the hospital, and there were specific data collection forms for gynecology and general surgery. The forms just collect data on events and do not check whether or not the events are Adept-related. It collected demographics, surgery performed, presenting conditions, and symptoms.

Dr. Peers addressed the Panel's question about the video audit procedure and the effect the process had on the outcomes of the study. The study was double-blind. Half of the patients had no reviews of their videos, and their results were the same as the half who did. Audits did not benefit Adept. Dr. Cedars asked further about the blinding process. Dr. Peers agreed that there was no blinding as to which video was first look and which second, since the procedure would have made that clear. Dr. Emerson asked about the second primary endpoint, the decrease in adhesions, and whether the process protected from bias on that endpoint. Dr. Peers said that if people expected fewer adhesions on the second look, that would affect both arms the same. Dr. Emerson pointed out that the secondary endpoint was a single-arm comparison. Dr. Davies said that those who have done adhesions studies before would be anticipating more adhesions on the second look.

Dr. Peers addressed the Panel question of how well matched the groups were for analysis of the secondary endpoints. The patients in the larger group and in the subgroups were approximately the same.

Dr. diZegra addressed the Panel's question about overlapping diagnoses. The distribution of the patients was well balanced. Generally, the more complex the adhesion-related diseases were, the better Adept did, compared to LRS.

Dr. Peers addressed the Panel's question about labial edema. All of the labial edema started within two days of surgery, and the majority resolved within three days. They were all resolved and were all mild. One started 30 days later and was severe, but it was probably not a related event. Dr. Luciano said that labial edema is related to the volume of fluid left inside. Under certain conditions, fluid can sometimes travel into the labia. The same mechanism can

cause vaginal swelling. The sponsor intends to include this in the labeling. Dr. Carey-Corrado asked about patient 637 at Site 13, who was readmitted for inability to void and labial swelling. Dr. Peers replied that the inability to void was severe but that everything else was moderate. The investigator reported the event as unrelated. Dr. Miller asked about the frequency of adverse events with Extraneal. Dr. Brown commented that peritoneal dialysis is more common in men, but men occasionally get scrotal swelling on one side.

Dr. Martin addressed the question of the irrigant and whether or not it was aspirated from the peritoneal cavity. The part of the irrigant placed in the cul-de-sac was aspirated immediately because it was used for cleaning as well as irrigation. The part that went over the pelvic brim into the abdomen could not be reached, but the patient was reversed to bring the solution back so it could be removed before the liter was instilled. In an experiment with a two-liter instillation of 4 percent Icodextrin, there is no increase in fluid over time. However, at 7.5 percent, there is a dialysis effect. That's why 4 percent is used, so that there can be a gradual volume decrease in the peritoneal cavity. At 2 percent, the decrease is not gradual enough.

Dr. Peers addressed the top 10 most common adverse events between surgeries. The reporting of adverse events in both the Adept and the LRS groups were statistically tested and were not found to be statistically significant.

Dr. Scrimgenour addressed the stratification issue. The randomization was not stratified by any patient characteristics, but it was stratified by center. The supplies were sent out in blocks of six.

Dr. diZegera addressed the Panel's question about data on inclusion of the irrigant. Previous studies had shown that frequent irrigation with a balanced solution that was isomatic and could absorb hydrogen ions would probably reduce adhesions. A study in rabbits using instillate only showed a benefit with Adept. Both Adept and LRS showed additional benefits with both the irrigation and instillate step. Dr. Snyder pointed out that the data does not show the value of using Adept for both as opposed to using LRS as an irrigant and Adept as the instillate. Dr. diZegera said that could be looked at going forward.

Dr. Martin addressed the Panel's question about labeling and training necessary for investigators. In Europe, there was no training. In the US, gynecologists were trained in the use of irrigator aspirators. There was no further training. Dr. Isaacson asked if there was any

training to prevent leakage from the incision or port sites. Dr. Luciano said that nothing was done beyond making sure the punctures were adequately closed.

Dr. Luciano addressed the Panel's question on uterine manipulations. Due to the number of adhesions in most patients, uterine manipulators were used nearly universally in operative laparoscopy.

Dr. Li addressed Dr. Weeks' question to the FDA regarding the center effect and how much of it was due to the small sample size. There was a significant center effect for all of the co-primary endpoints. The FDA adjusted for the center effect according to the protocol. However, in the sponsor's analysis of the difference in proportion and the confidence interval for the difference in proportion, the results were almost the same, were there adjustment or not.

Dr. diZegera addressed Dr. Chegini's question about patients with more than one diagnosis. Patients with adhesions but no endometriosis had a treatment effect of fifteen percent. Patients with endometriosis and adhesions showed a higher treatment effect. The study did not address infertility. Icodextrin does not contain glucose, so it does not leave glucose in the peritoneal cavity.

Dr. diZegeral addressed the Panel's question on how the scoring sheet was derived. The scoring sheet represents everything the sponsor thought would be useful for understanding an adhesion reduction device with a long interperitoneal dwell time and clinical benefit. The sheet captured 23 anatomical sites to see if the reduction was general or site-specific. The reduction was general. The sheet then looked at the types, severity, and extent of adhesions as well as the likelihood of reformation. Dense adhesions were, by definition, vascular. Last, the study looked at endometriosis, which two thirds of the patients had. The idea was to collect as much information as was possible in a reasonable amount of time. Dr. Isaacson asked about the statistical difference between the AFS and the modified AFS. Dr. diZegera explained that the AFS was developed in 1988, and the modified AFS was developed a few years ago. The idea was to use the severity and extent of adhesion to the ovary and tube. Those two parameters were then extrapolated to other sites. There was no statistical difference between the AFS and modified AFS. This relates to the large number of adhesions removed. Dr. Romero asked if the questionnaire is filled out interoperatively by dictation. It is done in that manner, with a research assistant present to read each of the sites to the investigator and to write down the investigator's responses.

Ms. Clinsby addressed the Panel's question relating to the labeling and incidence that was quoted, the 28 percent of adverse events in the ARIEL registry. That rate was in the general surgery laparotomy and included more surgeries that were not clean. The proposed labeling for Adept states that the safety and effectiveness has not been evaluated in clinical studies in the presence of rank infections in the abdominal pelvic cavity and that the safety of Adept has not been established after unintentional enterotomy or bowel perforation.

Dr. Romero asked the FDA why the pregnancy outcomes data was given, since the sponsor did not touch on the issue. Dr. Carey-Corrado responded that the pregnancy outcomes were discussed at the 2001 closed Panel meeting as an obviously meaningful clinical endpoint worth pursuing post market, but the Panel had agreed that it was not a practical primary endpoint for the pivotal clinical trial. The FDA was following up on the Panel's previous comments.

Dr. Miller asked Dr. Carey-Corrado to revisit the issue of the 5 percent threshold. Mr. Pollard responded that the Panel would have to decide whether or not the number had been set too high during the discussion. Dr. Emerson asked whether the number was due to the surrogacy of the endpoint and whether it is a pivotal trial. Mr. Pollard said that there were many factors, including those. The Panel will have to decide whether or not the results are clinically significant. Dr. Hillard asked about the use of LRS as a control and that one of the conclusions seems to be that LRS works pretty well. Mr. Pollard said that was a matter of discussion.

Dr. Snyder asked about patients with faster absorption rates and the effect on outcomes. Dr. Brown said that there was no ethical way to measure the residual volume in a patient in this study. However, he noted that there is a lot of variation. Dr. Snyder said that daily transvaginal ultrasound could have been done to determine at what point less than 30 ccs of fluid were left. Dr. Brown agreed that that could have been done and was not. That had been tried at the Imperial College in London, but the study was terminated early due to problems assessing the changes in volume over time and getting patients' approval, since this was not in the patients' clinical interest.

Panel Discussion

The Chairman called the Panel's attention to the discussion questions. The first question was, "Although the statistical

hypothesis for only one of the co-primary endpoints was met, please discuss each of the primary endpoints considering the objective, the statistical test, and the clinical significance."

Dr. Issacson stressed the difference between statistical and clinical significance. A 9.8 percent difference between the placebo and product is statistically significant, but it is not clinically significant. Dr. Sharts-Hopko disagreed, saying that the control device worked better than expected, but that should not work against Adept, since LRS was not really a placebo.

Dr. Emerson expressed concern about the need to maintain the integrity of the experimental process. He said that the P value does not match the confidence interval, probably due to strong effects in the center. As for the 5 percent threshold, he felt that pivotal studies should have stronger evidence than normal studies. The question is not so much meeting an arbitrary endpoint but meeting a meaningful endpoint that has a clinical effect. Adept shows fewer adhesions, but there is no way of knowing what that means.

Dr. Snyder said that the control did not turn out to be a placebo and there is evidence that Adept decreases the number of adhesions. However, Dr. Cedars said that without a control or placebo, there is nothing to make certain that the experiment is valid and to give some sort of parameter to judging improvement. LRS is already on the market for irrigation purposes, so Adept should show some degree of superiority. No matter how well LRS did, it is not a study without a control arm.

Dr Sharts-Hopko asked if the instillation of a 1,000 ccs, of anything was standard practice. The Chairman said it is not and that the problem seemed to be that the placebo worked better than expected in this procedure. Dr. Emerson replied that the problem was that there was not enough distance between the efficacy of the placebo and of the experimental arm. Had LRS done better, Adept would have had to have done better.

Dr. Emerson asked if anyone knew how good a measure AFS score is. The sponsor used it as a surrogate to predict fertility, and he wanted to know the validity of that. Dr. Issacson said that there is a correlation between adhesions and infertility, but it's not absolute and not linked to a number that indicates clinical significance. Dr. Emerson commented that relying on a correlation may be treating symptoms and not diseases. The Chairman said that AFS scores have been used for a long time but were not intended as an

evaluation, just a way of counting adhesions. Dr. Chengi commented on the subjectivity of the measurement, since it relies on observation and description. The Chairman reminded the Panel that infertility was not the only issue. Pain and other symptoms were also important.

Dr. Issacson said that the definition of success was very confusing and unclear. Dr. Snyder said that the product should not be expected to reform established dense adhesions. Dr. Cedars said that that was exactly what the product was supposed to do. The Chairman said that the product is supposed to improve all adhesions. Dr. Snyder said that part 3 of the first question focuses on fewer dense adhesions between the first surgery and the second one; however, AFS scoring looks at total adhesions. Dr. Cedars said that the differences in AFS scores achieved were not significant.

Dr. Sharp said that the data is clinically relevant, since the product prevents some of the damage done by surgery in making adhesions. If Adept did not go to market, He might use LRS to prevent adhesions. Dr. Miller added that the product may not meet all of the benchmarks of success, but there has been a trend toward helping women and reducing adhesions.

Dr. Weeks said that the data shows a reduction in the total number of adhesions, but mostly in the group with mild adhesions. Those are the adhesions that don’t make a clinical difference in terms of pain or endometriosis. While the product moves things in the right direction, it has not been shown to improve quality of life.

Dr. Hillard said that she could not separate safety from efficacy. Dr. Isaacson said that the study was excellent and difficult. The safety profile lowers the threshold for needing significant clinical benefit. The study was designed to show a statistical benefit, not a clinical one.

Dr. Sharp agreed that, in part three of the first question, dense adhesions are a problem, but it looks like the reduction was 50 percent. While there might not be much difference compared to placebo, it did seem to benefit the outcome. Dr. Emerson pointed out that if adhesions are reduced half the time, the other half of the time they are either the same or worse. He felt that a 50/50 shot doesn’t mean much.

Dr. Sharts-Hopko pointed out that there was a reduction in pain. Dr. diZergera said that eighty percent of patients with pelvic pain who received Adept had a reduction in pain. Still, the same effect was found with LRS.

The Chairman turned the discussion to co-primary 2, the number of sites with adhesions. Dr. Snyder said that regardless of the known clinical significance, he would prefer fewer adhesions to more. Dr. Weeks said that would depend on risk, but he was still uncertain that the reduction in filmy adhesions had a clinical effect. Dr. Miller commented that point 2 was the least controversial because the sponsor hit their target. Dr. Emerson said that point 2 may be clear, but it may not be relevant in an unblended assessment of the change. The Chairman summarized that the Panel seemed to believe the results and does not question the methods, but it is struggling with the issue of clinical significance.

The second question was: "Please discuss the statistical and the clinical significance of the above secondary outcomes. In particular, please focus on the data for subjects with primary focus on infertility." It was accompanied by a table. There were a number of secondary endpoints.

Dr. Emerson wondered whether there was a reason why the treatment would work better in patients who had adhesions causing infertility. Dr. Isaacson said that there's probably no reason and that he does not see a great difference in the modified AFS scores. Dr. Cedars said that people with pain were more likely to have more dense adhesions, while infertility patients might have less dense adhesions. He said that it is necessary to control for the multiplicity in the number of outcomes. Dr. Snyder commented that all of the outcomes were highly correlated, and that could reduce the necessary adjustment. He added that that AFS score is used for more than infertility patients, since it is a quantifiable measure.

Dr. Hillard commented that the infertility group might be different in that the adhesions are ovarian as opposed to the abdominal wall, and the mechanism of infertility is related to PID as opposed to endometriosis. Dr. Chegini agreed that that seems related to the percentage of patients with reductions. The separation caused by the volume of solution can prevent adhesions. The separation also would reduce pain. Additionally, there are nerve endings in some adhesions, so removing them would reduce pain.

The Chairman summarized that the Panel is not thrilled with the secondary endpoints. Some of the endpoints were interesting, but the primary endpoints were more important.

Question Three dealt with safety: "Please discuss the safety data from the pivotal trial and identify any adverse events,

including vulvar edema, you believe may be related to Adept. Also please discuss whether you believe that the risk posed by Adept is outweighed by the clinical benefit as discussed under questions 1 and 2 above."

Dr. Romero asked about the dramatic difference in the rate of vulvar edema in Europe as opposed to in the clinical trial. The Chairman speculated that vulvar edema can occur later than many adverse events, so it might have been underreported in the ARIEL registry. He asked the sponsor to comment. Ms. Clisby said that it is in the nature of trials to report every adverse event and in the nature of voluntary registries to underreport. Dr. Isaacson commented that it is a minor side effect that goes away quickly, so patients don't tend to report it.

The Chairman summarized that the Panel consensus is that Adept is a safe product.

Question Four said: "Please discuss whether the safety data from the Ariel registry supports the safe use of Adept as an adhesion prevention solution."

The Chairman said that a positive answer to number four logically flows from a positive answer to number three. Dr. Emerson said that the data is consistent with safe use, but it does not necessarily support it, since he was unsure of the accuracy of a voluntary registry. Ms. George commented that there is an MDR reporting process in Europe, so doctors are required to report injuries or deaths to their country, and the country notifies the manufacturer.

Question Five was on labeling and training: "Does the Panel have any comments on the labeling provided by the sponsor?"

Dr. Isaacson commented on Section One, draft labeling, suggesting that "a significantly greater percentage of patients, 45 percent versus 35 percent" be amended to say, "statistically significant greater." He also noted that the definition of success under A should be clarified. Dr. Emerson commented that "success" is not a good word to use on the labeling, since it is an editorial comment. It would be better to say that it met the threshold for reduction in lysis. Dr. Sharp pointed to language on page 3 of volume one: "It is to be used for reduction of post-surgical adhesions in patients undergoing gynecologic laparoscopic surgery which may include adhesiolysis." He wanted that language clarified, since the use described is broader than the use in the trial. Dr. Miller commented that the 9 percent reduction in de novo adhesions might make people want

to expand the therapies in which the device is used. The Chairman asked the sponsor for comment. Ms. Clisby said that the sponsor was seeking a broad indication for any gynecological surgery laparascopically performed in which it was felt that adhesions might form. Dr. Sharp was concerned about the infection rates in procedures involving a clean contaminated wound. The Chairman agreed that the ARIEL data on general surgery showed contamination to be a problem.

Dr. Snyder said that the device should be indicated for the population in which it was tested, though off-label use may occur. Dr. Isaacson said that clinical significance was already a struggle, so he wanted to see it limited to clean cases. Ms. George directed the Panel to the precautions on page 4 and said that might be the place to address clean contamination, under "the safety has not been established."

Dr. Chegini commented that the testing had been on adhesion reduction, not prevention, so there was no clear basis for using the device in patients who were not known to form adhesions. Dr. Weeks said that the patients in the study already had adhesions, and the device should be limited to use in similar patients. Dr. Cedars disagreed, saying that the inclusion criteria were too stringent for clinical use. Besides, it was chosen for statistical power rather than clinical importance. Dr. Miller suggested changing the labeling to indicate use in laparoscopic surgery requiring adhesiolysis. Dr. Emerson said that in the absence of clinical contraindications there was no reason to not use it for the prevention of adhesions. Dr. Isaacson said that the problem is that no patients were studied in many of the surgeries in which one would expect adhesions to form, so it is impossible to know whether it is safe or not. Dr. Snyder suggested specifically saying in the data that there is no data to establish safety in a clean contaminated case.

Dr. Emerson said he still didn't know whether or not treating adhesions matters, but preventing adhesions, if possible, is better than treating them. Dr. Romero suggested that the sponsor collect post-approval data before seeking to expand the indication. Dr. Emerson said that cherrypicking of which events are significant and which are not, as with vaginal bleeding, is inappropriate. Ms. George said that much of the data was inappropriate for labeling because it would be outdated soon. Mr. Pollard said that such labeling is common in implantable devices.

Dr. Chegini commented that, in table 4, "control" might be misleading, since a control could be nothing at all and is usually not something as effective as LRS.

Dr. Cedars wondered why vulvar edema was not in the list of things that occurred in more than 5 percent of patients below table one. Dr. Snyder suggested that vulvar edema and all adverse events that occurred in 5 percent or more of the patients be listed under precautions.

Dr. Isaacson noted that on page 9 only the secondary endpoints that favored Adept were shown, not the ones that showed no difference or worse.

Dr. Snyder pointed out that there was no evidence that Adept was a superior irrigant. Dr. Isaacson agreed but added that where Adept is used as an instillate, it should be used as an irrigant, since that was the procedure in the study.

Dr. Chegini wanted to see the pain reduction data on page ten handled in a more balanced way.

Dr. Cedars pointed out that the directions for use addressed removing packs and sponges, which is appropriate to laparotomy, not laparoscopy.

Dr. Weeks said that in the less than 1 percent group on page 6: urinary retention, vulvar edema, vulvar vaginal edema but severe enough to occasionally require cause urinary retention, should be included.

The Chairman stated that the FDA wanted more input on the problem about use in patients undergoing gynecologic laparoscopic surgery that may include adhesiolysis.

Dr. Sharp said it would include tubal sterilization, exploratory laparoscopy, diagnostic laparoscopy, tubal ligations, and Oophrectomy. Dr. Sharp said it could extend to removing an adnexa. When large portions of the peritoneum are exposed, you are likely to get adhesions.

The Chairman asked about situations in which the vagina or bladder is open but adhesions form. Dr. Sharp advocated limiting it to clean cases. Dr. Weeks said that the labeling should reflect what has been investigated and that expansion would occur naturally as clinical experience develops.

Question Six asked “Does the Panel have input regarding any issues that should be addressed in a post-approval study?”

Dr. Weeks asked about looking at future pregnancies in patients undergoing laparoscopy for infertility.

Open Public Hearing and Final Comments

The Chairman called for public comment. There being none, he opened the floor for final comments from the FDA and the sponsor. The FDA had no further comments.

For the sponsor, Dr. diZegera said that the Panel was considering issues the sponsor had spent years working on. The endpoint the sponsor is looking at is adhesions, and the evaluation of those endpoints was done in a blinded fashion. LRS had a statistically significant effect in reducing adhesions, and that made it an unusually active control. However, since LRS is not approved, the question is not whether Adept is better than LRS but whether Adept is better than nothing.

Adept showed many benefits. Fertility potential was preserved, demonstrated by lowered AFS scores. The sponsor's position is that all adhesions are important, and clinical consequences of adhesions become more apparent as the number of adhesions increase, so it is important that Adept showed benefit throughout all the groups of adhesions. Efficacy was maintained with increase in extent of endometriosis. Pelvic pain was reduced.

The fundamental issue with dense adhesions is subsequent surgery from the standpoint of causing additional problems on an ongoing basis, and there's a 50 percent reduction there, which this is the first time that degree of reduction has been shown.

The safety record is established, and the device is easy to use. The device fills an unmet medical need and shows an unusually high benefit to risk ratio.

Panel Deliberations and Vote

Dr. Bailey read the Panel recommendations options for Pre-Market Approval Applications. The Chairman called for a motion, and Dr. Sharp moved for approval with conditions. Dr. Isaacson seconded the motion.

The first condition, moved by Dr. Sharp, was that the device be indicated for clean cases and that the language of the labeling reflect that thus on page 4: "Adept Adhesion Reduction Solution is intended for use as an adjunct to good surgical technique for the reduction of post surgical adhesions in patients undergoing gynecologic laparoscopic surgery which excludes breach of the gastrointestinal tract or vaginal mucosa." Dr. Sharts-Hopko seconded the motion. After discussion of the limitations of the language, Dr. Sharp retracted the motion.

Dr. Cedars moved to take out the statement "surgery which may include," so that it reads "Adept Adhesion Reduction Solution is intended for use as an adjunct to good surgical technique for the reduction of post surgical adhesions in patients undergoing gynecologic laparoscopic adhesiolysis." Dr. Weeks seconded the motion and it carried unanimously.

Dr. Sharp moved to state under “precautions” that the use of Adept has not been studied in patients wherein the vaginal epithelium is breached. Dr. Cedars seconded the motion and it carried unanimously.

Dr. Snyder moved to include in the safety and effectiveness statement that Adept has not been studied for primary prevention. Dr. Isaacson seconded the motion and it carried unanimously.

Dr. Snyder moved to amend the precaution section to include the statement regarding labial edema or swelling, as well as urinary retention. Dr. Cedars seconded the motion and it carried unanimously.

Dr. Emerson moved to take out the language on the success rate, “decreased by at least three,” and "there was a success rate," and replace it with "first primary efficacy endpoint was defined as the proportion of patients for whom the number of sites with adhesions decreased by at least the larger of three sites, or 30 percent of the number of sites," at the bottom of page 7 of the labeling. Dr. Snyder seconded the motion, and it carried unanimously. However, after further discussion, Dr. Snyder suggested an amendment to Dr. Emerson’s amendment removing the material inside the parentheses on page 8 to clarify the meaning of success and eliminating A underneath. Dr. Emerson accepted the change and added that the language at the top of page 8, “significantly greater percentage of patients” should read “the Adept met this first primary endpoint. There was also discussion about changing the accompanying charts and graphs. The Chairman added the amendment to change the word “control” to LRS throughout the document, which Emerson accepted. When Emerson read back the motion, it read: “On page 7, it would be the first primary efficacy endpoint was defined as ‘the proportion of patients for whom,’ so I deleted the word ‘success rate which was.’ The top of page 8, ‘a significantly greater percentage of patients, 45.4 percent in the Adept group met the first primary endpoint compared to 35 percent.’ Notice at the top of figure 1, we just have to say ‘pivotal study first primary efficacy endpoint (percentage of patients).’ Similarly, the axis can be ‘percent of patients meeting first primary efficacy endpoint.’ Table 3, the title is okay. And then down, ‘success’ is replaced with ‘first primary efficacy endpoint.’ And you could say ‘difference in percent of patients meeting threshold.’ And under A say, ‘the first primary efficacy endpoint was met if the number of sites with adhesions decreased.’" Dr. Miller seconded the changes and the motion carried unanimously.

Dr. Isaacson moved to, at the bottom of page 9,

secondary efficacy, include the secondary endpoints in which there was no difference between Adept and LRS. Dr. Weeks seconded and the motion carried unanimously.

Dr. Cedars moved to remove, on page 9, the language in italics: “removed all packs and sponges.” The motion was seconded and carried unanimously.

Dr. Sharts-Hopko moved that on page 10 under secondary efficacy to indicate pain reduction two months post-procedure in the LRS group after the language “Eighty-three percent of Adept patients.” Dr. Emerson seconded. Dr. Isaacson pointed out that the change may be covered by her motion. Dr. Weeks said that the issue was that the statement concerning the 83 percent rate in the text favored Adept and should be eliminated. The motion was restated thus: to provide a table of the secondary efficacy endpoints along with P values comparing the control to treatment arms with an explicit denotation that it's not adjusted for multiple comparisons. Dr. Romero added that table 13 would be used to replace the narrative. The motion carried unanimously.

Dr. Emerson moved to remove the phrase regarding the attribution of the vaginal bleeding events on page 4 of 10. The specific phrase is the parenthetical: “The vaginal bleeding effects were not considered to be related to Adept or control, and none was considered severe.” Dr. Snyder seconded and the motion carried nine to one, Dr. Isaacson dissenting.

Dr. Emerson moved that there be a post-market surveillance database for infections following accidental bowel perforation. Dr. Sharp seconded the motion. Dr. Isaacson suggested that the database include intentional bowel anastomosis. Dr. Sharp suggested that the motion be made broad to address infection. After some discussion, including the question of whether Adept was contraindicated in cases of bowel perforation, the motion was withdrawn.

Dr. Snyder moved to require a post-market survey study on fertility rates following use. Dr. Weeks seconded. Dr. Romero suggested that a pregnancy study collect data on births. Dr. Isaacson suggested following to the point of intrauterine pregnancy. There was also the concern of ectopic pregnancy. After discussion of what to track and the burden to to sponsor as well as the usefulness of the data, Dr. Snyder withdrew the motion.

Dr. Hillard moved to have the product studied in a group for the primary prevention of adhesions. Dr. Emerson seconded the motion. The FDA commented that that is not the group included in the indication for use. Dr. Emerson added that is would be difficult to define a group that you’re sure

does not have adhesions. It would be a study for a new indication. The Chairman said that the Panel could suggest the study but that it might not be possible for the FDA to make the sponsor seek an indication. The FDA said that a different study for a different indication did not belong in this discussion, especially since the indication being sought was not yet approved. The Chairman noted that once the indication sought was approved, the meeting would be over, so there was no way to address the issue. Dr. Hillard withdrew the motion.

There being no further conditions, the Chairman called for a vote that on the motion that Innovata's Pre-Market Approval Application number P050011 for the Adept Adhesion Reduction Solution be conditionally approved with the above nine conditions that passed. The motion carried unanimously.

The Chairman then asked each Panel member to state the reason for his or her vote. Dr. Cedars stated that the safety data is reassuring, the data supports efficacy, and that there is no currently-available system for preventing adhesion formation during laparoscopy. Dr. Sharp said that the device is safe and that two of the three co-primary endpoints were satisfactory. Dr. Hillard cited the safety, statistical significance, and probable clinical significance. Dr. Chengini expressed reservations for the efficacy compared to LRS but acknowledged that the device does help some patients. Dr. Weeks was convinced about safety, but less about efficacy and voted to support the device because the indication was limited to adhesiolysis. Dr. Sharts-Hopko said that the safety data was compelling and that he anticipates the competition that will emerge. Dr. Snyder said that it will be years before medicine understands adhesions, but the trial showed efficacy in decreasing them and he would want this product to be available. Dr. Emerson said that clinical effectiveness was unclear due to the activity of the control, but the reduction was sufficient for approval. Dr. Isaacson said that there's no way to predict clinical significance at this point, but he felt compelled to vote for it because of Point Two. Dr. Miller echoed everyone's comments, adding that it is difficult to look at the fluid as a device. Dr. Romero spoke from the consumer perspective, citing the reassurance of the safety profile. He hoped that the manufacturer and clinicians would be responsible in what information they give the patients

regarding realistic expectations. Ms. George concurred with what the members had said and was glad that the conditions did not require a post-market study, since the sponsor already has an incentive to do the studies and try to expand the indications for use.

Adjourn

The day's agenda completed, the Chairman adjourned the meeting at 6:08 p.m.

I certify that I attended this meeting of the Obstetrics and Gynecology Devices Panel on March 27, 2006, and that these minutes accurately reflect what transpired.

Michael Bailey, Ph.D.
Executive Secretary

_____

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

_____
Kenneth Noller, M.D.
Panel Chair

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