

Lead Reviewer Summary Memo of Lifecore's PMA

DATE: To be presented at the Sept 6, 2001 Dispute Resolution Panel Meeting

SUBJECT: History of the Lifecore Biomedical PMA Application for Intergel® Adhesion Prevention Barrier Solution.

Introductory Remarks:

This memo summarizes the history of the PMA submission and the IDE study performed to support the safety and effectiveness of the Intergel® Solution. This memo is not intended to discuss the preclinical, statistical, or clinical issues in depth, but only to point out where and when issues arose. For details of preclinical issues see my preclinical review. For details of clinical issues, please see Dr. Horbowyj's review. For details of statistical issues, please see Richard Kotz' review.

Device Description:

INTERGEL® Adhesion Prevention Barrier Solution (Intergel Solution) is a sterile, nonpyrogenic, amber colored, viscous solution of 0.5% sodium hyaluronate, which has been ionically crosslinked with ferric ions and adjusted to isotonicity with sodium chloride to form a gel. The half-life of Intergel® Solution has been estimated to be approximately 51 h. The majority of a 300-ml instillate would be expected to clear the peritoneal cavity in 5 to 7 days via the lymphatic system. The solution is packaged in 300-ml low-density polyethylene bellows-type bottles. When stored at refrigerator or room temperatures the product has a proposed shelf life of 18 months.

Indications for Use:

Proposed in the Original PMA and at the January 20, 2000 General and Plastic Surgery Devices Advisory Panel (GPS Panel) Meeting:

Intergel Solution is indicated for use as a single use, intraperitoneal instillate for reduction of adhesions following gynecological pelvic surgery. It has been shown to reduce the incidence, extent and severity of post-surgical adhesions throughout the abdominal cavity when used as an adjunct to good surgical technique during laparotomy procedures.

Proposed in Amendment 11 in response to Panel Comments (From GPS Panel Meeting) and FDA Deficiencies:

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.

IDE Submission History:

The original IDE was for LUBRICOAT™ 0.5% Ferric Hyaluronate Gel (Lubriccoat Gel). The product is now referred to as Intergel® Solution (see above). It was submitted by the sponsor dated February 16, 1995 (received on February 17, 1995). The original IDE requested approval for a 1 institution, 25 patient, open label feasibility study to make a preliminary assessment of the safety and effectiveness of Lubriccoat Gel to reduce postoperative adhesions as compared to lactated Ringer's solution when applied following peritoneal cavity surgery. The feasibility study was approved in a letter dated June 1, 1995.

The results of the feasibility study showed that the Lubricat Gel and Control patients were similar in regards to number of sites with adhesions (3.55 and 4.33 respectively), number of lysed sites (2.82 and 3.78 respectively), and the number of primary surgical sites (5.36 and 5.56 respectively) at baseline. At 2nd look the number of possible sites was 17.18 for Lubricat Gel patients and 17.44 for Control patients, however, the Lubricat patients had adhesions at 6.09 sites (proportion of 0.364) and Control patients had adhesions at 11.0 sites (proportion of 0.629). There were no obvious differences in the safety profiles of the two treatments. The results of the feasibility study were used to calculate the sample size for the large-scale trial.

The proposal for a large-scale pivotal study was submitted in a supplement dated November 17, 1995 (received November 20, 1995). The supplement proposed a randomized, third-party blinded, placebo-controlled, multicenter clinical study of two parallel treatment groups. The study was to assess safety and effectiveness at 12 centers (11 US Centers were actually used) in the US (Protocol PTL-013) with a maximum of 350 patients (in order to obtain 200 evaluable patients) and there was to be a concurrent study performed in Europe (Protocol PTL-022) using the exact same protocol (There were 5 European Centers). The study proposed lactated Ringer's solution as the control treatment. The proposed large-scale pivotal clinical study was conditionally approved in the Agency's letter dated December 20, 1995. During the IDE review process, the Agency raised a number of issues that needed to be clarified.

The Agency's main concerns were as follows:

- The sponsor wanted to use a scoring system that was a modification of the American Fertility Society (AFS) scoring system. The concern was that the proposed method of scoring adhesions might not provide an adequate method for scoring the extent and severity of post-surgical adhesions as well as tallying actual sites with adhesions.
- The proposed scoring method had not been previously used to assess abdominal adhesions.
- The sponsor wanted to exclude all patients from the final effectiveness analysis if they failed to undergo a second look laparoscopy within 6 to 18 weeks after the original surgery.
- The sponsor was not planning to review second-look videotaped procedures.
- The European and US data were to be pooled and conditions of combinability were unclear.

During further discussions and correspondence, the Agency agreed to allow the sponsor to use the Modified AFS scoring system, but asked that the sponsor address the issue of validating this scoring method. The sponsor also agreed to perform an intent-to-treat (ITT) analysis including all patients that were treated in the final effectiveness analysis. This meant that all patients that did not complete the study would be considered treatment failures and would receive the worst possible score. The sponsor's proposal anticipated twice as many treatment patients as control patients not returning for the second-look laparoscopy. The sponsor further agreed to provide masked review of the second-look laparoscopy videotapes by an "Independent Medical Review Officer". Combinability (pooling) of the US and European studies was to be based on the following three factors:

1. There should be no significant interaction between location (US vs. Europe) and treatment efficacy.
2. The US and European populations should be similar on demographic and pre-treatment variables and the level of medical care. Variables included age, race, body weight, baseline adhesion score, previous and concomitant medications, endometriosis, surgical procedures performed, estimated blood loss, operative time, baseline clinical laboratory values, length of hospital stay, time to 2nd look laparoscopy and the number of patients lost to follow-up.
3. The US and European control groups should be similar on the 2nd look adhesion scores.

Once the sponsor had adequately addressed these issues the study was approved in a letter dated February 28, 1996.

In March of 1998, the sponsor submitted a supplement, which requested permission to halt enrollment of patients into the study because the sponsor felt that they had enough patients to combine the US and European studies with a combined enrollment of approximately 200 patients. At the time of submission this supplement, the sponsor was reporting on 104 US and 68 European patients, which was short of the 120 and 80 prescribed in the protocol for this analysis to justify pooling. On April 9, 1998, the Agency sent the sponsor a letter disapproving the supplement. The letter included the following Agency observations concerning the study.

- The average baseline number of adhesions for the US and European patients were significantly different (2.7 US vs. 6.5 European) and the proportion of sites with adhesions per patient and the Modified AFS score were similarly disparate at baseline between the US and European cohorts.
- The hospital stay was longer and timing of the 2nd look laparoscopy was later for the European subjects, while blood loss was significantly greater and operative time was significantly longer in the US.
- Significant differences in the racial make-up, previous and current medication regimens, and some of the baseline laboratory values existed when the US and European subjects were compared.
- Though the sponsor claimed that the interaction effect between either the US or European study group and efficacy was non-significant ($p = 0.085$), the analysis ignored the baseline adhesion scores for each subject and the potentially significant difference in the endpoint variance among evaluation cells.

The sponsor argued that the US and European data were still combinable in spite of the concerns voiced by the Agency. To clarify why this was the case, representatives of Lifecore met with the Agency in July and then submitted a follow-up supplement to answer questions raised by the Agency in the April 8, 1998 disapproval letter and at the July meeting. This supplement also requested permission to terminate enrollment of patients into the study.

The Agency responded to the July meetings and follow-up supplement with a letter, dated October 30, 1998 that granted the sponsor permission to stop enrollment, but also provided advice regarding the data presented to the Agency supporting combinability of the US and European. The advice given to the sponsor was as follows:

- The Agency expressed a concern that the data analyses presented, although intended to support pooling of the US and European studies, had not demonstrated that the Intergel™ Solution had been clinically effective in the patient population studied. The sponsor was advised that before the PMA could be approved the clinical data would need to demonstrate the clinical benefit of the product.
- The Agency stated that it was concerned that the differences in baseline number of adhesions obtained from the US patient cohort was different from the baseline number of adhesions obtained from the European cohort and that this difference could confound the analyses of the effectiveness endpoints. The sponsor was asked to be prepared to address this issue in the statistical analyses presented in the PMA.
- The Agency stated that it was not clear whether the differences between data obtained from the US cohort of the study and data obtained from the European cohort of the study would adversely effect the pooling analysis. The Agency went on to advise that any difference would have to be assessed as to its impact on the safety and effectiveness of the device for the proposed indications.
- Similarly, the Agency was concerned that the differences in data from the myomectomy and adhesiolysis patients might make those patient groups difficult to pool. The Agency felt that any

statistical analysis of these groups presented in the PMA needed to assess the poolability of the data.

PMA Submission History:

The PMA submission was received on March 8, 1999. The sponsor reported that a total of 303 (152 Intergel® Solution and 151 lactated Ringer's) female patients between the ages of 18.6 and 45.9 years of age undergoing peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy were randomized in the study. Following surgery each patient received an instillate of either 300 ml of Intergel® Solution or lactated Ringer's solution (Control Group). A return visit was conducted approximately 6 to 12 weeks after the initial surgery for a second-look laparoscopic procedure to evaluate effectiveness. The primary effectiveness variable was the Modified AFS score. Of the 303 patients randomized into the study 22 did not receive treatment and 281 did (143 Intergel® Solution and 138 Control). Of the 281 patients, 265 (131 Intergel® Solution and 134 Control) completed the study and 16 did not.

Briefly, the results for all patients (European and US) in the ITT analysis show that the baseline Modified AFS score for the Intergel® Solution patients was 1.01 and for the Control patients was 1.06 (out of a possible 16). Following surgery and either Intergel® Solution- or Control-treatment the score increased to 2.45 for the Intergel® Solution Patients and 2.58 for the Control patients, respectively (out of a possible 16). The number of baseline sites with adhesions for the 24 observed sites was 3.50 for the Intergel® Solution Group and 3.46 for the Control Group. Following surgery and either Intergel® Solution- or Control-treatment the number of sites with adhesions increased to 7.55 for the Intergel® Solution Group and 7.62 for the Control Group, respectively (out of 24). For Evaluable patients (all patients combined) the baseline Modified AFS score was 1.07 for Intergel® Solution Patients and 1.07 for Control Patients (out of a possible 16) while the second-look score was 1.21 for Intergel® Solution patients and 2.18 for Control patients (out of a possible 16). Baseline sites with adhesions were 3.65 for Intergel® Solution patients and 3.46 for Control patients (out of 24 sites) while the second-look adhesion scores were 6.05 for Intergel® Solution and 7.15 for Control (out of 24 sites).

The sponsor requested and was granted a 100th day meeting, which was held on August 17, 1999. At that meeting, the Agency informed the sponsor that the Agency felt the data presentation in the PMA was not complete and, based on the Agency's initial review, the effectiveness of the device was not clearly demonstrated.

During the pre-panel period, the Agency raised a number of concerns regarding the data in support of safety and effectiveness presented in the PMA and subsequent amendments. The Agency expressed the following concerns:

- Was the Modified AFS scoring system useful to assess success and what did a Modified AFS score mean?
- Was the data obtained from the European patients poolable with the data obtained from the US patients, based on the conditions of combinability described in the protocol?
- The patients in the Intergel® Solution Group had a higher infection rate than the patients in the control group.
- The animal study for potentiation of infectivity was inadequate because it had not been powered to detect as significant the 20% higher mortality rate seen in the Intergel Solution-treated rats than in the lactated Ringer's-treated rats.
- The sponsor had not met 2 point difference in Modified AFS score that they had predicted in their sample size calculation.

All of these concerns were presented to the GPS panel at the January 12, 2000 GPS panel meeting in the form of panel questions. The panel questions were as follows:

1. Data from Europe and the US has been presented in this application in patients with adhesiolysis as well as patients without adhesiolysis. When the data were compared between continents, there were substantial differences in distribution of baseline adhesion incidence, mAFS score, and race. Please discuss the poolability of data across continents and the poolability of data across surgeries (i.e., with adhesiolysis and without adhesiolysis).
 - a. from a clinical point of view, and
 - b. from a statistical point of view.
2. The clinical studies presented in this application include only non-cancer patients undergoing “procedures that would usually be classified as “clean.” Please discuss any clinical safety concerns with the use of this product in cases of any classification: clean, clean-contaminated, contaminated or dirty cases.
3. FDA 21 CFR 860.7(e)(1) for determination of safety and effectiveness states, “There is reasonable assurance that a device is effective when it can be determined, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

Does the data submitted in this application support:

- a. The mAFS scoring system to be a clinically meaningful and sufficient tool for assessing the number, extent and severity of peritoneal cavity adhesions during pelvic gynecologic surgery and evaluating the effectiveness of interventions for adhesions?
 - b. The ability of Intergel® Adhesion Barrier Solution to reduce the adhesion burden (number, extent and/or severity of post-operative adhesions) for treated patients?
4. The “Indication for Use” proposed by the sponsor states:

“InterGel Solution is indicated for use as a single use, intra-peritoneal instillate for reduction of adhesions following gynecologic pelvic surgery. It has been shown to reduce the incidence, extent and severity of post-surgical adhesions throughout the abdominal cavity when used as an adjunct to good surgical technique during laparotomy procedures.”

Please discuss the indications for device use that may be supported by the data presented in this application.

The summary of the panel’s responses to these questions were as follows:

1. The panel members agreed that there were clinical concerns about the poolability of the European and US data. However, the panel members felt that randomization within each center and stratification of analysis across sites were statistically appropriate.
2. The panel members voiced concerns about the potential problems of infection and the danger of potentially doing greater harm than benefit if the product were used on patients with cancer or those undergoing non-clean procedures. The panel members suggested that labeling should be modified to specify the specific population on which data are available, with an admonition not to go beyond this use.
3. The panel members expressed both statistical and clinical concerns about the mAFS scoring system as a clinically meaningful and sufficient tool for assessing effectiveness of the Intergel® Solution. Also, the panel members expressed concerns about the effectiveness of the Intergel® Solution itself in reducing the adhesion burden for treated patients.

4. The panel expressed serious concerns about the proposed indication for use. The panel members were concerned because of unclear data for the 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.

Following the discussion of the questions, the panel members voted 5-2 that the PMA was not approvable. The panel members indicated that they voted to recommend the PMA as nonapprovable because of issues with incomplete safety data and higher infection rates in treated patients over control patients. Also, the panel members expressed concerns in regards to the effectiveness of Intergel® Solution in adhesion prevention as well as the controversy over the use of mAFS scores as clinically meaningful surrogates.

Following the GPS Panel meeting the sponsor contacted the Agency and requested an opportunity to submit a major amendment to respond to the panel's concerns. The major amendment was submitted on June 2, 2000. The amendment contained a proposal for a revised "Indications for Use" Statement (Please see "Indications for Use" Section above), the repeated animal study showing no potentiation of infections in rats, some published clinical studies providing a background on the use of the AFS (not Modified AFS) scoring system, an analysis explaining the infection data observed in the clinical trial (still showing a 3:1 ratio of infections in Intergel® Solution-treated patients vs. control patients), and a reanalysis of the data using a retrospectively calculated AFS scoring. This was a reanalysis of data already presented to the January 12, 2000 Panel.

Following the review of this amendment, the Agency felt that the sponsor had not demonstrated the safety and effectiveness of the Intergel® Solution. The Agency sent the sponsor a not approvable letter on November 15, 2000. Upon receipt of the not approvable letter the sponsor petitioned for a hearing by the Dispute Resolution Panel.

This concludes the Agencies history of this submission.