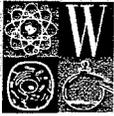


**SECTION I.**

**COVER LETTER**



## THE WEINBERG GROUP INC.

June 2, 2000

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Celia Witten, M.D., Ph.D.  
Director, Division of General and  
Restorative Devices (HFZ-401)  
Office of Device Evaluation  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Boulevard  
Rockville, MD 20850

Re: INTERGEL® Adhesion Prevention Solution, PMA 990015/A010  
Lifecore Biomedical Inc.

Dear Dr. Witten:

Enclosed please find a major amendment to the above referenced PMA. This amendment is in response to a deficiency letter dated December 7, 1999 and is also provided in response to unresolved issues regarding safety and effectiveness raised during the review of this PMA by FDA and the Advisory Panel convened on January 12, 2000. This submission provides for your consideration a revised statement of intended use, which we feel is adequately supported by valid scientific evidence, along with detailed information to address specific issues raised in the analysis of the data contained in this PMA. The following is a summary of our analysis and conclusions regarding these issues.

### **JUSTIFICATION FOR THE CLINICAL RELEVANCE OF THE METHOD USED TO SCORE ADHESIONS**

The sponsor conducted a high-quality pivotal trial designed to evaluate the incidence, extent, and severity of adhesions at sites in the peritoneal cavity following laparotomy and gynecological pelvic surgery. All aspects of the INTERGEL® Solution pivotal trial were designed in close collaboration with FDA, including selection of the primary endpoint and the method used to score this outcome. The method selected for evaluating the incidence, extent, and severity of adhesions in this trial was the American Fertility Society (AFS) adhesion scoring system, applied to 24 sites within the pelvic and peritoneal cavity.

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The INTERGEL® Solution pivotal trial incorporated all of the critical design elements available to minimize bias and control for confounders in a surgical trial (a double-blind, randomized, prospective, multi-center design with a concurrent control group, a standardized, quantitative means of assessing effectiveness and an appropriate sample size). We are gratified that the Office of Device Evaluation recognizes the considerable resources, time, and effort required to conduct a surgical trial of this quality and size in this field of medicine. The original Study Report of this clinical trial appears in Appendix D. As reflected in the original Study Report, every clinical efficacy endpoint prospectively identified and evaluated in this trial indicated a statistically significant difference between INTERGEL® Solution and the control treatment.

Nevertheless, we understand that, at present, concerns remain regarding the clinical utility of the product. This is because the AFS adhesion scoring system was originally developed for characterizing adnexal adhesions, and the clinical significance of adhesions evaluated at other sites utilizing this systematic method for scoring adhesion extent and severity has been questioned. Therefore, the sponsor proposes that the primary endpoint for consideration of the effectiveness of INTERGEL® Solution as determined in this pivotal trial be confined to adnexal adhesions utilizing the AFS adhesion scoring system. The alternative approach, a prospective outcome study to establish clinical significance, is not feasible in a pre-marketing setting for the following reasons: bowel obstruction is too rare; pain is multi-factorial and intermittent; fertility is multi-factorial.<sup>1</sup> Further, to the best of the sponsor's understanding, such a study was never proposed by FDA as a requirement for approval.

An amendment to the INTERGEL® Solution original Study Report, in which the primary endpoint has been restricted to a consideration of adnexal adhesions utilizing the AFS adhesion scoring system, is provided in this submission (Section III). These data are also contained in the original Study Report (Appendix D) and were presented by the sponsor at the General and Plastic Surgery Devices Panel meeting on January 12, 2000. Additionally, the present submission provides a systematic review of the clinical literature which confirms that the AFS scoring system for adnexal adhesions is a valid tool for patient management and fertility prognosis (Appendix A).

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<sup>1</sup> We note that none of the products approved by FDA as adjuncts intended to reduce and/or prevent surgical adhesions have relied upon clinical outcome data to establish effectiveness; rather, data on the incidence and severity of adhesions as a primary endpoint following surgery was considered sufficient to demonstrate clinical utility [INTERCEED; Septrafilm; ADCON-L; Biomatrix Hylasine 510(k) product].



## **MAGNITUDE OF CLINICAL EFFECTIVENESS OBSERVED WITH INTERGEL® SOLUTION VS. CONTROL**

Based on the data provided in the Amendment to the original Study Report (Section III), it can be concluded that INTERGEL® Solution reduces the incidence of adnexal adhesions when used as an intraperitoneal instillate following conservative gynecologic pelvic surgery, based on AFS adhesion scores. The magnitude of this effect is clinically significant, with the INTERGEL® Solution group showing a 5-fold lower risk of moderate or severe adhesions at second-look compared to controls. This endpoint (moderate/severe adhesions) is well-correlated with a poor fertility prognosis, as evidenced by a systematic review of the clinical literature (Appendix A). The difference observed is statistically significant, and the study was sufficiently powered to detect this difference with a high degree of confidence. Three patients in the INTERGEL® Solution group (2.3%) had moderate or severe adhesion scores at second-look, compared to 17 (12.7%) patients in the control group. Additionally, all 9 patients (100%) in the INTERGEL® Solution group that had moderate/severe adhesions at baseline improved at second-look (to minimal/mild), compared to 10 of 17 patients in the control group (59%). A subgroup analysis indicates that those patients most likely to benefit from INTERGEL® Solution were those presenting with adhesions treated with adhesiolysis, or those undergoing myomectomy.

Supportive evidence that the product prevents adhesion formation at sites other than the adnexa is provided by two secondary efficacy endpoints, both of which were also presented in the original Study Report. The proportion of patients with adhesion reformation and adhesions at the surgical site was significantly reduced (31% and 23%, respectively) in the INTERGEL® Solution group compared to control, a statistically significant result for both endpoints.

This product is intended to be used as an adjunct to good surgical technique. A revised product label for INTERGEL® Solution, based on restricting the primary endpoint to a consideration of adnexal adhesions utilizing the AFS adhesion scoring system, is provided in Section II.

## **SAFETY CONSIDERATIONS**

The randomized pivotal trial of INTERGEL® Solution identified no notable safety concerns compared to control. The product is a hyaluronic-based gel with a well-characterized safety profile. Concerns that the presence of this material might enhance the risk of infection led to the conduct of an animal study designed as requested by FDA, and follow-up analysis of post-surgical data on infection rates by the sponsor in consultation with expert clinicians. The results of this work are provided in Section IV. Given all of the available data from both animal and clinical studies, it can be concluded that the potential risks posed by INTERGEL® Solution when used as an adjunct according to the product label are comparable to control (lactated Ringer's solution).



## STATISTICAL ISSUES

The evaluation of the pivotal clinical trial data in this amendment addresses two statistical issues that require resolution. The first of these is the justification for utilizing data from all patients from all investigational sites. This was a randomized multi-center trial conducted at 11 sites in the United States and 5 in Europe utilizing a single protocol (PTL-0013/0022). Except for isolated protocol violations, all subjects met the inclusion/exclusion criteria and there were no demographic differences between the treatment and control groups. The two most powerful means of controlling for confounders in surgical trials were utilized in this pivotal trial: randomization and a multi-center design. Although baseline adhesion scores varied between sites -- an expected outcome that could not be avoided -- baseline adhesion scores were not significantly different in treatment vs. control groups. The clinical and statistical rationale for use of data from all clinical trial sites is provided in detail in the Amendment to the original Study Report (Section III).

The second statistical issue is consideration of the most meaningful and rigorous approach to evaluate data from subjects who failed to have a second-look laparoscopy. This study, as with most surgical trials, was prospectively designed (and powered) to include evaluable subjects in the effectiveness analysis, and all available safety data. At the request of FDA, and as an exploratory statistical evaluation, the sponsor agreed to include imputed values for subjects who failed to have a second-look laparoscopy. In order to avoid introducing bias into the analysis, this approach for the use of imputed values necessarily assumed that the lack of ascertainment at second-look would be independent of treatment and be evenly distributed between the two groups. Neither of these two assumptions were found to be valid upon completion of the trial, hence the original exploratory approach to evaluating data for patients who failed to have a second-look laparoscopy is no longer appropriate.

As an alternative, the sponsor developed an improved approach for analysis of data from subjects for whom there was incomplete ascertainment. This approach, along with clinical and statistical rationale and results, is explained and the data provided in detail in the Amendment to the original Study Report (Section III). The results of this analysis confirm that the possible introduction of bias due to incomplete ascertainment, if any, did not impact on the conclusions of the trial.

## CONCLUSIONS

The attached submission was designed to address all of the significant and important issues raised by FDA and the Advisory Panel regarding the above-referenced PMA. The proposed product label, which is adequately supported by valid scientific evidence, presents a significantly modified version of that originally proposed. Each of the scientific and public health concerns raised over the last year of which we are aware has been addressed in this submission, without the generation of new data (with the exception of the new safety study in rats). Taken together, the sponsor feels that these data provide reasonable assurance of safety



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and effectiveness with a favorable benefit-risk ratio. A revised Summary of Safety and Effectiveness, incorporating the new proposed indication for use, the results of the completed animal safety study, and highlighting the originally submitted data in support of the revised indication is provided (Appendix C).

As has been previously recognized by the Agency in granting this application expedited approval status, there is a compelling public health need for products that prevent or reduce the occurrence of surgical adhesions. At the present time, physicians in the United States have access to no products indicated for, and demonstrated to, reduce the risk of adhesions during gynecological pelvic surgery beyond the surgical site. It is our hope that this submission can be reviewed within the expedited approval framework, and that we can schedule a meeting with the review group to respond to any remaining questions within the next 60 days. A list of individuals who will be available to attend that meeting on behalf of Lifecore Biomedical is attached.

We look forward to speaking with you once you and the review group have had an opportunity to consider this amendment. Thank you in advance for your continuing assistance and consideration of this matter.

Very truly yours,



Karen M. Becker, Ph.D.

Worldwide Managing Director, Healthcare Products  
THE WEINBERG GROUP INC.

KMB/kh

Enclosure

cc: Stephen P. Rhodes, Ph.D.  
Georgiann Keyport, R.A.C.



**INTERGEL® ADHESION PREVENTION SOLUTION**

**Meeting Attendees**  
(Date to be determined)

James W. Bracke, Ph.D.  
President and CEO  
Lifecore Biomedical, Inc.

Georgiann Keyport, R.A.C.  
Director, Regulatory & Clinical Affairs  
Lifecore Biomedical, Inc.

Douglas B. Johns, Ph.D.  
Consulting Scientist, Growth Technologies & New Business Development  
Ethicon, Inc.

John D. Paulson, Ph.D. (Consultant)  
Vice President, Quality, Regulatory & Medical Affairs  
Ethicon, Inc.

Richard P. Chiacchierini, Ph.D. (Statistical Consultant)  
Senior Vice President, Statistics  
C. L. McIntosh, Inc.

Alan H. DeCherney, M.D. (Clinical Consultant)  
Department Chair  
UCLA, Dept. of OB-GYN

Gere S. diZerega, M.D. (Clinical Consultant)  
Professor, Department of Obstetrics & Gynecology  
University of Southern California

Karen M. Becker, Ph.D.  
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John H. Grossman III, M.D., Ph.D., M.P.H. (Clinical Consultant)  
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Professor of Microbiology and Immunology  
Professor of Obstetrics and Gynecology  
The George Washington University  
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