



THE WEINBERG GROUP INC.

HAND DELIVERED

January 4, 2001

Mr. Les Weinstein
CDRH Ombudsman (HFZ-5)
Office of the Center Director
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

RE: PMA990015
INTERGEL® Adhesion Prevention Solution
Lifecore Biomedical, Inc.

Dear Mr. Weinstein:

On behalf of Lifecore Biomedical, I respectfully request a review of certain scientific issues relating to the above referenced Premarket Approval Application (PMA) by the Medical Devices Dispute Resolution Panel. This request is in response to the letter received from Kimber C. Richter, M.D. dated November 15, 2000, in which the results of the review of this PMA by the Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH) are provided.

In accord with the April 27, 1999 Draft Guidance issued by your office entitled "Resolving Scientific Disputes Concerning the Regulation of Medical Devices," and your December 15, 2000 letter, the following information is provided in support of this request.

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STANDING

As the PMA applicant for the INTERGEL[®] Adhesion Prevention Solution (INTERGEL[®] Solution) for which there currently exist scientific disputes between Lifecore Biomedical and ODE as to the approvability of the PMA, Lifecore Biomedical has standing to submit this request.

SUMMARY OF ADMINISTRATIVE ACTIONS

FDA Action

CDRH has determined that the above referenced PMA is not approvable, based on the requirements of 21 CFR 814.44 (f) (letter from K.C. Richter to K. M. Becker dated November 15, 2000). The Sponsor, having consulted with numerous expert clinicians and regulatory counsel, disagrees. The data provided in this PMA and amendments provide reasonable assurance of safety and effectiveness for the proposed intended use.

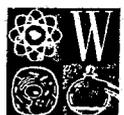
This PMA was filed on March 8, 1999.

CDRH, Division of General and Restorative Devices (DGRD), determined that the PMA was suitable for filing and granted expedited review status to this application on April 26, 1999, based on the determination that the product addresses an unmet public health need.

The Sponsor received a Major Deficiency letter from ODE dated September 8, 1999.

The Sponsor received a Major Deficiency letter from DGRD dated December 7, 1999.

The Sponsor submitted amendments to the PMA on May 12, August 25, September 10, September 13, September 21, September 29, December 15, December 16, 1999, and February 4, April 11, June 2, and September 12, 2000.



CDRH approved compassionate use of INTERGEL[®] in two patients (February 29 and July 24, 2000). There have been three emergency use notifications (July 24, 1995, January 27, 1997 and December 7, 1998).

Advisory Panel Action

On January 12, 2000, the General and Plastic Surgery Devices Panel convened and voted 5 to 2 against recommending approval of this PMA, under the conditions of use specified in the PMA as filed on March 3, 1999. This meeting was held prior to the submission of the Major Amendment dated June 2, 2000 with a revised intended use.

On January 25, 2000, the Obstetrics and Gynecology Devices Panel convened on January 25, 2000 to consider the Draft "Guidance for Resorbable Adhesion Barriers for Use in Abdominal and/or Pelvic Surgery" issued by ODE on December 16, 1999. FDA at that time convened a panel which the Agency believed was most appropriately suited, by qualifications and experience, to consider the clinical and study design issues particularly relevant to the revised intended use of INTERGEL[®]. The results of that panel meeting, convened to provide ODE with an expert discussion of the appropriate data sufficient to support approval of such products was not subsequently--to the Sponsor's knowledge--considered in the review of this PMA by ODE.

Previous Attempts at Dispute Resolution

1. Submission of Major Amendment June 2, 2000

The Sponsor diligently considered and responded to the unresolved scientific concerns expressed by both the reviewing Division and the Advisory Panel regarding the data provided in the PMA. A rigorous response to each scientific issue was developed, a supplemental animal safety study was conducted (as requested by FDA on December 7, 1999), and a revised product label was proposed to narrow the intended use from a general surgery to a gynecologic pelvic surgery indication. This new data and information were submitted to the Division in the June 2, 2000 Major Amendment.

Prior to preparation and submission of the June 2, 2000 Major Amendment, the Sponsor met with the Director of DGRD. The first meeting was with Mr. James Dillard on March 8, 2000, and the second with Celia Witten, M.D., Ph.D. on April 13, 2000. (Dr. Witten had subsequently been appointed Director.) In both of these meetings, the following topics were discussed:

- (a) Procedural and process irregularities that, in the Sponsor's judgment, had unfairly impacted on the review of the data contained in the PMA.
- (b) Consensus between the Sponsor and FDA regarding the most important scientific issues in dispute.



(c) A proposed revised intended use for the product.

(d) Consensus on the contents of the Major Amendment to be filed on June 2, 2000.

2. Response to Review of Major Amendment

On September 5, 2000, the Sponsor was notified by telephone that DGRD had completed the review of the June 2, 2000 Major Amendment and deemed the PMA to be not approvable.

On September 8, 2000, the Sponsor requested review of this decision by David W. Feigal, Jr., M.D., M.P.H., Director, CDRH. The matter was referred by Dr. Feigal to ODE.

On October 19, 2000, ODE informed the Sponsor by telephone that a not approvable letter had been signed, but not yet dated. At that time, Dr. K. C. Richter agreed to a meeting with the sponsor to discuss the scientific issues in dispute, which was held on October 27, 2000. Following this meeting with ODE, the Sponsor was informed that additional review of the PMA would be carried out.

On November 15, 2000, a not approvable letter was issued.

SUMMARY OF SCIENTIFIC ISSUES IN DISPUTE

In the opinion of Lifecore Biomedical and its expert consultants, the existing data provide reasonable assurance of effectiveness and safety of INTERGEL[®] Solution for its intended uses in conformity with applicable statutory and regulatory requirements. Specifically, Lifecore Biomedical and its experts believe that the available data show that: a) there exist statistically and clinically significant benefits in favor of INTERGEL[®] Solution as compared to control (lactated Ringer's solution) in reducing adhesion formation following pelvic surgery and b) this benefit is achieved without exposing the patient to any unacceptable risks, including infection. ODE, on the other hand, believes that the existing data do not provide reasonable assurance of effectiveness in that the differences observed between INTERGEL[®] Solution and control, while statistically significant, are not clinically significant and that the data raise, but do not resolve, the possibility that the use of the product may be associated with an unacceptable risk of infection.

SUMMARY OF ARGUMENTS

INTERGEL[®] Adhesion Prevention Solution is a sterile, nonpyrogenic amber colored, viscous solution of sodium hyaluronate, which has been ionically cross-linked with ferric ions and adjusted to isotonicity with sodium chloride via a proprietary process which avoids precipitation of insoluble ferric hyaluronate and results in gel formation.



INTERGEL[®] Solution is intended for use as a single use intraperitoneal instillate for reduction of adhesion formation following gynecological pelvic surgery. Lifecore Biomedical and experts consulted by the company are of the opinion the product has been shown by valid scientific studies to reduce the incidence, extent, and severity of post-surgical adhesions at the surgical site and throughout the abdominal cavity when used as an adjunct to good surgical technique during laparotomy procedures.

The proposed intended use for INTERGEL[®] Solution submitted in the PMA as amended is provided below, followed by a brief summary of the supporting data.

INTERGEL[®] Solution is a single-use, intraperitoneal instillate indicated to reduce the likelihood of developing moderate or severe postoperative adnexal adhesions in patients undergoing adhesiolysis or myomectomy during conservative gynecological pelvic surgery by laparotomy, when used as an adjunct to good surgical technique. INTERGEL[®] Solution was also shown to reduce adhesion reformation to sites in addition to the adnexa, and adhesion formation at surgical sites, including the anterior abdominal incision.

Safety and effectiveness of INTERGEL[®] Solution were evaluated in a prospective, multi-center, randomized, blinded, controlled clinical trial in female patients undergoing peritoneal cavity surgery by laparotomy. Effectiveness was evaluated approximately 6 to 12 weeks post-surgery during a second-look laparoscopy procedure. All 281 patients were evaluable for safety. There were 265 evaluable patients at second-look for effectiveness. The sponsor, utilizing appropriate statistical techniques, confirmed that a) the data from all study sites could be utilized in the final analysis of the trial, and b) there was no significant impact on the conclusions as a result of incomplete ascertainment of patient data at second-look.

The primary effectiveness endpoint was the mean modified American Fertility Society (mAFS) score, which provided a systematic method of recording the incidence, severity and extent of adhesions at 24 anatomical sites in the pelvis and abdomen. Also determined were the proportion of sites with adhesions (including *de novo*, reformed, surgical, pelvic vs. abdominal) and the standard American Fertility Society (AFS) score of adnexal adhesions. The primary effectiveness endpoint and secondary endpoints evaluated in the trial indicated a statistically significant difference between INTERGEL[®] Solution and the control treatment (lactated Ringer's solution). The incidence, severity, and extent of postsurgical adhesions, as assessed at 24 anatomical sites utilizing the mean modified AFS score, demonstrated a 45% reduction in the INTERGEL[®] Solution group compared to control. The proportion of sites with reformed adhesions was reduced by 31% ($p=0.001$). The proportion of surgical site adhesions was reduced by 23% ($p=0.003$).

A 59% reduction in the mean standard AFS score of adnexal adhesions was observed for INTERGEL[®] Solution compared to control. 100% of INTERGEL[®] Solution patients ($n=9$) with moderate/severe adnexal adhesions at baseline improved to the minimal/mild category at second-look, compared to 59% of control patients (10 of 17) ($p=0.003$).



For adnexal adhesions, the relative risk of treatment failure (defined as a moderate or severe AFS score) was five-fold lower in the INTERGEL[®] Solution group compared to control (82%; p=.003).

The incidence of adverse events was comparable in both groups, with the exception of allergic reactions reported to be higher in the control group. There was no statistically significant difference in the incidence of infection in the INTERGEL[®] Solution group compared to control (2.1% vs. 0.7%; p=ns).

Nonclinical studies confirmed the biocompatibility and lack of toxicity of INTERGEL[®] in *in vitro* and animal models (*in vitro* acute cytotoxicity; *in vivo* acute cytotoxicity; multiple dose sub-chronic toxicity; dermal sensitization; pyrogenicity; hemolysis; reproductive toxicity; absorption, distribution and excretion; infection potentiation).

ODE concludes that the above data fail to demonstrate reasonable evidence of either safety or effectiveness. The Sponsor disagrees.

Sponsor's Understanding of the ODE Position

To the best of the Sponsor's knowledge, ODE has raised the following as significant unresolved scientific issues with regard to the INTERGEL[®] Solution: a) use of adhesions as a primary effectiveness endpoint; b) the clinical significance of the differences observed between treatment and control; c) the validity of the adhesion scoring method; and d) the possibility of infection potentiation.

Based on the above data, it is the Sponsor's understanding that ODE is concerned that the manner of assessing effectiveness may not be valid, in that the adhesions evaluated have not been directly correlated with an outcome, such as pain, fertility, or bowel obstruction. The high incidence of, and risk of serious sequelae from, postsurgical adhesions is well documented.¹ As previously recognized by the Agency in granting this application expedited review status, there is a compelling public health need for products that prevent or reduce the occurrence of postsurgical 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. INTERGEL[®] Solution is available in 19 countries throughout the world, including Canada and the European Union.

The intended use of the product, to reduce the incidence of postsurgical adhesions, accurately represents the effectiveness data and claims provided by the sponsor. No product approved by FDA as an adjunct intended to reduce and/or prevent postsurgical adhesions has relied on clinical outcome data to establish effectiveness; rather, data on the incidence and severity of

¹ Ellis H, Moran BJ, Thompson JN et al. 1999. Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study. *The Lancet* 353: 1476-1480.



adhesions as a primary endpoint following surgery was considered sufficient to demonstrate clinical utility (INTERCEED; Seprafilm).

Further, a systematic review of published and unpublished data found that no randomized, controlled clinical trials have been conducted of any pharmacologic, barrier, liquid, or fluid agents for preventing adhesions in which fertility or pain was an endpoint.² This reflects the significant practical obstacles to be managed in clinical research of adhesion prevention. Assessing adhesions post surgery requires an invasive procedure, a fact that presents ethical constraints and severely limits subject accrual. Trials that would incorporate pain, fertility, or bowel obstruction as effectiveness measures must account for the multifactorial nature of these outcomes, include long-term (multi-year) follow-up and very large sample sizes to compensate for loss to follow-up and the anticipated incidence of the outcome.

The pivotal INTERGEL[®] Solution clinical trial was designed in collaboration with CDRH in 1995. This study is an unusual and outstanding example of a rigorous surgical trial, incorporating all of the critical design elements available to minimize bias and control for confounders (a double-blind, randomized, prospective, multi-center design with a standardized, quantitative means of assessing effectiveness and an appropriate sample size). Four years were required to accrue a sufficient number of subjects to this study and the Sponsor has invested to date over \$25M in this state-of-the-art clinical research program. ODE, retrospectively, asserts that this clinical trial design is not adequate to support approval of a product intended for use as an adjuvant in the prevention of postsurgical adhesions. Based on extensive consideration of the clinical literature and consultation with experts in the field, the Sponsor concludes that this trial design is not only adequate, but optimal. ODE has actively considered this matter in public forums and in discussions with the Sponsor, but to date has failed to identify any significant improvements to this study design that are feasible, ethical and will meet the as yet unarticulated Agency standard for approval of adjuvants for adhesion prevention.

The Sponsor also understands that, although statistically significant, ODE questions the clinical relevance of the effectiveness results. The magnitude of the changes observed in the incidence, severity and extent of adhesions from baseline to second-look for INTERGEL[®] Solution are comparable or greater than the differences observed for previously approved surgical site-specific adhesion reduction products (INTERCEED; Seprafilm). Unlike previously approved products, effectiveness data for INTERGEL[®] Solution is available on both surgical site-specific adhesions and non-surgical site adhesions. The results are consistent, and taken together add to the weight of the evidence in support of the

² Farquhar C, Vandekerckhove P, Watson A, Vail A, Wiseman D. Barrier agents for preventing adhesions after surgery for subfertility (Cochrane Review). In: The Cochrane Library Issue 4: 2000. Oxford: Update Software.

Watson A, Vandekerckhove P, Lilford R. Liquid and fluid agents for preventing adhesions after surgery for subfertility (Cochrane Review). In: The Cochrane Library, Issue 4, 2000. Oxford: Update Software.



determination of effectiveness. The sponsor also notes that INTERGEL[®] Solution is an adjuvant, not a cure nor a prophylactic. It has been designed, tested, and labeled as such.

ODE has expressed the concern that the use of the standard AFS score to assess adnexal adhesions in the patients enrolled in the INTERGEL[®] Solution trial represents a retrospective analysis of the data. This is incorrect and more importantly, obscures the recognition and consideration of clinically relevant, reliable data. Adnexal adhesions were among the 24 sites prospectively identified in the study protocol for evaluation with respect to incidence, severity, and extent. AFS scores for all subjects were originally presented in the INTERGEL[®] Solution PMA. Additional analysis of these data was *required* by the reviewing Division during the review of the PMA as stated in Major Deficiency letters received from DGRD (September 8, 1999; December 7, 1999). The AFS scores observed in the INTERGEL[®] Solution trial, and in particular the impact the product had on patients with moderate or severe adnexal adhesions is, in the opinion of the Sponsor and experts in the field, a compelling and clinically meaningful demonstration of clinical utility. This statistically significant demonstration of effectiveness *further validates* the statistically significant differences observed in the mean modified AFS score, reformed adhesions, and surgical site adhesions.

The AFS score is the most widely used system in the published literature for classification of adnexal adhesions.³ In the INTERGEL[®] Solution trial, adnexal adhesions were assessed using this scoring system, determined from evaluations at three sites on each ovary and two sites on each fallopian tube. ODE is concerned that the scores determined may not be "actual" AFS scores, because more than one site on each anatomical structure was assessed. The adhesion data for each site was combined, based on anatomical considerations and confirmed as valid via a series of sensitivity tests. It is important to recall, when considering the manner in which adhesions are evaluated in any trial, that the method used should be uniform and systematic to reduce the risk of bias and minimize variability across multiple investigational sites. The AFS scores in the INTERGEL[®] trial were obtained prospectively in the same manner at baseline and at second-look for all subjects.

In considering the safety of INTERGEL[®] Solution, the Sponsor has been informed by ODE that the risk of infection may be higher compared to control. The difference between groups is not statistically significant, but ODE has nevertheless concluded that use of the product may pose a risk of infection. The sponsor evaluated this data carefully. The appropriate statistical test was applied to determine that the infection rate reported between groups (Fisher's exact-test) is not different. A review of the case reports confirmed that all infections in both groups were resolved without sequelae. The entire data set of adverse events from the trial was independently evaluated by two leading experts in the field, both of whom concluded that there is no increased risk of infection with INTERGEL[®] Solution. There is no

³ American Fertility Society. 1988. The American Fertility Society classification of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies and intrauterine adhesions. Fertil. Steril. 49:944-955.



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suggestion from postmarketing experience with INTERGEL[®] in 19 countries of an infection risk. Finally, results of two studies in an animal model indicate that the product does not potentiate infection risk. The second animal study, which confirmed the lack of infection potentiation risk in the first study, was designed and carried out as *required* by the reviewing Division (Major Deficiency letter dated December 7, 1999).

The Sponsor suggested to the reviewing Division that a post-approval study could be undertaken to evaluate the potential for infection potentiation in a larger population. ODE rejected this approach to resolving the scientific issue, as well as the possibility of additional animal research. No alternative methodology or approach to explain or resolve this concern have, to date, been proposed by ODE.

ACTION REQUESTED

The applicant requests that you refer this dispute to the Dispute Resolution Panel. The PMA applicant and ODE have a fundamental disagreement as to whether or not the scientific data in the PMA as amended provide reasonable assurance of the safety and effectiveness of the device for its intended use as an intraperitoneal instillate for reduction of adhesion formation following gynecologic pelvic surgery. The applicant pursued internal appeals to the ODE Director level, but ODE ultimately issued a not approvable letter.

The applicant requests that the Dispute Resolution Panel review the PMA data and consider the opinions of well-qualified clinical experts who are of the view that the PMA data support the safety and effectiveness of the product for its intended use. The applicant believes that ODE's not approvable determination is arbitrary and incorrect based on the scientific data in the PMA as amended. Accordingly, the applicant seeks a determination from the Center Director that the PMA as amended should be approved.

Respectfully submitted,



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Worldwide Managing Director, Healthcare Products
THE WEINBERG GROUP INC.

KMB/kh

cc James W. Bracke, Ph.D.

