

**SUMMARY MINUTES OF THE**

**GENERAL AND PLASTIC SURGERY DEVICES PANEL OF THE**

**MEDICAL DEVICES ADVISORY COMMITTEE**

**OPEN SESSION**

**JANUARY 12, 2000**

**Conference Room 020 B  
Corporate Building  
9200 Corporate Boulevard  
Rockville, Maryland**

**GENERAL AND PLASTIC SURGERY DEVICES PANEL ROSTER****January 12, 2000****Panel Chair**

Thomas V. Whalen, M.D.  
Robert Wood Johnson Medical School at Camden

**Voting Members**

David L. DeMets, Ph.D.  
University of Wisconsin Medical School

Robert L. McCauley, M.D.  
Shriners Burns Hospital and University of Texas Medical Branch

**Temporary Voting Members**

Mary E. Davis, Ph.D.  
West Virginia University

Charles E. Edmiston, Jr., Ph.D.  
Medical College of Wisconsin

Barbara Levy, M.D.  
Yale University School of Medicine and University of Washington School of Medicine

Subir Roy, M.D.  
University of Southern California School of Medicine

Mark A. Talamini, M.D.  
Johns Hopkins University School of Medicine

**Consumer Representative**

Maxine F. Brinkman, RN  
North Iowa Mercy Health Center

**Industry Representative**

Marcia Yaross, Ph.D.  
Allergan, Inc.

**FDA Personnel**

David Krause, Ph.D.  
Panel Executive Secretary

Jim Dillard  
Acting Director, Division of General and Restorative Devices

Nancy Pluhowski  
Panel Coordinator

Stephen P. Rhodes  
Branch Chief, Plastic and Reconstructive Surgery Devices Branch

Roxolana Horbowyj, M.D.  
Medical Officer, Division of General and Restorative Devices

Richard Kotz  
Statistician, CDRH/OSB

**OPEN SESSION**

The meeting was called to order at 10:32 a.m. **Dr. David Krause, Panel Executive Secretary**, read appointments to temporary voting status for Drs. Davis, Edmiston, Levy, Roy, and Talamini and an appointment as chair for Dr. Thomas Whalen. Dr. Krause also read the conflict of interest statement, noting that waivers had been granted for Drs. DeMets and Talamini and that matters concerning Drs. Levy, McCauley, DeMets, Roy, and Talamini had been considered but their full participation allowed.

**Panel Chair Dr. Thomas Whalen** noted that the panel would be discussing premarket approval application (PMA) P990015 for Lifecore Biomedical's INTERGEL Adhesion Prevention Solution. He asked the panel members to introduce themselves.

**Stephen P. Rhodes, chief of the Plastic and Reconstructive Surgery Devices Branch**, gave an update on activities in that branch and the General Surgery Branch since the last panel meeting in June 1999. He noted that the last panel meeting had discussed Intuitive Surgical's Endoscopic Surgical Control System, and that the General Surgery Branch and that sponsor had subsequently been working to finish the premarket approval application. Mr. Rhodes stated that on August 19, 1999, the Plastic Surgery Branch published a Final Rule requiring the submission of saline-filled breast implant PMAs within 90 days and in October released for public comment a draft guidance on preclinical and clinical data and labeling for breast prostheses. That comment period has just ended. Mr. Rhodes also said that in November 1999 four types of wound dressings were classified as Class I devices, exempt from premarket notification, as the panel had recommended at its November 1998 meeting: These were nonresorbable gauze/sponge for external use, hydrogel, occlusive, and hydrophilic, all of which have no biologic or animal source material. Mr. Rhodes notified the panel that a draft guidance for resorbable adhesion

barrier devices for use in abdominal and/or pelvic surgery has just been released and will be discussed at the upcoming January 2000 OB/GYN panel meeting, which will include some members of the General and Plastic Surgery Devices Panel because of the overlap with adhesion barrier products. Mr. Rhodes announced that the next meeting of the General and Plastic Surgery Panel is scheduled for March 1-3, 2000.

### **OPEN PUBLIC HEARING**

There were no requests from the audience to address the meeting.

### **OPEN COMMITTEE DISCUSSION**

#### **Sponsor Presentation—Lifecore Biomedical, Inc.'s INTERGEL Adhesion Prevention Solution, PMA P990015**

**Ms. Georgiann Keyport of Lifecore Biomedical** began the PMA sponsor application by introducing the sponsor team members.

**Dr. Douglas Johns** described the device, which is a sterile, viscous, nonpyrogenic solution of hyaluronic acid crosslinked with ferric chloride that claims to reduce the incidence, extent, and severity of adhesions following gynecologic surgery. He summarized the device's history, noting that it had been previously marketed as Lubriccoat, and he presented pilot study results from a one-center, open label study on 23 patients of the INTERGEL device versus lactated Ringer's as control. The pilot study found device safety to be comparable to control, with no clinically significant differences in serum chemistry or hematology and no serious adverse events, and effective in significantly reducing proportion, extent, severity, and total score of adhesions.

Dr. Johns also described the objective and design of a pivotal third-party, blinded, parallel, randomized controlled study in 11 U.S. and 5 European centers that assessed safety and

efficacy of INTERGEL solution in reducing adhesions in female patients undergoing peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy. He explained the protocol and exclusion criteria, as well as blinding techniques and postoperative procedures. The primary efficacy variable was a modified adhesion scoring method of the American Fertility Society (mAFS), which Dr. Johns explained. Of a total intent-to treat population of 281 treated patients, the total evaluable efficacy population was 265 patients. Dr. Johns described the statistical methods used on the data and presented the following efficacy results. INTERGEL Solution was shown to reduce the incidence, extent, and severity of adhesions compared to control. The mean mAFS score was reduced by 44%, the AFS score was reduced by 61%, and the proportion, severity, and extent of post-surgical adhesions were reduced. De novo, reformed, and surgical site adhesions were reduced, and the reduction was consistent for sites throughout the abdomen. The reduction was observed for all surgical procedures studied and was observed in the groups listed as all patients, U.S. patients only, and European patients only. Analysis of individual patient outcomes showed that, in comparison to the control group, more INTERGEL Solution-treated patients were totally adhesion-free; fewer INTERGEL Solution-treated patients had a moderate or severe outcome; and fewer INTERGEL Solution-treated patients had a severe outcome.

**Dr. Gere diZerega** described safety results in terms of adverse events, pre and postoperative laboratory test evaluations, concomitant medications, and gross observations at second look. No significant differences were found between device and control groups in adverse events, concomitant medications, or laboratory values, except for elevated white blood cell (WBC) counts in the device group. The sponsor considered the elevation in WBC levels to be a

brief, subclinical response of no clinical significance and stated that there was no evidence of foreign body reactions.

Dr. diZerega concluded that adhesion-free patients were twice as likely not to develop adhesions with the device and that it helps patients by reducing the chance of failed postoperative therapy from postsurgical adhesions.

Questions from the panel to sponsor presenters concerned whether the mAFS score is a ranking or an actual numerical score and whether it was fair to categorize that score as a prognostic indicator. The panel also discussed the elevated WBC counts, and it was hypothesized that the device might be a barrier to peritoneal healing mechanisms because of microbial organisms adhering to the device surface. Possible allergic reactions and blinding techniques used during the study were also discussed.

### **FDA Presentation**

**Nancy Pluhowski, Panel Coordinator**, served as Executive Secretary for this portion of the meeting. **Dr. David Krause**, the lead PMA reviewer, introduced the FDA review team and read the proposed indications for device use and device description. He listed the toxicity and biocompatibility studies, which were extensive, and noted that there were no observable deleterious effects when used in amounts similar to the clinical trials. For smaller animals, however, high doses caused some fatalities and produced signs of toxicity. Dr. Krause also described reproductive studies performed with rats, noting a potentially deleterious effect and a proposed solution. No statistical significant treatment-related changes were observed in animals treated with the clinically equivalent instillate. On infectivity studies, Dr. Krause noted a difference between sponsor and FDA interpretations, in which the sponsor found no statistical difference, and the FDA concluded that the study was insufficiently powered to detect the 20%

difference observed. Subsequently, the sponsor has submitted an acceptable protocol for a second study powered to determine a 25 % difference, and to assess abscess formation.

**Dr. Roxi Horbowyj** presented the FDA clinical perspective. She discussed the objective design, effectiveness outcomes, and safety outcomes of the clinical study. Dr. Horbowyj described the target population and study design and listed the safety and efficacy endpoints. No safety issues were identified during the pilot study, which she described, and significant differences in effectiveness endpoints were found.

Dr. Horbowyj also discussed the pivotal study, stating that the clinical significance of an mAFS score and of a change in mAFS score is not known. Dr. Horbowyj noted that device use was studied in clean class, non-cancer and relatively low baseline adhesion burden patients in otherwise good health. After examining this study in detail, she stated that baseline evaluation differences between continents, per treatment group, were greater than differences within a continent, per treatment group for race and adhesion evaluation. She also noted that effectiveness outcomes per treatment group are not consistent between continents. Dr. Horbowyj observed that the U.S. safety outcome on wound infection rate was 3.9% for device, as opposed to 1.0% for control, and that the differences in effectiveness outcome measures between U.S. INTERGEL and control cohorts were generally less than one unit of measure.

**Mr. Richard Kotz** gave the FDA statistical review. He discussed sample size, the sponsor's proposed protocol, and actual protocol, and the issue of pooling data across continents, noting that the FDA and the sponsor had disagreed about the combinability of data across continents, so the sponsor enrolled a total of 200 U.S. subjects. The sponsor also presented evaluable patients and excluded subjects lost to follow-up, whereas the FDA represented intent-to-treat analysis, with patients lost to follow-up assigned the worst scores. In addition, the

sponsor presented a parametric analysis, while the FDA presented a nonparametric analysis. Because the FDA thought it unclear that pooling was appropriate, it presented results stratified by continent and surgery type (adhesiolysis and nonadhesiolysis). The resulting Intent-to-Treat tables presented results that indicated, when analyzed according to the statistical plan proposed by the sponsor, there is not a statistically significant difference between the INTERGEL patients and the lactated Ringer's patients with respect to mAFS score and incidence of adhesions.

**Dr. David Krause** read the FDA questions for panel consideration.

### **Panel Deliberations**

**Panel lead clinical reviewer Barbara Levy** stated that a device must make a clinical difference to be considered clinically different from a control. She thought the difference in mAFS scores presented was clinically meaningless, and she noted that whether the statistics are those analyzed by the FDA and or by the sponsor, the difference shown between device and control is minimal. From a clinical standpoint, she therefore felt hard-pressed to say that the device makes a difference.

**Panel lead statistical reviewer Dr. David DeMets** discussed three issues—the mAFS scores, the intent-to-treat populations, and pooling of data. He considered the mAFS a ranking rather than a continuous scale and was not convinced that this measure provided a good validation of the outcome. On intent-to-treat population, he thought the sponsors used the term incorrectly, and should have analyzed all patients with all outcomes, rather than just those who got the treatment device. He thought this produced a potential for bias because the lost patients should be accounted for, and was concerned about an additional potential bias because some patients did not get the second look required by protocol. Dr. DeMets discussed the historical perspective on intent-to-treat populations and the dangers of retrospective assessment, especially

when lack of protocol compliance or not receiving the full treatment can scramble the results.

He emphasized the importance of following all patients from the beginning of the randomization process and the importance of proper blinding, because both introduced the potential for bias. On data pooling, Dr. DeMets noted the mixed messages produced by pooling qualitative and quantitative data and stressed that randomization within each center is critical. He encouraged stratified analysis, noting that a small study made subgroup analysis difficult, but stratified analysis provides a consistency check. He concluded by suggesting that a reduction in mAFS score is artificial because the scale itself is artificial.

The sponsors asked the lead reviewers to comment on the appropriate way to treat patients who do not return for a second-look laparoscopy or to treat those who feel fine or are pregnant. It was suggested to use both ITT and evaluable patient analysis to look at the data in a best and worst case analysis.

### **FDA Questions**

The panel agreed that there were clinical concerns about the poolability of data, although randomization within each center and stratification of analysis across sites were statistically appropriate.

On use of this product with cancer patients or those undergoing non-clean procedures, the panel voiced concerns about problems of infection and the danger of potentially doing greater harm than benefit. Labeling should be modified to specify the specific population on which data are available, with an admonition not to go beyond this use.

The panel expressed both statistical and clinical concerns about the mAFS scoring system as a clinically meaningful and sufficient tool for assessing effectiveness of this device, and about the effectiveness of the device itself in reducing the adhesion burden for treated patients.

Serious concerns were voiced about the proposed indication for use, both because of unclear data for the initially proposed indication of gynecological pelvic surgery and because the second part of the second sentence (to reduce the incidence, extent and severity of post-surgical adhesions throughout the abdominal cavity) could be construed as a subtle introduction to other, off-label treatments not indicated or intended for use.

### **OPEN PUBLIC HEARING**

**Jack Lazarus, a venture capitalist with an interest in Lifecore,** expressed his concern about the suggestions made by the panel. He noted the difficulty of assessing patient benefit when dealing with relatively small increases in effectiveness, given that most patients do not get adhesions. He also noted the difficulty of performing an ITT analysis in a surgical study as opposed to a drug study and the difficulty of finding reasonable surrogate endpoints.

### **FDA SUMMATION**

**Dr. Dillard** expressed appreciation that the panel had clarified the issues for the FDA on how to look at the data, and he noted that the FDA was not asking for a determination on surrogate endpoints but on whether the data presented a reasonable demonstration of safety and efficacy.

### **SPONSOR COMMENTS**

Sponsor representatives stressed the importance of the clinical significance of the device and the value of reducing adhesions, even to a small degree. They noted a consistency between and among sites in response to device use and stressed the ease and efficacy of the device.

### **CONCLUDING PANEL DELIBERATIONS AND VOTE**

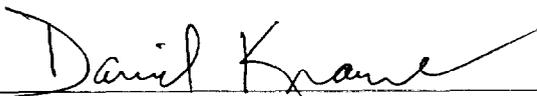
**Dr. Krause** read the voting instructions to the panel.

A motion to recommend the PMA as approvable was made but failed from lack of a second.

A motion to recommend the PMA as nonapprovable was made, seconded, and passed by a vote of five to two, with Drs. Roy and Davis as the opposing votes. Those who supported the motion stated that they voted to recommend the PMA as nonapprovable because of issues with incomplete safety data and high infection rates, as well as controversy over the use of mAFS scores as clinically meaningful surrogates. Those who opposed the motion stated that they were prepared to recommend approval with conditions that a subset of the patient population should be analyzed or a clinical study be performed to look more closely at results in the target population.

Both Mr. Dillard and Dr. Whelan thanked all those present for their participation. Dr. Whelan adjourned the session at 3:50 p.m.

I certify that I attended the Open Session of the General and Plastic Surgery Devices Panel Meeting on January 12, 2000, and that this summary accurately reflects what transpired.

  
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David Krause, Ph.D.  
Executive Secretary

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

  
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Thomas V. Whalen, M.D.  
Panel Chair

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January 24, 2000

## INVOICE

Summary Writer Services to provide technical scientific summary minutes of the General and Plastic Surgery Devices Panel Meeting, January 12, 2000

Attendance at meeting (based on 5 and 1/2 hrs. @ \$40/hr.)	\$ 220.00
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