

**SUMMARY MINUTES**

**OF THE**

**ORTHOPAEDICS AND REHABILITATION DEVICES**

**ADVISORY PANEL MEETING**

**OPEN SESSION**

**January 19, 2001**

**9200 Corporate Blvd.  
Room 20 B  
Rockville, Maryland**

**Orthopaedics and Rehabilitation Devices Advisory Panel Members  
January 19, 2001**

Michael J. Yaszemski, M.D., Ph.D.  
Mayo Clinic  
Panel Chair

Albert Aboulafia, M.D.  
Emory University School of Medicine  
Voting Member

Edward Y. Cheng, M.D.  
University of Minnesota  
Voting Member

Maureen Finnegan, M.D.  
U.T. Southwestern Medical Center  
Voting Member

Stephen Li, Ph.D.  
Dana Center  
Voting Member

Harry Skinner, M.D., Ph.D.  
University of California, Irvine  
Voting Member

Floyd Larson, Ph.D.  
PaxMed International  
Industry Representative

Karen Rue  
Arcadian Health Care Alliance  
Consumer Representative

Jens R. Chapman, M.D.  
Harbor View Medical Center  
Consultant, deputized to vote (participation by phone)

Fernando Diaz, M.D., Ph.D.  
Wayne State University Health Center  
Consultant, deputized to vote (participation by phone)

Richard Simon, Ph.D.  
National Cancer Institute  
Consultant, deputized to vote

Timme Topoleski, Ph.D.  
University of Maryland, Baltimore  
Consultant, deputized to vote.

### **FDA Participants**

Hany Demian, M.S.  
Executive Secretary  
Orthopaedics and Rehabilitation Devices Advisory Panel

Celia Witten, Ph.D., M.D.  
Director, Division of General, Restorative, and Neurological Devices (DGRND)

Mark Melkerson, M.S.  
Deputy Director, Division of General, Restorative, and Neurological Devices (DGRND)

Barbara Zimmerman, B.S.  
Branch Chief  
Orthopedic Devices Branch

Holly Rhodes, B.S.  
Reviewer  
Orthopedic Devices Branch

Gene Pennello, Ph.D.  
Statistician, Division of Biostatistics

Martin Yahiro, M.D.  
Medical Officer, Division of General, Restorative, and Neurological Devices (DGRND)

**OPEN SESSION—JANUARY 19, 2001**

**Hany Demian, Executive Secretary of the Orthopaedics and Rehabilitation Devices Panel**, called the meeting to order at 9:37 a.m. and read a statement deputizing temporary voting members Jens Chapman, M.D., Fernando Diaz, M.D., Ph.D., Timme Topoleski, Ph.D., and Richard Simon, Ph.D., noting that Dr. Simon was also a voting member on a panel of the Center for Drugs Evaluation and Research. Mr. Demian read the conflict of interest statement, noting that waivers had been granted for Edward Y. Cheng, M.D., Stephen Li, Ph.D., Harry B. Skinner, M.D., Ph.D., and Jens Chapman, M.D., who had declared interests in firms potentially affected by the day's deliberations and that matters involving Dr. Li, Dr. Chapman, and Michael J. Yaszemski, M.D., Ph.D., had been considered but their full participation was allowed. He asked the panel members to introduce themselves, including Drs. Chapman and Diaz, who were participating by telephone conference.

**Panel Chair Michael J. Yaszemski, M.D., Ph.D.**, noted that the voting members constituted a quorum and stated that the charge to the panel was to consider a premarket approval application (PMA) for the Sulzer Spine-Tech BAK/C Interbody Fusion System intended for the treatment of cervical degenerative disc disease with radiculopathy.

**Mark Melkerson, M.S., Deputy Director of the Division of General, Restorative, and Neurological Devices (DGRND)**, introduced three new reviewers in the division, Glenn Steigman, Michelle Mattera, and Sam Kim, and the new Branch Chief of the Orthopedics Devices Branch, Barbara Zimmerman.

**OPEN PUBLIC HEARING**

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

## **SPONSOR PRESENTATION**

**Dan Mans, director of Clinical and Regulatory Affairs at Sulzer Spine-Tech,** introduced the sponsor representatives and explained the rationale for the device, noting that although there are several approaches to cervical spine fusion, the BAK/C device addresses some deficiencies that exist with current treatments such as morbidity associated with bone graft harvest. He reviewed the history of the PMA, noting that the submission was granted expedited processing due to the potential for clinically meaningful benefits associated with elimination of autograft harvest.

**Steven Griffith, Ph.D., from Sulzer Spine-Tech Research,** explained the design rationale and preclinical testing of the device. He listed the design characteristics and showed the device, which consists of a threaded hollow porous uncoated titanium cylinder or a hydroxyapatite (HA) coated version to enhance fusion and osseointegration. Dr. Griffith described goals and results of preclinical mechanical strength and fatigue testing for a minimum design load of 80 pounds and biomechanical testing done in two separate labs to show cadaveric flexibility and stability results. He stated that preclinical animal studies done on goat and sheep models showed bone growth with mature trabecular bone inside the cage at three months, no HA-related adverse events, and no device-related fractures, extrusions, or collapse. Dr. Griffith concluded that the preclinical experimentation demonstrated high mechanical strength and integrity, positive rigid biomechanical fixation, bone growth and fusion, and safety with no unanticipated adverse events.

**Robert Hacker, M.D, a neurosurgeon consultant for the sponsor,** explained the design of the clinical study and summarized its results. He listed various treatment

options for cervical degenerative disc disease and stated that the purpose of the study was to demonstrate the safety and effectiveness of the BAK/C and BAK/C-HA Interbody Fusion System for the treatment of this disease with radiculopathy. The study was a prospective, randomized, multicenter equivalence trial intended to show 1:1:1 randomization, with 578 patients enrolled at 28 investigational sites and a long-term follow-up of more than two years. Dr. Hacker explained patient selection procedures and listed inclusion and exclusion criteria. He concluded that the study showed the device is safe, as demonstrated by a low rate of complications; effective, as demonstrated by immediate and sustained relief of pain, improved quality of life, and fusion success rates; and clinically useful as shown by reducing the need for autograft harvest.

Dr. Hacker explained that study patients were randomized into coated and uncoated device groups and a control group treated with anterior cervical discectomy and fusion (ACDF). These groups were further stratified into one-level and two-level patients. HA coated and uncoated study cohorts were combined for statistical analysis; Dr. Hacker stated that statistical presentation would show coated and uncoated devices perform comparably. He explained patient demographics for one-level and two-level patients in all groups, noting no significant differences among the cohorts. Surgical technique consisted of standard anterior cervical decompression with the Interbody cage in the treatment arm or bone graft in the control arm.

Study results showed no significant differences between control and experimental groups in the one-level patients in terms of serious complications, although some required additional surgery. In the two-level patient group, there was a statistically significant difference between device and control group involving the implant itself, in

that the control group showed significantly more graft collapse. Effectiveness was evaluated for fusion using flexion-extension radiographs, neck pain using a visual analog scale, radicular pain using a pain and strength assessment, and function using the SF-36 general health survey. Fusion results showed comparable or superior results for the experimental group versus control, as did pain and function scores. Clinical utility was assessed in terms of surgical variables, donor site pain, employment status, and patient perception, with most results very similar for both groups, except for donor site pain and blood loss, both of which favored the experimental group.

Dr. Hacker concluded that the BAK/C Interbody Fusion system is safe and effective for use in treating patients with discogenic radiculopathy from C3-7, with fusion and clinical outcomes comparable or superior to those of traditional anterior cervical discectomy and fusion. He stated that the BAK/C provides the distinct benefits of a noncollapsing columnar support, autograft biology, and elimination of donor site pain.

**Kinley Larntz, Ph.D.**, gave the sponsor's statistical analysis. He provided an introduction to Bayesian techniques, in which data are collected over time, and in which Bayesian inference allows probability statements about model parameters conditional on the data. The BAK/C Bayesian model provides a linear model for log odds of success for each outcome and includes a random effect for center outcome success probability and for center treatment effect. Dr. Larntz showed various comparisons that can be done on the BAK/C-HA versus control or on one versus two level patients. He explained multivariate longitudinal modification, which permits inclusion of 12-month and long-term data in the same model and gives more precise estimates of long-term effects while accounting for missing long-term data. He also explained the protocol definition of

equivalence and showed a posterior distribution example. After explaining study objectives and outcome measures, Dr. Larntz looked at long-term effectiveness for a restricted cohort, noting that an intensive effort was made to increase compliance for the patients due for 24-month follow-up on November 15, 1999, with compliance at 81.3 % for this cohort.

Dr. Larntz discussed results of these statistical analyses, which showed that for one-level patients, equivalence criteria were satisfied for all outcomes and both uncoated and coated devices were superior to control in fusion, with the uncoated version also superior to control in overall success. For two-level patients, equivalence was satisfied for the coated device for function and overall, with an 80% or better probability of equivalence except for uncoated device radicular outcome.

Dr. Larntz also performed a sensitivity analysis to explore the extent to which missing data would need to differ from obtained data in order to change the study conclusion. He stated that this analysis demonstrated that the missing data are unlikely to affect study conclusions. Safety analyses using the same delta as the effectiveness analysis and using a Bayesian analysis for complication incidence and a Kaplan-Meier method for time to event analysis showed that the BAK/C device is superior to control in overall complication rate and in complications requiring additional surgery. Overall, therefore, Dr. Larntz concluded that the BAK/C and BAK/C-HA devices are safe and effective at one level for the stated indications. Two-level performance is similar to one-level performance, but two-level data alone do not establish equivalence. He reiterated that missing data are unlikely to affect study conclusions.

In conclusion, **Dan Mans** stated that the device had proven safety and effectiveness for use as indicated and showed a clinically meaningful benefit over existing technology by minimizing need for autograft harvest.

## **FDA PRESENTATION**

**Holly Rhodes, lead PMA reviewer**, introduced the members of the FDA review team. She also described the static and fatigue mechanical testing of the six mm implant, stating that the bench testing indicated that the device is strong enough to withstand anticipated physiologic loading. She stated that in vitro flexibility and stability testing were done on human cadaveric spines at C4-C5 and C6-C7, with no differences in initial range of motion or stiffness compared to the intact spine, but data were not stratified based on level of implantation. Ms. Rhodes also described results of the animal testing in goats, which found no statistically significant differences in stability between uncoated and HA-coated devices. Animal testing in sheep assessed fusion rates radiographically and compared device with autograft (67%), anterior plate with autograft (100%), and autograft alone (67%). She noted that in all three groups many deemed radiologically fused were not fused from a histological standpoint.

**Martin Yahiro, Medical Officer in the DGRND**, gave the FDA clinical review, noting that the protocol defined overall success as achievement of radiographic fusion; pain, functional, and radicular success; and absence of additional surgery. The rate of long-term overall patient success was 65.9%, 61.1%, and 53% for the one-level BAK/C, BAK/C-HA and control groups respectively, and 42.1%, 58.6%, and 46.7% respectively for the two-level BAK/C, BAK/C-HA, and control groups. Radiographic fusion rates for all groups were good, especially for one-level fusions. According to the sponsor's

Bayesian statistical analysis, the device group fusion success rates were “superior “ to that of control for one-level fusions but inconclusive for two-level fusions. For overall success, the results were “superior” for the one-level uncoated device and equivalent for the coated device one-level and two-level groups, but inconclusive for the two-level uncoated group. Dr. Yahiro noted, however, that the FDA raised concerns about the sponsor’s definition of statistical superiority.

FDA concerns with the effectiveness analysis included the fact that safety and effectiveness analyses were performed on different data sets, there were missing data, patients were not missing at random, and a disproportionate number of control patients withdrew following randomization but prior to surgery. Dr. Yahiro explained these concerns in detail, noting FDA questions for panel consideration in each area.

Dr. Yahiro summarized the safety evaluation in terms of data on adverse events associated with use of the device compared to control treatment. These adverse events were categorized as implant-related, surgery-related, additional surgeries, and other. He presented the total number of each of these events, as well as the type for one- and two-level fusions for BAK/C, BAK/C-HA, and control device groups. According to the sponsor’s Bayesian statistical analysis, the overall complication rates were equivalent between the one- and two-level BAK/C groups compared to the control, but the BAK/C-HA one-level and two-level BAK/C groups had superior overall combination rates compared to control. The implant related complication rates of the BAK/C and BAK/C-HA groups were superior to the control for one-level cases. Comparisons between the BAK/C group for two-level fusions were inconclusive, but showed equivalency for the

BAK/C-HA group compared to control. Again, however, the FDA had concerns about the definition of superiority.

FDA concerns regarding the safety analysis were that the safety and effectiveness analyses were performed on different data sets, that the safety data accountability analysis shows low follow-up rates at six, 12 month and longer follow-up evaluations, that disproportionate control group withdrawal is a concern, and that there was no sensitivity analysis to determine effects of missing data on safety conclusions. Dr. Yahiro described these concerns in detail, noting FDA questions for panel consideration.

**Gene Pennello, Ph.D., from the Division of Biostatistics,** gave the statistical review of clinical data, beginning with an explanation of the trial design. He noted that the effectiveness analysis was made on the restricted cohort because the rate of follow-up was higher for the restricted rather than the unrestricted cohort and the restricted cohort results were slightly less favorable than the unrestricted cohort. He explained the difference between a Bayesian and non-Bayesian analysis and defined equivalence and superiority hypotheses, as well as the log odds scale for probability of success. He also explained the Bayesian logistic model on success rate for each endpoint, and showed that exchangeability allows pooling of data across effects. Dr. Pennello explained his analysis of long-term effectiveness in the restricted cohort on one-level patients for uncoated versus control, coated versus control, and uncoated versus coated, which showed that coated and uncoated are equivalent to control in all endpoints and in some endpoints superior to control. The coated device was not superior to uncoated in any of the effectiveness endpoints, in his analysis. For two-level patients, only two conclusive

results could be obtained, in part because of lower power to detect equivalence. The coated device was equivalent to control in function and overall success rates.

Dr. Pennello also looked at the effect of missing data on Bayesian long-term analysis of effectiveness, noting that the missing patients will appropriately influence the analysis against BAK because of their long-term prognosis. A sensitivity analysis of the one-level patients only considers how the conclusions would change if the missing control patients were more successful and the missing device patients were less successful than the model would have predicted. It found that for all endpoints except neck pain, the conclusion of equivalence would be maintained even if the odds of success among missing patients relative to non-missing patients was 1000 times greater for control than the device.

Dr. Pennello noted that safety analyses on the unrestricted cohort only show an incidence rate with no adjustments for missing data and no consideration of time to complications. Looking at time to complication by Kaplan Meier curves shows that the uncoated and coated devices are superior to control in overall and implant-related complications and equivalent to control in surgery-related complications and additional surgeries. The results are inconclusive for other-related complications. Longer-term complication incidence rates in the unrestricted cohort for one and two-level patients showed the coated device superior to the uncoated in implant-related complications. Dr. Pennello observed that the submission did not include a descriptive table of complications per person-year by device. He added that clinical utility variables favored the experimental device only for donor site pain because few patients with device needed donation of bone harvested from the iliac crest.

Dr. Pennello concluded that for one-level patients, the uncoated and coated devices are equivalent to control in all safety and effectiveness endpoints. The two-level data were inconclusive. The one-level effectiveness results were adjusted for missing data and insensitive to missing data deviating from the model. For safety the missing data may not be an issue for surgery-related, implant related, and additional surgeries. Limitations on the data are that discontinuations were found disproportionately among controls and low follow-up rates led to analyses of different cohorts. Also the Bayesian safety analysis does not consider time to complication.

#### **Panel Preclinical Review**

**Dr. Topoleski** gave the preclinical panel review, noting that five major preclinical tests were done: ultimate strength, fatigue strength, stability, a surgical implantation instrumentation study, and two animal studies. He described the methodology of these tests, stating that he found them adequate for and specific to the particular implant.

#### **Clinical Panel Review**

**Dr. Diaz** gave the panel clinical review, in which he concluded that the only clear benefit in any area is for the one-level patients. He also found the only objective analysis to be fusion; all other analytical endpoints are softer. He thought the safety concerns well presented and well analyzed, and that the procedure is safe. He thought that graft collapse using the iliac bone harvest was predictable and that using a patellar allograft might have provided a better comparison. Problems with the study included the withdrawal of patient from follow-up and the use of an overall efficacy analysis, which he said created a wastebasket analysis. His major concern was with the overall

improvement of radicular symptoms, and he speculated about the beneficial effect of decompression alone versus the effect of fusion.

### **Panel Statistical Review**

**Dr. Simon** gave the panel statistical review, stating that he would have liked an analysis to show that the control itself is effective at eliminating neck pain. His second issue was the number of control patients who dropped out of the trial, especially two-level patients; he would have liked a sensitivity analysis in regarding to refusing randomization. Dr. Simon thought the Bayesian versus non-Bayesian analysis overemphasized, and he questioned whether enough patients were available for follow-up.

### **DISCUSSION OF FDA QUESTIONS**

- 1) Did Sulzer Spine-Tech demonstrate effectiveness of the BAK/C with and without the HA coating? And 2) Does the one- and two-level combined data set apply to two-level patients?*

The panel considered questions 1 and 2 in conjunction. Noting problems in interpreting the data because of the post-randomization dropout rate of control patients who did not receive the device, the panel agreed that equivalence in effectiveness was demonstrated for one-level patients but not for two-level patients.

- 3) Did Sulzer Spine-Tech demonstrate safety of the BAK/C with and without the HA coating?*

The panel expressed concern about needing to look separately at certain issues involving the coating (such as mechanical testing data after steam sterilization and other loading modes in vivo), but they agreed that safety was established.

**4) *What, if any, long-term questions does the panel think it would be important to answer in a post-approval study?***

Although some failed to see benefit in a postapproval study because of the long time involved to see small effects, others on the panel suggested possible topics such as radiographic and motion studies to assess implant longevity, subsidence, effect at other levels such as C4-C5 and C5-C6, effect on possible revision surgery, adverse events, changes in hormonal level in postmenopausal women affecting bone density, and relationship of study outcomes to implant size and level, spinal stenosis, revision of titanium after 12 months, and the need for more information on implant in a living, moving body.

**5) *Please give guidance on how to answer questions regarding a potential post-approval study in terms of assessment parameters, study duration, and any other elements of study design.***

The panel suggested five years for study duration and recommended radiographic and motion studies on the topics given above. Use of the Odom scale and assessment by a research nurse rather than by surgeon should be considered. One suggestion was to consider implants with the HA coating as a subset.

**6) *Are there any questions which related to the effect of the HA coating that the panel believes need to be addressed in a postapproval study?***

Some panel members suggested perhaps studying the HA coating group of patients separately from the uncoated implants. Other questions that could be addressed include preclinical testing on crackling off and abrasion of titanium, titanium wear, and effect of steam sterilization on the coating.

## **OPEN PUBLIC HEARING**

There were no requests to address the panel.

## **SPONSOR FINAL COMMENTS**

**Mr. Mans** suggested that the panel consider approval for one- and two-levels with a precaution on two-level patient data. This would allow clinicians to review the data for themselves in the package insert.

## **PANEL RECOMMENDATIONS AND VOTE**

**Mr. Demian** read the voting instructions and options. A motion was made and seconded to recommend the PMA as approvable subject to conditions. The motion passed. The conditions, each of which passed individually, were as follows:

- 1) That the device be approved for one-level usage only and that the package insert note that the data for two-level usage provided by the company were deemed not evaluable.
- 2) That a sensitivity analysis be performed on patient drop-out in the control group at a level the FDA will decide upon.
- 3) That a postapproval study as described in discussion of the FDA questions be performed.
- 4) That the sponsor make a distinction in the postapproval study between coated and non-coated devices and look separately at clinical variables such as the rate of integration of both devices and different rates of ingrowth, incorporating European study data.
- 5) That further mechanical testing of the HA coating be done
  - a) Along the lines of the testing already done on the uncoated device

- b) For all sizes of the device
- c) With fatigue tests as described above
- d) To show results on HA integrity after the sterilization procedure recommended by the sponsor, excluding testing data already in the master file
- e) Using a test method and loading more relevant to living bodies by reproducing loadings in flexion, extension, rotation, and lateral movement

The motion to recommend the PMA as approvable subject to the above specific conditions was made, seconded, and unanimously approved.

Mr. Demian thanked the panel and sponsor representatives, and the session was adjourned at 2:15 p.m.

I certify that I attended the Open Session of the Orthopaedics and Rehabilitation Devices Advisory Panel Meeting on January 19, 2001, and that this summary accurately reflects what transpired.

\_\_\_\_\_/s/\_\_\_\_\_  
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Hany Demian, M.S.  
Panel Executive Secretary

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

\_\_\_\_\_/s/\_\_\_\_\_  
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Michael J. Yaszemski, M.D., Ph.D.  
Panel Chair

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