important or not? Does this substance delay this effect?

DR. CERFOLIO: Can I answer that? Unpublished literature that's coming looking at I think 1,400 patients that we've done lobectomies on, large percentages were sent home. These have no sealants. These are just my patients over the last four or five years where we didn't have any sealant.

A large number of patients go home with pneumothoraxes, which I term fixed pleural space deficits, and about one or two percent will come back with subcutaneous emphysema, require a chest tube, either because they're symptomatic and they feel it, or you see them -- they're asymptomatic and you see them back at a month.

So it still happens, but it's pretty small; two or three percent probably.

DR. BIRNBACH: LoCicero?

DR. LOCICERO: We've been dealing with chest tubes since Hippocrates put a quill

in somebody. And we probably have not progressed any further than Hippocrates in our -- in our reuniform management of chest tubes.

So I think we're having a problem here, because despite the fact that thoracic surgeons do the same procedure all over the country, all over the world, our management is very different. How long it stayed it stayed on suction, how long it stays after there's no air leak is extremely variable and essentially based on gut.

To give you a completely different experience, we recently had a patient we were trying a new device, where you digitally see an air leak. There's no bubbles.

The device read zero. I didn't believe it. We left the tubes in for four days. It really -- it's just totally based on the way we feel about the patient, and if there's no air leak at one day, and we can take the tube out at one day, we're too nervous. So we're not going to do it.

And so we're getting hung up here on hours after the air leak stops, and whether or not the tube is going to come out sooner, and there may be other reasons why the tube is staying in when there's no air leak. It might be because there's increased drainage and the patient is not going home because they can't get into a rehab facility, or because they don't have a ride home, or because they haven't met their financial obligation, or because they're got atrial fibrillation or a thousand other reasons.

So we really have to deal specifically with did this product stop and air leak period? I think we're off into areas that are giving us some issues. So in terms of this, we need to look at the data that's listed here on -- by the FDA and by the -- by the sponsor in terms of air leaks.

And then looking at the residual space issues, they're almost all in upper lobe patients, which tells us that this is a

problem with upper lobe resection. It's not necessarily a problem with a device.

Now we have to deal with the issue of a number of patients who had these Heimlich valves as whether or not that was appropriate or not. And you know, the observation of the Heimlich valve as a patient comes in the office, we place the tube under water and ask them to cough and see if they bubble. And if they don't bubble, then the air leak is gone. If they bubble, the air leak is still there, and they go home, come back the next week.

So we're back to the question that we had before, which is when does the air leak really stop? And I don't know that we have the data from the sponsor to tell us that exactly. So we're --

DR. BIRNBACH: We're sort of circulating back to the same.

DR. LOCICERO: I was just going to say if I can try to stop the circle a little bit to summarize what I believe I'm hearing

from the panel, and then I will give you opportunity to tell me whether or not you agree with my summation.

It's that based on the data we have now, which is somewhat inconclusive, we can't actually comment on effectiveness at decreasing air leaks.

DR. CASSIERE: I'd like to comment on that. I think it's pretty clear that contaminated air in the pleural cavity is bad. If you could decrease the contamination of air, contaminated air in the pleural cavity, that would be good.

I think the sponsor showed some adequate data to show that it actually decreases the amount of contaminated air into the chest, and you're left with residual space that's not contaminated. That's the first thing.

So looking at the literature, having contaminated air in the chest is going to cause pneumonia empyema and death. So I

think what some of us are asking the sponsor is to prove that gut feeling, or thing that's based in medicine, that having contaminated air in the chest is bad.

I think we should come to the conclusion, and we can discuss it amongst ourselves and clinicians if we believe that's a true statement. I personally believe that's a true statement. So once you get over that hurdle, the next step is, well, what are some of the safety issues that I see with this product?

We haven't really mentioned does this product exacerbate hypovolemia after surgery? We have patients who have oliguria. We have some data that shows that this product can actually absorb -- potentially absorb fluid.

So I mean I'm looking at the issues differently. Clinically, it looks like it stops air leaks. Great. And then we have to make an assessment: do we actually believe the

literature that we read that an air space that's left over that's not contaminated is bad. I happen to believe that it's not. And I'm interested to see what some of the other panel members have to say about that.

DR. JEEVANANDAM: I agree with you. I think that air space that has contaminated air is bad, and an air leak that has contaminated air is bad. I just think with this device, coming out of the operating room and the recovery room it certainly stops air leaks. But if you look at the data within four days, the amount of air leaks, whether you have it with the device or with control is the same.

So it's probably only at that point that you start getting real contaminated air because you're now out of the operating room and the recovery room setting. So I think there's no question it stops air leaks in the immediate post operative period, probably just reflects the fact that if you don't use the

device after four days, most air leaks stop anyway.

So I think I agree with you that contaminated leaking air is bad. But does this device after four days prevent that from happening? The data shows that it doesn't. It prevents it before, but after four -- after four days, the control group catches up.

DR. CASSIERE: Well, if you take a look at the -- the percentage of patients that had air leaks to controls, at least from looking at the data, the -- the sponsor has actually shown that there's actually a decrease in the number of patients who have air leaks when they have the sealant.

So I think it does show that there's decreased contamination in the pleural space from the air leak unless you're viewing it differently.

DR. JEEVANANDAM: Right. I mean you're right in that if you look at the number of patients who've never had an air leak,

there is -- it is higher in the sealant group. But after four days, the numbers are equivalent. And numbers are equivalent in that after four days, the same number of patients have no air leaks.

DR. BIRNBACH: So let me revise my summary. It appears that the sponsor has shown that this does decrease perioperative air leaks in the acute period after several days. We're not quite sure whether or not this is effective, or whether this changes the clinical course. So it's pretty clear that based on that inconclusiveness that we are going to ask for more data. Are there any opposing opinions about that?

DR. WILCOX: That's why it was the design of the study to show that it -- it decreases air leaks. That was the point of the design, was it not? And we don't know about future --

DR. BIRNBACH: Well, it was --

DR. WILCOX: -- empyema or anything

like that. That was not build into the --

DR. BIRNBACH: As suggested by the FDA, the bigger question may not be to look at air leaks in the recovery room, but rather how this device is going to be used out there, and that may mean that we need to ask the question, "Does this device stop air leaks period?" rather than looking at the primary end point per se. Does anyone on the panel have any other opinions about that? Dr. Ries, your head is shaking.

DR. RIES: I'm basically agreeing with you. I mean I think I'm very sympathetic to surgical colleagues, and don't -- any more than they do, I understand their frustration at seeing bubbles in the chest tube when you come in, and post-operatively.

But I think to me, what the sense I'm getting is the product makes the surgeon feel better, the physician feel better. You see less air leaks in the immediate post operative period. But I'm not sure that it

helps the patient because within -- within six days, 85 percent of the control patients had no air leak, and 75 percent of the treated patients had no air leaks.

So actually more of the control patients were air leak free within the first week. And the chest tubes similarly came out sooner in the control patients.

DR. CASSIERE: Well, if we could, look at slide 57. It has under the section here, "No air leaks for one-month follow up from the recovery room," 35.6 percent of the sealant patients, and 14 percent of the control patients are air leak free for that entire period.

DR. NORMAND: That's the question. The question is it's not measured at 30 days for everybody. And there's the question that we really wanted to see. So I find that statistic difficult to interpret because we know for a fact that it's not one month for everybody. For some people it's two weeks.

For some people it's 30 days plus two weeks. And therein lies the problem of using this 01 variable. So I think that's very misleading.

One has to assume -- one can't interpret that without correcting for the fact that the date of ascertainment of that information varies from patient to patient.

DR. BIRNBACH: Can I -- can I suggest that we do this one at a time through the chair so that we don't turn into the Wild West? Dr. Ries?

DR. RIES: I believe that the difference is that the primary outcome variable is based on continuous absence of air leak, and as we know, air leaks can be somewhat intermittent.

So presumably, what's happening in terms of the -- the -- when the patient reaches a stayable state of having no air leak is different than looking at someone who has had absolutely no air leak through those first few days.

DR. CASSIERE: Well, that's what this data is saying, that no air leak through one month from the recovery room: 35.6 percent sealant, 14 percent control. And I understand your concern about the variability and the days of follow up.

DR. BIRNBACH: Dr. Normand?

DR. NORMAND: Again, it's not just a concern. It's how you interpret that finding. And I'm not saying the finding is wrong, because I don't know, because I haven't been provided with -- it could be most of them are assessed for the sealant group at 16 days, and most of them -- now I know on means they were the same, but it's very difficult. I don't want to guess at the answer as opposed to looking at something I know is not correct.

DR. CASSIERE: Well, you'd have to say then that the way the data could be skewed is you'd have to say then at their far .4 to six weeks down the road, you'd expect a big spike in leaks from the sealant patients, as

opposed to the control, which clinically doesn't make much sense, actually. You're going to have more of an up front than later on.

DR. BIRNBACH: Rather than allowing this to self perpetuate, let me ask you. You said you have alternative summary to our panel answer for question one?

DR. CASSIERE: Well, the only summary is that I think that the sponsor has shown that the -- the sealant decreases leaks. That's convincing to me. The second thing, though, that I need to come to grips with is the safety part of it.

The safety part of it for me is two things: one, in relation to Dr. Loeb's comment, changing the approach to the patient. We're used to taking care of these patients and seeing the leaks early on, and not later. That may be a whole different approach to how thoracic -- maybe not surgeons take care of the patient, but thoracic residents.

If you're in an academic institution, the residents are usually being trained to take care of air leaks early on. It may be a surprise to say that we're using a product, and you may see late air leaks after the fact.

The second thing has to do with the issue of the renal problems -- so called renal problems with the product, which may be related to fluid management, as was ascertained earlier. We try to keep these patients dry initially post op, and does this product exacerbate hypovolemia? That's the issue that's going through my mind.

DR. BIRNBACH: So is the panel okay with our consensus, including Dr. Cassiere, that we do need more data before we can conclusively state that the sponsor has shown that this is safe and effective at reducing air leaks?

DR. CASSIERE: I think it reduces air leaks. In terms of the safety, I'm

actually looking forward to hearing some of the panel members' opinions about the renal component. That's my take on the renal component is there's really a volume issue, not really a toxicity issue.

DR. BIRNBACH: All right, let's go onto question two, then. Actually, have we addressed the FDA issues on question one to allow us to go to question two?

MR. MELKERSON: I believe you've given us enough to consider, yes.

DR. DURFOR: Question two: ProGEL Surgical Sealant is comprised of compromised of bifunctional polyethylene glycol cross linker and human serum albumin. Clearance studies of the C14 label sealant in rats revealed that urine was the primary route of excretion with the majority of clearance occurring in one to three days after implantation.

In the second study over 50 percent of the C14 label device was excreted after one

day, and virtually all radioactivity was recovered 14 days after implantation.

In the PMA study, post-operative renal dysfunction, oliguria, acute renal failure, abnormal renal function was observed in nine of 103, or 8.7 percent of the sealant, and two of 58, or 3.4 of the control patients. While three of nine sealant, and one of two control subjects who had an adverse event related to renal function also had a pre-existing renal disease, severe adverse renal events occurred in five of nine sealant, and one of two control subjects.

Considering the device composition, the pre-clinical data on renal excretion, the clinical data on renal dysfunction, and the information on renal adverse events presented in the executive summary, and the patient population in the study intended for commercial use, please discuss the clinical significance of these findings and the possibility that renal events that occurred

during the clinical study were device related.

DR. BIRNBACH: So the panel also had some concerns about renal function as relates to use of this device. Anyone on the panel have any comments about the renal issues? Yes, Ms. Petersen?

MS. PETERSEN: I have a question for the clinicians and surgeons who would actually be using the product in the operating room. I'm wondering in this study, as I understand it, the product was used to seal known air leaks, things that were detected following the suturing in the procedure. Is it possible that in -- as the FDA suggested earlier when the product is in use by the average surgeons, in average people outside the tertiary care environment, is it possible that patients could be exposed to considerably more sealant in the -- in the actual use real world of the product, and that we could see additional renal adverse effects as a result of greater exposure, or the implementation in

the real world?

And I'm asking because not being a clinician, I don't know what you would actually do with it in the OR.

DR. BIRNBACH: So the question would relate to do we think that renal function abnormalities were directly due to the device, or is this an indirect action as Dr. Cassiere has suggested previously? Anyone on the panel have any comments about what they think is going on? Dr. Lillard?

DR. LILLARD: I don't know exactly what's going on, but I think it's also interesting if you look at table 37 on the sponsor's summary, the clinical data. I've been looking over this table, and there's also a significant amount of adverse cardiac events as well.

Look at atrial fibrillations, cardiac arrests, arrhythmias, cardiac failure, myocardial infarction. It adds up to 7.8 percent in the sealant groups and 3.4 percent

in a control group, much similar to the adverse renal events of 39 -- I'm sorry, 3.8 percent for the sealant groups, and 1.7 percent.

And if you consider that this PEGylated product is excreted within -- 50 percent is excreted in the first 24 hours, we're not seeing similar types of toxicities to the liver. This further points to some -- some component causing these toxicities in both cardiovascular as well as the renal --

DR. BIRNBACH: Dr. Normand, the statistics of that suggestion, is that "kosher," to take a look at all of those various side effects and now say there may be a safety issue in the cardiac realm?

DR. NORMAND: You see, I was quiet. I wasn't going to say anything. I'm just being very quiet here. Again, obviously this study is not powered to detect adverse events. So I think you can look at them by looking at them, and making comments that way. But we

know that you can't -- you don't have a power -- the power to test here. But these are just lists to provide insights, so.

DR. BIRNBACH: Okay, so let's go back to insight. Do we believe, or is there any discussion that would allow us to believe that the "renal failure," or the renal function abnormalities are somehow related to the sealant, rather than an indirect effect. Anyone on the panel have any thoughts on that?

DR. JEEVANANDAM: I don't know if we ever really know the answer. I guess polyethylene glycol, if it's excreted in the kidney, is going to have some kind of adverse renal effect.

I mean the only thing that worries me is I was on the panel a couple of times for Aprotinin. And Aprotinin in all its randomized clinical trials had suggestions of renal dysfunction, but there was nothing ever shown to be statistically significant. And then once it got used very often in cardiac

surgeries, as you know it's now pulled of the market because of renal dysfunction.

So I know this study wasn't powered to look at renal dysfunction, but it is excreted in the kidney, and there's a suggestion of -- of renal effect. So I don't know if we'll ever know the answer from this study.

We will never know the answer from this study, but we're looking at efficacy. We're looking at safety. And I guess there's a balance. And if something was supremely efficacious, so to speak, and you can accept a little bit of risk, I guess. I'm trying to balance the efficacy and safety issue here.

DR. BIRNBACH: Well, do we really believe that there's a safety issue? The sponsor led us to believe that this renal function abnormality was not very serious, was short lived. It was probably due to other factors. So what do we think about that? Dr. Lillard?

DR. LILLARD: Even a short-lived renal insult could have repercussions later. So in fact, I wanted to ask that question to put this in the proper context. How sick exactly are these patients? What's their mean survival term? I wanted to get a sense of that as well.

DR. BIRNBACH: So would that be a question for us, or rather for the sponsor?

DR. LOCICERO: I think we can answer that.

DR. BIRNBACH: Okay.

DR. LOCICERO: In looking at this study design, this clearly was an effort by the sponsor to get the study done in a short period of time, accrue a number of patients rapidly. And they went to big centers that are tertiary care facilities.

These patients in general are sicker than the general population of patients that you would see for a standard operation. The other problem with this study is that the

resection type of totally heterogeneous. So you get some wedger sections, you get lobectomies, you get some extended stuff. The only thing that's not included is pneumonectomy.

So you have a very heterogenous population of sicker patients, and now you're trying to work with that. So a lot of what we're dealing with on safety issues here are going to be rely skewed, and it's not powered to study it anyway.

DR. BIRNBACH: But Dr. LoCicero, you're not concerned about the renal -- our question here is renal. And so I'm trying to bring it back to that very specific question.

DR. LOCICERO: Okay. So just to finish that, these centers are also the centers that believe, like many of us, that these patients require fluid restriction during the operation, and post operatively. And so these are going to be the patients who would see renal failure more than others.

So I think it's totally confounded. And I can't tell.

DR. BIRNBACH: Dr. Wiswell, you had a comment?

DR. WISWELL: In a simple way of looking at it, I was looking at dose response to the amount, the quantity of sealant. And then just looking at the tables, I really don't see a dose response. Those were a fairly high proportion, 7.2 ml or more, and they were no more likely to get acute renal failure.

Two of the patients with acute renal failure had a very low amount of the sealant going in, and so I'm at the point that I think that there is probably not a true relationship with this sealant, but more of a relationship with the perioperative management, the fluids.

DR. BIRNBACH: And wouldn't the perioperative management of people in the control group be the same in those

institutions as people in the sealant group?

DR. WISWELL: I would think so, but I think --

DR. BIRNBACH: I mean you keep them dry in that hospital. Wouldn't you keep everybody dry?

DR. WISWELL: Right. I agree with you, but I think this is such a heterogenous group of very sick patients, and we're only talking about a fairly small population; one or two patients either way having acute renal failure to make it look or appear to be something really bad.

So they're going to be more prone to it, and I just need something that's more striking to me in terms of the renal function tests, or acute renal failure to really convince me that there is a direct relationship.

DR. BIRNBACH: Dr. Normand?

DR. NORMAND: I'm obviously not going to comment on whether or not this is an

issue, but the one comment I wanted to raise, which is along with something Ms. Petersen raised, was the issue of having the sealant applied to air leaks that otherwise could not be treated.

And so we are, if there is a -- or isn't a dose response relationship, this is important to know because in theory, we know that it'll be -- the average patient now will be getting more than currently just because this device can be applied to air leaks that currently can't be treated.

And again, I don't know if that's a good thing or a bad thing, but I just wanted to raise that in terms of the discussions that the clinicians are having.

DR. BIRNBACH: Dr. Ries?

DR. RIES: I was just going to agree with some of the other comments. But I wouldn't fear this as a great safety -- a large safety issue. I mean there is -- if we trust the randomization and the control

aspects of the study, then there are some trends of differences in renal function in the -- in the treated patients, which we should attribute to the intervention.

I would say it's of concern, and I think Ms. Petersen raises a very valid point. It's very likely that in general practice this product would be used in larger doses than it was being used in this study. And if there is a concern, it would -- it's something that would really warrant close monitoring.

DR. BIRNBACH: Dr. Jeevanandam?

DR. JEEVANANDAM: I think -- I mean this study is not going to answer the question now. It has to do a much larger study. It's not going to answer a question. The only solution may be to mandate post-approval surveillance or a database of these products being used and look at renal dysfunction.

DR. BIRNBACH: Okay, so -- Dr. Stoller.

DR. STOLLER: So let me say that I

share the committee's sense that renal dysfunction related to the device itself is unlikely. Having said that, I'm still stuck on some discordant data in the various reports that allow me to address this.

In particular, we're told that among the deaths, for example, there was multiple organ system failure in -- in several of the sealant patients that -- that exceeded the percentage in those of the control group, the ARDS patients in particular.

And one has to imagine that renal failure was part of that scenario, and yet I'm struck that that doesn't necessarily appear in the reporting of renal failure in the outcome measures, number one. And then number two, on page 56 of the -- of the sponsor's report, table 37, the same table that Dr. Lillard referred to, the incidence estimates or the prevalence estimates more precisely of ARDS are said to be the same in both groups, one and one.

And so I find it very difficult to kind of weigh in on the safety issues when I actually don't -- I don't have a real feel for the consistency of the data about events that I would regard while biologically being unlikely to be related, nonetheless have a prevalence maldistribution between the two groups, mainly the ARDS issue.

So while not an issue of renal dysfunction per se, there is a certain relationship between renal dysfunction that doesn't appear in the renal dysfunction data as we see it reported. So I find myself confused about being able to answer the question.

DR. BIRNBACH: Dr. Topoleski?

DR. TOPOLESKI: I just wanted to say that one thing going for this is that there's a lot of experience in other biomaterials with PEG and even serum albumin, and they don't seem to have any problems. And in fact, going back to the question of dose,

it doesn't appear to be so much a dose as the molecular weight of the polyethylene glycol, which is why I asked the question before, and this is well below what is pretty well known that the kidneys can handle successfully.

DR. LILLARD: I would agree with that, but this is a -- this is a unique product that is -- it's forming a gel as it's being cleared. So very different from some of the other PEG related proteins that are on the market.

DR. TOPOLESKI: Is it forming a gel as it's cleared? I thought it degraded, and you had the separate products that are cleared separately? Or maybe --

DR. LILLARD: I thought it formed -- it starts to form a gel within the first --

DR. TOPOLESKI: It forms a gel, but then when it's degraded, you get -- maybe we can ask the sponsor? You get the isolated PEG and the serum --

DR. BIRNBACH: That is my

understanding as well. Does the sponsor want to --

DR. TOPOLESKI: It goes back to your comment about how sick are these patients, and in other uses of the biomaterials, the patients would not be that sick.

DR. BIRNBACH: Go ahead.

DR. PARKS: Your understanding is correct.

DR. BIRNBACH: So once again I will attempt to summarize what is probably a gray zone. If I understand what we have said, it's that the renal dysfunction is probably not directly related to the device, however, the renal dysfunction may or may not be a concern.

We are somewhat concerned, especially in light of the fact that when used outside, this may be used by different people in different amounts. But that looking at the level of dysfunction that we saw now,

clinically, we are not terribly concerned by these numbers. Would that be a reasonable consensus of what was discussed here? Dr. Ries?

DR. RIES: I would agree with one exception. I think that we don't have a great deal of concern, but the concern we do have, I would think is related to the device because it was a randomized controlled trial.

DR. BIRNBACH: And I believe that we're also suggesting potentially that that concern would translate into some level of post marking surveillance. Anyone have any opinions that are otherwise? Is that okay Mr. Melkerson?

MR. MELKERSON: That addresses our question. Thank you.

DR. BIRNBACH: Question three?

DR. DURFOR: The results of the randomized two to one ration controlled multi-center study, in which 103 patients were treated with ProGEL Surgical Sealant, and 58

received control treatment R.

And at this point, this slide provides for you a summation of the primary and secondary end points. Air leak free through one month, 35 versus 14 percent; duration of post operative air leaks and days median and mean values are displayed. Duration of chest tube placement median and mean values are displayed.

There was an asterisk there. On that asterisk is part of what we ask you to consider, which is the non-equal use of Heimlich valve in sealant and control patients in considering that in terms of your consideration of those end points, and length of hospital stay in the median and mean values are also displayed.

Partial lung expansion, once again as we've discussed before, was 33 percent in the sealant patients, and 12 percent in the control patient.

Do the data presented in PMA 010047

demonstrate a 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?

DR. BIRNBACH: So related to question 3, which is the presence or absence of clinically significant and meaningful results. Does the panel have any comments? And if I might, I would like to ask Dr. Normand about -- just to summarize the many conversations that we've had thus far today about how we should be looking at the length of stay data or not, as the case may be.

DR. NORMAND: The way we should be looking -- so I think we've determined that length of stay is measured from hospital discharge. Oh, no, I'm not taking about the one-month follow up. So length of stay. So we should be looking at length of stay using a

Kaplan-Meier.

DR. BIRNBACH: And if indeed way more patients in one group got a Heimlich valve than in the other group?

DR. NORMAND: Then that -- my understanding is that was treated appropriately in the statistical analysis by assuming that they were censored due to Heimlich.

So I would believe -- my understanding of what the FDA showed, which did show a PF.04 in terms of a benefit of length of stay, in my opinion, that seems the way we should be looking at it.

DR. BIRNBACH: Okay. So now, does the panel have any comments on clinically significant and meaningful results as related to air leaks? Maybe I should make it a clinical question. You want to use it in your practice?

DR. CASSIERE: Well, I'll -- I'll -- if you look at the air leak-free through one

month, it's 35 percent in the sealant, 14 percent in the control group, which is statistically significant. The next question is do you think not having an air leak is significant? And my opinion is yes.

DR. BIRNBACH: And thoracic surgeons?

DR. JEEVANANDAM: That is being truly air leak free. But if you look after four days, again, the number of air leaks in both groups were the same. And the question is clinically significant and meaningful results. Yes, this thing definitely stops air leaks. And if that's what end point is, I think that is true that it stops air leaks.

Now, does that lead to clinically better results? We haven't shown it in this study.

DR. BIRNBACH: Any other comments? Dr. Normand?

DR. NORMAND: Again, I'm -- just because it's sort of I just have to remind

everybody at least in terms of the one-month of follow up. Again, it's statistically significant if the assumptions are met for using that test, and my claim, the assumptions are not met for that test. So judging at least we don't -- we have every reason to believe the statistical assumptions for that test aren't met. Therefore, it's very difficult to interpret that P value.

DR. BIRNBACH: Dr. LoCicero?

DR. LOCICERO: All thoracic surgeons seek the holy grail of no air leak. And expanded space? No space issues. It makes our pulmonologists happy. It makes us happy. So I think in terms of would we use this in our practice, we certainly would. But now we're putting the burden of proof on the individual surgeon, and their own experience with the product.

DR. BIRNBACH: Any other comments? We're still talking about whether or not there's a clinically significant and

meaningful result. Dr. Wiswell?

DR. WISWELL: A couple of thoughts. For me, going home two days earlier is a good thing. So I think that's clinically significant. To me, not having an air leak and a certain portion of the population for roughly four days, a four day period, even though it's a short period, is probably also a good thing.

There is that potential for a contaminated air leak, potentially to cause some severe problems, and perhaps even death. So those are two good things.

DR. BIRNBACH: Dr. Loeb, I saw your head shaking. Do you have any comments? No. All right, so if I were to summarize question three, any other comments before I attempt to summarize this?

I believe the sponsors did clearly show that this product stops air leaks in the perioperative period, defining whether there's a different at four days versus 30 days, and

there were some issues about the 30-day measurement. Whether or not there are clinically better results, the suggestion is that there may very well be, and some of the things that we saw, such as hospital stay that we believe is reduced may actually be clinically significant for patients.

So while we have to stop somewhere short of jumping up and down and saying, "This is going to revolutionize the practice of thoracic surgery," it is clear that it may have some clinical advantages. Would that be an overall summary of what we've been discussing? Any opposing opinions?

Okay, Mr. Melkerson, is that adequate?

MR. MELKERSON: Thank you very much.

DR. BIRNBACH: Question 4?

DR. DURFOR: Do the data -- excuse me. Do the data presented in PMAP010047 for ProGEL Surgical Sealant used with standard

care, compared to controlled standard care alone, adequately demonstrate a reasonable level of risk of adverse events, illness or injury associated with the use of a device for its intended uses and conditions of use?

DR. BIRNBACH: Okay, so question four. Not that these aren't all related to one another, but this one asks us to discuss the reasonable level of risk of adverse events, illness or injuries associated with the use of this device for its intended uses. Any comments for the panel? Dr. Stoller?

DR. STOLLER: I'll just revisit. Again, I'm of two minds. On the one hand, I find it difficult -- this regards the ARDS occurrence. On one hand, I find it difficult to implicate this from a biological plausibility point of view in causes acute respiratory distress syndrome.

On the other hand, there is a maldistribution in the death rates with regard to ARDS. So at the bare minimum, I would say

that one can't ignore a somewhat small signal. At the bare minimum, it would require some post marketing assessment of that, but one could say that the severity of that outcome is such that it might actually rise to a level of a higher concern.

DR. BIRNBACH: Any other comments? Ms. Petersen?

MS. PETERSEN: I think we can say that they demonstrate a particular level of risk of adverse events when used to treat non-air leaks.

I don't think we can say that they adequately demonstrate any particular level of risk for adverse events if they were used more broadly, or perhaps even to coat the entire surgical incision as a preventative measure, which is admittedly not necessarily the question asked by this particular study, but does reflect how the project might be used in the at-large population not being treated at tertiary care academic medical centers.

DR. BIRNBACH: Any other comments? Dr. Loeb?

DR. LOEB: I'm not -- I'm with Dr. Stoller in that he said, "I don't it's very plausible that the product causes -- has a great biological risk." And I actually looked at table 36, the sealant and control adverse affects greater than two percent, and across the board on almost every road, the sealant had a higher adverse effect, the numbers are higher, than with the controls.

And my reading of that is that somehow or another sicker patients were involved in the sealant group. So my -- because it's not in any one area that I'm seeing that there are higher -- higher numbers.

So my reading of the adverse effects and my knowledge of the biological affects are that it doesn't pose any great risk, and -- and --

DR. BIRNBACH: So if I were to

attempt to -- Dr. Lillard?

DR. LILLARD: Well, could someone define what is a reasonable level of risk? Does that --

DR. BIRNBACH: Well, I think we'd all have to be concerned with a risk-benefit ratio here. What is the risk of having an air leak that was preventable, versus what is the risk of having either renal toxicity or ARDS secondary to the device? That's the way I would define it, unless anyone on the panel has another definition.

If I were to summarize, I would suggest using the FDA's wording that we were adequately shown a reasonable level of risk. However, we also can't ignore a possible trend, and post marketing surveillance would be necessary to see if that actually existed or not. Any opposing opinion or other comments? Dr. Normand?

DR. NORMAND: I just wanted to follow up on the comment that was made

regarding perhaps the assumption that the sealant patients were generally sicker than the control patients. I think that was your suggestion of what might be related to the adverse events.

And I just wanted to -- I know when we looked at the observables in terms of the characteristics of the two cohorts, I believed there wasn't anything there that would indicate that, but I may be misremembering.

And so the fact that they were randomized within -- within institution, it sort of makes that argument less plausible, I think, unless the randomization is supposed to balance on measureables, either.

So I find that -- I'm just sort of giving you the context that I can't believe that would be the reason. There's everything pointed against that for that being the reason that that is they're just sicker based on both the observables and the fact they were randomized within centers. So I just wanted

to put that out.

DR. BIRNBACH: Dr. Domino, did you have a comment?

DR. DOMINO: I just wanted to -- again, I'm sort of hung up with the fact that this is a really small study. It's underpowered to detect complications. There's some trends that are somewhat disturbing, and so I just wanted to point that out.

DR. BIRNBACH: So as far as I see it, the summary still exists that we believe that they have demonstrated a reasonable level of risk. However, we can't ignore the possibility that there may actually be a risk that we did not see based on the size, the sample size and the fact that is was not powered to look at this, and the fact that we do have this trend, and we would need more information about renal function and renal failure.

Do I have agreement from the panel that that's actually what we said?

DR. STOLLER: And ARDS.

DR. BIRNBACH: And ARDS, sorry. Dr. Lillard?

DR. LILLARD: And cardiac.

DR. BIRNBACH: ARDS, renal and cardiac. Okay, Mr. Melkerson, is that adequate?

MR. MELKERSON: That is. Thank you.

DR. CASSIERE: Actually, I'm just curious about the cardiac effects. It's because I'm not clear on looking at what I was looking at if there was an increase in the cardiac. Because the atrial fibrillation looked in the same group, and I'm going down the list on the cardiac things. It's not anything that I would expect out of the ordinary from post-thoracic surgery, unless there's something I'm missing in terms of --

DR. LILLARD: No, I understand, and you may very well be correct. I'm not a physician. But when I add up the A's

attributed to cardiac function, 7.8 percent for the sealants, and 3.4 --

DR. BIRNBACH: And that may just be based on the fact of the sample size. I don't know that we can make any statement here that there is some issue that we believe that the patients who have the device had a big risk. I don't think we can say that. But unless someone on the -- yes?

DR. WISWELL: Just one quick comment. I don't think you can just add them up, because the same patient can be counted as having several different ones, so the same patient can be counted multiple times in that table for the serious adverse events. And so we don't know if it's a true increase, or if it's the same patient having a couple of those.

DR. BIRNBACH: Dr. Stoller?

DR. STOLLER: I would just again add the asterisk comment with regard to my ARDS comments, that -- that there's a

discordance between the prevalence as recorded in the deaths and the actual prevalence in the data. So that if uncertainty on the committee's part with regard to the accuracy of the reporting feeds into somehow the level of confidence in the conclusion, I would have to say that if I were to apply a level of confidence to the -- not only should we give a yes/no answer, but we should apply a level of confidence to the degree we have in that answer. And I would say my level of confidence is very low.

DR. BIRNBACH: Any other comments from the panel? Mr. Melkerson, you're still okay with that summation?

MR. MELKERSON: I was just reminded by our post approval study group that when you're referring to these things as being post approval, are you truly saying that these are things that do not need to be addressed pre-market versus post-market? Post-market says it can be things like you address things like

you see a trend that you're not comfortable with, and the data can't answer that.

If I were to guess what we haven't discussed that the panel has been subtly saying is that this particular question can be handled in a post-market fashion. But I'm not quite sure because Dr. Stoller's last comment suggests otherwise.

So while that had been my thought, your comment suggests maybe that you believe that we would need more data with a much larger study pre --

DR. STOLLER: So the issue comes down to clinical significance. And it's kind of like the standard gamble question. How much risk are you willing to take to develop an outcome that is catastrophic, which is ARDS?

And so while on the one hand, let me reiterate that from a biologic plausibility point of view, it's hard for me to relate this gel to the development of ARDS. Nonetheless,

I think the history of medicine is full of lapses between our biologic understanding and phenomenon that we observe in randomized trials. And I think it would arrogant to ignore the trend.

Having said that, I would say that given the level of severity of ARDS as an outcome would be one that might cause me to say I wouldn't be comfortable with allocating this to post-marketing approval, but that it might be a question I'd like to have answered up front, even though my level of biologic concern, given my current knowledge in 2008 is low.

DR. BIRNBACH: Dr. Wiswell?

DR. WISWELL: I don't know if we have enough information about ARDS, and -- and how it was diagnosed. I don't know if in the -- obviously we had some data that the FDA presented in their presentation, and the sponsor, and there is -- I don't know if it's the standard definition for ARDS that came

about 14 years ago, and specific P/F ratios, et cetera, and you have to meet all those criteria.

This is a high risk population for ARDS, also. So I don't know if we have enough information about it in both groups to have a major concern now or not. And I guess that's a quandary that we're in.

DR. BIRNBACH: Dr. Spindell?

DR. SPINDELL: Getting back to Dr. Stoller's comment, and Dr. Wiswell, we had one slide that showed one ARDS in the control, and three in the sealant group. And then we saw another slide from the manufacturer that said three in the control group, and three in the sealant group. So I -- I think that ought to be rectified before somebody makes a judgment.

DR. BIRNBACH: Assuming that the data is straight, the question from the FDA, however, still says, "If we believe that there is even a trend here, is this something that needs to be addressed pre-approval, or is this

something that in our minds is of a low enough level to allow it to occur post-market surveillance?" Yes, Dr. Spindell?

DR. SPINDELL: What gets back to Dr. Wiswell's comments is if we look at this slide that the manufacturer presented, there is no trend in ARDS. Both sides had three people with ARDS. And these people are high risk populations; it's semi-understandable.

If the FDA slide is the correct slide, but one in the control and three in ARDS, that -- that might be a different evaluation. And I think that's one of the things that needs clear.

DR. BIRNBACH: Right. So what I was saying is since we won't be here when we figure that out, if the FDA's data at the end of the day is considered correct, and there is a trend at best, is that something that needs to be evaluated pre-approval or not? Ladies and gentlemen, any comments? Dr. Ries?

DR. RIES: Well, I would think it

can probably be handled post market. The issue of death certificates and how things are coded is -- is quite variable. Fundamentally, if we look at all causes of mortality, there wasn't -- the trend was in the other direction. The trend was more of a higher death rate in the control groups. So I wouldn't be terribly worried about it.

DR. BIRNBACH: Dr. Wilcox?

DR. WILCOX: Can we not ask someone to clarify that beforehand? I understand the difference in the two slides had to do with the deaths to which one penetrated for diagnoses, rather than just looking at the death certificate. And so that in two slides, two bits of data may be absolutely compatible. Could not someone from the FDA clarify that for us?

DR. BIRNBACH: Can we go back to the FDA and try to get --

MR. MELKERSON: I'll try to paraphrase this. Dr. Horbowyj presented that

our calling was based on cause -- would be the identified cause of death. The second part of the table had contributing factors. So the discrepancy could've been related to the sponsor looking at attributing factors, versus the actual -- what was listed as cause of deaths in the separate column. But when we went back and looked at that, it had deferred to Dr. Horbowyj, and the actual summation of that.

DR. BIRNBACH: Dr. Stoller?

DR. STOLLER: Not to be persnickety, but again, we have different estimates. Table 37, row 13 talks about the equal prevalence in both groups of ARDS. And yet, the death data, whether it's contributing or real, talks about different number estimates.

So I find myself again looking at the data, and being unable, whether or not its PF ratio is less than 200, and unless they feel pressures less than 18, and all of that;

however it's being counted it's not being counted consistently. And so if I'm asked to weigh in on my level of concern, I have to say I really don't know.

DR. BIRNBACH: Dr. Loeb?

DR. LOEB: There may be some more information that we've overlooked, and that is on pages 60 through 63, there is a narrative of each patient who died. And given what I'm hearing, maybe it would be worthwhile for us to try to review that, and come to some conclusion ourselves as to whether or not ARDS is the primary reason for death. That might be helpful.

DR. STOLLER: Let me say also that I'm not necessarily only talking about it as being causal of death, because we know that currently 30 percent of patients die. But I'd rather not develop it at all. I would say that put against the background of a two-day accelerated discharge from the hospital, the possibility of developing ARDS, it's clear

what my choice would be. I'd rather stay in the hospital two days longer and not get it.

So I think I did review those narratives with that in mind, and I -- I take your point. I'm not sure that that's going to really answer the question I've posed in terms of the prevalence of the event, whether or not it was causal to death.

DR. CASSIERE: Well if you were to think that the ARDS was developing, you'd expect that to impact the length of stay though. Because if someone develops ARDS, it's usually -- if it's mild, maybe it'll dissipate in a couple of days. But if it's moderate to severe, you expect these patients to be trached in the intensive care unit.

So the length of stay data kind of shakes that out. And yes, I agree they -- who is to find the ARDS? Is it -- you're looking at death certificates. So I can't remember the last patient that died of atrial fibrillation. So you have to look at these

things with a grain of salt.

But if you look at the length of stay data, and the narratives, it's pretty clear that the patients who died, died of multiple reasons.

DR. DOMINO: Since we're on page 60 with table 30, the day of death in two of the sealant groups with ARDS, one of them was post-op day seven. One was on post-op day six. So they wouldn't really be -- you wouldn't see that longer length of stay then since they were dead.

DR. CASSIERE: No, we're talking about in the table when it looks at the incidence of ARDS in either group, not the cause of death but the incidence of the ARDS as an adverse event.

DR. BIRNBACH: Dr. Normand, was that your hand up? No? It looked like you wanted to say something.

DR. NORMAND: Yes. I was just trying to -- I don't think looking at length

of stay would do it is I guess what I wanted to say. Because you know, if somebody did, even at the prevalence estimate, if they're all dying very soon, the length of stay is going to look short.

So I think using the length of stay data to justify or as a solution to determining whether the prevalence of ARDS is correct, I don't think that's the right -- that's not the right tool to look at it.

DR. CASSIERE: Well, no, because ARDS is an -- it's a disease that when you get it, it's debilitating usually, and it will affect the length of stay if you don't die.

DR. NORMAND: Yes.

DR. CASSIERE: If you get ARDS and you die the next day, you have a short length of stay. But if you have a product that's going to cause ARDS, and it causes it in -- it's going to impact the length of stay because that diagnosis in and of itself is going to change how you get treated

clinically, and then you're going to be in the hospital longer.

DR. NORMAND: No, I understand. But there's going to be some that die, and some that -- that don't die. I'm just saying on average, I don't think it's --

DR. CASSIERE: No, I'm saying but we know the patients who died and we have a description of it. So the other issue is the -- if -- does this product pre-dispose or cause ARDS? You'd expect to see that in the sealant group. And if it does, you'd expect that to impact on their length of stay; the ones who survived.

DR. NORMAND: Yes, I guess I'm not being clear, or perhaps I'm being dense. And it could be both of them. But it seems to me that I understand what you're saying, but if you're going to take -- because the people who die are in there, and it's just -- it's just pretend everybody had ARDS, and you're averaging short -- people who are really sick

and die early, versus those that have some debilitating disease and you want to do that comparison.

That's the wrong thing to look at is I guess what I really wanted to make a point of. To use length of stay to say, "Well, we really see it in length of stay."

The other thing I wanted to ask, and I don't think anybody answered that question, is that for those that get discharged, I'm presuming they all get discharged to home. Because maybe the people are really debilitated get discharged to go somewhere else. And so sometimes that's the real issue with these lengths of stay. It's a very biased measure in terms of they don't all go home.

So that's another way length of stay might not be appropriately utilized to assess sickness in two groups.

DR. BIRNBACH: So Mr. Melkerson, I am going to summarize. We have a little bit

of a split jury on this one with some people believing that this is a significant enough problem that you would need more information pre-approval, and others on the panel believing that you can go ahead assuming all the other issues are settled and do this as a post-market surveillance. Would that work for the panel?

That said, we are now going to take a ten-minute break.

(Whereupon, the above-entitled matter went off the record at 3:25 p.m., and resumed at 3:37 p.m.)

DR. BIRNBACH: We are going to now resume the meeting. We'll proceed with the second open public hearing of this meeting. Is there anyone who would like to address the panel at this time? Being not, we will proceed to the FDA and sponsor summations. Is there any further comment or clarification from the FDA?

MR. MELKERSON: No, there is not.

DR. BIRNBACH: Is there any further clarification from the sponsor?

MR. MELKERSON: The sponsor is not back in the room yet, and they had mentioned that they did want to make some summation comments. I'll see if I can find them.

DR. BIRNBACH: That would be great. Thank you very much. Is the sponsor ready for giving us any further comment or clarification?

DR. CERFOLIO: First of all, I want to thank everybody's attention. You've been here a long time. I know it's hard to do. As you recall, I've sat in that seat, and I also know the responsibility that goes on your shoulders when you sit there, that you don't want to approve something you think is going to hurt patients.

I just wanted to really review the data. I think all the answer is immersed in the data. And the study that would be nice to maybe go back and redo, but it was a study

that we showed the FDA or the company, not me, the company showed to the FDA and did and met their primary end point.

But let's go through the safety. I think you very nicely handled the issue about the renal problems. I think you've come to a reasonable conclusion as we have that really we don't see any evidence there's any renal problems, and we're okay there.

We spent some time on the ARDS, and I think we've lost sight of the fact that we had two independent reviewers go back and look at the deaths. And if you go back and look in your summary packages, you'll see that there are ARDS deaths in the controls, and there are ARDS deaths in the patients that got the sealant.

There's at least two patients in the control that had ARDS, and three in the sealants. So we don't think that there's a difference. Moreover, there's more deaths in the control group.

So I agree with your comment, Dr. Stoller, very much, that if I had an option, I'd rather spend two extra days in the hospital than be dead also. But this device wasn't causing deaths. There were less deaths in the patients that got the sealant.

So I do not think that the evidence, if you look at the data, you look at the pneumonia rates, and we all know that ARDS are very difficult to even come to a definition. But pneumonia is a little easier. But there really was even more pneumonias in the patients that got the controls than got the sealant.

So I wouldn't get hung up, or I wouldn't allow the ARDS issue to create us to have to do more data, because I don't think if you look at the data that is a correct conclusion. If you really look at the data and the analysis of the deaths, and in either the narratives or in some other package that you have, and those were based from

independent reviewers.

So in terms of safety, I think I've addressed the renal, the ARDS, and I think you've talked about the lung, and I think we're all okay with this idea that there's persistent space in the chest.

Finally, we come to efficacy. I think the FDA and the company got together, and set up a primary end point. Whether it was perfect or not, I think your issues are very good and I agree with a lot of your comments. But the primary end point was met by the study from a multi-institutional prospective randomized study. And it was a positive study.

I think we have to come back to that. That's how the study was designed and it showed a difference. And finally, we have to go back to ask ourselves what are we going to do with patients now?

Our patients deserve a product like this. Our patients deserve to have their tube

out a couple days earlier. As you mentioned, Dr. Wiswell, it does make a difference to have your chest tube out two days earlier. That's probably why the pneumonia rate was less in the sealant. If the tube comes out, the patient is less pained. They can breathe better. They get a better result.

It's not just a matter of going home two days earlier. Having the tube in longer, having the air leak longer, leads to real problems like you heard Dr. Walsh say.

So my passion for my patients is I think this is a good product. Does it need further studies after it's approved? Does it need to be carefully monitored? Absolutely. And I would tell you I think that's a very reasonable thing to do. But I think if you look at the data, the answer for safety are in the data. It's safe. There's less deaths in the patients that got the sealant, and it's efficacious. Thank you.

DR. MILLER: Can I just make one

comment just in regards to the review of the deaths? They were blinded to the review. They did not have any operative reports. They were all -- they had the preoperative data, and they had the postoperative data. There was no information on if sealant was used or not, the ones who reviewed the final deaths that was summarized in your narrative.

DR. BIRNBACH: Thank you. Before we proceed to the vote, I would like to ask Ms. Petersen, our Consumer Representative, and Dr. Spindell, our industry representative if they have any additional comments. Ms. Petersen?

MS. PETERSEN: Thank you. I just had one comment relative to question number four, which was asking if we could -- if the product had adequately demonstrated a reasonable level of risk of adverse events, illness and injury.

I know several times today from both FDA and the sponsor, as well as some of

the people on the panel, we have mentioned that this study was neither designed nor powered to assess adverse events and adverse effects in patients.

So I'm concerned about question 4 because we have already established that this study was not designed to answer that question.

DR. BIRNBACH: Thank you. Dr. Spindell?

DR. SPINDELL: And I would like to say that with question 4, if we review the data that was -- even though it was underpowered, there was no statistical trend that says there was a higher risk of adverse events in the group, and I do point -- I agree with Ms. Petersen's earlier comment that something that is used in a larger population, maybe that is something that a post-market study would be appropriate for. Not for adverse events, but for the larger population of use.

DR. BIRNBACH: Thank you. We're now ready to vote on the panel's recommendations to FDA for this PMA. Mr. Patel will not read the panel recommendation options for Premarket Approval applications. Panel, please refer to the voting procedure flow chart in your folder. Mr. Patel?

MR. PATEL: The medical advice to amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990 allows the Food and Drug Administration to obtain a recommendation from the Expert Advisory Panel on designated medical device Premarket Approval application that are filed with the agency.

The Premarket Approval must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in application, or by applicable publicly available information.

The definitions of safety, effectiveness and valid scientific evidence

are as follows: safety as defined in 21 CFR, section 860.7(d)1, There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness as defined in 21 CFR 860.7(e)1: There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid scientific evidence as defined in 21 CFR Section 860.7(c)2, evidence from well-controlled investigations, partially

controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

Isolated case reports, random experience, reports lacking sufficient details to permit scientific valuation and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

Your recommendation options for the vote are as follows: Number one, approval, if there are no conditions attached. Two, approvable with conditions. The panel may recommend that the Premarket Approval be found approvable subject to specified conditions

such as physician or patient education, labeling changes, or a further analysis of existing data.

Prior to voting, all the conditions should be discussed by the panel. And the third option is not approvable. The panel may recommend that the pre-market application -- or Premarket Approval application is not approvable if the data do not provide a reasonable assurance that the device is safe, or the data do not provide a reasonable assurance that the device is effective under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Following the voting, the chair will ask each panel member to present a brief statement outlining his or her reasons for the vote. Dr. Birnbach?

DR. BIRNBACH: Are there any questions from the panel about these voting options before I ask for a main motion for this PMA? That said, is there a motion for

either approval, approvable with conditions, or not approvable from the panel?

DR. CASSIERE: Approvable with conditions.

DR. JEEVANANDAM: I second.

DR. BIRNBACH: Is there a second for this motion?

DR. JEEVANANDAM: Second.

DR. BIRNBACH: Is there any discussion on this motion?

DR. CASSIERE: The approval with conditions, the condition that contemplating is limiting the number of applications since this particular study looked at a maximum three applications of the -- of the device. And I believe it's reasonable to limit the application to no more than three applications.

DR. BIRNBACH: Yes?

DR. JEEVANANDAM: The condition --

DR. BIRNBACH: Wait. So we're limited to that condition. We're going to

discuss that condition, vote on that, and then move onto the next condition. So any discussion on that condition? Oh, I need a second for that motion. Does anyone second that motion?

DR. BRUNSON: I second.

DR. BIRNBACH: Okay. Discussion? Dr. Loeb?

DR. LOEB: It's already in the precautions statement on page 3 of the proposed instructions for use to limit the amount. I missed where it is, but there's a limitation on the amount that can be used. It says, "The safety of the sealant has not been evaluated in patients receiving more than 30 mls of the sealant." Does that -- I would propose that that satisfies, unless there's some stronger language that we want to put into limit how much can be used.

DR. BIRNBACH: Dr. Cassiere?

DR. CASSIERE: Yes, that would be adequate.

DR. BIRNBACH: So any other discussion? Yes, Ms. Petersen?

MS. PETERSEN: I'm wondering if it would be appropriate to clarify that the device could be applied for the therapeutic use of air leaks, as opposed to the prevention of air leaks, where they maybe thought that they could --

DR. BIRNBACH: I think that would be a new condition.

MS. PETERSEN: Okay.

DR. BIRNBACH: And we need to wait until we bring up new conditions. Dr. Normand?

DR. NORMAND: I just wanted to clarify. Is that per leak, that's 30 -- per leak just in general overall? I'm sorry. I don't know the units. It may be a stupid question, but I just wanted to --

DR. BIRNBACH: Dr. Cassiere?

DR. CASSIERE: My understanding would be total.

DR. BIRNBACH: Sponsor, are we okay on total? Okay, do I have a -- I guess we're going to take a vote. All in favor of --

DR. LOCICERO: The language here says that it's not -- it's now known, right? Run that again. It says, "Safety of the sealant has not been evaluated in patients receiving more than 30 ml." So what you're asking for is a label that says, "No more than 30 ml." Is that correct?

DR. CASSIERE: That's correct.

DR. BIRNBACH: All in favor of this condition, please raise your hand. Okay, so for the record, we've got Dr. Ries, Dr. Jeevanandam, Dr. Wilcox, Dr. -- I knew it would happen some time today, LoCicero, Dr. Wiswell, Dr. Loeb. Dr. Domino, I didn't see your hand. It was covered. Dr. Domino, Dr. Brunson, Dr. Cassiere, Dr. Stoller, Dr. Lillard, Dr. Normand and Dr. Topoleski all voting for that motion.

So any against? That would be a

hard call since all of you raised your hands. And that means no abstentions. So are there any other conditions?

DR. JEEVANANDAM: I'd like to add a condition of post-market surveillance.

DR. BIRNBACH: Okay.

DR. JEEVANANDAM: Specifically regarding the issues of cardiac outcomes, renal outcomes, and perhaps ARDS -- ARDS.

DR. BIRNBACH: So Dr. Jeevanandam wants a post-market surveillance for ARDS for cardiac and for renal issues. Do I have a second for that motion? Motion is seconded. Discussion? Dr. Stoller?

DR. STOLLER: So I would concur with that, and I would perhaps add the notion that the data be evaluated around standard criteria for ARDS so that this area of uncertainty that we have as to whether ARDS has or has not happened could be in fact objectively assessed by the European-American consensus criteria with PF ratios and so on.

There are standard definitions that all of us apply, and I think it's reasonable to think that the data would be characterized by those standard definitions in this data set. And it may have been the case, but we're not assured of that from the information available.

MR. MELKERSON: This is Mark Melkerson. I just wanted to clarify if you are doing a -- recommending a post approval study, make sure you give explicit statements of what questions you would like addressed. Is it trends of adverse events? Like for example, I'm just leaving it that way. And if you want some further input on other suggestions, I can refer to our post approval study staff.

DR. BIRNBACH: Your motion, would you like to be more specific to the FDA on what that condition is?

DR. JEEVANANDAM: I guess the problem is you don't have a control arm to

look at what you compared this to, unless you want to look at --

DR. BIRNBACH: Okay. Dr. Normand?

DR. NORMAND: I think they need to have a comparison group. Otherwise we're going to be stuck not knowing whether or not -- you know, they'll find something and everybody will think, "Oh my god. It's too hard. We needed comparison groups." So they aren't burnt if they -- if they find something and it's sort of not that much different than what we'd expect in a control arm.

DR. BIRNBACH: So this would be a post market surveillance for adverse events, including cardiac events, renal dysfunction, ARDS. And there would also need to be a comparison group. Any other comments?

DR. JEEVANANDAM: Could you use the control arm of this present study as historical control?

DR. NORMAND: I'm sorry. Okay, the only issue would be if the standard -- if

things change over time, and that's -- that's not a good idea to use a historical control group. It's to the benefit of the sponsor really to have a concurrent comparison group. I wouldn't recommend a historical group.

DR. BIRNBACH: Okay. Any other discussion? Yes, Dr. LoCicero?

DR. LOCICERO: Do we have to define a control group now? Should we define it?

MR. MELKERSON: Any suggestions you can make at this point in time will make discussions with the sponsor much easier.

DR. LOCICERO: Okay. In lieu of the randomized control trial, the Society of Thoracic Surgeons, thoracic surgical database, is collecting data on all -- on a large number of patients.

There's been a recent report that this is now becoming robust, similar to the SDS database for cardiac surgery, and might be a way to compare so that this were some defined level of standard deviation above what

we're seeing in that database. Then that might be a trend that needs to be looked at.

DR. BIRNBACH: Dr. Normand?

DR. NORMAND: Okay, I'm not sure how much time you want us to spend on designing their post-market study. But probably based on the conversations we heard today with regard to practice style and the use of various chest tube placements and things like that, it would be nice if they could use perhaps a database, but try and get comparisons within the same institution at the very least, to mitigate some of the practice patterns that might rise and the results.

So they could potentially utilize the data collection instrument in that database, but I would again recommend using a concurrent comparison group, and that comparison group could be people or patients treated within the same institution, which is available in that database.

DR. MARINAC-DABIC: The other thing

to think about with regard to suggesting the use of the SDS data is what is the duration of the follow up you're considering? Because SDS doesn't have long-term follow up. It ends with 30 days post-op.

DR. BIRNBACH: Any discussion about duration of follow up?

DR. LOCICERO: The concern we have are all under 30 days. These are things that develop even in the hospital or out to 30 days in comparison to what we have right now, unless we decide that we need to make it different.

DR. BIRNBACH: Dr. Normand?

DR. NORMAND: Again, I don't know if this is maybe something the FDA needs to assess, but I think sometimes we worry about things beyond 30 days. And to the extent we would worry about -- I know I do not being a clinician, but again that's something that if you had the hospital -- if you know where the patient is treated, you could link to state

databases.

It could be cheap to get longer term follow up as long as you have the identifiers. And I run the SDS in our State, so I know that's doable and it could be done. I guess long-term would be important to determine from the clinicians whether or not you are absolutely comfortable saying 30 days and that's it.

I know in other studies, we want to go longer than 30 days. So I just want to ask the group to think hard whether 30 days really is it.

DR. BIRNBACH: Dr. Ries?

DR. RIES: I think particularly for the renal issue, a longer term follow up would be appropriate because the unsigning event may be within 30 days, but really the issue is whether there's any long-term consequence of renal dysfunction.

DR. BIRNBACH: Any further discussion? So the motion that we're going to

vote on is that this will require post-market surveillance for trends of adverse events, including ARDS, renal function or dysfunction, and cardiac issues; that we'll also have a comparison group hopefully within the same institution and will go for at least 30 days, but hopefully for a longer period than that, maybe up to perhaps 90 days.

Is that the consensus of the motion on the table? Okay, all in favor? Okay, that's everyone. So for the record here we go again: Dr. Ries, Dr. Jeevanandam, Dr. Wilcox, Dr. LoCiciero, Dr. Wiswell, Dr. Loeb, Dr. Domino, Dr. Brunson, Dr. Cassiere, Dr. Stoller, Dr. Lillard, Dr. Normand and Dr. Topoleski have all voted yes.

There are no no's, and there are no abstentions. Are there other conditions?

DR. CASSIERE: I'm not sure if this is appropriate, but we haven't talked -- we've talked about open thorocotomy. Should there be a limitation on although this device

physically can't be stuck through a VATS, should there be a limitation on using this device or similar technology from a company to do it via VATS thoracotomy, or is that off-base?

DR. BIRNBACH: Say again?

DR. CASSIERE: This product is approved for -- the way it's given is with open thoracotomy.

DR. BIRNBACH: Correct.

DR. CASSIERE: Most -- some of these surgeries are done through VATS. Should there be a limitation? I know technologically it probably won't be for long. But instilling this -- this device through a VATS thorocotomy as opposed to an open thorocotomy.

DR. BIRNBACH: So the motion on the table is to limit the use to open thorocotomies? Is there a second for that motion?

DR. JEEVANANDAM: Could I ask a question? Why would you want to limit it to

open? I mean I think if they did, they'd develop a delivery system where you can give it into a VATS -- during a VATS procedure. You may actually have more utility in a VATS procedure to prevent air leaks.

DR. CASSIERE: Well, the reason is because the original study looked at just open.

DR. LOCICERO: Well, I mean I don't know that we're -- we have only looked at one device here. There's only one device with one applicator. We haven't seen any other information. I'm unaware of any other information.

DR. BIRNBACH: Well, I believe that we need to have a second for this motion actually if -- because if no one is going to second the motion, then --

DR. TOPOLESKI: I'll second.

DR. BIRNBACH: Okay, so we have a second to the motion. So is there any discussion?

Dr. Wilcox?

DR. WILCOX: There is some confusion as to what is open and what is not. And many VATS procedures are also accompanied by a small thorocotomy through which this applicator could be -- deliver it's material. So I'm not quite sure how to -- how to define this to make it do what you would like it to do.

DR. BIRNBACH: Dr. Loeb?

DR. LOEB: Just as a point of discussion, I think it might be important also since I heard in the motion the word thorocotomy, which would limit its use for abdominal procedures, and we do know that there potentially would be problems with putting it into the perineum for the animal studies.

So my understanding is if you put this up without a limitation of where it can be used, clinicians may think, "Oh, gee, this is a sealant that can be used in other areas."

And we do note there is a problem in the perineal cavity.

DR. BIRNBACH: And how would you modify this condition?

DR. LOEB: I wouldn't modify it because if you're only using it in open thorocotomies, in addition to the fact that you're precluding VATS, you're also precluding abdominal procedures.

DR. BIRNBACH: Dr. Brunson?

DR. BRUNSON: I think the important thing is that the application is designed for the surface of the lung. And I think if we want to say something, maybe we ought to have a condition that limits it to usage on the surface of the lung, and then it's up to the surgeon to decide how I guess they put it there. And that way we don't get into those kinds of issues.

DR. BIRNBACH: Dr. Wilcox?

DR. WILCOX: I think that's an important point because we haven't talked

about this being applied to a bronchial stump, and that would be an entirely -- would have entirely different implications than what we talked about all day. So I think if the consideration touches that it would be important.

But I'm also -- this -- your motion wouldn't preclude someone using it if they used VATS, scopes and so forth to do the resection. You had applied this through an open thorocotomy, is that correct? I mean that would be my choice if --

DR. CASSIERE: Well, I threw it out there because there's been no discussion of the way the surgery is done, whether it's open or whether it's VATS or a combination of the two. And is that relevant? And it may, it may be relevant. I'm interested to see what -- that's why I threw it out there as a motion.

DR. BIRNBACH: Dr. Stoller?

DR. STOLLER: So I would support the notion of limiting its use to the surface of

the lung. I would speak against constraining it to VATS because the surgeon wishing to be in compliance would in fact then me incented to make an incision in order to be in compliance with the indication that would not otherwise occur.

So I think that that constraint might have the unintended consequence of driving more incisions than would otherwise occur. I recognize that that's a potentially unlikely scenario, but I think that we have to be mindful of the downstream impact of what committees such as this recommend. So I would speak against that.

DR. BIRNBACH: And in turn perhaps put that forward as another condition. So right now, the condition on the table that we need to vote for would limit the use of this device to open thorocotomy, thus precluding its use for VATS. All those in favor of this condition raise their hand.

All those opposed raise their hand.

Okay, so for the record -- oh, keep your hands up because not everybody raised their hand. So Dr. Ries, Dr. Jeevanandam, Dr. Wilcox, Dr. LoCicero -- I'm sorry, it's been a long day. Dr. Wiswell, Dr. Loeb I can't tell. Dr. Domino is. Dr. Birnbach doesn't vote. Dr. Brunson, Dr. Cassiere, Dr. Stoller, and then we've got two, no -- none of you have your hands up, correct?

Okay, so all those against -- all those abstain? Got three abstentions and that's Dr. Lillard, Dr. Normand and Dr. Topoleski. Okay, are there any other conditions?

DR. JEEVANANDAM: Well, as a corollary to that I guess we would put the condition that this is for the surface of the lung.

DR. BIRNBACH: Okay. So we have a motion for limiting this to the surface of the lung. Is there any discussion on that? All those in favor of limiting its usage to the

surface of the lung? All hands are up. So do I have to go through this every time? Sooner or later I'm going to get LoCicero right.

Okay, so for the record, Dr. Ries, Dr. Jeevanandam, Dr. Wilcox, Dr. LoCicero, Dr. Wiswell, Dr. Loeb, Dr. Domino, Dr. Brunson, Dr. Cassiere, Dr. Stoller, Dr. Lillard, Dr. Normand and Dr. Topoleski all voted for limiting this to the surface of the lung. Are there any other conditions? Yes?

MS. PETERSEN: I suggest a labeling indication, noting that the product is for use of therapy of existing air leaks and not for the prevention of potential air leaks.

DR. BIRNBACH: Is there a second for that? We have a second. Is there any discussion? Dr. LoCicero?

DR. LOCICERO: The intended use states that as an adjunct to standard tissue closure techniques for sealing or reducing air leaks incurred during pulmonary surgery -- I'm not sure this is different from the proposal.

DR. BIRNBACH: So what you're suggesting is since it's already written there, we don't actually need to have this condition? Okay.

DR. JEEVANANDAM: It doesn't -- it says as an adjunct, but it doesn't -- what she was implying is that you do your standard procedures. You check the lung. If there's a leak, then you go ahead and put this device on. That just says as an adjunct that one could interpret, "Well, I've stitched it. I'm just going to reinforce it now." And then before you even check for a leak.

So I think your implication was you need to check for a leak, make sure there's a leak, and then put the device on.

DR. BIRNBACH: Now, how about this? The discussion we had this morning about the fact that sometimes the leaks are so small in the area you can't do anything now, but they would want to put that on. Is that something anybody wants to discuss?

MS. PETERSEN: My intent is to be clear for surgeons that the product is to be applied to known leaks and small things that you can't suture or staple in other ways, not as something that you apply across the entire suture line to prevent anything just in case. Because we acknowledge we are concerned about the level of exposure of the patient to the substance.

DR. BIRNBACH: Okay, so the motion on the table would limit the use to air leaks that you've got, and to small areas that you otherwise can't suture, but not to prevent by wholesale administration to the suture line. Dr. Brunson?

DR. BRUNSON: I'm not clean on that. So if there are small areas, as you say, that cannot be sutured, do you have to demonstrate the air leak? If you demonstrate the air leak, then that covers it all anyway. See, I'm confused because there will be areas that you can't get to that you can use it on, even

though you haven't demonstrated the air leak, I guess.

DR. BIRNBACH: Perhaps I could restate your condition that this agent not be applied to the suture line to prevent air leaks.

MS. PETERSEN: That would convey the intent, yes.

DR. BIRNBACH: Dr. Wilcox?

DR. WILCOX: I'm real concerned about being too instructive to the surgeon. I mean I'd be much more concerned about saying that -- in changing the instructions on the insert that this not be applied to bronchial stumps because there is some evidence that that can give problems. But not to apply it -- to say not to apply it to the suture line, I think, is extending a little too far.

DR. BIRNBACH: Okay.

DR. WILCOX: If I can add without demonstrated air leak, or something like that.

DR. BIRNBACH: Hold on. Who

seconded your original motion? Dr. Ries, do you accept the amendment to that original motion?

DR. RIES: Yes.

DR. BIRNBACH: Great. Now, we can continue the discussion.

DR. LOEB: I'm satisfied with limiting the total dose and don't feel that the other limitation is necessary, and I think it's too intrusive into clinical practice.

DR. BIRNBACH: Okay. So let's move onto a vote. Those in favor of limiting this so that it cannot be applied to the suture line raise their hands. Those against this limitation raise their hands. So for the record, everyone has raised their hands other than one. So we've got positive votes for Dr. Ries, Dr. Jeevanandam, Dr. Wilcox, Dr. LoCicero, Dr. Wiswell, Dr. Loeb, Dr. Domino, Dr. Brunson, Dr. Cassiere, Dr. Stoller. Dr. Lillard is not voting for; Dr. Normand and Dr. Topoleski are. Dr. Lillard, are you

abstaining? We have one abstention.

DR. RIES: And one correction. I actually wanted to vote for the motion.

DR. BIRNBACH: I'm sorry, I missed that. Who voted for the -- okay, so we have one vote for the motion. That's Dr. Ries. We have all the other votes against the motion except for one abstention, which is Dr. Lillard. Okay, are there any other conditions? Dr. Ries?

DR. RIES: I'd like to suggest a discussion on a condition regarding the primary outcome of a possible post marketing surveillance study that it not be -- that it be something different than what was used in the -- in this study.

DR. BIRNBACH: Such as?

DR. RIES: Such as a time to event analysis since we're interested primarily in clinical -- clinical outcomes, and the -- it seemed to be based on the sponsors that the most important clinical outcomes were -- were

the absence of air leaks in the removal of a chest tube that those be -- those be the kind of clinical outcomes that be considered, and it be a time to event analysis.

DR. BIRNBACH: So the motion on the table is that the post marketing study should have a different primary outcome than the studies that have been presented us today, and should include a time to event analysis. Is there a second for that motion? We have a second, Dr. Normand. Any discussion on that motion?

Okay, let's vote. All those in favor of requesting that the primary outcome of the post-marketing surveillance be different raise your hands.

Okay, so this one I'll have to go more slowly. This is -- okay, Dr. Ries says yes. Dr. Jeevanandam says yes. Dr. Wilcox says yes. Dr. LoCicero says yes. Dr. Loeb says yes. Dr. Domino says yes. Dr. Brunson says yes. Dr. Stoller says yes. Dr. Lillard

says yes. Dr. Normand says yes, and Dr. Topoleski says yes.

All of those against the motion? Okay, so we've got one, Dr. Wiswell says no. All of those -- oh, two, sorry. Dr. Wiswell and Dr. Cassiere say no. All of those abstaining? No one, okay.

Are there any other conditions? Yes, Dr. Stoller?

DR. STOLLER: I would suggest that if in fact a post marketing study evaluated a time to event analysis that the ascertainment of the air leak be done by an independent blind observer.

DR. BIRNBACH: In a post market surveillance. Do we have a second? Dr. Normand seconds. Discussion? Could you elucidate a little bit more perhaps on how you would design this post market? Since now anyone can use this, would you only select one subgroup that would have to -- because they'd have to blind this. You would have a very

difficult time telling surgeons you can start using this, but every time you use it you're going to have to find a blinded observer in your hospital after --

DR. STOLLER: Right.

DR. BIRNBACH: Is that actually what you want?

DR. STOLLER: I'm fully aware of how confusing the recommendation is. It's meant to weight in on my level of confidence as I alluded to before. The dichotomous yes/no assessment doesn't quite allow for an assessment of confidence in the outcome. And so I'm trying to communicate that in a somewhat unconventional manner.

So I'm not sure I could design the study, but I'd like at least to be part of the record as to reflect the comments that I think occupied most of the committee's discussion for most of the day.

DR. BIRNBACH: All right, so discussion? Yes, Dr. Loeb?

DR. LOEB: Yes, I'm not sure how that would look in a typical post market surveillance, but I think we can expect that when this product is released that there will be additional studies that are done either with the support of the company or without the support of the company, looking at other types of efficacy.

And I don't know if we have a role and the power to suggest or to mandate that the company perform additional studies. I would not suggest linking that type of a study to the adverse events study, which is going to by necessity be very large.

But if we can suggest a study smaller in scope that would look at some of the things that -- that I know have been raised, and that I still wonder about in terms of when the air leaks might occur after application when they hadn't been there, total time of air leaks, some of the -- some of the things that we haven't seen. But I don't

think that that would belong in a -- in an adverse event type study.

DR. BIRNBACH: Just for clarification, Mr. Melkerson, can this panel require a second post study?

MR. MELKERSON: There's nothing wrong with having multiple post market surveillance studies to address different questions. The question the FDA would have to the panel would be what question are you trying to address with that study, or that condition?

DR. BIRNBACH: Dr. Normand?

DR. NORMAND: I wasn't going to answer that question, so maybe somebody else wanted to. I was going to make a different point.

DR. BIRNBACH: Make a different point. We'll go back to that.

DR. NORMAND: Again, I think it's difficult as a group of us to sit around here and design a post market study that would be

efficient and rigorous. With that said, there are some designs you could capitalize on the -- the original study we talked about where you might do some sub-sampling and be efficient, so not having to go to an entirely new population.

And so although I understand people were worried about the amount of resources it would take to do that, but two studies doesn't make much sense to me. You could do one study, do some sub-sampling, get an independent trainer that's going to go around and do it for some sub-studies, and it's doable. It's not going to break the bank. So that's my sense.

DR. BIRNBACH: All right, so the motion on the table, for the record is that --

DR. NORMAND: It'd be blinded.

DR. BIRNBACH: -- post surveillance -- the post release surveillance would be required to have a blinded observer. Dr. Stoller?

DR. STOLLER: So let me own that. In response to the question, I would say that I think that from my own point of view, the sponsor needs to be given credit for having satisfied the primary outcome measure, and I would argue in retrospect that the rigor around the primary outcome measure would not necessarily satisfy my own standards for approvability.

So in that context, I would argue that the question to be answered is the -- the occurrence of the actual efficacy question of does it stop the post -- post op air leaks, and over what time frame? Which I think is incompletely evaluated, admittedly a fundamental question to this -- to this application, but not completely elucidated in my view.

DR. JEEVANANDAM: I think it's a post market surveillance, and then we had talked about three adverse event issues that need to be tracked. I think if anything, the

sponsor has shown that this device does stop air leaks. So I don't know if we need to have air leaks as a part of the post surveillance study.

I think we should just track the adverse events that we had doubts about --

DR. BIRNBACH: The motion that we're discussing is whether or not to have a blinded observer, not what the post market surveillance is going to be.

DR. JEEVANANDAM: But if -- if -- sorry.

DR. BIRNBACH: So if you're saying you want a blinded observer, but not to look at air leaks, is that --

DR. JEEVANANDAM: Okay, I'm saying we don't need to look at air leaks. We don't need to look at air leaks. You need a blinded observer, because if you're going to look at the other adverse events, the -- unless the surgeon is putting it out, it's going to be pretty blinded.

DR. BIRNBACH: Dr. Normand?

DR. NORMAND: That's what I was -- I was agreeing if you're going to look at air leaks, it needs to be blinded.

DR. BIRNBACH: So let's vote on this independent blinded observer. Those in favor? Okay, Dr. Wiswell, Dr. Stoller, Dr. Lillard, Dr. Normand, Dr. Topoleski vote yes. All those against? Dr. Ries, Dr. Jeevanandam, Dr. Wilcox, Dr. LoCicero, Dr. Loeb, Dr. Domino, Dr. Brunson, Dr. Cassiere vote no. All those abstaining? None, and what was that vote since I wasn't counting? Did anyone actually from the FDA count?

MR. MELKERSON: Five-eight.

DR. BIRNBACH: Five-eight, so no need for me to vote. Okay. Are there any other conditions?

DR. CASSIERE: I think one of the things we forgot to add on besides the renal, the ARDS and the cardiac is readmission rate in 30 days. Because we're concerned about the

late pneumothoraxes, and then if you take a look at re-admission to the hospital, the assumption would be if someone developed a pneumothorax they'd be re-admitted to the hospital within 30 days. I think that may be a reasonable thing to tack onto the surveillance.

DR. BIRNBACH: So the motion on the table is that we add re-admission to our previous list of what we're going to do. That was number 2, motion number 2 about post market surveillance. Is there a second for evaluating readmission rights?

DR. BRUNSON: Second.

DR. BIRNBACH: Any discussion? Yes?

DR. SPINDELL: Is it re-admission specifically for pneumothorax or all re-admissions?

DR. CASSIERE: All re-admissions.

DR. BIRNBACH: We ready to vote? All of those in favor of adding re-admission say aye or put up your hand. Okay, so we have

to do this again here. So much fun.

Dr. Ries, Dr. Jeevanandam, Dr. Wilcox, Dr. LoCicero. Let's see, Dr. Wiswell, that was a yes, right? I can't see; Dr. Loeb is hiding you. Dr. Loeb, Dr. Domino, Dr. Brunson, Dr. Cassiere, Dr. Stoller all vote yes. Dr. Lillard is voting yes. Dr. Normand is, and Dr. Topoleski is yes or no? Yes.

So everybody is voting yes except for Dr. Normand. Dr. Normand is voting to abstain or no. Okay, so one vote for no and no abstentions. Are there any other added conditions? Dr. Loeb?

DR. LOEB: I'd like to have I guess under precautions a statement that -- that the sealant is effective for short-term closure of air leaks, and in the weakest language possible, "may," I guess, "cause later air leaks," or may -- yes, something --

DR. BIRNBACH: Maybe associated with delayed air leaks?

DR. LOEB: Delayed air leaks, thank

you. "May be associated with delayed air leaks." Just something in there to alert clinicians that -- to be a little bit wary of that. And I would tack on that I think that I've heard some indication that that might be lifted after successful completion of a post -- a later study that would prove that that's not a problem.

DR. BIRNBACH: Okay, so the motion on the table would be for a temporary precautionary statement that this is short-term, and may be associated with delayed air leaks, or some language that conveys that.

Is there a second to that motion? Dr. Ries seconds it. Any discussion? Those in favor of adding the temporary precaution that this may be associated with a delayed air leak? We're voting.

Okay, so here we go again. Dr. Ries, Dr. Jeevanandam, Dr. Wilcox, Dr. LoCicero, Dr. Wiswell, Dr. Loeb, Dr. Domino, Dr. Brunson, Dr. Cassiere, Dr. Stoller, Dr. Lillard and Dr.

-- oh, I thought -- you didn't? Okay, let's go back again. You didn't vote? Okay.

So Dr. Ries votes yes. Dr. Jeevanandam votes yes. Dr. Wilcox votes yes. Dr. LoCicero votes yes. Dr. Wiswell votes yes. Dr. Loeb votes yes. Okay, now, Dr. Brunson votes yes. Dr. Cassiere votes yes. Dr. Lillard votes yes and Dr. Topoleski votes yes.

Those who vote no? Okay, Dr. Domino votes no. Dr. Stoller votes no, and Dr. Normand votes no. That leaves no one left to abstain. Are there any other conditions? Dr. Topoleski?

DR. TOPOLESKI: I would like to move that perhaps somewhere either under the warnings or precautions a statement that the time dependence of the strength and the adhesive properties of this sealant have not been evaluated.

DR. BIRNBACH: So the motion on the table is that we add language saying that the

duration -- would that --

DR. TOPOLESKI: Well, the time dependence.

DR. BIRNBACH: Time dependence. That's why I asked.

DR. TOPOLESKI: Well, duration is how long it will maintain a certain strength. Time dependence refers to a functionality. Could be one percent per day, ten percent per day, 30 percent per day. Duration is the clinical term, but a scientific engineering term would be time dependence, I think.

DR. BIRNBACH: Do I have a second for the motion that we add that the time dependence is unknown? No one has seconded the motion. Are there any other conditions? Hearing none, I assume that we're ready for the main motion vote.

We will now vote on the main motion. With a show of hands, please indicate if you concur with the recommendation, that the above named PMA be found approvable with the

conditions that we discussed.

Voting members who are raising their hands indicating that they concur with the recommendation are, in no particular order: Dr. Ries, Dr. Jeevanandam, Dr. Wilcox, Dr. LoCicero, Dr. Wiswell, Dr. Loeb, Dr. Domino, Dr. Brunson, Dr. Cassiere, Dr. Stoller, Dr. Lillard. Dr. Normand, is that up or not? Down. Dr. Topoleski.

All of those against the motion? Dr. Normand votes against. And there are no abstentions. Now, I would like to go over each of you, and have you tell us -- actually before I do that, I have to announce the decision.

It is the recommendation of the panel of the FDA that the PMA P010047, for the ProGEL Surgical Sealant from NeoMend, Incorporated, be found approvable with the stated conditions. I would now ask each panel member to state the reason for his or her vote, starting with Dr. Ries.

DR. RIES: I think my vote was based as much on hope as substance. I am swayed by the sponsor's argument that this is an important problem and a compelling need for a product such as this. And I think the product does control leaks.

And I think if, as Dr. Cerfolio said in his summary, if the data really supported that you could reduce air leaks and remove chest tubes sooner, that this would be a no-brainer. I don't think the current data actually support that because it doesn't seem to be a difference. But I certainly would think this is a promising product that deserves more attention.

DR. JEEVANANDAM: I concur. I think this -- this study shows that this will decrease air leaks, will eliminate air leaks in a significant proportion of patients. However, I was just concerned about a couple of issues, particularly residual space at the 30-day chest x-ray, potential cardiovascular

effects and the potential renal effects.

So that's why we had -- I recommended post market surveillance.

DR. BIRNBACH: Dr. Wilcox?

DR. WILCOX: This product in my opinion has answered the old admonition about first do no hard. So I think it's been demonstrated that it's a safe product.

The beneficial effects are less obvious. Having not been, the evidence strongly suggested that it will be a benefit to patients undergoing pulmonary resection. So I voted yes.

DR. BIRNBACH: Dr. LoCicero?

DR. LOCICERO: All thoracic surgeons seek the holy grail of no air leak after thoracic surgery. This may or may not be the product.

DR. BIRNBACH: Dr. Wiswell?

DR. WISWELL: I think we've seen that the major end point was clearly answered an achieved. I'm quite hopeful that the post

approval study will show perhaps that we are going to prevent some empyemas, maybe some other complications by not having those air leaks.

So I'm -- I'm hopeful about that. I shared some concerns, but a low level of that concerning the ARDS, renal, cardiac, etcetera issues. And so I think that they, in my mind, have potential benefits. And benefits outweigh the risks.

DR. BIRNBACH: Dr. Loeb?

DR. LOEB: I felt that the pre-clinical studies did a good job of demonstrating that it was a safe product. I thought that the clinical study did achieve the initial objectives of which it set out, and like every good study, raised a lot of other questions that we wrestled with.

I think that this product has a relatively low chance of causing injury, and some chance of improving care for patients.

DR. BIRNBACH: Dr. Domino?

DR. DOMINO: I felt that the clinical study, these kinds of studies, are very difficult to do. And it was small, and it didn't address all the questions, and I -- on the other hand, I think that it demonstrated a reduction in leaks, in at least the initial perioperative, I would say, several day period. And I look to the post approval surveillance data to really test the idea about safety issues.

DR. BIRNBACH: Dr. Brunson?

DR. BRUNSON: I think that this product addresses an important clinical problem that we deal with in medicine. Besides that, with the evidence that was presented, while we did have questions, I'm satisfied that with the post market surveillance study that we will do, that it will address some of those concerns. And I think overall, it has shown its efficacy, and I think will be a good addition to the clinical practice.

DR. BIRNBACH: Dr. Cassiere?

DR. CASSIERE: My positive vote for this product was based upon the fact that the primary end point was clearly shown by the company. And also given the fact that there really is no adequate therapies for air leaks post thoracic surgery, I'm confident that the safety profile will bear out with the post marketing set up that we have.

DR. BIRNBACH: Dr. Stoller?

DR. STOLLER: I voted for based on again the great promise of the product. I think that the sponsor needs to be given credit for having satisfied the agreed upon primary outcome measure, but I would argue that in some ways the primary outcome measure and the design of ascertaining it is less than ideal.

In fact, were I to do this recognizing that the retrospectoscope is 20/20. I would insist on blinded ascertainment of the outcome. I would do it

in a time dependent manner, and I would have independent radiographic ascertainment of all films in a blinded way over time so that one could really sink one's teeth into the efficacy of the primary outcomes.

So my vote is yes. My level of confidence in the yesness is rather low.

DR. BIRNBACH: Dr. Lillard?

DR. LILLARD: My vote in favor was based on the fact that the -- I felt the sponsor addressed or proved the primary end point of effectiveness. While this initial study hadn't been powered for determining the complete safety, I think the relative safety questions we have, we address with post markets.

DR. BIRNBACH: Dr. Topoleski?

DR. TOPOLESKI: I voted yes because I was convinced by the sponsor that the product had an affect on reducing air leaks. I had a small concern that we know very little about how the strength or the adhesiveness and

thereby the effectiveness degrades. But I'm sure that the sponsor would recognize that that would be valuable data to produce in the future.

DR. BIRNBACH: Dr. Normand?

DR. NORMAND: I voted no, and the reason why voted no were probably the reasons listed by my colleague down the row. And that relates to A, the lack of blinding of the primary end point introduces such bias into the -- to that particular end point. Even though that's the way it was designed, the fact of the matter is it's biased, and so it's very -- poses lots of difficulties interpreting the primary end point.

From a statistical standpoint, whether the primary end point was met or not is questionable. I worry when my colleagues see a P value of .005 and think that it's been shown and get you P value for anything. We just have to make sure it's the right tests, so I'm worried about that.

I think that we didn't see any benefit in lengths of stay based on sort of the correctly done statistical analysis. But I think that primarily summing it all up, it seemed to me that the efficacy did not outweigh the potential safety concerns. And by that, I mean we're introducing a gel into a patient's body. Now we have the potential for air leaks that never in the past had been treated, to now be treated.

I don't know if that's a good thing by the way. And so the efficacy end point wasn't reached in sufficient, in my mind, to outweigh the potential harms and the unknowns. And I based -- my assessment is based on the data presented and not necessarily on any hopefulness that I may have.

DR. BIRNBACH: And our Industry and Consumer Representatives, if you'd like to give your opinions? Dr. Spindell?

DR. SPINDELL: No comment.

DR. BIRNBACH: And Ms. Petersen?

MS. PETERSEN: I would recognize the desire to do something about air leaks, that it is a great concern of thoracic surgeons and also of patients. I think we have seen some positive indications in the data that was presented today, although like many panel members, I have some concerns about some of the secondary end points, and also about the statistical analysis and the blinding.

I hope that as the FDA goes forward in looking at ways to get the product to be approvable, that there is attention paid to the use of the quantity administered to patients as we learn more about the product to ensure consumer safety.

DR. BIRNBACH: At this -- I'd like to take this opportunity now to thank the panel, the FDA and the sponsor. Mr. Melkerson, is there anything the FDA would like to add?

MR. MELKERSON: I'd would just add I'd like to thank the sponsor on their

presentation, as well as the staff for putting their time and effort, as well as your time and effort to come here. Thank you very much.

DR. BIRNBACH: The June 12th, 2008 meeting of the Anesthesiology and Respiratory Therapy Devices Panel is now adjourned. Thank you all.

(Whereupon, the above-entitled matter went off the record at 4:41 p.m.)