

**SUMMARY MINUTES OF THE**

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

**MEDICAL DEVICES ADVISORY COMMITTEE**

**FIFTY-SEVENTH MEETING**

**OPEN SESSION**

**MAY 8, 2000**

**Gaithersburg Marriott Washingtonian Center, Salons F and G**  
**9751 Washingtonian Blvd.**  
**Gaithersburg, Maryland**

**GENERAL AND PLASTIC SURGERY DEVICES PANEL ROSTER**  
**May 8, 2000**

Thomas V. Whalen, M.D.  
Chair

Joseph V. Boykin, Jr., M.D.  
Voting Member

Phyllis Chang, M.D.  
Voting Member

David L. DeMets, Ph.D.  
Voting Member

Susan Galandiuk, M.D.  
Voting Member

Robert L. McCauley, M.D.  
Voting Member

Robert J. Cerfolio, M.D.  
Temporary Voting Member for FocalSeal-L

Mark K. Ferguson, M.D.  
Temporary Voting Member for FocalSeal-L

Thomas Lee Kurt, M.D., M.P.H.  
Temporary Voting Member for FocalSeal-L

Steven I. Reger, Ph.D.  
Temporary Voting Member for Apligraf

Maxine F. Brinkman, R.N.  
Consumer Representative

Sally L. Maher, Esq.  
Industry Representative

**FDA Personnel**

David Krause, Ph.D.  
Panel Executive Secretary

Celia Witten, Ph.D., M.D.  
Director, Division of General and Restorative Devices

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

Charles N. Durfor, Ph.D.  
Lead Reviewer, Division of General and Restorative Devices

Katharine Merritt, Ph.D.  
Office of Science and Technology

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

Phyllis M. Silverman, M.S.  
Statistician, Division of Biostatistics

**SPONSOR REPRESENTATIVES**

Mary Lou Mooney, M.S., R.A.C.  
Focal, Inc.

Bradley Poff, D.V.M.  
Focal, Inc.

Joseph LoCicero III, M.D.  
Independent Study Monitor, Focal, Inc.

John Wain, M.D.  
Principal Study Investigator, Focal, Inc.

Mathias Hukkelhoven, Ph.D.  
Novartis Pharmaceuticals Corporation

Vincent Falanga, M.D.

Michael L. Sabolinski, M.D.  
Organogenesis, Inc.

## **OPEN SESSION**

The meeting was called to order at 8:05 a.m. **Dr. David Krause, Panel Executive Secretary**, read appointments to temporary voting status for Drs. Cerfolio, Ferguson, Kurt, and Reger. Dr. Krause also read the conflict of interest statement, noting that a waiver had been granted to Dr. Boykin for his interest in a firm potentially affected by issues under discussion and that matters concerning Dr. McCauley had been considered but his full participation allowed.

**Panel Chair Dr. Thomas Whalen** noted that the panel would be discussing two premarket approval applications (PMAs). He noted that the members present constituted a quorum and asked the panel members to introduce themselves.

**Stephen P. Rhodes, Chief of the Plastic and Reconstructive Surgery Devices Branch**, gave the branch update since the last panel meeting of March 1-3, 2000, which considered three PMAs for saline-filled breast implants. He stated that the panel had recommended two of the PMAs as approvable with conditions and one as nonapprovable. Also, there were two recent reclassifications from class III to class II, one for the Gore suture and one for esophageal and tracheal devices.

## **OPEN PUBLIC HEARING**

There were no requests to speak.

**OPEN COMMITTEE DISCUSSION—PMA P990028 FOR FOCAL, INC.’S  
FOCALSEAL-L SYNTHETIC SEALANT**

**Sponsor Presentation**

**Ms. Mary Lou Mooney, vice president for regulatory/clinical affairs of Focal, Inc.,** began the PMA sponsor application for the device by defining the device and giving its regulatory history.

**Mr. Bradley Poff, director of preclinical services for Focal, Inc.,** read the intended use, which is as an adjunct to standard closure of visceral pleural air leaks incurred during pulmonary resection, and described the product, which is based on hydrogel technology. He explained the sealant molecule and its life cycle, analyzed the components and formulation excipients, and described application and polymerization. Mr. Poff showed an *ex vivo* porcine lung application demonstration and a clinical application demonstration. He also summarized the preclinical data analyses that showed that FocalSeal-L sealant has a favorable biocompatibility profile without evidence of mutagenic or carcinogenic risk. He described a long-term implant profile in multiple species where the FocalSeal-L Sealant tissue response was similar to that of other resorbable devices and indicated that preclinical efficacy results show adherence and 100% sealing efficacy in multiple *in vivo* lung studies.

**Dr. Joseph LoCicero III, an independent data monitor,** discussed the clinical need for the device and the study design. He reviewed the objectives and current limitations of pulmonary resection, noting the clear need for better surgical tools to control and prevent air leaks. Dr. LoCicero explained the study design, which was an open label, prospective, randomized multicenter study that compared standard tissue

closure versus standard closure plus the product. The 180 patients were stratified pre-randomization into high and low risk strata based on preoperative and intra-operative risk factors. He assessed the appropriateness of a six-month follow-up period as allowing adequate safety assessment and described the intent to treat scheme. Efficacy endpoints included percentage of patients air-leak-free from skin closure through hospital discharge and time to air leak cessation as well as percentage of patients air-leak-free at skin closure. Chest tube removal and hospital discharge times were assessed for trend patterns. Dr. LoCicero described intra-operative and post-operative air leak assessments and minimization of bias during the procedure. He concluded by describing safety assessments and study monitoring and documentation.

**Dr. John Wain, principal investigator,** described clinical results, charting patient accountability, enrollment by center, and protocol compliance. Analysis of patient demographics showed no statistically significant differences between control and device groups, as did analysis by primary surgical diagnosis, concomitant pulmonary problems, preoperative or intra-operative risk factors, risk stratification results, surgical procedure, or air leaks per patient. Mean application time was 12.7 minutes.

Dr. Wain summarized that clinically and statistically significant differences were achieved for all study endpoints, with percentage of air-leak-free patients increased more than threefold, and duration of air leaks reduced by almost one full hospital day. He noted favorable trends in chest tube removal and hospital discharge times and no significant differences in incidence or severity of adverse events.

Questions from panel members to the sponsors included whether allergic reactions had been noted, whether the device generates heat, whether there is autopsy data, and whether chest radiographs show the material.

### **FDA Presentation**

**Charles N. Durfor, Ph.D., FDA lead reviewer for the PMA**, summarized the device's regulatory history and described the device. He also introduced the review team.

**Dr. Katharine Merritt** gave the FDA perspective on preclinical studies. She explained the biocompatibility testing, noting that testing procedures for materials that polymerize in situ are not yet described and pose a challenge. She stated that implantation tests were done creatively and well; they showed that the material is slowly resorbed and there is an active inflammatory response for over 20 months. Genotoxicity and carcinogenicity testing provided weak evidence for a genotoxic effect, and carcinogenic effect was similar to that of controls (incidence and timing), but the study had limited power.

**Dr. Roxi Horbowyj, medical officer**, discussed the FDA's clinical perspective on the device. She described the device and the objective and design of the clinical study. Effectiveness results showed that, based on the whole cohort treated, the FocalSeal cohort had an increased proportion of patients with no air leak at skin closure and no air leak from the time of skin closure to discharge as compared to control. There was also a reduced time to no air leak. There was no difference in the percentage incidence of patients with air leak recurrence and with no air leak recurrence between treatment groups, and therefore, based on the cohort of patients per treatment group, who were air leak free at skin closure, there was no difference in the percent incidence of patients who

became air leak free and remained air leak free; there was also no difference in the median time to chest tube removal and time to hospital discharge. She noted that the learning curve and any covariate or confounding effects are not known, and the clinical benefit of the device is unclear. On safety, the FocalSeal group had a greater percentage and several-fold higher incidence of wound infection and empyema as compared to control. There was a small but not remarkable increase in the percentage incidence of cancer progression percentage during six-month follow-up in these small cohorts. Dr. Horbowyj also noted that the effect of FocalSeal-L, as a polymerized resorbable device, on the incidence and progression of cancer in humans is not known beyond six months.

There were no panel questions to the FDA presenters.

### **Panel Clinical Review**

**Panel Member Dr. Mark K. Ferguson** gave the panel clinical review. He listed strengths and weaknesses of the information presented. Strengths included the choice of centers, study performance, good distribution, completion of data collection, low toxicity, and good sealing efficacy. Weaknesses included the poor choice of primary endpoint. He noted a potential bias in that there was no stated definition of air leak, and no algorithm for chest tube removal or hospital discharge, and also noted the potential for observer variation. He suggested that a more meaningful primary endpoint might have been the proportion of patients who were air leak free at time zero that remained air leak free until discharge. Dr. Ferguson's concerns also involved toxicology, potential for adhesion formation, effects on lung cancer patients for chronic inflammation, higher incidence of wound infection, and lack of demonstrated clinical advantage in device use supported by  $X^2 = 0.106$ ;  $p = 0.745$  which Dr. Ferguson calculated for the endpoint he suggested:

proportion of patients who were air leak free at time zero that remained air leak free until discharge.

### **Panel Preclinical Review**

**Panel Member Dr. Thomas Lee Kurt** gave the panel preclinical overview, noting that none of the substances was in the list of carcinogens and possible sensitizers were present only in low amounts. He observed that his job was to describe the worst possible case scenario. Toxicological considerations concerned multiple package or dosage use, sensitization issues, and exposure of hospital personnel to components given off during device application. He saw no acute toxicological considerations but stated that potential sensitization was more likely with repeated use. Chronic health questions include sensitization, retention in the body, and possible tumor promotion. His questions concerned unapproved or off label use, use of multiple packages in a single patient, mixing the device with other components, possible hazards to the surgical staff, and whether a radiographic substance could or should be added to the product. He recommended further in vivo chronic studies on cancer promotion using larger numbers of animals and a postmarket reporting requirement that all reactions be reported in the first two years.

Panel discussion focused on use of the product in cancer patients on chemotherapy, wound infection rates, compatibility with antibiotic mixes, and possibility of cancer promotion.

### **FDA Questions for the Panel**

Dr. Durfor read the FDA questions to the panel.

The panel expressed a general level of satisfaction with the adequacy of preclinical testing and the safety profile but noted that three areas needed emphasis: tumor progression; residual material, and the propensity of infection. The panel emphasized concern over tumor progression regarding the cumulative and additional effect of therapies in the neoplastic process.

The panel came to consensus that reasonable assurance of safety had been demonstrated. The panel was in general agreement that further data were needed before answering the safety of device use relative to cancer progression, but there was no agreement on the duration of follow-up. Suggestions ranged from six months to five years. The panel agreed that effectiveness and clinically significant results were demonstrated.

#### **OPEN PUBLIC HEARING**

There were no requests to speak from members of the audience, the sponsor team, or the FDA.

#### **FDA Summation**

FDA representatives thanked the panel for its consideration.

#### **Sponsor Summation**

Sponsor representatives stressed that there was no statistically significant incidence of additional cancer progression or of carcinogenic possibilities.

### **Panel Recommendations and Vote**

Panel Executive Secretary Dr. Krause read the voting instructions. A motion was made and seconded to recommend the application for approval subject to the following conditions:

- 1) The sponsor would recommend maximum dosage limitations for one-time use and specify the number of syringes/patient weight in the package insert.
- 2) The product label would include a warning that there may be a higher rate of infection with this product.
- 3) The labeling would include a statement that the use of additives and their effectiveness has not been studied.
- 4) The sponsor would perform a follow-up postapproval study with longer follow-up time for tumor and infection rates. There was an interest in collection of additional information about complications, oncological developments, and infection. Details of the study would be worked out between the FDA and the sponsors.

(A motion that further animal studies be performed as a postmarket approval condition to reassure the FDA regarding carcinogenicity or tumor promotion with a combination of substances failed. A motion that the manufacturer provides a video or educational materials for required training failed for a lack of a second.)

The motion to recommend the PMA as approvable subject to the above four conditions was unanimously passed. Dr. Whalen thanked the panel reviewers and adjourned the Open Session for lunch at 11:50.

The Open Session resumed at 1: 15 p.m. Dr. Whalen noted that the charge for the afternoon was to review a PMA from Organogenesis for a cultured skin construct,

Apligraf. He observed that Drs. Cerfolio, Ferguson, and Kurt had left and that Dr. Steven Reger had joined the panel, and he asked Dr. Reger to introduce himself.

#### **OPEN PUBLIC HEARING**

**Dr. Lawrence Harkless of the University of Texas Health Science Center**, who stated that he owned some stock Organogenesis, reviewed statistics on the cost of diabetes-related complications such as foot ulcers. He stated that understanding the ulcerative process and its prevention, detection, and treatment are critical. Dr. Harkless spoke in favor of Apligraf and hoped the panel would agree to approve the device.

#### **OPEN COMMITTEE DISCUSSION—PMA APPLICATION P950032/S16 FOR ORGANOGENESIS INC.'S APLIGRAF**

**Mathias Hukkelhoven, Ph.D., vice president and U.S. Head of Drug Regulatory Affairs of Novartis Pharmaceuticals Corporation**, introduced the PMA by reading both approved and proposed indications for use. He noted that the device has been used commercially more than 10,000 times and introduced the sponsor representatives.

**Dr. Vincent Falanga** discussed diabetic foot ulcers and their pathogenesis. He presented statistics on the significance of diabetic foot ulcers and survival rates after amputation, as well as the etiology of diabetic foot ulceration and methods of treatment. He also noted that neuropathic foot ulcers are difficult to heal even with good standard care and may be associated with lack of progression through the normal wound-healing process. Dr. Falanga described the device and its application, noting that as a viable, bi-layered skin construct that is also capable of stimulating a healing response, Apligraf may be of benefit to patients with diabetic foot ulcers.

**Dr. Michael Sabolinski** discussed safety and efficacy as shown in protocol 95-DUS-001, a multicenter prospective randomized controlled clinical trial. The study was designed to compare the efficacy and safety of Apligraf therapy plus standard care to standard care alone for the treatment of neuropathic diabetic foot ulcers. After reviewing the study timelines, Dr. Sabolinski looked at key inclusion and exclusion criteria and described the Apligraf treatment and supportive therapies. A total of 208 patients were treated at the 24 sites, with roughly half in the device and control groups.

Dr. Sabolinski defined the primary efficacy endpoint (complete wound closure by week 12) and explained how wound closure was assessed. After a discussion of statistical methodology used (which included Fisher's exact test and Cochran-Mantel-Haenszel tests), he summarized that Apligraf improved the frequency of complete wound closure, reduced the time to complete closure, increased the probability of healing over 12 weeks, and showed a comparable incidence of recurrence.

Dr. Sabolinski noted that the purpose of the trial was to determine the effectiveness of Apligraf in the overall target population and not in individual subgroups. Subgroup analyses were needed to identify possible candidate risk factors for Cox's proportional hazards analysis. When adjusted for the multiple risk factors, the Apligraf treatment effect remained, leading him to conclude that the differences between Apligraf and control were not due to an imbalance in risk factors. Subgroups studied included Charcot joint deformity and study ulcer location. Any explanation for the apparent differences between Apligraf and control remains speculative in these small subgroups, but he concluded that after adjusting for risk factors the significance of effectiveness data remained in the overall target population for Apligraf versus control.

On safety, Dr. Sabolinski noted that no direct correlation exists between the number of Apligraf applications and adverse events. Adverse events are comparable between Apligraf and control. Serious infections at the study ulcer were comparable, as were additional safety parameters.

Dr. Sabolinski concluded that for the patient population defined in the protocol, Apligraf provided effective treatment and did not pose any increased risk. The device has a valuable risk/benefit ratio compared to standard treatment in patients with neuropathic diabetic foot ulcers.

Questions from the panel concerned the relationship of ulcer size to healing, the definition of wound infection, and whether this skin graft should be compared to other standard forms of treatment.

**Dr. Celia Witten, director of the Division of General and Restorative Devices,** clarified that the device was not claiming to be an alternative to saline-soaked dressings or to grafts but should be evaluated as indicated in the claim.

#### **FDA Presentation**

**Dr. Charles Durfor** read the device description and the indications for use before introducing the review team.

**Dr. Roxi Horbowyj** described the Apligraf market experience and the clinical study. She outlined the study objectives and target population as well as its design. Safety endpoints included laboratory assessments and evaluations of vital signs, immunology, and adverse events. The primary effectiveness endpoints were time to and incidence of complete (100%) wound closure, and secondary endpoints included recurrence and wound characteristics. Population outcomes showed no remarkable differences between

Apligraf and control distributions of demographics, age, gender, race, BMI, smoking history, ulcer size, or location. Effectiveness outcomes varied between pooled centers for both Apligraf and control groups. Dr. Horbowyj stated that Apligraf-treated patients showed increased incidence of 100% wound closure with number of Apligraf applications and decreased median time to 100% wound closure. She noted that difference and trend for difference do not persist in patient subgroups with ulcer location on toes, Charcot's disease, or multiple ulcers on target foot, but commented that these were very small subgroups. On safety, infection rate increases with number of Apligraf application, but incidence of infection in Apligraf and control patients is comparable. Dr. Horbowyj observed that ulcer recurrence as well as lab and vital sign profiles in Apligraf and control treated patients are comparable, and no immunologic response to Apligraf is evident.

**Phyllis M. Silverman** presented the FDA statistical review. She discussed randomization, noting that screening failures did not meet the inclusion criteria, but the remaining cohorts were very comparable. The sample size was adequate. She concluded that data are poolable for analysis and showed protocol violations removed and discontinued patients, which caused no appreciable bias. Ms. Silverman also concluded that the primary endpoints were well defined, that accountability at 12 weeks is greater than 84%, that Apligraf is superior to control for total population, and that there could be bias from the unmasked nature of the study, but it cannot be evaluated objectively.

There were no panel questions to the FDA presenters.

### **Panel Clinical Review**

**Dr. Boykin** listed the strengths and weaknesses of the device, noting that the device design is ingenious and the technology good. He thought, however, that there were significant concerns about study design factors and comparable groups and that the device should be compared to autografts. He was concerned both about evaluation of cost and the effect of treatment on quality of life. He thought it a very valuable product.

### **Panel Statistical Review**

**Dr. DeMets** listed four issues involving the basic design, the intention to treat, unbiased evaluation, and poolability. He noted that the study was not really a randomized study because of the loss of comparability and expressed concern about masking and unbiased evaluation. He was not sympathetic to the effort to pool data; although he thought the results generally consistent, the centers or subgroups should not be pooled too much. He agreed that the small numbers of various populations are too limited to draw many conclusions.

In panel discussion, members focused on whether antimicrobial agents could be combined with the device and why the device had been used so often in Canada and so little in the United States.

### **FDA Questions to the Panel**

The panel agreed with the statistical concerns expressed that the small numbers of difficult populations require further study and that the numbers are too small to draw conclusions. Similarly, on the impact of ulcer location, the panel consensus was the numbers were too small to draw distinctions, particularly without knowing prior podiatric experience. On whether the safety data provided a reasonable assurance of device safety, the panel answered an unqualified yes. The preponderance of panel opinion was that the

device was also effective although questions as to degree and reservations about prior podiatric procedures remain.

### **OPEN PUBLIC HEARING**

There were no requests to speak.

### **FDA and Sponsor Summary**

FDA and sponsor representatives thanked the panel.

### **Panel Recommendations and Vote**

**Dr. Krause** read the panel voting instructions and options. A motion to recommend the PMA as approvable with conditions was made and seconded. The conditions were as follows:

- 1) The issue of applicability of the device in the overall treatment of the diabetic patients should be clarified—that the device is one that should be sought after the failure of standard therapy.
- 2) The FDA should significantly evaluate how efficacy is portrayed in the labeling.
- 3) The labeling should clearly indicate that studies about the graft in neuropathic diabetic ulcer treatment were not compared to the standard human allograft treatment but to standard saline dressings.

The motion to recommend the PMA as approvable subject to the above conditions was unanimously passed.

Panel members commented that there were many strengths to the study but also some serious flaws and questions on the size of the effect. The device was thought to be a novel and safe and effective approach, but alternative methods should be encouraged.

The chair thanked all those present and adjourned the session at 4:45 p.m.

I certify that I attended the Open Session of the General and Plastic Surgery Devices Panel Meeting on May 8, 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

Summary minutes prepared by Aileen M. Moodie  
9821 Hollow Glen Pl.  
Silver Spring, MD 20910  
301-587-9722

Summary minutes edited by David Krause  
Executive Secretary, General and Plastic Surgery Devices Panel  
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