

UNITED STATES DEPARTMENT OF
HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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MEDICAL DEVICES DISPUTE RESOLUTION PANEL

+ + +

THURSDAY,
SEPTEMBER 6, 2001

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The panel met in Salon E at 9751
Washingtonian Boulevard, Gaithersburg, Maryland, at
8:00 a.m., Scott Ramsey, M.D., Ph.D., Acting Panel
Chairman, presiding.

PRESENT:

SCOTT D. RAMSEY, M.D., Ph.D., Acting Chairman

MARK D. CARLSON, M.D., M.A., Standing Voting
Member

RALPH B. D'AGOSTINO, Ph.D., Temporary Voting
Member

GERALD J. SHIRK, M.D., Temporary Voting Member

KIM L. THORNTON, M.D., Temporary Voting Member

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PRESENT (Continued):

HECTOR HUGO GONZALEZ, R.N., Ph.D., Nonvoting
Member

JUDY GORDON, D.V.M., Nonvoting Member

ALSO PRESENT:

ROXOLANA HORBOWYJ, M.D., FDA

RICHARD KOTZ, FDA

DAVID KRAUS, Ph.D., FDA

CELIA WITTEN, M.D., FDA

KAREN M. BECKER, Ph.D., LifeCore

JAMES W. BRACKE, Ph.D., LifeCore

THEODORE COLTON, Sc.D., LifeCore

ALAN H. DeCHERNEY, M.D., LifeCore

SEBASTIAN FARO, M.D., Ph.D., LifeCore

DOUGLAS B. JOHNS, Ph.D., LifeCore

LUIGI MASTROIANNI, JR., M.D., LifeCore

STEVEN PIANTADOSI, M.D., Ph.D., LifeCore

DONALD B. RUBIN, Ph.D., LifeCore

RICHARD P. CHIACCHIERINI, Ph.D.

GERE diZEREGA, M.D.

LENA HOLMDAHL, M.D., Ph.D.

L. MICHAEL KETTLE, M.D.

L. RUSSELL MALINAK, M.D.

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PRESENT (Continued):

MARK G. MARTENS, M.D.

JOHN SEVER, M.D.

BESS WEATHERMAN

AUGUSTA SISLER

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P-R-O-C-E-E-D-I-N-G-S

(8:08 a.m.)

CHAIRMAN RAMSEY: I'd like to call to order the Medical Devices Dispute Resolution Panel.

I'm Scott Ramsey. I'm the Acting Chair of the panel.

This meeting is being held at the request of LifeCore Biomedical to resolve a scientific dispute between LifeCore, the sponsor of premarket approval application PMA 990015, as amended, for INTERGEL adhesion prevention solution, and the Office of Device Evaluation in FDA Center for Devices and Radiologic Health.

On November 15th, 2000, ODE sent LifeCore Biomedical a not approvable letter regarding its PMA, as amended, for INTERGEL adhesion prevention solution. The letter states that there is not sufficient information directly relating to the performance of this device to its indication for use to demonstrate reasonable assurance of safety and effectiveness.

The indication for use as described in LifeCore's amendment to the PMA, which is Amendment

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1 11, dated June 2nd, 2000, is for use as an
2 intraperitoneal instillate for reduction of adhesion
3 formation following gynecologic pelvic surgery.

4 This amendment modified the indication for
5 use that was proposed in the original PMA, which was
6 for a general surgery indication.

7 LifeCore disagrees with ODE's decision to
8 issue the not approvable letter and the reasons for
9 issuing it as enumerated in their letter. It's
10 LifeCore's opinion that the existing scientific data
11 provides reasonable assurance of safety and
12 effectiveness.

13 Specifically, LifeCore believes the PMA as
14 amended should be approved because the available data
15 shows that, first, there exists a statistically and
16 clinically significant benefit in favor of INTERGEL
17 solution as compared to control, lactated Ringer
18 solution, in reducing adhesion formation following
19 gynecologic pelvic surgery.

20 And, second, that the benefit is achieved
21 without exposing the patient to any unacceptable risk,
22 including infection.

1 Thus, this panel to whom LifeCore has
2 appealed the not approval letter is charged to
3 answering the following question and to make
4 recommendations to the Director of the Center for
5 Devices and Radiologic Health as to how this
6 scientific dispute should be resolved.

7 In particular, the question is whether the
8 PMA as amended provides reasonable assurance of the
9 safety and effectiveness of INTERGEL for its intended
10 use as an intraperitoneal instillate for reduction of
11 adhesion formation following gynecology pelvic
12 surgery.

13 In answering this question, the panel
14 should determine whether there are statistically
15 significant differences between INTERGEL solution and
16 control, whether those differences can be considered
17 clinically significant, and, second, whether the
18 benefits of the product outweigh the potential risks,
19 including potential risks of infection.

20 Our panel will discuss this question, and
21 then when the panel votes on a recommendation to the
22 Center Director on approvability of this PMA, as

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1 amended, that vote will constitute our answer to the
2 question.

3 I'd like to note for the record that the
4 voting members present constitute a quorum as required
5 by 21 CFR, Part 14, and at this point I'd like each
6 panel member to introduce him or herself, also
7 designating their specialty, position title, and
8 status on the panel.

9 And I'll start with Dr. Carlson.

10 DR. CARLSON: My name is Mark Carlson.
11 I'm a cardiac electrophysiologist by training, and by
12 trade I'm Professor of Medicine at Case Western
13 Reserve University Medical School in Cleveland.

14 CHAIRMAN RAMSEY: And please also state
15 whether you're a voting, a nonvoting, standing or
16 temporary member.

17 DR. CARLSON: I am a voting standing
18 member.

19 DR. D'AGOSTINO: Ralph D'Agostino,
20 statistician from Boston University. I'm a temporary
21 voting member.

22 DR. GORDON: Judy Gordon. I'm the

1 industry representative to this panel. I'm a
2 regulatory consultant. I've spent the last 20 years
3 directing clinical trials of medical devices and
4 pharmaceuticals and representing companies, more
5 recently largely small device companies to the FDA.

6 DR. KIM THORNTON: Kim Thornton. I'm an
7 Assistant Professor in the Division of Obstetrics,
8 Gynecology and Reproductive Biology at Harvard Medical
9 School and also reproductive endocrinologist at Boston
10 IVA. I'm a voting non-temporary or temporary member.

11 DR. GONZALEZ: I'm Hector Gonzalez. I'm
12 a registered nurse. I'm the consumer representative
13 on the panel, nonvoting, and I'm the CEO for the San
14 Antonio chapter of the Hispanic Nurse Association and
15 Chairman and Professor Emeritus of Nursing at San
16 Antonio College.

17 DR. SHIRK: I'm Gerry Shirk. I'm a
18 private gynecologist in practice in Cedar Rapids,
19 Iowa, and a clinical Associate Professor at the
20 University of Iowa, and I am a temporary voting
21 member.

22 CHAIRMAN RAMSEY: And I'm Scott Ramsey.

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1 I'm an Associate Professor at the University of
2 Washington and the Fred Hutchinson Cancer Research
3 Center. I'm a standing voting member, but I will be
4 serving as the Acting Chair in this case voting only
5 in case of a tie.

6 I'll now ask Les Weinstein, the CDRH
7 ombudsman and Executive Secretary of the panel, to
8 make a few comments.

9 MR. WEINSTEIN: Thank you, Dr. Ramsey.

10 The next item of business are statements
11 that I will read into the record. The first is an
12 appointment to temporary voting status.

13 Pursuant to the authority granted under
14 the Medical Devices Advisory Committee charter, dated
15 October 27th, 1990, as amended on August 18th, 1999
16 and November 16th, 1999, I appoint the following
17 people as voting members of the Medical Device Dispute
18 Resolution Panel for this meeting on September 6th,
19 2001:

20 Gerald J. Shirk, M.D.;

21 Kim L. Thornton, M.D.;

22 Ralph B. D'Agostino, Ph.D.

1 For the record, these people are special
2 government employees and are consultants to other
3 panels under the Medical Devices Advisory Committee.
4 They have undergone the customary conflict of interest
5 review and have reviewed the material to be considered
6 at this meeting.

7 In addition, I appoint Scott D. Ramsey,
8 M.D., Ph.D., to act as Temporary Chair for the
9 duration of this meeting.

10 Signed David Feigal, M.D., M.P.H.,
11 Director, the Center for Devices and Radiological
12 Health.

13 The second statement is a conflict of
14 interest statement.

15 The following announcement addresses
16 conflict of interest issues associated with this
17 meeting and is made part of the record to preclude
18 even the appearance of impropriety. To determine if
19 any conflict exists, the agency reviewed the submitted
20 agenda for this meeting and all financial interests
21 reported by the committee participants.

22 The conflict of interest statutes prohibit

1 special government employees from participating in
2 matters that could affect their or their employer's
3 financial interests. However, the agency has
4 determined that the participation of certain members
5 and consultants, the need for whose services outweighs
6 the potential conflict of interest involved, is in the
7 best interest of the government. Therefore, a waiver
8 has been granted for Dr. Ralph D'Agostino for his
9 interest in a firm that could potentially be affected
10 by the panel's recommendations.

11 Copies of this waiver may be obtained from
12 the agency's Freedom of Information Office in Room
13 12A15 of the Parklawn Building in Rockville.

14 We would like to note for the record that
15 the agency took into consideration other matters
16 regarding Drs. Mark Carlson and Ralph D'Agostino.
17 These panelists reported interests in firms at issue,
18 but in matters that are now concluded, unrelated to
19 today's agenda or imputed from an employing
20 institution.

21 The agency has determined, therefore, that
22 they may participate fully in all discussions.

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1 In the event that the discussions involve
2 any other products or firms not already on the agenda
3 for which an FDA participant has a financial interest,
4 the participant should excuse him or herself from such
5 involvement, and the exclusion will be noted for the
6 record.

7 With respect to all other participants, we
8 ask in the interest of fairness that all persons
9 making statements or presentations disclose any
10 current or previous financial involvement with any
11 firm whose products they may wish to comment on.

12 Also, anyone who will be making a
13 presentation to the panel today should provide copies
14 of your remarks, including overheads unless you have
15 already done so. They will be collected from you when
16 you go up to the podium.

17 In addition, after the meeting, Dr. Ramsey
18 and I will be available to respond to questions from
19 the press.

20 CHAIRMAN RAMSEY: Before we have
21 presentations from the sponsor and from the FDA, we're
22 going to start with an open public hearing. So at

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1 this time we're going to open the floor to anyone from
2 the public who would like to address the panel and
3 present data, information, or views on the issues
4 pending before our committee.

5 I'd ask that all of the persons who do
6 address the panel come forward to the microphone and
7 speak clearly for our transcriptionist.

8 We also request that persons making
9 statements either during the open public hearing or
10 any other portion of the meeting disclose whether they
11 have any involvement, including and not limited to
12 financial interests in any medical device company,
13 including LifeCore or one of its competitors.

14 So before making your presentation to the
15 panel, please state the nature of your interest,
16 including such things as whether the company, LifeCore
17 and other companies, paid for your expenses to attend
18 the meeting and whether your organization receives
19 funding from LifeCore or another device company.

20 I'll ask Mr. Weinstein to present the
21 speakers who have beforehand requested a chance to
22 address the panel in response to the Federal Register

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1 notice.

2 MR. WEINSTEIN: The following people have
3 requested time to speak. I'll read their names, and
4 that will be the order in which you may come up to the
5 podium to make your presentation.

6 Dr. Michael Kettel.

7 Dr. Lena Holmdahl.

8 Dr. Russell Malinak.

9 Dr. Melvin Thornton.

10 And Ms. Bess Weatherman, who will be
11 speaking this afternoon.

12 So if we can begin with Dr. Kettel, is he
13 here?

14 CHAIRMAN RAMSEY: Because of the number of
15 speakers we have at this open meeting, I'm going to
16 ask if at all possible to try to limit your comments
17 to five minutes. I'll raise my hand when you have one
18 minute left just so you'll know approximately where we
19 are.

20 DR. KETTEL: Thank you, Dr. Ramsey.

21 My name is Michael Kettel, and I am
22 presenting today my views on the approvability of

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1 INTERGEL.

2 In introduction, I was a participant in
3 the clinical trial that will be presented today and so
4 I did receive some financial remuneration from
5 LifeCore for that participation. However, they have
6 not paid for my travel today.

7 I am a private practicing reproductive
8 endocrinologist in San Diego, California, and have had
9 extensive experience treating fertility patients with
10 a variety of different disorders, including pelvic
11 adhesions.

12 In our center, we treat over 2,000
13 patients a year between my partner and I with various
14 causes of infertility. We perform over 400 surgical
15 procedures per year, and have a variety of experiences
16 in dealing with pelvic adhesive disease.

17 I, for the sake of my comments today, did
18 a short analysis of our experience from last year just
19 to give a sense to the panel of the significance of
20 publications to the infertile population here in the
21 United States.

22 We did 408 surgical procedures last year

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1 between two gynecologic surgeons. Of those 408
2 patients, there were over 200 of them that had pelvic
3 adhesive disease, but there were 114 of them for which
4 the pelvic adhesive disease was deemed probably the
5 sole cause of their individual infertility.

6 That represents 28 percent of the surgical
7 patients in our practice with infertility solely
8 attributable to pelvic adhesive disease, certainly not
9 a clinically insignificant problem.

10 Lastly, I would make a second point, and
11 that has to do with experiences that I've gained over
12 the years participating in clinical trials. I've had
13 the opportunity and pleasure to participate in
14 clinical trials for several devices which have been
15 brought before the FAA and have gained approval for
16 adhesion prevention.

17 There are currently three products that
18 I'm aware of that have gained approval by the FDA for
19 adhesion prevention and gynecologic health surgery.
20 All of these three other devices have been proven to
21 be effective, but limited, and tier limitation is
22 based on their site of application. They're all

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1 devices which are placed on the surgical side
2 exclusively and are, in fact, effective at producing
3 adhesions at the surgical site.

4 However, for the members of the panel and
5 others who are experienced with surgical procedures,
6 one is -- and you will become, I think aware of later
7 today -- aware of the fact that adhesions don't always
8 just limit themselves to surgical site applications,
9 and that INTERGEL is the only product thus far that's
10 been brought before the FDA which has the potential
11 applicability of also preventing adhesions at non-
12 surgical sites.

13 Non-surgical site adhesions are clearly as
14 important as surgical site adhesions, particularly as
15 it pertains to disease around the fallopian tubes.

16 Thank you very much for allowing me this
17 opportunity to speak.

18 CHAIRMAN RAMSEY: Thank you.

19 MR. WEINSTEIN: Ms. Holmdahl.

20 DR. HOLMDAHL: I have some overheads that
21 I would like to show if possible.

22 CHAIRMAN RAMSEY: While we're getting

1 started, would you state your institution and name and
2 nature of interest?

3 DR. HOLMDAHL: My name is Lena Holmdahl.
4 I am Associate Professor of Surgery at the University
5 of Goteborg, with a special interest in information
6 both from a scientific and clinical standpoint.

7 And the focus has been mainly on
8 pathogenesis, but also on iteration of adhesion
9 reduction produced in therapies, including design and
10 production of such trials.

11 I have no financial interest in the
12 sponsor, but the sponsor has admittedly reimbursed me
13 for my time.

14 And what I'm going to say is in the very
15 limited is I will try to show that clinical outcome
16 studies when it comes to adhesion formation are either
17 unsafe to prove efficacy or not feasible, at least not
18 in the pre-market period.

19 The next one, please.

20 For the following reasons. The clinical
21 outcomes that we would like to assess when it comes to
22 adhesion relation is either small bowel obstruction,

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1 infertility, or positive pain.

2 And from a scientific standpoint there is
3 an established relationship between small bowel
4 obstruction and adhesions, and about 60 to 70 percent
5 of small bowel obstruction is related to post surgical
6 adhesions.

7 And when it comes to infertility that
8 figure is lower, but there is an established
9 relationship by the theorists, about 20 percent.

10 And when it comes to pain, from a
11 scientific standpoint, it's very hard to get evidence
12 that adhesions actually can cause pain. So I would
13 say that there is no established relationship with the
14 outcome variable.

15 The next one, please.

16 When we're assessing small bowel
17 obstructions, we actually consider the assessment
18 tools. That would be either abdominal surgery or
19 clinical and radiological evidence of small bowel
20 obstruction, but then we would have to relook at the
21 other factors that possibly might cause small bowel
22 obstruction.

1 And the incidence rate of small bowel
2 obstruction after surgery is very low. From the
3 literature it can be estimated to be 3.6 percent, and
4 using the standard that is statistical in a sample
5 size of consultations to test such a hypothesis.

6 Next one, please.

7 The same is true for gynecological
8 surgery, and there the incidence is even lower. So
9 the sample size increases, and it will be more like
10 40,000 patients.

11 Next one, please.

12 Even if we consider pain, the family would
13 have the event rate, which is very poorly documented
14 in the literature, and we would also have troubles in
15 assessing pain after any clinical trial.

16 But if we assume that the event pain is
17 intangibly a lot of major complications after surgery,
18 the sample size would be very large and would be more
19 like 36,000 patients.

20 Next one.

21 The event tree is likely to be higher
22 after pelvic surgery, and is likely to decrease the

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1 sample size, but still it would be very much.

2 Next one, please.

3 If we could consider pregnancy as a
4 lifetime variable, the event rate is much higher, and
5 that would then decrease the sample size. So we're
6 approaching figures that we could handle, and the
7 sample size would be close to 1,600 patients.

8 But the problem is that they will now --
9 they would like to have pregnancy as an outcome
10 variable because there is an alternative treatment,
11 which is ILEA (phonetic), and it's very likely that
12 many of these patients would have benefitted from
13 being referred to ILEA in the first place.

14 Next one.

15 So to summarize, clinical outcome
16 variables, additional models directed at fertility or
17 pain are difficult to handle because of the
18 subjectivity. There is delayed appearance of the
19 outcome. We have large assessment tools. The
20 incidence is poorly documented. They would require
21 very large sample sizes, and there are alternative
22 treatments available.

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1 So the conclusion is that outcome --
2 clinical outcome studies are not feasible.

3 Thank you.

4 CHAIRMAN RAMSEY: Thanks for your comments
5 and coming all the way from Sweden.

6 MR. WEINSTEIN: Dr. Malinak.

7 DR. MALINAK: I'm Russell Malinak. I have
8 no financial interest in the sponsor. However, my
9 expenses and trip have been paid and my professional
10 time.

11 I'm Emeritus Professor of Obstetrics and
12 Gynecology at Baylor College of Medicine. I recently
13 retired from a gynecologic surgery practice of 35
14 years in that institution's related hospitals where my
15 principal interest has been in reproductive surgery.

16 Thus the majority of operative procedures
17 I have performed have been to restore or enhance
18 fertility or to relieve chronic pelvic pain.

19 Included in my job as full-time faculty
20 has been teaching of medical students, residents, and
21 fellows in conducting research in women's health
22 issues. A major focus of my teaching and research has

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1 been in the realm of post surgical peritoneal adhesion
2 formation, in attempts to understand pathogenesis and,
3 more importantly, to search for ways to reduce or
4 eliminate these adhesions.

5 They remain an inevitable sequel to any
6 operative procedure.

7 To that end, I have participated in
8 multiple clinical trials of the application of new
9 materials or methods to accomplish our goal. Of
10 particular note, I participated in the pivotal trial
11 of INTERCEED, the first adhesion prevention barrier
12 approved by the FDA.

13 To my frustration, each promising new
14 method has failed in one way or another. During my
15 tenure at Baylor College of Medicine, I have observed
16 and been privileged to participate in many phenomenal
17 advanced in the science and art of obstetrics and
18 gynecology.

19 Yet effective reduction in postoperative
20 adhesions has eluded us and remains the largest unmet
21 need in the entire realm of women's health care.

22 Several years ago I participated in the

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1 randomized clinical trial to evaluate the
2 effectiveness and safety of INTERGEL. I was
3 particularly pleased to join this study because it was
4 the best designed clinical trial of an adhesion
5 prevention product I had ever seen, and in contrast to
6 the limitations of INTERCEED, it provided a method to
7 reduce de novo adhesions, as well as surgical site
8 adhesions.

9 A tremendous amount of time and resources
10 were expended in executing this protocol, which
11 typical of any randomized trial and surgery is among
12 the most difficult to carry out in all of medicine.

13 I was pleased that the outcome measure was
14 the adhesion itself rather than pregnancy or pelvic
15 pain, both of which are multifactorial in origin and,
16 therefore, provide less rigorous analysis.

17 Upon completion of the study, I was
18 gratified to see clinically significant reduction in
19 adhesions secondary to the product, which was also
20 proven safe. In a patient population which had an
21 uncharacteristically low incidence of adhesions, there
22 was a five-fold reduction in moderate to severe

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1 adhesions in the study group as compared to control,
2 and a 31 percent reduction in reformed adhesions.

3 This reduction is clinically quite
4 significant and would most likely be more impressive
5 in a patient population at high risk for adhesion
6 formation.

7 In the amended material, I was further
8 pleased to see the focus. The fallopian tubes and
9 ovaries are the organs most vulnerable to distortion
10 by adhesions and, therefore, most likely to be
11 associated in infertility and/or pelvic pain when
12 significant adhesions form.

13 In the analysis of the data from this
14 study, I have seen for the first time a simplified and
15 clinically meaningful way to portray the results of
16 adhesion studies in patients, not in animals, that is
17 in the shift tables developed by the sponsor in
18 conjunction with the FDA. This approach will aid in
19 interpretation of future adhesion prevention trials.

20 In closing, it is my opinion that an
21 adhesion reduction product has been identified by very
22 good science, has been evaluated in a rigorous

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1 clinical trial, and has been shown by critical
2 statistical analysis to be safe and effective.

3 It will be a disservice to women's health
4 if this product is denied our patients in the United
5 States of America.

6 Thank you for the opportunity to speak.

7 CHAIRMAN RAMSEY: Thank you, Dr. Malinak.

8 MR. WEINSTEIN: Dr. Thornton.

9 DR. MELVIN THORNTON: Good morning. My
10 name is Dr. Melvin Thornton, and I'm Assistant
11 Professor at Columbia University and currently the
12 Medical Director of the Center for Women's
13 Reproductive Care at Columbia University.

14 And I was a participant in the clinical
15 trials for INTERGEL, and I did not receive financial
16 assistance for being here today.

17 I came here today because I feel this is
18 the most important meeting that is going to happen
19 this year in women's health care because, as you heard
20 from the previous speakers, adhesions are a major
21 problem with surgery for women, and as a reproductive
22 surgeon, it's difficult to train residents and teach

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1 them about adhesion prevention when there are no
2 products out there that I can feel confident in giving
3 the patient, knowing that when I leave the OR she's
4 going to have a reduction in her adhesions.

5 But the reason for this, because the
6 products that are approved are very difficult to use
7 and take a lot of time to use, the majority of the
8 physicians out there choose not to even attempt to use
9 these products. So these patients are leaving the
10 operating room with nothing to prevent adhesions from
11 forming.

12 This INTERGEL has been shown to be
13 effective and has been shown to be safe, and as a
14 participant in clinical trials, I know for a fact that
15 it works, and it's easy to use.

16 So this, if it's approved, the majority of
17 physicians out there will definitely use this because
18 it's easy for them to use, and using something is
19 better than using nothing.

20 And I'd like to say thank you for the
21 time.

22 CHAIRMAN RAMSEY: Thanks, Dr. Thornton.

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1 Is there anyone else who would like to
2 speak at this portion of the hearing? Anyone else?

3 (No response.)

4 CHAIRMAN RAMSEY: I'll turn it over to Les
5 then.

6 MR. WEINSTEIN: I have two comments that
7 were submitted before the meeting that was originally
8 scheduled in June, and those comments were submitted
9 for the June 4th meeting that was rescheduled to
10 today, and I've been asked to read these portions of
11 those two comments into the record.

12 One comment was submitted by the American
13 Society for Reproductive Medicine.

14 The American Society for Reproductive
15 Medicine and the Society of Reproductive Surgeons are
16 pleased to submit comments to the Dispute Resolution
17 Panel on the top of postoperative adhesions. Our
18 intent is to emphasize to the committee the clinical
19 importance of postoperative adhesions and devices and
20 agents designed to reduce the development of these
21 adhesions.

22 Postoperative pelvic and abdominal

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1 adhesions are a common problem. It is estimated that
2 more than half of the more than three million women
3 who undergo gynecologic surgery every year will
4 develop some postoperative adhesions.

5 These postoperative adhesions can lead to
6 significant medical complications, chronic pain,
7 reduced quality of life, and increased cost of medical
8 care.

9 Common examples of medical complications
10 include bowel obstruction and infertility. In
11 addition to these complications, postoperative
12 adhesions may produce chronic pelvic pain, which may
13 be mild and a nuisance for some, but severe and
14 disabling for others.

15 Clearly, impaired fertility and chronic
16 pelvic pain may reduce the quality of life experienced
17 by those who develop adhesions. Furthermore, the
18 diagnostic tests and surgical therapies performed to
19 evaluate and treat the infertility and pain are costly
20 and sometimes ineffective.

21 Finally, pelvic adhesions may also
22 complicate and increase the morbidity of any

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1 subsequent pelvic surgeries. We see these clinical
2 consequences of postoperative adhesions every week in
3 our clinical practice. Good surgical techniques and
4 the products that are currently on the market will not
5 always prevent the development of postoperative
6 adhesions in many of our patients.

7 As a result, there is a need to develop
8 additional and effective methods to reduce the
9 occurrence of adhesions after surgery. The
10 development and use of new devices and agents that are
11 capable of reducing the incidence, extent, and
12 severity of adhesions are likely to reduce
13 postoperative complications, pain, decreased quality
14 of life, and the cost of subsequent medical and
15 surgical care.

16 Signed by Dr. William R. Keye, spelled K-
17 e-y-e, and Dr. R. Dale McClure. Dr. Keye is the
18 president-elect of ASRM. Dr. McClure is the president
19 of SRS.

20 The next comment was submitted by Dr.
21 Barry Stewart of the Pacific Gynecology Specialists
22 Group in Seattle, Washington.

1 As one of the principal investigators of
2 INTERGEL prevention solution, I have had the
3 opportunity to experience its characteristics and
4 efficacy first hand. Its ease of application in gel
5 form and the widespread surface coverage that it
6 provided in confined spaces seemed particularly
7 advantageous over other products available.

8 I also found it to be clearly helpful to
9 my patients in preventing pelvic adhesions after
10 myomectomy relative to Ringer's lactate.

11 I do not have the experience of the panel
12 in analyzing the test data presented, but if safety
13 and efficacy in the range of other such products can
14 be demonstrated, the gel form in which INTERGEL is
15 utilized would increase its application and the
16 potential benefits derived for a large number of
17 patients undergoing abdominal pelvic surgery.

18 I personally look forward to its approval
19 and to my utilization of it in my surgical practice.

20 Signed Barry C. Stewart, M.D.

21 Those are the only comments that I've
22 received.

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1 CHAIRMAN RAMSEY: Let me ask the panel if
2 they have any questions that they'd like to ask to any
3 of the speakers during the open presentation.

4 DR. D'AGOSTINO: Can I?

5 CHAIRMAN RAMSEY: Yes.

6 DR. D'AGOSTINO: The speaker who said that
7 you can't measure clinical outcomes in a particular
8 premarket phase, is the suggestion then that we should
9 rely on a surrogate? I mean, she didn't say that, but
10 is that the implication?

11 DR. HOLMDAHL: Yes, I would propose that
12 in the premarket period, to rely on adhesion
13 information.

14 DR. D'AGOSTINO: Even though you don't
15 know that pain relates, the surrogate relates to
16 relieving pain?

17 DR. HOLMDAHL: That is true, but if you're
18 looking into efficacy or an adhesion reducing, ending
19 therapy, then I would suggest that it's better to look
20 at the -- to measure adhesion in the postoperative
21 period.

22 DR. D'AGOSTINO: Thanks.

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1 CHAIRMAN RAMSEY: Any other questions?

2 (No response.)

3 CHAIRMAN RAMSEY: Okay. We're now going
4 to move on. We're a little ahead of the time, which
5 is great, but we're going to go ahead and move on to
6 the presentations by the parties in dispute, and we're
7 going to start with LifeCore's presentations.

8 As with the open hearing, everyone who
9 comes up, I'd ask that you please speak clearly into
10 the microphone for our transcriptionist, and also as
11 before, before making your presentation, please state
12 your name, affiliation, and any financial interest
13 with the company.

14 Just to remind you, the definition of
15 financial interest includes compensation for time and
16 services or expenses of those and your assistance and
17 staff in conducting a study, preparing a report, or
18 appearing at the panel meeting on behalf of the
19 sponsor, including paid travel. If you're an employee
20 of the company, obviously you don't have to make those
21 type of disclosures.

22 DR. BRACKE: Good morning, ladies and

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1 gentlemen. I am Jim Bracke. I am president and chief
2 executive officer of LifeCore Biomedical, the sponsor
3 organization.

4 I would like to start by thanking the FDA
5 on behalf of LifeCore for making the Dispute
6 Resolution Panel option available to sponsors of PMAs.

7 I would like to further thank Les
8 Weinstein for a very extensive effort in coordinating
9 this first Dispute Resolution Panel unit with the
10 sponsor.

11 I would also like to thank all of the
12 experts involved in this entire process who have put
13 in considerable effort in preparing for today's
14 meeting.

15 I would now like to introduce you to Dr.
16 Karen Becker, who is representing LifeCore in this
17 matter before the FDA. Dr. Becker is worldwide
18 managing director of health care products at the
19 Weinberg Group. She has worked for 15 years on the
20 clinical evaluation of implanted medical devices, pre
21 and post marketing and has published a textbook on the
22 subject.

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1 Dr. Becker.

2 DR. BECKER: Thank you, Jim.

3 I have no financial interest in LifeCore,
4 and I'm being compensated for my time.

5 May I ask for a clarification before I
6 begin my remarks? The questions to be asked of the
7 panel, would you repeat those?

8 MR. WEINSTEIN: I think that they were
9 misread.

10 CHAIRMAN RAMSEY: Okay. Sorry. Let me
11 try that again.

12 It says: "whether the PMA, as amended,
13 provides reasonable assurance of the safety and
14 effectiveness of INTERGEL for its intended use as an
15 intraperitoneal instillate for reduction of adhesion
16 formation following gynecologic pelvic surgery. In
17 answering this question, the panel should determine
18 whether a statistically significant difference between
19 INTERGEL solution and control can be considered
20 clinically significant; and, second, do the benefits
21 of the product outweigh the potential risks, including
22 any risk of infection?"

1 DR. BECKER: Thank you.

2 MR. WEINSTEIN: Does that clarify?

3 DR. BECKER: Yes.

4 Well, I want to first thank Les and CDRH
5 for giving the sponsor the opportunity to talk to you
6 today in a fair and open scientific forum about the
7 scientific issues in dispute.

8 The sponsor's presentation today has four
9 parts. I will provide a summation of the sponsor's
10 position on the scientific issues with regard to the
11 INTERGEL PMA as amended in June 2nd, 2000.

12 Dr. Johns will then present the results of
13 the INTERGEL clinical trial. His presentation will be
14 followed by a consensus comment on safety and
15 effectiveness of INTERGEL by independent, well
16 qualified clinical experts who are here today.

17 Lastly, a consensus statement will be
18 provided to you by independent experts on the
19 statistical issues.

20 First slide, please.

21 It is the sponsor's position that valid
22 scientific evidence has been submitted to FDA

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1 sufficient to establish reasonable assurance of safety
2 and effectiveness for INTERGEL adhesion prevention
3 solution for the labeled indication in accordance with
4 requirements enumerated in the federal Food, Drug and
5 Cosmetic Act and applicable regulations.

6 We respectfully disagree with the
7 determination by OBE that premarket approval
8 requirements for this product have not been met.

9 This product is safe and effective. This
10 submission has been thoroughly peer reviewed by well
11 qualified experts. Today we will provide you with a
12 summary of the data submitted as part of this project,
13 the scientific basis for the sponsor's position, and
14 independent expert opinion in support of the sponsor's
15 conclusions.

16 Next slide, please.

17 As you have heard and as you are well
18 aware, post surgical adhesions following gynecological
19 surgery caused significant morbidity. Over three
20 million gynecologic pelvic surgeries are performed
21 annually in the United States according to the
22 National Center for Health Care Statistics.

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1 From 60 to 90 percent of these cases
2 result in post surgical adhesions. Adhesions are
3 responsible for infertility, bowel obstruction,
4 complications of additional surgery, and in some cases
5 chronic pelvic pain.

6 These outcomes are not self-limiting, do
7 not resolve without intervention, and are difficult to
8 manage. Over 400,000 women undergo adhesiolysis
9 surgery every year in the United States. It has been
10 reliably estimated that at least five percent of all
11 hospital readmissions or due to complications from
12 post surgical adhesions.

13 The rate of readmissions post surgery due
14 to post surgical adhesions does not decline over time,
15 but continues over ten years. This conclusion is
16 based on the work of Dr. Harold Ellis and colleagues
17 in the U.K. utilizing the Scottish National Health
18 Service medical records and linkage database, which is
19 the largest verifiable database on hospital
20 readmissions due to adhesions. There were
21 incorporated 30,000 patients followed for ten years.

22 The cost to the U.S. health care system of

1 managing co-surgical adhesions is estimated to be \$1.6
2 billion. This figure has been replicated on a per
3 capita basis by data from the U.K.

4 I would point out though that this is a
5 gross underestimate because it relies only on
6 peritoneal adhesiolysis surgery.

7 Two products are available in the United
8 States for reducing the risk of surgical site
9 adhesions as adjuncts to good surgical technique. No
10 adjuncts are available for reducing the risk of
11 adhesions beyond the surgical site.

12 INTERGEL, the product under consideration
13 today, is available to women in Canada, the European
14 Union, and in many other countries throughout the
15 world.

16 Next slide, please.

17 As you know, the clinical evaluation of
18 post surgical adhesions is extremely difficult.
19 Products approved for use by FDA have thus far been
20 restricted to two site specific adhesions. Both of
21 these approvals rely on adhesions as the endpoint.

22 Almost two years ago, FDA convened a

1 meeting of the Obstetrics and Gynecology Devices
2 Advisory Panel to consider the premarketing data
3 requirements for adjuncts to reduce the risks of post
4 surgical adhesions in gynecologic surgery. This
5 meeting considered a draft guidance on barrier
6 adhesion products. The focus of the expert testimony
7 provided and the panel discussion which ensued was on
8 the design of clinical trials for adhesion barrier
9 products.

10 Some of you on the panel today were on
11 that panel in January 2000: Dr. D'Agostino, I
12 believe, and Dr. Shirk. Many other people present in
13 the room today were on that panel. It was a very
14 snowy day. Dr. Alan De Cherney provided testimony.

15 This meeting yielded three very important
16 conclusions regarding the state of the clinical
17 science and recommendations with regard to regulatory
18 standards to be applied to these products in the
19 United States.

20 First, the experts agreed that adhesions
21 are an endpoint and not a surrogate. This position
22 was expressed by leaders in the field, including Dr.

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1 De Cherney, Dr. Steven Schwaitzberg (phonetic), and
2 the panel chair, Dr. George Blanco (phonetic), in his
3 summation of the testimony and panel discussion.

4 Secondly, there was agreement that these
5 studies, even with adhesions as the endpoint are
6 extremely difficult to do. Outcome studies to assess
7 fertility, bowel obstruction, and pain cannot be
8 conducted pre-marketing.

9 Thirdly, there was a consensus that
10 adhesion assessment in any given study should be
11 uniform and systematic, considering such features as
12 location, extent, incidence, and severity.

13 No single adhesion assessment tool is used
14 by investigators uniformly, but the American Fertility
15 Society scoring system for adnexal adhesions was cited
16 as the method most commonly employed by gynecological
17 surgeons.

18 Next slide, please.

19 Now, I will review for you how we ended up
20 here today. The following is a synopsis of the
21 regulatory history of the submission under
22 consideration.

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1 In 1995, following a pilot study to assess
2 safety and to gauge sample size calculations, FDA
3 cleared an IDE for the INTERGEL pivotal trial. This
4 slide is the study hypothesis for the clear protocol
5 developed in collaboration with FDA.

6 The objective of this multi-center trial
7 is to assess the safety and efficacy of INTERGEL in
8 preventing or reducing adhesions in patients
9 undergoing peritoneal cavity surgery.

10 The study protocol cleared by the division
11 as the basis for a pivotal trial in support of the PMA
12 was clearly designed to measure adhesions. The
13 INTERGEL clinical trial utilized the AFS scoring
14 system to assess in a systematic and uniform manner
15 the incidence, extent, and severity of adhesions at 24
16 anatomical sites, prospectively in all patients in a
17 blinded manner at every center in the same way. A
18 reduction in the mean score of all 24 sites evaluated
19 was designated as the primary endpoint for this trial.

20 The INTERGEL trial was multi-center,
21 prospective, randomized, controlled, blinded. It
22 required two invasive procedures: a laparotomy

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1 followed by a second laparoscopy.

2 This was an extremely resource intensive
3 trial. It required over two years to accrue subjects
4 to this study. It could not be repeated today given
5 the minimally invasive surgical techniques used and
6 increasing reliance on in vitro fertilization.

7 Further, I must point out that investing
8 in the development of adhesion prevention problem
9 products is problematic when six years after the
10 initiation of a study, such as this one, we are still
11 discussing whether or not adhesions are an endpoint.

12 At least six products of which we are
13 aware are in various stages of development for
14 nonsurgical site adhesion prevention as adjuncts to
15 good surgical technique. These development programs
16 are on hold, pending a consensus by the regulatory --
17 pending action by the regulatory community that is in
18 agreement with clinical experts on this matter.

19 Next slide, please.

20 In 1999, the INTERGEL PMA was filed with
21 FDA and granted expedited approval status on the basis
22 of an unmet public health need. The proposed intended

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1 use was supported by statistically significant
2 differences in a prospectively identified primary
3 endpoint and secondary endpoints. That proposed
4 intended use was as follows.

5 As a single use IP instillate reduction of
6 adhesions following gynecologic pelvic surgery. It
7 has been shown to reduce the incident, extent, and
8 severity of post surgical adhesions throughout the
9 abdominal cavity when used as an adjunct to good
10 surgical technique during laparotomy procedures.

11 In the course of the review of this PMA,
12 FDA asked for additional information. In December of
13 1999, about one month before the General and Plastic
14 Surgery Devices Advisory Committee was going to
15 consider the approvability of this PMA, the sponsor
16 received a letter from the agency requiring more
17 information, including, number one, a supplemental
18 infection potentiation study in rats, a larger study
19 than the previous one that was negative.

20 Secondly, FDA required that the sponsor
21 submit AFS scores. These were part of the conditions
22 of approval.

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1 Obviously with one month prior to a panel
2 meeting, the animal safety study -- there was not
3 enough time to conduct the animal safety study.

4 Next slide, please.

5 When the general Plastic Surgery Devices
6 Panel convened to consider the original INTERGEL PMA
7 in January of 2000, as I said, a supplemental
8 infection potentiation study in rats was not yet
9 completed. As you will note from having read the
10 panel transcripts, FDA questioned the clinical
11 significance of the study hypothesis developed in
12 1995, adhesion reduction.

13 At that panel meeting, the required
14 analysis of AFS scores was not considered due to time
15 constraints. That is also reflected in the record.

16 Finally, as noted in the panel
17 transcripts, FDA had concluded that the rate of
18 infection with INTERGEL was higher than that in
19 control. That panel was told that among the four
20 cases cited in the INTERGEL group -- I'm sorry -- the
21 panel was not told that among the four cases of
22 postoperative infection cited in the INTERGEL group,

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1 the panel was not told that one was a case of chicken
2 pox and one was a head cold. This was an unfortunate
3 misunderstanding that had a significant impact on the
4 vote.

5 The panel voted five to two against
6 approval of the PMA, citing concerns about safety, the
7 need for the completion of an additional animal
8 infection potentiation study, and questions about
9 clinical utility.

10 Interestingly, just two weeks later, a
11 different advisory panel convened by FDA, the
12 Obstetrics and Gynecology Devices Panel that I've
13 previously mentioned, met and agreed that adhesion
14 reduction is, in fact, a suitable endpoint as an
15 adjuvant for this intended use.

16 Next slide, please.

17 In June of 2000, the sponsor, following
18 discussions with FDA, submitted an amended PMA to
19 address each of the concerns raised by the GPS Panel
20 at FDA. That is the submission before you today.

21 No FDA advisory panel has ever considered
22 this submission or these data in the context of this

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1 intended use.

2 The product has a revised intended use
3 narrowed to reflect the adhesion assessments in the
4 pivotal trial that speak directly to clinical outcomes
5 of accepted importance to gynecologic surgeons:
6 namely, adnexal adhesions, reformed adhesions, and
7 surgical site adhesions. This is an OB-GYN indication
8 as opposed to a general surgery indication. The
9 adhesion assessment data in support of this intended
10 use were prospectively gathered and provided in the
11 original PMA.

12 The PMA as amended provides a systematic
13 review of the clinical literature validating that
14 assessment of adnexal adhesion scores using the AFS
15 score as a valid prognostic tool. INTERGEL

16 The PMA as amended also provides the new,
17 larger infection potentiation study in rats, which was
18 required by FDA. It was negative, as were the results
19 of an earlier, smaller study.

20 Since this meeting almost two years ago,
21 INTERGEL has been marketed all over the world, with
22 approximately 35,000 units sold. So we now have the

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1 benefits of more clinical experience. This broad
2 clinical experience confirms the safety and
3 performance of the product. There is no data to
4 suggest that there is an increased risk of infection.

5 The PMA as amended also provides
6 statistical analyses and resolution of statistical
7 issues raised by the advisory panel and FDA, including
8 the issues of poolability and incomplete
9 ascertainment, although we note that at the original
10 panel, Dr. Metz concluded that the data can be pooled.

11 Today you have the benefit also of expert
12 opinion. These data -- this peer review of the
13 clinical trial was not available two years ago to FDA
14 or to the original GPS Advisory Panel. Leaders in the
15 field of reproductive medicine, obstetrics, and
16 gynecology, adhesion pathophysiology management, and
17 postoperative infection have reviewed this submission
18 before you in depth and agree that the product is safe
19 and effective for the intended use.

20 It has also been peer reviewed by a panel
21 of experienced and well qualified statisticians who
22 conclude that the sponsor's analysis is sound.

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1 And finally, very importantly, you are the
2 first panel to consider an adhesion prevention
3 adjuvant following the consensus reached by the OB-GYN
4 Advisory Panel on barrier adhesion products. At that
5 panel it was agreed that adhesions are an endpoint,
6 not a surrogate.

7 This is the first opportunity to act on
8 that medical consensus in a forum that contributes
9 directly to an improvement in public health.

10 Next slide, please.

11 There is consistent evidence, as you will
12 hear, that INTERGEL is effective. The product has
13 been shown to be effective in a well designed,
14 controlled clinical trial. The primary and secondary
15 outcomes of the study endpoints, all measures of
16 adhesion incidents, it's extent and severity
17 consistently demonstrate an improvement compared to
18 control, which was lactated Ringer's solution.

19 The effectiveness established in the
20 pivotal trial for INTERGEL confirm the findings of the
21 pilot study in which reduction and adhesion formation
22 was observed.

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1 Review of these data by leaders in the
2 field led them to conclude that the manner of
3 assessing adhesions in this trial is, in fact,
4 appropriate. The magnitude of the changes observed
5 compared to control are clinically significant and
6 meaningful. A substantial proportion of the
7 population benefitted, and the benefits of the product
8 outweigh the risks.

9 You have their consensus report in writing
10 for the record, and they are here to speak with you
11 today.

12 In addition to the clinical data, the
13 effectiveness of INTERGEL in reducing adhesions is
14 supported by data gathered in animal models and the
15 mechanism of action, that is, as a resorbable barrier
16 adhesive, a mechanism of action that shares in common
17 with the two site specific products on the market.

18 Next slide, please.

19 The evidence is consistent that INTERGEL
20 is safe. The product has been shown to be safe both
21 in clinical use and in animal studies. The pilot
22 study of INTERGEL was a safety study. It generated no

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1 data of concern with regard to infection or any other
2 adverse event.

3 The pivotal trial of INTERGEL confirms the
4 safety of the product. No adverse events, including
5 postoperative pelvic infections occurred at a higher
6 rate compared to control.

7 The post marketing experience with
8 INTERGEL, approximately 35,000 units sold as Iaset
9 (phonetic) confirms the safe profile and has over the
10 last three years raised no issues of concern. The
11 infection potentiation study in rats was negative the
12 first time and the second time.

13 FDA has raised the concern that patients
14 treated with INTERGEL may have increased risk of
15 postoperative infections despite the data I have just
16 summarized. As part of the clinical review of these
17 data by experts, a complete and independent review of
18 the patient records from the pivotal trial was
19 undertaken to examine the safety results.

20 Dr. Sebastian Faro and Dr. John Sever
21 developed a protocol and a criteria for the review of
22 these data. The conclusion of their exhaustive review

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1 is that the postoperative pelvic infection rate
2 between INTERGEL and control is not different, and
3 differences in the absolute number of cases reported
4 are not clinically meaningful.

5 You will have an opportunity to hear from
6 them directly today.

7 Also, I will note what you are well aware
8 of, that within our common adverse event occurring at
9 less than five percent incidence, a clinical trial of
10 approximately 12,000 subjects would be required to
11 determined the true incidence of postoperative
12 infection. Such a study could never be conducted
13 premarketing and is not warranted by this body of
14 evidence.

15 Next slide, please.

16 The statistical methods used in this trial
17 are salient. FDA has questioned many aspects of the
18 statistical method applied to the INTERGEL pivotal
19 trial. Some questions were discussed at the advisory
20 panel meeting and during the review process of the
21 PMA.

22 The statistical methods applied to the

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1 analysis of this data set are entirely appropriate.
2 The sponsor has responded thoughtfully and rigorously
3 to every concern raised by FDA.

4 The sponsor requested a peer review of
5 these data by three well qualified experts who
6 confirmed that the analysis as presented in the PMA,
7 the analyses, are appropriate, and the results of the
8 trial robust.

9 Their opinion has been provided to you in
10 writing for the record, and you will hear from them
11 directly today.

12 The sponsor did adhere to the data
13 analysis plan in the study protocol. All data
14 analyses were conducted in accord with good
15 statistical practices, ICH standards, and sound
16 clinical and statistical rationale.

17 It is appropriate to utilize the data from
18 all centers. The sponsor properly considered the
19 impact of missing data at second look in complete
20 ascertainment, including utilizing a worst case
21 imputation methodology required by FDA in the protocol
22 cleared in 1995.

1 You should note that this worst case
2 imputation methodology has no sound clinical or
3 statistical rationale, but was provided as required by
4 FDA.

5 This is the misnamed ITT analysis that you
6 have seen referred to in documents from the agency.
7 You will note that even with application of this
8 unscientific worst case imputation, the primary
9 endpoint of the INTERGEL trial was still statistically
10 significant compared to control.

11 We conclude that the statistical questions
12 related to this trial have been resolved and welcome
13 your experienced peer review of the methods utilized.

14 Next slide, please.

15 Finally, I have put up here the intended
16 use for the submission under consideration today. It
17 is very important to distinguish correctly between the
18 intended use of a product and a study hypothesis. The
19 data gathered in a trial or trials and all of the
20 available data is what drives the statement of
21 intended use of a product, and of course, it is the
22 data that determines the labeling in its entirety,

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1 including adequate directions for use, warnings,
2 precautions and claims.

3 The original intended use for this product
4 is, in the opinion of the sponsor, well supported by
5 the data in the original PMA. However, since the GPS
6 Advisory Committee and FDA questioned the clinical
7 utility of adhesion reduction, the sponsor proposed a
8 more narrow intended use from the same data set.

9 Specifically a new intended use, a new
10 product was provided to the agency and is the
11 submission under review today. The intended use is as
12 follows.

13 INTERGEL solution is a single use IP
14 instillate indicated to reduce the likelihood of
15 developing moderate or severe postoperative adenocele
16 adhesions in patients undergoing adhesiolysis or
17 myomectomy during conservative gynecologic pelvic
18 surgery by laparotomy when used as an adjunct to good
19 surgical technique.

20 INTERGEL solution was also shown to reduce
21 adhesion reformation to sites in addition to the
22 adnexa and adhesion formation at surgical sites,

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1 including the anterior abdominal incisions.

2 I want to emphasize that this is not a
3 subset analysis. This is not a retrospective
4 analysis, and this is not an inappropriate ad hoc
5 analysis. This intended use reflects the data
6 prospectively gathered in all study subjects. Ten of
7 the 24 anatomical sites assessed were the tubes and
8 the ovaries.

9 These data were provided in the original
10 study cohort, and additional analyses were provided in
11 the PMA as amended to support this label.

12 The submission you're considering today
13 provides a scientifically sound resolution to
14 questions of clinical utility, safety, and statistical
15 methodology.

16 Last slide, please.

17 Finally, this slide summarizes for you the
18 primary and secondary endpoints prospectively
19 identified in the INTERGEL clinical trial. It also
20 provides the endpoints relied upon in the approval of
21 INTERCEED Seprafilm for comparison.

22 All of these products rely on adhesions as

1 the endpoint. The magnitude of the effects reserved
2 for these adjuvants is comparable. The data on
3 INTERGEL is consistent and, in the sponsor's opinion
4 and in the opinion of experts in the field,
5 compelling.

6 The AFS scores listed here were provided
7 in the original clinical study report and were
8 required by FDA.

9 Adhesions following gynecologic surgery is
10 an important problem for women that requires attention
11 now. Your due consideration of this submission is
12 very much appreciated.

13 I will now introduce you to Dr. Doug Johns
14 from Gynecare/Ethicon R&D, who designed the INTERGEL
15 pivotal trial with Dr. Gere diZerega.

16 DR. JOHNS: Good morning. My name is Doug
17 Johns. I'm an employee of Gynecare and a consultant
18 to LifeCore Biomedical.

19 I will be presenting an overview of the
20 INTERGEL pivotal clinical trial design and the data.

21 A pivotal multi-center study was initiated
22 to assess the safety and efficacy of INTERGEL in

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1 reducing adhesions in patients undergoing peritoneal
2 cavity surgery by laparotomy, with a planned second
3 look.

4 The study was a third party blinded,
5 randomized, concurrent control design. It was carried
6 out at 11 centers in the United States and give
7 centers in Europe.

8 Female patients 18 to 45 years of age
9 undergoing peritoneal cavity surgery by laparotomy
10 with a planned second look received 300 milliliters of
11 INTERGEL or lactated Ringers just prior to closure.

12 The analysis plan and the protocol
13 specified all treated patients were to be evaluated
14 for safety and all evaluable patients were to be
15 evaluated for efficacy, and an evaluable patient was
16 defined as all patients that completed the second look
17 laparoscopy.

18 The protocol also included an FDA required
19 intent to treat analysis, which required a worst case
20 imputation for missing data at second look.

21 In addition, the protocol also defined a
22 subset of this previous group which excluded subjects

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1 who refused second look for reasons unrelated to the
2 device and informed censoring analysis.

3 It is important to note that the protocol
4 did not identify the intent to treat population as the
5 primary analysis; that this worst case was done
6 because the agency insisted upon seeing it; and at the
7 same time encouraged us to do other analyses, which we
8 felt were more appropriate.

9 This presentation will focus on the
10 evaluable population for efficacy and all treated
11 patients for safety. The intent to treat analyses
12 referred to will be discussed in detail by our
13 statistical experts later.

14 Adhesions were assessed at 24 anatomical
15 sites at the initial laparotomy procedure and, again,
16 at second look. The 24 sites throughout the
17 peritoneal cavity included 16 pelvic sites and eight
18 abdominal sites. The 24th site, the interior
19 abdominal incision, was the laparotomy incision from
20 the first surgery. So there were 23 sites assessed at
21 the first operation and 24 assessed at the second
22 look.

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1 An adhesion assessment chart was used by
2 investigators to capture the data. If an adhesion was
3 present for each site, it was marked yes or no. If an
4 adhesion was present, the severity of that adhesion
5 was then determined. Filming avascular adhesions were
6 considered mild, while organized, cohesive, vascular
7 and/or dense adhesions were considered severe.

8 Extent was also captured for each site
9 where an adhesion was present. Adhesions were
10 considered to be localized if less than one third of
11 the site was involved with adhesions. It was moderate
12 if between one third and two thirds of the site was
13 involved with adhesions, and extensive if more than
14 two thirds of the site was covered. This, in fact, is
15 the AFS methodology.

16 After the characteristics of the adhesion
17 were established, the surgeon would indicate whether
18 or not the adhesion was lysed and, if so, by which
19 method. The methods included sharp dissection,
20 cautery, laser, or blunt dissection.

21 In addition to adhesiolysis, other
22 surgical intervention at each of the anatomical sites

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1 was captured. The presence of endometriosis was
2 specifically noted if it was surgically treated, and
3 if so, how, which method.

4 If other surgery was done, that is, other
5 than adhesiolysis or other than surgical treatment of
6 endometriosis, this was also noted, and the use of
7 sutures at each of the anatomical sites was also
8 noted.

9 From this data, all of the primary and
10 secondary endpoints prospectively identified in the
11 protocol can be calculated.

12 Postoperatively, patients were monitored
13 for adverse events and medications were tracked
14 throughout the study. Laboratory evaluations and
15 abdominal auscultation percussion were carried out at
16 day three, and between days seven and 28, and finally
17 a second look was carried out at six to 12 weeks
18 following the initial surgical procedure.

19 The primary efficacy identified in the
20 protocol, which was intended to support a general
21 surgery label, was an adhesion score using the
22 adhesion scoring method of the American fertility

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1 society applied to these 24 sites. We've termed this
2 the modified AFS score, of mAFS.

3 The focus of the analysis for the June
4 2nd, 2000 amendment was changed to provide our results
5 in a clinically relevant context, that is, the AFS
6 score for adnexal adhesions. It is important to note
7 that the AFS data was required by FDA. Data from all
8 patients who had second look were included, and the
9 data used to calculate the score was prospectively
10 collected and presented in the original clinical trial
11 report.

12 The June 2nd amendment also includes
13 additional analyses of these data in response to the
14 points raised by the panel and FDA and as Dr. Becker
15 alluded to earlier.

16 Secondary endpoints included adhesion
17 incidents which was expressed as a proportion of sites
18 with adhesions as determined by the number of sites
19 divided by the number of possible sites with
20 adhesions.

21 Adhesion extent was determined using a
22 three point scale, and adhesion severity was

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1 determined using a three point scale as well.

2 Other secondary analyses specified in the
3 protocol included the different adhesion categories,
4 of course, all adhesions, reformed adhesions, de novo
5 adhesions.

6 The de novo category included surgical
7 site and nonsurgical site de novo adhesions.

8 And finally, all surgical site adhesions,
9 which includes both free formed adhesions and de novo
10 surgical site adhesions.

11 We also did analysis by surgical
12 procedure. This was not specified in the protocol,
13 but was done at the request of FDA.

14 Turning to the study results, 281 of the
15 303 patients that were randomized for the study were
16 treated. Two hundred and 65 of these patients
17 completed the study which included a second look
18 laparoscopy. That leaves 16 patients, which is less
19 than six percent, who discontinued from the study
20 after receiving treatment.

21 The reasons patients did not return for
22 second look is shown for you here. One patient was

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1 pregnant. One patient had a failed laparoscopy due to
2 obesity. Seven patients had no complaints, but simply
3 did not want a second surgery. Six other patients had
4 some complaints, but also did not want a second
5 surgery, and one patient was truly lost to follow-up.

6 So if you exclude patients who did not
7 return for reasons unrelated to the device, you're
8 left with four treatment patients and three control,
9 the ones on the bottom.

10 Surgical procedures. Myomectomy was by
11 far the most common procedure performed.
12 Approximately 70 percent of the patients in the study
13 had a myomectomy procedure.

14 Adhesiolysis was second. Approximately 50
15 percent of the patients.

16 Ovarian procedures and tubal procedures
17 were also fairly common, as was surgical treatment of
18 endometriosis.

19 Dr. Becker has already mentioned pooling
20 of the data, and our experts will be discussing that
21 topic in more detail in a little while, but it's
22 important to note some of the primary considerations,

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1 and to this end, I would like to share some of the
2 European and U.S. data as it is appropriate.

3 As you'll see on this slide, myomectomy
4 was the most common procedure in the United states,
5 around 70 percent of the patients, followed by
6 adhesiolysis, which was on the order of 35 to 40
7 percent.

8 This trend was reversed in Europe.
9 Approximately 40 percent of the patients in Europe
10 underwent myomectomy, and approximately 70 percent of
11 the patients underwent adhesiolysis.

12 However, these surgical procedures carried
13 out in the U.S. and in Europe were anticipated and
14 allowed for under the protocol. They involved similar
15 surgical technique and differed only in their overall
16 percentages in the two populations.

17 Now, for the data. At baseline patients
18 in the INTERGEL group were similar to patients in the
19 lactated Ringer's control group. The number and
20 proportion of adhesions and the modified AFS score,
21 severity, extent, and AFS scores were all similar,
22 indicated here by the nonsignificant p values.

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1 Therefore, the amount of adhesions
2 remaining after surgery was also similar following the
3 surgical intervention shown for you here. Most of the
4 adhesions were lysed. Similar amounts of additional
5 surgery were done. So what was left behind was a
6 small number of adhesions.

7 At second look, the original primary
8 efficacy variable, the modified AFS score was reduced
9 from 2.18 to 1.21. This result was highly significant
10 and amounted to a 44 percent reduction.

11 The modified AFS score was also
12 significantly reduced in the U.S. and European
13 populations. That data is shown here. Note that the
14 treatment group and control group baseline in the
15 United States is similar. The treatment group and
16 control group baseline data in Europe is similar.

17 However, the baselines in Europe were
18 higher than that in the U.S. The different baseline
19 starting points are a direct result of the difference
20 in the percentages of the surgical procedures carried
21 out.

22 Patients undergoing myomectomy procedures

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1 tend to start out with a very low baseline modified
2 AFS score, and this score goes up at second look.
3 INTERGEL significantly reduces adhesions, however, for
4 the myomectomy population shown through here.

5 Now, considering the myomectomy patients
6 in both the U.S. and Europe, you can see that similar
7 trends are observed. In the U.S. and in Europe, both
8 populations start off with a low baseline and increase
9 at second look. In both populations INTERGEL reduces
10 adhesions.

11 Patients undergoing adhesiolysis tend to
12 start off with a higher baseline adhesion score, as
13 shown for you here, and INTERGEL significantly reduces
14 adhesions at second look compared to control.

15 As you would expect, baseline adhesion
16 scores for the U.S. and European patients followed the
17 same trend. Again, similar control and treatment
18 groups at baseline and similar trends in the U.S. and
19 Europe.

20 Now, to the AFS score. At baseline, the
21 treatment and control groups were similar, as I told
22 you, and at second look, the AFS score was reduced by

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1 61 percent, from a mean score of 4.23 to a mean score
2 of 1.67. This result was highly significant.

3 The secondary efficacy variables were also
4 reduced by INTERGEL. The proportion, extent, and
5 severity were reduced by 17 percent, 27 percent, and
6 32 percent respectively.

7 Reductions for each adhesion type were
8 also observed. The proportion of reformed adhesions
9 was reduced by 31 percent. Surgical site de novo
10 adhesions, 23 percent.

11 The reduction in the proportion of de novo
12 adhesions was not statistically significant, although
13 the trend was in favor of INTERGEL. However, the
14 extent and severity of each adhesion type as shown for
15 you here was significantly reduced in all cases.
16 These numbers ranged in the 30 percents for reduction
17 across the board for the different adhesion
18 categories.

19 The modified AFS score, the primary
20 variable for all of these adhesion types, was also
21 reduced for each of these adhesion types. These
22 reductions ranged from 45 to 49 percent. These

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1 results were all statistically significant.

2 Now, while these averaging techniques can
3 be used to compare treatment and control adhesion
4 reduction, they tend to obscure individual patient
5 benefits, and you're left with the question: what
6 does it mean to reduce a mean score from a two to a
7 one?

8 The means can be looked at to test for
9 statistical difference between the treatment and
10 control groups, and I've just shared that with you.
11 to answer the question of clinical significance, one
12 must look at the results on a patient-by-patient
13 basis.

14 Individual patient results can be
15 ascertained by evaluating the number of patients who
16 shift from one AFS category to another. Now, recall
17 the AFS score for adnexal adhesions was developed to
18 provide a way of assessing the patient's adhesion
19 status, but also to provide a prognostic indication.

20 The prognostic indication is shown for you
21 here. Minimal adhesions are defined as AFS scores
22 between zero and five; mild, AFS scores between six

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1 and ten; moderate, AFS scores between 11 and 20; and
2 severe, AFS scores between 21 and 32.

3 Note in the INTERGEL group, 109 patients
4 started off with minimal adhesions. Of these 109, 103
5 remained minimal; four became mild; one became
6 moderate; and one became severe.

7 Similarly, 109 patients in the control
8 group had minimal scores at baseline. Of these, 96
9 remained minimal; six became mild; three became
10 moderate; and four became severe.

11 Overall, at second look there are more
12 INTERGEL patients in the minimal category -- next
13 slide, Gary -- compared to control. There were 121
14 patients with minimal compared to 105 in the control
15 group, and there were fewer patients in each of the
16 mild, moderate, and severe categories.

17 In fact, the number of patients with
18 moderate and severe adhesions was reduced -- next
19 slide, Gary -- from 17 in the control group to only
20 three in the INTERGEL group, 17 moderate and severe to
21 three moderate and severe.

22 Analysis using the Cochran-Mantel-Haenszel

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1 test controlling for baseline level indicates a highly
2 significant p value.

3 Now, the published literature indicates
4 that patients with minimal and mild adhesions tend to
5 do well compared to patients with moderate to severe
6 adhesions. Our clinical experts agree with this
7 conclusion as well, and as a result, we've combined
8 these groups into what we've termed a binary analysis
9 where patients with moderate to severe adhesions are
10 considered to be treatment failures.

11 Only three of the 122 patients, INTERGEL
12 patients, shifted from the minimal-mild category to
13 the moderate-severe category compared to ten of the
14 117 control patients.

15 All nine patients in the INTERGEL group
16 that started off in the moderate-severe category
17 improved to the minimal-mild category. This is
18 compared to only ten of the 17 control patients.

19 Overall, only three patients in the
20 INTERGEL group had moderate or severe adhesions. This
21 is two percent compared to 17 percent or 13 percent of
22 the control population.

1 The reduction in treatment failures from
2 13 percent to two percent is not only statistically
3 significant; it is clinically significant as well.

4 I think it's also important to note that
5 ten, over half of the control group treatment
6 failures, came from patients who started out with
7 minimal or mild adhesions or patients who did not have
8 an adhesion problem prior to their first surgery.

9 Analysis of the failure rate by surgical
10 procedure was also carried out. In all cases the
11 INTERGEL patients' risk of treatment failure was
12 reduced compared to control. For the two most common
13 procedures, myomectomy and adhesiolysis, this result
14 was highly significant.

15 Now, as previously mentioned, the FDA was
16 concerned about the continent enrollment, U.S. and
17 Europe, and the adhesiolysis status, that is, whether
18 the patient had no adhesions, minimal mild adhesions
19 at baseline or moderate or severe adhesions.

20 To respond to this, a Cochran-Mantel-
21 Haenszel analysis was performed that evaluates the
22 percentage of patients with moderate or several AFS

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1 scores at second look stratified by continent of
2 enrollment and adhesiolysis category. This table
3 presents those results.

4 Note that the computation of the common
5 relative risk is justified by the nonsignificant
6 Breslow-Day (phonetic) test of homogeneity and after
7 adjustment for continent and for adhesiolysis
8 category, there remains a fivefold reduction in the
9 risk of moderate or severe adhesions, and that result
10 is highly significant.

11 This is consistent with the same CMH
12 analysis stratified for an adhesiolysis subgroup only,
13 as well as the unstratified analysis. The similarity
14 and consistency of these results indicate that the
15 adjustment for continent and/or adhesiolysis status
16 had little impact on the risk of developing moderate
17 or severe adhesions at second look.

18 Turning now to safety, the safety
19 assessment of INTERGEL includes the preclinical
20 studies, the adverse events, laboratory evaluations,
21 medications, and gross observations from second look
22 from the clinical studies, as well as our INTERGEL

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1 post marketing experience.

2 You've heard most of this previously from
3 Dr. Becker, but I'd like to review the adverse event
4 data from the pivotal study in a little more detail.

5 I apologize for the busy slide.

6 The incidence of commonly reported adverse
7 events is shown for you here, presented by body
8 system. This list includes all AEs that were reported
9 for five percent or more of the patients in either
10 group. The only event that reached statistical
11 significance was allergic reaction.

12 However, it was the lactated Ringer's
13 group that at a higher proportion of this event, upon
14 closer scrutiny, however, you'll note that it was, in
15 fact, seasonal allergies that were being coded under
16 this heading and not actual allergic reactions to the
17 product.

18 You'll also note that infection was not
19 listed in this table because it was not observed in
20 five percent of the patient population, and this is
21 not surprising as our clinical experts have advised
22 us. They would expect infection rates for the

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1 gynecologic surgery population in this study to range
2 from between 2.4 to 3.3 percent.

3 At the previous GPS panel meeting, the
4 agency reported a four to one risk of increased
5 infection for the INTERGEL patients. The data that
6 led to this statement was the adverse event code for
7 infection, for the body as a whole system, for the
8 U.S. population only.

9 In fact, there were four INTERGEL patients
10 and one control patient in the patient listing. The
11 event that led to two of the INTERGEL patients being
12 coded as having an infection were chicken pox and a
13 head cold.

14 Subsequently, we have reviewed the data in
15 detail, and we have had independent clinical experts
16 that you will hear review the data in detail. If you
17 include all wound infections and all infections coded
18 by the investigators as possibly being related to
19 treatment, you will find ten INTERGEL patients and
20 four control patients.

21 This still includes patients being coded
22 as having an infection who had chicken pox and a head

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1 cold, as well as a patient with a bladder infection,
2 a patient with a positive chlamydia culture at the
3 time of surgery, and a patient with a vaginal fungal
4 infection. Clearly some of these infections are
5 unrelated to the device.

6 In fact, the investigators coded only four
7 of these events as being possibly related, three
8 treatment and one control. As you will hear from our
9 clinical experts, when the data are considered
10 appropriately there is no difference in the infection
11 rate between INTERGEL and control.

12 In summary, I'd like to remind the panel
13 that the primary and nearly all of the secondary
14 variables were significantly reduced by INTERGEL and
15 that the safety of INTERGEL in this surgical
16 population was comparable to lactated Ringers.

17 The mAFS scores and the AFS scores were
18 all reduced. The proportion of adhesions was reduced.
19 The number of treatment failures was reduced, and
20 different types of adhesions were all reduced.
21 Clearly, the data obtained in this prospective,
22 blinded, multi-center trial demonstrated that INTERGEL

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1 adhesion prevention solution reduced adhesions
2 compared to good surgical technique plus Ringer's
3 lactate.

4 That these reductions are clinically
5 meaningful will now be assessed by our clinical
6 experts, and thank you for your attention.

7 I'd now like to introduce Dr. Luigi
8 Mastroianni, who is the William Goodell Professor of
9 Obstetrics and Gynecology and the former chairman of
10 obstetrics and gynecology from the University of
11 Pennsylvania School of Medicine.

12 Dr. Mastroianni.

13 DR. MASTROIANNI: Good morning.

14 May I have the microphone here?

15 DR. JOHNS: It works.

16 DR. MASTROIANNI: Yes. As you've heard,
17 I'm Luigi Mastroianni, and I'm Professor of OB-GYN at
18 the University of Pennsylvania, where I've been
19 working in the field of infertility and in basic
20 aspects of reproductive biology for at least three
21 decades.

22 My areas of interest are fallopian tube

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1 function and the function of the adnexas specifically,
2 and clinically I've been vitally interested in the
3 surgical approaches to infertility and to the
4 reproductive tract.

5 My introduction to INTERGEL came when I
6 was asked to join a group of clinical experts to
7 consider issues related to INTERGEL this last year.
8 I have no financial interest at all in INTERGEL or in
9 the company, nor do I have any financial interest in
10 any device companies. I'm being compensated for my
11 time and being reimbursed for my expenses.

12 Well, we were asked to review voluminous
13 data most of which has been reviewed in previous
14 presentations, and we were asked to look at the
15 clinical data on safety and effectiveness and to
16 consider the study design and methodology for
17 assessing adhesions and clinical significance of the
18 findings and also the potential for increased risk of
19 infection.

20 The clinical experts who were involved in
21 this endeavor included Alan De Cherney, professor and
22 chairman at the University of California in Los

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1 Angeles; Harold Ellis from the University of London;
2 Sebastian Faro from the University of Texas Health
3 Sciences Center; and Lena Holmdahl from Goteborg
4 University in Sweden; and Russ Malinak from Baylor
5 College of Medicine; Mark Martens, who's Chairman of
6 Obstetrics and Gynecology of Franklin Square Hospital
7 in Baltimore; and John Sever, Professor of Pediatrics,
8 Obstetrics and Gynecology, Microbiology and Immunology
9 at George Washington University in this city.

10 And each panel member independently
11 reviewed all of the relevant data, and it was
12 voluminous, many inches, and the data which we
13 considered and the documents which we considered are
14 listed in this slide, and I won't read them, but the
15 panel met and jointly provided a consensus opinion,
16 which you have, I think, in your packets.

17 And actually the consensus opinion found
18 that there was a valid and reliable body of evidence
19 which had been provided to support the conclusion that
20 INTERGEL is an effective adjunct for the reduction of
21 post surgical adhesions in gynecologic surgery, and
22 the study design, execution and analysis provide valid

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1 data to support the proposed intended use.

2 And finally, the benefit of INTERGEL use
3 for the labeled indication outweighs any potential
4 risks.

5 The sponsor has provided valid scientific
6 evidence to demonstrate that the product does not pose
7 an unreasonable risk of injury or illness.

8 Well, today we are going to focus on four
9 areas. We'll review the validity of the study design.
10 I'll do that, and then Dr. DeCherney will discuss
11 methodology for assessing adhesions, and the clinical
12 significance of same.

13 And then Dr. Faro will speak specifically
14 to the issue of increased infection or infection
15 overall associated with the use of the product.

16 Now for the validity of the study design.
17 The committee found that it was really exceptionally
18 good. It was a multi-center, randomized, prospective,
19 blinded, controlled trial in women undergoing pelvic
20 gynecologic surgery by a laparotomy. The study
21 included centers in the U.S. and Europe. European
22 patient characteristics were reviewed, demographics,

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1 baseline adhesions, surgical procedures, results, and
2 they do not confound or bias the study.

3 There was randomization at each study
4 center. Adhesion assessment procedures were uniform.
5 Baseline adhesions were comparable between INTERGEL
6 and control group, and there was a single protocol
7 which was used.

8 The design addresses clinical utility.
9 Adhesions are a clinically valid endpoint, in our
10 opinion, and not a surrogate. Adnexal adhesions do
11 impair fertility. Reformed adhesions, de novo
12 adhesions, adhesions at the surgical site, other
13 anatomical sites are undesired. Adhesions are the
14 enemy in reproductive surgery.

15 Other outcome studies premarketing are
16 really not feasible, and this has been spoken to by
17 earlier presenters. I mean, bowel obstruction is very
18 rare. It's clearly a major complication of
19 myomectomy, an operation which I've been involved in
20 for many, many years. It's so important to give women
21 an option of preserving their reproductive function
22 even into the late reproductive years in the times,

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1 and myomectomy is an operation which is increasingly
2 used for that purpose, and adhesions are still one of
3 the major complications.

4 And bowel obstruction, although it does
5 not occur very commonly, is a serious, serious issue.

6 Fertility is an endpoint. Well, it's
7 multi-factorial, very long in duration. There are
8 alternative treatments.

9 Pain can be transient, subjective,
10 variable in its etiology and be very hard to use that
11 as an endpoint, the improvement of pain.

12 And as for the logistics, the accrual
13 rate, sample sizes, and duration of studies, using any
14 of those endpoints would be just outrageously
15 prolonged and inexpensive and, I think, impossible.

16 Well, at this point I think we ought to
17 turn to the issue of the validity of the methodology,
18 and you know, we all look at data as we ready articles
19 and consider in each case the methodology which was
20 used to acquire those data.

21 And so Dr. DeCherney will speak to the
22 validity of the methodology for assessing adhesions.

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1 DR. DeCHERNEY: Thank you.

2 I'm Alan DeCherney. I have no financial
3 interest in INTERGEL or companies associated with
4 INTERGEL.

5 And today I'll address the American
6 Fertility Society evaluation of adhesions and
7 effectiveness as far as adhesion reduction and
8 INTERGEL as an adjunctive therapy.

9 Adhesions were evaluated in the INTERGEL
10 trial from observation at three sites on the ovary,
11 two sites on the fallopian tube, which is consistent
12 with the AFS method. This was published in 1988. It
13 is a scoring system which was a consensus statement by
14 the American Fertility Society, now the American
15 Society for Reproductive Medicine.

16 The data was prospectively gathered,
17 uniformly in both groups, and was an anatomically
18 correct calculation. Clinical literature and
19 experience indicate that the extent and severity of
20 adhesions correlates with fertility prognosis. This
21 is pretty much based on the surgical literature where
22 lysis of adhesions occurs and fertility is increased

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1 in patients. So it's based pretty much on the
2 surgical literature of which there is extensive
3 information.

4 The AFS scoring system provides a
5 standardized, functionally sound basis for quantifying
6 the impact of pelvic adhesions or fertility potential.
7 There's only one study that looks at this precisely.
8 This was published in Fertility and Sterility in 1994.
9 This, too, was a consensus statement, and found that
10 the interobservational correlation coefficient was 0.7
11 as far as the scoring system was concerned, and
12 actually when you looked at the high end, patients
13 with severe adhesions, the correlation coefficient for
14 observation was even higher.

15 The next slide just looks at three groups
16 of patients, all patients with myomectomy and
17 adhesiolysis, the two most commonly reported
18 procedures in this study utilizing INTERGEL and
19 compared to lactated Ringers as a control, and as
20 mentioned before, you can see the results are
21 statistically significant, and certainly clinically
22 significant as far as reduction of adhesions in those

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1 patients that have moderate and severe adhesions,
2 which are those patients most -- who have the most
3 compromised fertility because of the inability of the
4 ovary in the tube to be juxtaposed as far as ovulation
5 induction, ovulation and ovary capture is concerned.

6 The risk of moderate and severe adnexal
7 adhesions was reduced fivefold in the INTERGEL group
8 compared to the control group, as shown in the
9 previously slide, 13 versus two percent. Patients
10 with moderate to severe adnexal adhesions have little
11 to no likelihood of natural conception because of this
12 barrier that's presented between the two and the OS
13 site.

14 Now, the changes observed in the modified
15 AFS score, 61 percent reduction, for patients with
16 baseline to second look the shift scores that we just
17 demonstrated were statistically significant and
18 clinically meaningful. Obvious, those patients with
19 the most severe adhesions are those that have the most
20 compromised in their fertility.

21 The reason for the modified AFS score in
22 the original study was to make this a comparable study

1 for surgeons, as well as gynecologists. Other sites
2 included the bowel and omentum, things that were more
3 pertinent to the general surgeon than to the
4 gynecologic surgeon as far as postoperative adhesions,
5 especially bowel adhesions and bowel obstruction in
6 the future.

7 The effectiveness of INTERGEL in reducing
8 the risk of adnexal adhesion formation was observed
9 for all patients in subgroups of surgical procedures
10 in the trial as demonstrated with the all patients,
11 myomectomy and adnectal surgery.

12 So in conclusion, a consistent response in
13 reduced adhesion incidence was seen in other endpoints
14 as well. Certainly a 31 percent reduction in
15 reformation adhesions is impressive, as are the de
16 novo or surgical site adhesion reduction of 24
17 percent.

18 These, of course, are clinically important
19 results, as mentioned by the other panelists and the
20 speakers in the beginning of the program, as far as
21 fertility is concerned. The results are comparable to
22 previously approved adjuncts for site specific

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1 adhesion reduction.

2 And now Dr. Faro will discuss the risks.

3 DR. FARO: I'm Sebastian Faro,
4 obstetrician, gynecologist with a special interest in
5 infectious diseases, and I have no financial interest
6 in LifeCore, and they are reimbursing me for expenses
7 and paying for my professional time.

8 Dr. Sever and I independently reviewed the
9 clinical report forms of all patients with a mention
10 of infection in the report, and there were 30 INTERGEL
11 and 20 in the Ringer's lactate group. We identified
12 patients with possible treatment related pelvic
13 infections using predetermined diagnostic criteria and
14 clinical judgment, and we compared rates between
15 groups and drew conclusions.

16 The diagnostic criteria for pelvic
17 infection are well documented in our literature, and
18 to document a postoperative pelvic infection is more
19 subjective than it is on documented clinical findings,
20 but we do use criteria that are available to us.

21 Elevation in temperature and co-elevation
22 in pulse rate, elevated white count or a left shift

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1 with an increase in immature band forms, purulent
2 drainage from the site, and cellulitis are the
3 criteria that we use and will publish in our
4 literature.

5 The consensus agreement of patients with
6 possible treatment related postoperative pelvic
7 infections, in the INTERGEL group we have three, one
8 pelvic infection and two wound infections. In the
9 Ringer's lactated group there were three, one wound
10 infection -- correction -- two wound infections and
11 one pelvic infection.

12 When we compare the infection rates
13 between the study PI, the FDA auditor, and Dr. Sever
14 and myself, you can see in this table relatively there
15 were really no differences in the infection rates
16 between any of the analysis and between the two groups
17 in study.

18 The comparison of infection rate
19 assessment, the difference in number of possible
20 treated related pelvic infections between INTERGEL and
21 the control group are not statistically significant.
22 However, the conservative estimates for the

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1 gynecologic surgery were found, which ranged from 2.4
2 percent to 3.3 percent.

3 Febrile morbidity is a more common
4 diagnosis that's made in our patients after surgery,
5 and oftentimes misconstrued as infection. The
6 phenomenon is observed in women undergoing pelvic
7 surgery by laparotomy. Oftentimes this is due to the
8 surgical procedure itself or accumulation of blood.

9 Some patients with fever may have been
10 diagnosed with postoperative pelvic infection in the
11 absence of sustained elevated white counts and
12 clinical signs of infection, and these patients were
13 probably in the febrile morbidity group.

14 This slide characterizes what I'm talking
15 about and the difference. If you look at patients who
16 have fever and elevated pulse rate in the infected
17 patients, there is a parallel between the two. The
18 two findings actually parallel each other throughout
19 the course of the illness.

20 Where in the febrile morbidity group,
21 there's an elevation in temperature, but the pulse
22 rate tends to remain within the normal range.

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1 When we looked at adverse effects not
2 related to treatment, chicken pox is certainly not
3 related to the surgical procedure or Ringer's lactate
4 or INTERGEL. A head cold should not be construed as
5 a complication of the surgical procedure, nor should
6 cystitis or a urinary tract infection since most of
7 these patients, I would assume all of these patients
8 were catheterized at least once and had an ingrowing
9 Foley. So that's the risk factor for that.

10 Potentially significant adverse effects
11 that I would look for in using an agent instilled into
12 the peritoneal cavity would be the occurrence of
13 postoperative or interoperative pulmonary edema, which
14 there was none. There was no electrolyte imbalances.
15 There were no cases of anuria, and there were no cases
16 of immunosuppression. All of these factors would be
17 complications associated with infection.

18 So safety conclusions. Using accepted
19 clinical criteria for the diagnosis of pelvic
20 infection, we determined that the rate of treatment
21 related pelvic infection was comparable among INTERGEL
22 patients and controls. No other important adverse

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1 events were noted.

2 Concern over infection risk was not borne
3 out in the post marketing experience, two events out
4 of more than 35,000 units sold. The animal
5 potentiation study in a large number of rats was
6 negative and was not available to the GPS panel.

7 If you want to say that the rate model
8 that was used was a high risk, intra abdominal sepsis
9 model first described by Annie Honordunk (phonetic)
10 and John Bartlett and Sherry Gorbach, and not to find
11 an increase in that model with the INTERGEL group, I
12 think, is really important because that is a definite
13 significant high risk study model to be using for
14 intra abdominal sepsis.

15 And with that I would conclude.

16 Oh, I have one more slide. The study
17 design, execution, and analysis of the INTERGEL
18 adhesion prevention solution provides valid, reliable
19 data sufficient upon which to base the conclusions
20 supported for the proposed intended use. The benefit
21 of INTERGEL used for the label indications outweighs
22 any probable risk and the sponsor had provided valid

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1 scientific evidence to demonstrate that the product
2 does not pose an unreasonable risk of injury or
3 illness.

4 I'd like to close with one statement in
5 that. In the surgical procedures done in this study,
6 they are all low risk for infection because of the
7 nature of the surgery that was performed. The
8 evidence provided is reasonable and sufficient to
9 establish that the product is effective and that the
10 nature, extent, and magnitude of the reductions
11 observed are clinically significant.

12 There was no increase in infection among
13 those with INTERGEL. The absolute number of patients
14 who benefitted is a significant portion of the study
15 population.

16 Thank you, and I will pass on.

17 DR. COLTON: My name is Ted Colton, and I
18 have no vested interest for the sponsor, and I do hope
19 that the sponsor will pay for my expenses for coming
20 to this meeting.

21 I will give my credentials in just a
22 minute. I just want to note I don't know how often

1 statisticians are in the enviable position of being
2 the last in a presentation, having the wind-up
3 position at least with regard to the sponsor's
4 presentation, but in the unenviable position unless
5 things have changed of being what stands between a
6 much needed break after we finish.

7 In any event, I want to summarize a
8 consensus report that you all have, I believe, that I
9 and my two colleagues who looked at the INTERGEL
10 pivotal trial wrote after we had examined all the
11 accompanying documentation.

12 There are three parts to our presentation.
13 I want to describe briefly our credentials, again very
14 quickly go over what we reviewed, and unlike our
15 clinical colleagues, we identified six issues, six
16 statistical issues. I have four clinical issues, and
17 then each of us, each of the three of us will address
18 each of these six specific statistical issues, and
19 finally I will summarize our conclusions.

20 Next slide, please.

21 Okay. I'm Professor and Chair Emeritus,
22 meaning a step-down chair -- I'm not retired though --

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1 in the Department of Epidemiology and Biostatistics at
2 Boston University School of Public Health.

3 My colleague to the right, Steve
4 Piantadosi is Director of Biostatistics at the
5 Comprehensive Cancer Center at Johns Hopkins School of
6 Medicine.

7 And finally, last on my right is Don
8 Rubin, who is Professor and Chair of the Department of
9 Statistics at Harvard University.

10 I think you heard this before. I'll just
11 say we reviewed what we believe are all of the
12 relevant data of the PMA, as amended, et cetera.
13 You've heard this before. And after we did our
14 independent review, we convened and we jointly forged
15 the consensus opinion that we wish to present to you.

16 Our opinion concludes, our report
17 concludes that the trial provides valid scientific
18 evidence to base conclusions regarding the
19 effectiveness and safety of INTERGEL prior to
20 marketing. We concur with the sponsor that the trial
21 is well designed, and the analysis described in the
22 PMA as amended is scientifically sound.

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1 The analysis proceeded as described in the
2 protocol. Additional analyses were carried out at the
3 request of ODA, and we believe in accord with
4 appropriate statistical practices.

5 The results are statistically robust and
6 sufficient to support approval, and we did not
7 identify any methodologic or statistical issues that
8 were sufficiently critical or problematic that would
9 undermine the validity of the results.

10 We looked at all of the methodology and
11 data analysis. We looked at one numbers and our
12 clinical colleagues did, and we looked at the
13 questions that were posed by ODE on the statistical
14 issues.

15 The six statistical issues that we
16 identified and that we will discuss are the pivotal
17 trial design, adherence to the protocol and pooling,
18 which Dr. Piantadosi will handle. I'll say something
19 about statistical power. Dr. Rubin will say something
20 about incomplete ascertainment and the intention to
21 treat analysis.

22 So let me turn now to Dr. Piantadosi for

1 the first three issues.

2 DR. PIANTADOSI: Thank you, Dr. Colton.

3 I have no financial interest in the
4 company, only an intellectual interest in the topic,
5 and like nearly everyone else in the room, I'm not
6 working for free.

7 (Laughter.)

8 DR. PIANTADOSI: I'm going to discuss the
9 first statistical issue, which deals with the pivotal
10 trial design, and I want to emphasize what you've
11 already heard, that being the critical features that
12 this study has incorporated to eliminate selection
13 bias and control the precision of estimation of the
14 treatment effect.

15 You've heard that the study was masked.
16 This is unusual for a surgical trial. It's unusual
17 for a device trial. The very size of this study and
18 rigor with which it was done is unusual in this kind
19 of setting.

20 The trial is what might be conventionally
21 referred to as triple masked. The surgeon, the
22 evaluator of adhesions postoperatively at the second

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1 look, and the patient herself are unaware of the
2 treatment assignment.

3 The study was a multi-center study, the
4 state of the art for providing a heterogeneous enough
5 cohort to support the external validity of the
6 findings. This is a strength, not a weakness of this
7 study.

8 Within each center participating in the
9 trial there was a blocked and stratified randomization
10 which provides multiple independent and unbiased
11 estimates of the treatment effect at each center,
12 which can then be pooled across center under
13 appropriate conditions that I'll discuss in a moment
14 to provide an overall, unbiased, valid, and precise
15 estimate of the treatment effect.

16 We found in our review that the study
17 design was scientifically valid, and it meets the
18 scientific and regulatory standards that might be
19 applied in this setting.

20 The second issue that we addressed had to
21 do with adherence to the protocol plans for the
22 statistical analyses and concerns that the products of

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1 those analyses might be deemed post hoc or data
2 dredging. This is not the case.

3 The PMA as amended presents all of the
4 analyses that are set forth in the study protocol.
5 The secondary endpoints about which you've heard were
6 prospectively defined in the study protocol, and we
7 have been able to identify no issues of multiplicity
8 of analysis that would invalidate any of the type one
9 error or significance levels that have been presented
10 to you.

11 You've heard that the AFS is an
12 appropriate endpoint. I think that whether we
13 describe it as a surrogate or clinical endpoint is
14 semantic. In this case it's clearly the appropriate
15 one, and the data that comprise the score of the AFS
16 were prospectively collected.

17 The indication that's being asked for is
18 new, but the data set is not. It is the data set that
19 was submitted as part of the original PMA.

20 There were additional analyses that were
21 requested and performed by the sponsor, requested by
22 the FDA and agreed upon. These analyses have been

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