

SUMMARY MINUTES

OF THE

ANESTHESIOLOGY AND RESPIRATORY THERAPY DEVICES PANEL

OF THE

MEDICAL DEVICES ADVISORY COMMITTEE

OPEN SESSION

June 12, 2008
Hilton Washington DC North/Gaithersburg
Gaithersburg, Maryland

Attendees
Anesthesiology and Respiratory Therapy Devices Panel Meeting

Open Session

June 12, 2008

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Voting Members:

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CALL TO ORDER

Panel Chair David J. Birnbach, M.D., called the meeting to order at 8:06 a.m. and noted that the voting members present constitute a quorum as required by 21 CFR Part 14.

Panel Executive Secretary Neel Patel noted that due to an unexpected emergency Dr. Gerald Schulman would not be present at the meeting. Mr. Patel read the conflict of interest statement. No conflict of interest waivers have been issued based on the meeting agenda. Mr. Patel then read a statement appointing Joseph LoCicero, Benson Wilcox, Valluvan Jeevanandam, Andrew Ries, Tim Topoleski, and Sharon-Lise Normand as voting members for the duration of the meeting. He also read a separate statement appointing James Lillard and James Stoller as temporary voting members.

Dr. Birnbach said the purpose of the meeting is to make a recommendation on pre-market approval application PMA P010047 for the NeoMend, Inc., ProGEL Surgical Sealant. He then asked the panel members and FDA staff seated at the table to introduce themselves.

POST APPROVAL STUDIES UPDATE

Dr. Marinac-Dabic discussed the need for post approval studies and the transformation of the post approval studies program. She noted that post approval studies should not be used to evaluate unresolved issues for the pre-market phase that are important for initial establishment of device safety and effectiveness.

OPEN PUBLIC HEARING

No members of the public came forward to speak.

SPONSOR PRESENTATION

Dr. Mezger introduced the sponsor representatives and provided an overview of NeoMend, Inc. The ProGEL sealant was acquired from 3M in 2007 and used the same

technology being developed independently by NeoMend since 1999 to address the need for better surgical sealants, particularly for lung air leaks (ALs) following lung resection surgery.

Dr. Walsh described the clinical need for the device. Currently, around 100,000 surgical procedures for lung cancer are performed, but that number is likely to increase with earlier detection of tumors. Around 40 percent of thoracic surgical cases are complicated by ALs. ALs result in longer hospital stays, prolonged need for chest tube, and greater risks of complications. There is confusion regarding the difference between pneumothorax and residual space, but residual space after pulmonary resection with no AL is not a problem. Current options for dealing with ALs include staples, sutures, pleural tents, muscle flaps, and phrenic nerve crushes, but they are not always effective and can have negative consequences. Thoracic surgeons also use available sealants off label. A sealant that is easy to apply and cost effective is needed.

Dr. Parks discussed product design and preclinical studies. The design uses two well known components, polyethylene glycol (PEG) and human serum albumin (HSA). The material mixes and polymerizes in vivo and was designed as an adjunct to standard closure for sealing ALs. Performance objectives were for sealing strength to withstand three times the pressure observed in a routine clinical environment while remaining compliant during lung expansion and contraction; gel target time of eight to 40 seconds; to achieve acceptable gel strength within two minutes; and residence time in the body less than 30 days.

Preclinical studies focused on device performance, biocompatibility, and results in animals. In design verification, the gel exceeded the 90 millimeters of mercury (mm Hg) burst strength criteria at 114.2 mm Hg and met the criteria for gel time with an average of 13.7 seconds. Preclinical studies showed that the sealant polymerizes rapidly in situ and adheres to tissue, consistently seals lung ALs, degrades within 30 days, has excellent biocompatibility, and

results in normal tissue healing with no evidence of any immune response.

Dr. Miller discussed the study design and results. The study was an open label, prospective, randomized controlled multi-center study, with a control of standard methods of closure and a treatment group of standard methods plus the sealant. There were 103 subjects in the sealant arm and 58 in the control arm. Sealant was only applied to observed ALs and not to other portions of the lung. Chest tubes were placed on suction, 20 to 25 centimeters for the first 24 hours and then placed on water seal at the investigator's discretion. Tubes were removed when no ALs were present, if there was insignificant stable residual space, or when drainage was less than five cubic centimeters per kilogram for 24 hours or 2.5 cc/kg for 12 hours. Heimlich valve use was allowed in the study according to standard U.S. practice.

The primary efficacy endpoint was the proportion of subjects who remain AL free from the recovery room (RR) through one month follow-up. Secondary endpoints included the proportion of intra-operative ALs (IOALs) sealed, proportion AL free in the RR, duration of post-operative ALs, chest tube duration, and the length of hospital stay. Safety endpoints were adverse events (AEs) through one month as well as laboratory results including standard blood tests and immunologic assays.

Baseline characteristics were similar, but there was a slight increase in sealant group patients with chronic obstructive pulmonary disease (COPD), renal disease, and who had undergone neo-adjuvant chemotherapy prior to surgery. In terms of the procedures performed, there were more patients in the sealant group who underwent an extended resection. There was a statistically significant difference in terms of multiple ALs: 70 percent of subjects in the sealant group compared to only 50 percent in the control group. The initial size of the ALs was similar. There were multiple different sources for the ALs, and there were no statistically significant

differences. In greater than 93 percent of sealant group subjects, the ALs were successfully sealed with either one or two applications of the sealant.

As for the results, the primary efficacy endpoint was achieved, favoring the sealant group 35 percent compared to only 14 percent in the control group, a statistically significant difference. Significant differences in secondary efficacy endpoints were seen in the measures of IOALs sealed in the operating room (OR), subjects who were AL free in the RR, and hospital stay, all in favor of the sealant group. There were no statistically significant differences in any clinical AEs or laboratory values. There were no device-related deaths, empyemas, significant changes in regards to immunity, physiologic or other physical findings of statistical or clinical concern, or acute or chronic effects. There were five deaths in the sealant group (4.9 percent) and four in the control group (6.9 percent). After a review by two of the investigators, the majority were found not to be pulmonary related, and there was no difference between the two groups.

A post hoc analysis was performed in response to an FDA concern regarding partial lung expansion. Partial lung expansion can occur following extended resection and does not mean the lung is trapped or there is any clinical problem. The preferred term rather than partial lung expansion is residual pleural space, which does not imply partial lung collapse. If there is no AL, no treatment is required. A post hoc subgroup analysis was performed looking at one month chest x-rays (CXRs). Looking at all study subjects, partial lung expansion was noted in 33 percent of all sealant patients and 23 percent of control patients, and there was no difference with regard to pneumothorax. A radiologist reviewed a subset of CXRs from 40 sealant patients and 20 control patients and found six sealant subjects had pneumothorax compared with none of the control patients. However, five of the six had a reduced residual pleural space at the time of follow-up, and only one, who had had an extended resection, upper and middle lobectomy, as

well as five previous thoracotomies and radiation treatment, required a chest tube at one month follow-up. Furthermore, the average time to one month follow-up was 13 days shorter for the sealant group, so they did not fall in the four to six week period in which the residual space would normally resolve.

There were higher numbers of patients with renal issues, but there was no statistical significance compared to the control group. Extensive renal toxicity preclinical testing was negative. There was more pre-existing renal disease in the sealant group (13 percent) compared with the control group (nine percent), and keeping patients dry to limit pulmonary edema in the peri-operative period may have led to increases in creatinine and transient oliguria.

Dr. Cerfolio presented the sponsor's conclusions. FocalSeal, which was previously approved by FDA, was difficult and cumbersome to use; because surgeons never adapted to it and due to other problems, FocalSeal is no longer available.

The sponsor's prospective, randomized, multi-institution study has demonstrated significant p values for the primary endpoint as well as three of the five secondary endpoints. There has been no evidence of device-related AEs. Regarding pneumothorax, they are hard to read, difficult to interpret on portable CXRs, and really have no clinical significance. Furthermore, there was no statistically significant difference in pneumothorax, so there is no evidence that the device traps the lung. There was also no statistically significant evidence of renal toxicity. Although there were some empyemas in the FocalSeal data, there were none with ProGEL. The device is very safe and shows high efficacy, and the data meet the burden of reasonable assurance of safety and efficacy. The clinical benefit to patients cannot be underestimated.

Dr. Normand asked who actually counted the number of ALs after the sealant is applied.

Dr. Miller said it was the surgeon. Dr. Normand was concerned about the lack of blinding related to counting ALs and removing chest tubes. She requested the specific duration of follow-up for each individual patient.

Dr. Cassiere asked for a breakdown of control versus sealant on how many hours patients were on positive pressure ventilation. Dr. Miller said they do not have that data but that median operating time for both groups was the same.

Dr. Wilcox asked about maintaining consistency in operative procedures. Dr. Miller said the surgical techniques were the same across all five institutions. Three institutions used an Ethicon stapler and two used Eurosurgical, but there was no difference in post-operative ALs based on the stapler used.

Mr. Melkerson noted the PMA must stand on its own and should not be viewed in comparison to another approved product and that there was data presented on Heimlich valves that has not been reviewed by FDA.

Dr. Domino asked about observed incidences, outside of the study, of renal insufficiency after thoracotomies and lung resections. Dr. Walsh said five to 15 percent of patients will have a transient bump in creatinine as a result of the relative hypovolemic state thoracic surgeons keep patients in to avoid the problem of pulmonary edema.

Dr. Jeevanandam noted that no clinical benefit was shown in terms of length of stay or the amount of time chest tubes were used. Dr. Cerfolio said it is hard to show a statistically significant difference in chest tube duration with ten different surgeons. Length of stay is also a difficult measure because patients may have longer stays for many reasons unrelated to their condition. However the data do show benefit in getting tubes out and patients home quicker.

Dr. Ries asked if randomization was site specific; Dr. Walsh said it was. Dr. Ries asked

why there were significantly more multiple ALs in the sealant group. Dr. Walsh said the randomization happened to result in more extended resections in the sealant group.

Dr. LoCicero asked when the gel reached acceptable strength, and Dr. Parks said in one to two minutes. Dr. LoCicero asked about the length of the study. Dr. Miller said it lasted 15 months, ending in late 2001.

Regarding post-operative renal function, Dr. Stoller asked for data on volume management. Dr. Cerfolio said they do not have that data but said reviewers were very cautious given that creatinine bumps from 1.2 to 2 were labeled AEs. There was no real difference between the two groups in terms of changes in creatinine.

Dr. Lillard asked about numbers and distribution of minority subjects in the study. Dr. Parks said there was less than five percent minorities at each center. Regarding preclinical hypersensitive response, Dr. Lillard asked about the hypersensitivity metric in the clinical study. Dr. Parks said the anaphylaxis reactions seen in guinea pigs were type I hypersensitivity and was looked for in the clinical study during the operation. With regard to a delayed type IV hypersensitivity reaction, investigators depended on immune studies and subsequent follow-up.

Dr. Normand asked for clarification on when the randomization occurred. Dr. Miller said that following the procedure ALs were counted, standard techniques were applied to repair those ALs, and then patients were randomized to either sealant or control, and then ALs were counted again for both groups. Dr. Normand asked if the surgeon could apply the sealant to places other than where ALs were spotted, and Dr. Miller said it was only applied to recorded ALs. Dr. Normand also asked if everyone with an AL gets a chest tube, and Dr. Miller said yes.

Dr. Topoleski asked how burst strength was measured and whether it was the material itself bursting or the adhesive bond between the material and tissue. He also asked whether there

was a range of molecular weights and in particular regarding degradation products. Dr. Parks said burst strength is the strength of the material. Regarding PEG breakdown, he said they occasionally found a single succinate molecular weight but otherwise it was 3,500. No smaller fractions were found. Dr. Topoleski asked if an adhesive strength test was performed. Dr. Parks said adhesive testing was done as part of the development of the burst strength testing profile.

Dr. Lillard asked if there was any gender or ethnicity bias in the observed renal failures, and Dr. Miller said there was not.

Regarding the statements that the sealant group had more extensive surgery, Dr. Loeb inquired whether any subsequent analysis breaking down those groups was performed. Dr. Miller said there is no subgroup analysis and that it was a very small percentage.

Dr. Wiswell asked whether it is true that of the six that had prolonged AL, only one had had an extended resection. Dr. Miller clarified that they did not have prolonged ALs but were deemed to have a pneumothorax or residual pleural space at follow-up. Dr. Wiswell then asked for the definitions of oliguria and acute renal failure used in the study. Dr. Miller said oliguria was defined as less than 30 cc an hour of urine output over a 24 hour period, even though in clinical practice more than 10 cc is generally deemed to be okay. Acute renal failure was defined as those patients requiring dialysis to treat it. Dr. Wiswell finally asked for data on the length of time patients had oliguria or were considered to have acute renal failure. Dr. Miller said oliguria resolved within one or two days after surgery.

Dr. Jeevanandam wondered about the clinical benefit given that no patients in the control arm developed bronchopleural fistula or needed to have chest tubes reinserted and their ALs stopped on their own, albeit not as fast as with the sealant. Dr. Miller said the study was not powered to look at complications but there was more pneumonia and death in the control arm,

and the literature shows that prolonged ALs do lead to more complications, longer hospital stays, and death.

Dr. Normand asked for clarification whether the sealant was applied to sites which the surgeon did not close with the standard technique because the AL was too small or the tissue too fragile, and Dr. Miller said that is correct but noted that it was not used prophylactically on areas where no AL was found. Dr. Cerfolio said one of the important clinical benefits of the product is that it can be used on ALs that otherwise could not be treated.

Dr. Stoller asked whether the primary outcome was based on the surgeon's assessment at one month, and Dr. Miller said it was the surgeon and the research coordinator, who he agreed were not blinded.

Dr. Brunson asked about the impact of the product on ALs not detected until post-op. Dr. Cerfolio said it is an important question the study did not address since the sealant was not used prophylactically over the staple line, and he noted that many surgeons used the previous product and currently use off-label products prophylactically in that way. Dr. Walsh elaborated that chest tubes stay in for reasons other than ALs.

Dr. Cassiere asked for the definition of partial and complete lymphadenectomy and whether there is any clinical significance to the fact there was no lymphadenectomy in 29.1 percent of sealant and 19.3 percent of control patients and a complete lymphadenectomy in 41.7 percent of sealant and 56.1 percent of control patients. Dr. Miller said a complete removes all lymph nodes from the peratracheal, subcarinal, and hilar areas, but if the patient does not have a primary malignancy, lymph nodes are not evaluated. Dr. Cassiere clarified that with more lymphadenectomies and more manipulation of the pleural and lymph nodes, one would expect more ALs. Dr. Miller said lymphadenectomy is a mediastinum lymph node dissection that has

no effect on the lung.

Dr. Domino inquired about differences in terms of those extubated at the end of the case versus those intubated for a day or longer. Dr. Walsh said patients were extubated at the end of the case and didn't have mechanical ventilation unless they needed it some time later. Dr. Domino asked whether with a CPAP or BiPAP device one might have an increase in an AL. Dr. Walsh said with CPAP or positive pressure ventilation you will increase your AL, but there was no difference in the number of people who needed positive pressure ventilation.

Dr. Birnbach asked why they did not exclude patients with renal failure nor blind the study. Dr. Walsh said they wanted the subjects to represent the patient population the device would be used for. He said they thought the assessments would be the most consistent with having the surgeon and research personnel be the only ones to determine whether there was an AL and said that surgeons err on the side of leaving tubes in longer in case there is an AL.

Regarding between center differences, Dr. Ries asked if the same proportion of patients who were determined not to have an AL and thus not randomized was seen across centers, and Dr. Miller said yes. He also noted there was no concern about preclinical renal toxicity and that renal data was only presented to address FDA's concerns on the post-hoc analysis.

Dr. Cerfolio said the surgeon performed a routine follow-up at one month and that it was really the radiologist reading the CXR who identified potential ALs and was blinded to the study. Dr. Stoller wondered if they could see data from the radiologists on air in the pleural space at one month. Dr. Spindell asked if the determination of AL at one month was just CXR, and Dr. Miller said it was CXR and clinical exam. Dr. Spindell asked if residual space in the follow-up CXR would indicate the presence of an AL, and Dr. Miller said if it is decreasing rather than increasing in size, there is no AL. He said there is no way to accurately measure the pleural

space in a CXR because it is a three-dimensional volume. Dr. Stoller suggested they consider a later session with three endpoints for the one month follow-up: the prevalence of air in the pleural space, the presence of air in the pleural space deemed to be of decreasing size compared to the prior film, and the surgeon's assessment of whether or not there was an AL.

Dr. Ost emphasized that when the standard techniques were applied to close ALs, no one knew whether the individual patient would be randomized as a sealant or control patient. He also said assessment of persistent AL, while not blinded, is fairly objective and simply involves looking for any bubbles in the chest tube container. He also noted that the primary outcome measure effect size was large in addition to being statistically significant.

FDA PRESENTATION

Dr. Durfor outlined the FDA presentation and discussed preclinical studies and clinical immunology. In subchronic toxicity studies in situ polymerization resulted in slight to moderate inflammation on the small intestines, associated with microscopic signs of inflammation, neo-vascularization, and hemorrhage, but the cause is unclear. In a standard irritation study, moderate to severe irritation was observed when polymerized in rats. Wound healing was not delayed in pig lung studies, and the product was largely absent by four days and not observed at all by 14 days. Inflammation and squamous metaplasia were common near the surgical closure site on days four and seven. In pharmacokinetic studies, the product cleared rapidly, over 50 percent during the first day, with urine as the primary clearance route. Clinical data on immunology testing presents no concern for FDA.

Dr. Horbowj discussed clinical study design, demographics, and operative parameters. Of note, there were slightly more control patients who had had previous thoracic surgery. A recently proposed idea to retrospectively regroup patients by procedure is inappropriate because

the volume of resected lung in partial resections was not recorded.

Dr. Lao presented the statistical perspective. For the primary efficacy endpoint, the statistically significant combined odds ratio was 3.34 with a 95 percent confidence interval from 1.4 to 9.1, which does not include one, in favor of the sealant group. IOALs sealed and RR POALs sealed favored the sealant group. There was a marginally significant difference in length of hospital stay. There was no significant difference in duration of POALs sealed from time of surgery or probability of chest tube removal.

Dr. Horbowyj discussed clinical study outcomes. Incidence of AL free patients through one month as determined from the RR was 21 percent greater in the sealant group and, when determined from the OR, 30.1 percent greater. The incidence of AL free status in the OR was 60 percent greater and in the RR 23.9 percent greater in the sealant group; the endpoint was met statistically, but the AL recurrence rate is clinically notable. The time to discharge endpoint was met, but evaluation was confounded and potentially biased by Heimlich valve use with no prospective plan. No difference was found in time to AL sealed or time to chest tube removal, and the evaluation of these was also confounded by Heimlich valve use.

Late onset AL occurred in six percent more sealant patients. Prolonged AL occurred in two percent more sealant patients at post-op day seven and in 7.5 percent more through post-op day 11 and thereafter. Pneumothorax occurred at a comparable incidence, but five of nine sealant patients and only 1 of 5 control patients required invasive intervention, and one of those sealant patients died. According to the treating physician and study monitor, incomplete lung expansion occurred in 11 percent more sealant patients; but according to independent, masked radiologic assessment, in 17 percent more sealant patients. Renal AEs occurred in 5.7 percent more sealant patients.

Dr. Krulewitch presented potential post-marketing issues. Since the PMA was submitted prior to 2005, the sponsor has not submitted a post-approval protocol and an epidemiologist was not included in the review team. Discussion of a post-approval study should not be interpreted as a suggestion that the panel find the device approvable, and a plan to conduct such a study does not change the threshold of evidence required. Objectives include evaluation of device performance and potential device-related problems in a broader population treated by average physicians over an extended period of time, evaluation of any training programs, evaluation in patient subgroups, and monitoring of AEs, particularly rare ones not observed in clinical trials.

Dr. Normand asked if it is correct that the primary efficacy endpoint was measured at one month follow-up so time wasn't taken into consideration. Dr. Lao said the primary endpoint was measured at one month follow-up or at the time of patient discharge depending on which one was longer. Dr. Normand asked if the conclusion would then be different if one used a Kaplan-Meier analysis rather than the binary endpoint, and Dr. Lao said yes.

Dr. LoCicero asked whether there is any way to separate the effect of the staples from that of the sealant in pig studies. Dr. Durfor said each pig had seven surgical sites: five closed with staples followed by sealant, one closed only with staples, and one with sealant put into the wound, closed with staples, followed by sealant. He said his interpretation was that it appeared as if the sealant had pretty much covered all of the sites. Dr. Parks agreed and said the response to the sealant could be distinguished where it was mechanically distant from the staple.

Dr. Spindell asked if anything on Slide 71 from Dr. Horbowyj's second presentation reached statistical significance. She said they may not even have been evaluated statistically because sample sizes were small and the study was not adequately powered.

Dr. Topoleski asked about data on the time dependent strength or adhesive strength of the material or cyclic or fatigue loading of the material that would simulate the in vivo environment. Dr. Durfor said no and that it is a difficult environment to simulate.

Dr. Loeb pointed to the differences between FDA slide 34 and the sponsor's slide 52 on intra-operative parameters and asked if there is any possibility of conducting an analysis looking at the amount of tissue removed. Dr. Horbowyj said the issue with grouping procedures the way the sponsor presented the data is the inability to compare individual procedures based on how much tissue is removed as well as clinical translation into CXR reports.

Dr. Birnbach asked whether there is any statistical difference in how sick the patients were or whether they had had previous surgery. Dr. Horbowyj said there is not.

Regarding slide 64 and the independent radiologic assessment at one month, Dr. Stoller asked if there are statistics suggesting an 11 percent excess of non-complete lung expansion in the sealant group. Dr. Horbowyj said she could get that information but noted the studies were not powered to look at that. Dr. Stoller asked if a complete independent radiologic assessment of all 161 patients would look any different. Dr. Horbowyj said they tried to carefully choose a representative sample by going across three large centers. There did seem to be a disparity in the group with right upper lobe resection compared to the overall cohort.

Dr. Jeevanandam noted that the study shows the sealant stops ALs early, but, although the pneumothorax incidence was the same, more sealant patients required therapy for their pneumothorax and there were more patients in the sealant group with incomplete lung expansion. He wondered if it could be an effect of the sealant itself.

Dr. Domino wondered if there is any physiologic mechanism that could explain why there were three cases of acute respiratory distress syndrome (ARDS) in the sealant group and

none in the control group.

Dr. Normand asked if all patients were discharged home. Dr. Horbowyj said she thought most patients went home but would try to out.

Comparing the sponsor's slide 77 to FDA slide 69, Dr. Stoller asked if ARDS was a cause of any deaths in the control group as stated in the sponsor's slide. Dr. Horbowyj said they listed the etiologies as they were presented to FDA. Dr. Stoller asked if there was any independently assessed attribution of death. Dr. Horbowyj did not believe so.

Referring to FDA slides 64 and 65, Dr. Loeb asked about the difference in incidence of incomplete lung expansion in the group of 149 patients, with 33 percent in the treatment group and 22 percent in the control group, and in the independent radiologic survey of 59 patients, with 17 percent in the treatment group and none in the control group. Dr. Horbowyj said the difference is a function of sample selection. Dr. Jeevanandam asked why the sub-analysis of 59 patients was performed. Dr. Horbowyj said FDA asked for an independent assessment to try to confirm and hopefully understand the results, and FDA and the sponsor agreed on a cohort of 60 patients since not all CXRs were available and to avoid being overly burdensome.

Dr. Walsh addressed outstanding questions. Regarding incomplete expansion, he said most lobectomy patients will have a residual pleural space, and, if there is no AL, it is of no clinical significance. Comparing the 32 partial expansion sealant patients to the 12 partial expansion control patients, there was a lower complication rate in the sealant group, no increase in hospital stay, nor a lower rate of AL free one month analysis. In the independent review of 60 patients, all six in the sealant group with partial lung expansion had shrinking residual spaces at one month follow-up, and only one of the 40 sealant group patients, who had had a bilobectomy, had an increasing airspace. Also, the 40 patients happened to include more patients who had

right upper lobe resections. Dr. Walsh emphasized there is clinical benefit to the product and that chest tube duration cannot be the sole measure taken into consideration.

Dr. Lao clarified an earlier response to Dr. Normand and said his review was time to event Kaplan-Meier analysis. Dr. Normand asked if AL free and chest tube removal are equivalent, and if so, what would be the equivalent of the time to event analysis on the primary outcome. Dr. Lao said he did not see the analysis trying to link the two outcomes together. Dr. Walsh said stopping the AL can not be equated with chest tube removal given different chest tube management and patient differences. Chest tubes are used not only for air but also for fluid drainage. Dr. Normand asked how they determined patients were AL free. Dr. Walsh said every morning patients performed standard maneuvers to see if any air bubbles came out.

Dr. Horbowj addressed an earlier question on death etiologies and said the causes in the PMA are as listed in the agency presentation. For the control group, no etiology of death was attributed to ARDS, but ARDS was listed as a contributing factor for one patient. Three instances of ARDS were reported as cause of death in the sealant group, and two instances of ARDS were reported with multi-system failure as a cause of death.

Dr. LoCicero asked if between 50 and 60 percent of all partial expansions really occurred in upper lobectomy patients, and Dr. Walsh said that is correct.

PANEL DELIBERATIONS

Dr. Topoleski wondered if it would be helpful to know the probability of success at various time points rather than simply knowing that one can close ALs right away. Dr. Parks said it would have been very difficult to do that experiment. Dr. Cerfolio said such information would not alter patient management. Dr. Walsh said whatever ALs can be controlled will help get chest tubes out faster and that the product is especially important in difficult to seal areas like

the hilum.

Dr. Loeb was concerned about the potential for late pneumothorax or late AL. He thought it would be safer for patients to have an AL and watch it disappear rather than not have an AL, manage the patient as if there's no potential for an AL, and then have an AL appear.

Dr. Jeevanandam noted that the sponsor's data does not support the conclusion that ALs prolong chest tube placement. There is a difference in length of stay, but the ten treatment patients on a Heimlich probably could have been discharged early anyway. Dr. Spindell recalled a slide showing that omitting Heimlich patients length of stay was still shorter, and Dr. Miller said that was true. Mr. Melkerson noted that FDA has not had been able to evaluate that data.

Dr. Ries agreed with Dr. Jeevanandam; he was convinced the product controls ALs in the OR and in the immediate post-op period but was unsure of the clinical significance. He said time to cessation of AL is really no different and that there was a subset of sealant patients with prolonged AL and chest tube. Dr. Cerfolio one reason that is true is there were ten sealant patients who got a Heimlich and only one control, which might be explained by the sealant making the AL small enough that the patient could get a Heimlich and go home. He emphasized that the study was not designed to look at chest tube removal since the ten surgeons all manage chest tubes differently and that the study was positive in terms of freedom from AL. Dr. Ries pointed to slide 59 showing that within the first six to eight days after surgery, around 85 percent of control patients had no AL compared with 75 percent of sealant patients.

Dr. Normand again requested data on when the one month follow-up was actually obtained; she said a binary endpoint is inappropriate and that she needs to see an analysis that takes into account the different durations of follow-up. Dr. Cerfolio said average time to one month follow-up was shorter in the sealant group possibly because patients who went home on a

Heimlich valve had to return. This shorter time would explain why sealant patients had more space since they were seen before such space problems tend to resolve. Dr. Walsh said the sponsor tried to get it within the four to six week time frame but had to make allowances for patients who had to travel long ways to get to a particular center.

Dr. LoCicero asked if one month follow-up was calculated from operation or discharge. Dr. Walsh said mean follow-up for the sealant group was 41.5 days plus or minus 14.4 and 39.1 days plus or minus 14.6 for the control group, and with the length of stay approximately five to seven days, follow-up would be approximately one month after discharge.

Dr. Birnbach asked how patients were selected for the post hoc analysis . Dr. Mezger said three of five sites had digital x-rays and it was decided for expediency to do the subgroup analysis with digital x-rays that could be forwarded to one blinded radiologist. The sponsor tried to find pretty complete sets of x-rays for as many patients as they could and then settled on 60 so as to maintain the two to one randomization.

Dr. Jeevanandam asked if they had considered reanalyzing all the x-rays after the 11 percent difference became 17 percent. Dr. Mezger emphasized that the subgroup analysis was meant to determine if there was any investigator bias in reading the x-rays. Dr. Loeb asked how the assessment of no bias was made given there was a better outcome in the control group and a worse outcome in the sealant group. Dr. Walsh said the difference was likely due to selection bias in selecting more treatment patients with more anatomic resections.

Dr. Normand reiterated her desire for an analysis using the actual time of the assessments. Dr. Ost said they do not have a Kaplan-Meier analysis but said the survival curves would not cross.

FDA QUESTIONS

1. Please discuss the clinical significance of the preclinical and clinical findings and their impact on the clinical safety and effectiveness of ProGEL Surgical Sealant as an adjunct to standard care, compared to control (standard care alone).

Panel members were concerned about the lack of expansion in the sealant group, the fact that within four days the control group caught up in terms of number of patients with no AL, the potential for late pneumothorax occurring outside the hospital, and the lack of any difference in chest tube duration. One member said without a Kaplan-Meier analysis it is unclear whether the study met the primary endpoint. There was discussion whether the difference in expansion might be related to chest tube management and whether patients were on suction.

Regarding late pneumothorax, a sponsor representative said there was one patient who had a pneumothorax after hospital discharge but before one month follow-up, but she had had multiple thoracotomies as well as radiation therapy. Another representative of the sponsor said that four other patients had been listed as having delayed pneumothorax when in fact they simply got Heimlich valves attached to their chest tubes.

One member talked about the problems with evaluating chest tubes and suggested the panel should focus on whether the product stopped ALs. One member felt the panel could not comment on efficacy with the existing data. One member said contaminated air in the pleural cavity is bad, that there was data that the product does decrease contaminated air in the chest, and that a residual, uncontaminated air space is not bad. Another member noted that within six days, 85 percent of control patients had no AL compared with only 75 percent of treated patients. There was discussion around the meaning of the primary endpoint data and the varying time of ascertainment of one month follow-up. There was concern the product could change clinicians' approach to patient management.

The chair summarized that more data is needed before the panel can conclusively state that the product is safe and effective at reducing ALs.

2. Please discuss the clinical significance of these findings and the possibility that renal events that occurred during the clinical study were device-related.

There was discussion whether patients might be exposed to more of the sealant post approval and whether the renal function abnormalities were directly due to the device. One member suggested the product might be responsible for higher levels of cardiac AEs. Another noted that the study was not powered to detect adverse events. One member said there is a suggestion of renal effect, as was the case in the clinical trials for aprotinin, which was eventually taken off the market because of renal dysfunction. Another panel member said that even a short-lived renal insult could have repercussions later on. Another member said the sponsor attempted to get the study done quickly by using large tertiary care facilities, so the subjects were sicker; heterogeneity of resection types is also problematic. Furthermore, the results are confounded by the requirement for fluid restriction during and after the operation. Looking at dose response another member said it does not appear that acute renal failure was device-related and thought it was related to fluid management. One member thought renal function warrants close monitoring but did not think it was a particularly important safety issue. Another said a much larger study would be needed to answer the question and thought it would be worthy of study post-approval. There was discussion of prior experience with PEG and serum albumin not being a problem. There was disagreement as to whether the product degraded into the two components before being cleared, and the sponsor said it does.

The panel felt the renal events were probably not directly device-related, but renal dysfunction nevertheless may be a concern. The potential for the product to be used in larger quantities is also concerning. Panel members were not overly concerned with the observed renal dysfunction. One member thought the concern was device-related given that it was a randomized controlled trial. The panel felt renal effects deserved some level of post marketing

surveillance.

3. Do the data presented in P010047 demonstrate reasonable assurance of effectiveness (i.e., in a significant portion of the target population, the use of ProGEL Surgical Sealant for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings will provide clinically significant/meaningful results)?

A panel member reiterated that a Kaplan-Meier analysis should have been used for length of stay and that patients with a Heimlich valve were appropriately censored in the statistical analysis.

The panel felt the sponsor clearly showed that the product stops ALs in the perioperative period, whether for four or 30 days, and there were some issues with the 30 day measurement. There is a suggestion of clinically better results, and some measures such as reduced hospital stay may be clinically significant for patients.

4. Do the data presented in P010047 for ProGEL Surgical Sealant use with standard care compared to control (standard care alone) adequately demonstrate a reasonable level of risk of adverse events, illness, or injury associated with the use of the device for its intended uses and conditions of use?

One panel member felt that it was biologically implausible for the product to cause ARDS, but given the maldistribution of ARDS-related deaths, it requires at least post marketing assessment but may rise to a higher level of concern. Another member noted that since the sealant group seemed to have higher AEs overall sicker patients had simply been enrolled in the treatment group. However, another member said there was no observed difference that would indicate that and it is implausible given the within institution randomization.

The panel felt the sponsor had demonstrated a reasonable level of risk but could not ignore the possibility there may be a risk that was not seen given the size of the study and the lack of power. More information is needed regarding ARDS and renal effects.

One member was not entirely comfortable with allocating ARDS to post marketing surveillance given its level of severity as an outcome. There was discussion about the lack of coherence between the FDA slide showing one instance of ARDS in the control and three in the

treatment group versus the sponsor slide showing that both arms had three people with ARDS.

The chair summarized that the panel is somewhat split with some believing it is a significant enough problem to require more information prior to approval and others believing that it could be addressed in post market surveillance.

SECOND OPEN PUBLIC HEARING

No members of the public came forward.

FDA AND SPONSOR SUMMATIONS

FDA had no further comments.

Dr. Cerfolio said there is not evidence of any renal problems. Regarding ARDS, two independent reviewers looked at the deaths; there were at least two patients in the control group and three in the sealant group, and there are more deaths overall in the control arm. The primary endpoint was met in a multi-institution prospective randomized study. Patients deserve to have access to such a product, and getting a chest tube out two days earlier does make a difference and may explain the sealant group's lower pneumonia rate. Dr. Miller pointed out that those who conducted the independent review of deaths had only the preoperative and postoperative data and were blinded to whether sealant had been used.

PANEL RECOMMENDATION AND VOTE

Dr. Birnbach asked the consumer and industry representatives for any additional comments. Ms. Petersen expressed concern about FDA question four given that the study was neither designed nor powered to assess AEs. Dr. Spindell said even though the study was underpowered, there was no statistical trend of a higher risk of AEs.

Dr. Cassiere moved that the device is approvable with conditions, and Dr. Jeevanandam seconded the motion.

Dr. Cassiere proposed a condition limiting the product to no more than three applications, and Dr. Brunson seconded. Dr. Loeb noted that issue was already addressed in the precautions statement. The condition was approved unanimously.

Dr. Jeevanandam proposed a condition of post-market surveillance regarding the issues of cardiac outcomes, renal outcomes, and ARDS, and Dr. Normand seconded. Dr. Stoller proposed evaluating the data using standard criteria for ARDS. Dr. Normand added there would need to be a comparison group, and Dr. Jeevanandam suggested using the control arm of the clinical study as a historical control. Dr. Normand said that since things change, it would be to the sponsor's benefit to use a concurrent comparison group. Dr. LoCicero suggested the Society of Thoracic Surgeons (STS) database as a control. Dr. Normand proposed using a concurrent comparison group of patients treated within the same institutions from that database. She also said that with patient identifiers one could link to state databases to get longer than the 30 day follow-up available in the STS database. Dr. Birnbach clarified that the motion is for post market surveillance of trends of AEs, including renal function, ARDS, and cardiac issues with a comparison group hopefully from within the same institution at least out to 30 days, but hopefully longer. The motion passed unanimously.

Dr. Cassiere proposed limiting use to open as opposed to VATS thoracotomies, and Dr. Topoleski seconded the motion. Dr. Wilcox was unsure how to define such a condition given the confusion around what is open and what is not. Dr. Loeb proposed limiting where in the body the device can be used given that animal studies suggested problems in the perineum. Dr. Brunson suggested limiting its use to the surface of the lung. Dr. Stoller supported Dr. Brunson's suggestion but was opposed to limiting use to open procedures because of the possible unintended consequence of otherwise unnecessary incisions. The motion failed.

Dr. Jeevanandam made a motion to limit use to the surface of the lung. There was no discussion, and the motion passed unanimously.

Ms. Petersen made a motion that the product be used for therapy of existing ALs and not for prevention of potential ALs, and Dr. Ries seconded the motion. There was confusion about the precise meaning of the condition, and Dr. Birnbach restated it to be that the agent not be applied to the suture line to prevent ALs, and both Ms. Petersen and Dr. Ries agreed. Dr. Loeb was satisfied with simply limiting total dose. The motion failed with one in favor, eleven opposed, and one abstention.

Dr. Ries moved that the primary outcome of the post marketing study should be different than in the clinical trial and should include a time to event analysis. Dr. Normand seconded the motion. There was no discussion. The motion passed with eleven in favor and two opposed.

Dr. Stoller moved that ascertainment of AL in a time to event analysis in a post marketing study be done by an independent blinded observer, and Dr. Normand seconded. Dr. Birnbach noted the challenge if surgeons were allowed to use the device but always had to find a blinded observer. Dr. Stoller said the motion was meant to reflect his level of confidence given the problems with the binary outcome measure. Dr. Loeb suggested not linking that type of study to the AE study and proposed a smaller study to look at other issues. Dr. Normand said there could be one study with an independent blinded observer who would do some sub-sampling. The motion failed with five in favor and eight opposed.

Dr. Cassiere moved to add readmission rate within 30 days to the PAS measures, and Dr. Brunson seconded. Dr. Spindell asked if it was readmissions for pneumothorax, and Dr. Cassiere said it was all readmissions. The motion passed with twelve in favor and one abstention.

Dr. Loeb moved to add a temporary precautionary statement that the sealant is for short-term closure and may be associated with delayed ALs. Dr. Ries seconded the motion. There was no discussion. The motion was approved with ten in favor and three opposed.

Dr. Topoleski made a motion to add a statement that the time dependence of the strength and the adhesive properties of the sealant have not been evaluated. There was no second.

There were no additional conditions, so Dr. Birnbach called the question on the motion of approvable with the above conditions. The motion passed with twelve in favor and one opposed.

Dr. Ries said his vote was based as much on hope as substance but believed the product does control ALs.

Dr. Jeevanandam concurred and said he recommended a PAS because of issues such as residual space at 30 days and potential cardiovascular and renal effects.

Dr. Wilcox said the product was shown to be safe and the evidence strongly suggests it will be a benefit to patients.

Dr. LoCicero said all thoracic surgeons seek to have no AL after surgery and that this may or may not be the product to deliver that.

Dr. Wiswell said the major endpoint was clearly achieved and that the benefits outweigh the risks and was hopeful that the PAS would demonstrate prevention of some empyemas and other complications.

Dr. Loeb said the product has a relatively low chance of causing injury and some chance of improving care.

Dr. Domino noted that such studies are difficult to conduct and do not address all questions but thought the study demonstrated a reduction in ALs at least in the initial perioperative period.

Dr. Brunson said the product addresses an important clinical problem and has been shown to be effective and was satisfied the PAS would address some of the remaining questions.

Dr. Cassiere's vote was based on the sponsor having met the primary endpoint and the lack of adequate therapies for ALs.

Dr. Stoller voted in favor because of the great promise of the product but argued that the primary outcome measure and the design were less than ideal.

Dr. Lillard voted in favor because the sponsor met the primary endpoint, and he thought the remaining safety questions could be addressed with a PAS.

Dr. Topoleski voted yes because the product has an effect on reducing ALs.

Dr. Normand voted no because it is questionable whether the primary endpoint was met because the lack of blinding introduces bias. She said the efficacy did not outweigh potential safety concerns.

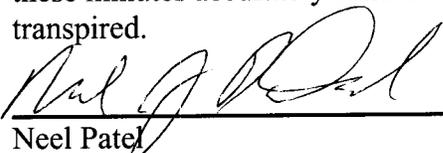
Dr. Spindell had no final comments.

Ms. Petersen said there are some positive indications in the data presented and hoped attention would be paid to the quantity administered

ADJOURNMENT

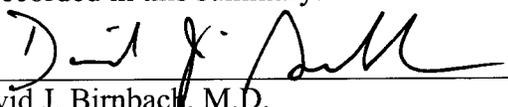
Dr. Birnbach adjourned the meeting at 4:41 p.m.

I certify that I attended this meeting of the Anesthesiology and Respiratory Therapy Devices Panel on June 12, 2008, and that these minutes accurately reflect what transpired.



Neel Patel
Executive Secretary

I approve the minutes of the June 12, 2008, meeting as recorded in this summary.



David J. Birnbach, M.D.
Chairperson

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