Incomplete lung secured between one month in the sealant patient is unknown and adverse events of renal etiology occurred in five percent more sealant patients than in control, as has been described.

This completes the FDA presentation of this pre-market application. Thank you for your attention. We look forward to your comments. Now, it's my pleasure to introduce to you, Dr. Cara Krulewitch who will present potential post-marketing issues for you to consider if a case A post-marketing study may be suggested.

DR. KRULEWITCH: The joys of technology. Thank you. Good morning. As Dr. Marinac-Dabic noted earlier, as of 2005, all new PMA submissions include epidemiologic input.

Since this PMA was submitted prior to 2005, we slightly deviated from that procedure and the sponsor has not submitted a post-approval protocol as part of the PMA

submission, and an epidemiologist, as you noted on the list, was not included in the PMA review Panel.

However, should a decision be made that a post-approval study is recommended, we have prepared a number of questions for the Panel consideration and we will provide input into development of the post-approval study.

Additionally, just to remind you that the discussion of post-approval studies prior to a formal recommendation as a recommendation on the approvability of the PMA should not be interpreted to mean that FDA is suggesting the Panel find the device approvable.

The plan to conduct a post-approval study does not decrease the threshold of evidence required to find the device approvable and the post-market data submitted to the agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order

for the device to be found approvable.

Just a little about the general principles for post-approval studies. As we know, pre-market clinical data are collected from patients that are highly selected and treated by the best trained physicians.

In contrast, when a device is permitted to be on the market, patients that received the device are less restricted and physicians who treat these patients are not limited to the best trained physicians.

Additionally, some rare adverse events that were not observed pre-market might present in the post-market phase as the observation period extends and patient populations broaden.

Therefore, the main objectives of conducting post-approval study is to evaluate device performance and potential device related problems in a broader population over an extended period of time after pre-market establishment of reasonable device safety and

effectiveness.

However, post-approval study should not be used to evaluate unresolved issues from the pre-market phase that are important to the initial establishment of device safety and effectiveness.

The reasons for conducting post-approval studies are to gather longer term post-performance -- longer term performance of the device, data on how the device performs in a broader patient population where treated by average physicians, as opposed to highly selected patients treated by leading physicians and clinical trials.

Post-approval studies are also needed to evaluate the effectiveness of training programs for the uses of devices. Evaluation of device performance in sub-groups of patients, since clinical trials tend to have limited numbers of patients, which may not include all sub-groups of the general patient population.

In addition, post-approval studies are needed to gather real world experience and monitor adverse events, especially rare adverse events that are now observed in the clinical trials.

Another reason for post-approval studies is to address issues and concerns that Panel members may raise on their experiences and observations.

This concludes the FDA presentation. Thank you.

CHAIR BIRNBACH: Thank you. I'd like to thank the FDA speakers for their presentations. Does anyone on the Panel have any questions for the FDA, and remember, you may also ask the FDA questions later and the questions should only go to the FDA at this time. Dr. Normand.

DR. NORMAND: I have a question for the FDA statistician, Dr. Lao. I have a question with regard to the finding that -- just clarification more or less, I think.

In figure one, slide 51, you have indicated that probability of chest tube removal, there's no statistical difference using sort of that Kaplan-Meier analysis.

However, the primary endpoint, effectiveness endpoint, efficacy endpoint is looking at no air leak and there, we do find a statistical difference and my understanding -- and this is where I want the clarification.

My understanding is the primary efficacy endpoint is basically measured at one month follow up, so time isn't taken into consideration. Is that correct?

DR. LAO: Primary endpoint at the one month follow up or at the time the patient was discharged, depending on which one was longer.

DR. NORMAND: Okay. So it looks like you -- is it fair to say, you would get a different conclusion if you used a Kaplan-Meier analysis versus if you use the endpoint of air leak free, yes or no?

DR. LAO: Well, the Kaplan-Meier analysis included all the patients, one to three patients versus 58 patients.

DR. NORMAND: But the question really is, do you get a different conclusion? I realize you're including all the patients and using some sensory mechanism and what not, but is it fair to say, if I interpret the data, slide 51 says you don't get any benefit whereas the binary endpoint analysis, granted they're including different patients, but you would get a conclusion that says it was clinically efficacious?

DR. LAO: Well, you ask for the Kaplan-Meier analysis, Kaplan-Meier analysis included all the randomized patients.

DR. NORMAND: I realize that, but just very succinctly, and perhaps I'm not being clear, do you get two different conclusions if you use a Kaplan-Meier -- based on what you've presented, get a different conclusion, based on a Kaplan-Meier analysis

versus the binary endpoint, and I understand --

DR. LAO: Yes.

DR. NORMAND: Yes, you get a different conclusion?

DR. LAO: Yes.

DR. NORMAND: Thank you.

CHAIR BIRNBACH: Dr. LoCicero.

DR. LOCICERO: A question for Dr. Durfor. Looking at the animal studies, the wound healing in pigs, as you analyzed this, this was sealant placed over a staple line and we have, in the clinical study, sealant over staple line and sealant over no staple line.

Going to the animal study though, is there a way to separate the effect of the staples from the effect of the sealant?

DR. DURFOR: In what respect?

DR. LOCICERO: In respect to the -- if we saw a staple line with no sealant, is there a difference from the staple line with sealant? In other words, was that in the

study?

DR. DURFOR: Okay, yes, there were -- each of the pigs had seven surgical sites and five of the sites were closed with staples followed by sealant, one site was closed with just staples and one had sealant put into the wound, closed up and then staple and then sealant, to sort of simulate a sealant trapped inside a wound.

My interpretation of the reports -- and actually, I would welcome Dr. Parks' comment as well, but my interpretation of what I've seen from the pathology reports was that if one looks at the tracings of sealant at day one, when it was clear where it was, that it looked like the sealant had pretty much covered all of those sites.

So it may not be easy to say -- to take a value and say what does the histopathology look like at a staple only site versus a staple site covered by sealant? That was my reading of the pathology report.

If Dr. Parks wants to say otherwise, I would be happy to hear his comment.

DR. PARKS: I agree with that. I think it was difficult to separate that out where the staple was placed. We found areas of atelectasis as a consequence of mechanical compression.

At the point where the sealant was placed, it was -- we could find the sealant. The response to the sealant, with respect to fibrosis, was no different than what we saw with the staple.

So I would say that the response to the sealant, where it was mechanically distant from the staple, could be distinguished, but in areas where the staple was present, those areas underwent mechanical compression and fibrosis, as we would have anticipated.

CHAIR BIRNBACH: Dr. Spindell.

DR. SPINDELL: Yes, this is -- I apologize, Dr. Horbowyj, on slide 71, if you

could -- I understand these are concerns we're going to be speaking about later on. Were any of these issues reached with statistical significance? That was the summary slide.

DR. HORBOWYJ: All of the issues we saw on the summary slide may not have been actually evaluated statistically because they were small sample sizes, so we do not necessarily evaluate all of them for statistical significance.

Those that were, I think were not, but we don't again, look at that that way because the study was empowered to six sealant. So the evaluation in the statistical significance may be misleading, if it's not statistically significant. If it were statistically significant, it may have value.

CHAIR BIRNBACH: Dr. Topoleski.

DR. TOPOLESKI: Thank you. I was looking at the data you presented and there seems to be a time dependent decrease in the incident of air leak free patients, which

suggests something about -- potentially, about the strength and the time dependent behavior of the material.

Were you able to evaluate or did you have any data on either the time dependent strength of the material, the time dependent adhesive strength of the material or a cyclic or fatigue loading of the material that would simulate the in vivo environment?

DR. DURFOR: I think the quick answer is probably no. It's a very difficult environment to simulate. The studies that we have that looked at resorption, I've tried to give you that sense, in terms of what was done in pigs and the histopathology that went with it.

There was also an in vitro study where essentially, the disks were made up of the material, placed in a solution that was physiologically relevant. That certainly doesn't give you the stress and the strain of a lung or anything like that, and in that case

-- and I believe Dr. Parks discussed that, that the disks essentially resorb somewhere between seven and 14 days.

So in terms of the data and in terms of the mechanical strength of the product, it's a function of time during resorption, I don't believe we have those data.

CHAIR BIRNBACH: Dr. Loeb.

DR. LOEB: I'd just like to have people maybe look at slide 34 that was presented by the FDA, about intra-operative parameters in contrast to slide 52, presented by the sponsor of the same thing of procedures, and it points out -- it's sort of a follow up of what I asked before, about the magnitude of the surgeries potentially being different between the two groups.

The way the slides are set up is, I guess something that is increasing my confusion about it because the sponsor sort of -- the sponsor grouped together bi-lobectomy,

lobectomy with a segment and a lobectomy with wedges and multiple wedges, as indicating larger surgeries.

Whereas, on the FDA slide and the way I'd seen the data presented before, the -- it looks like bi-lobectomy and lobectomy are bigger procedures, and then the group of things at the bottom look like smaller procedures.

I believe I heard it stated during the FDA presentation that the amount of tissue removed was not something that was measured and that seems to be the indication of why there can't be an analysis that looks at the magnitude of a surgical procedure as impacting some of the late complications, not necessarily complications, but the later findings of residual volumes and air leaks.

So sort of an open-ended question, is there any potential for doing a subsequent analysis? Do we just not have the data or are there a number of ways of looking at the

surgery that was done, that again, precludes further analysis?

DR. DURFOR: Could you clarify, is that question to FDA or is that a question for Panel discussion?

DR. LOEB: It's for the FDA.

DR. HORBOWYJ: The idea to group the different procedures was recently brought up by the sponsor and when we looked at this, one of the questions that comes up is whereas -- and that anatomically, so by extent of surgery, it's possible to envision what a bi-lobectomy and a lobectomy may encompass.

However, specifically, segmentectomies and wedgectomies, I think, present an issue because we don't know necessarily how much tissue is removed and how to go back and get a quantitative amount to know that a segmentectomy performed in any given patient, whether they were in control or if they were in the sealant group, were comparable and then to then translate that

into an interpretation of the chest x-rays, I think is complicated and I don't know how true that would be.

The same issue comes to wedgectomies, where wedgectomies can be very small, wedgectomies can be pretty large, and multiple wedgectomies, if they're from the same part of the lung or different parts of the lung, depending on their anatomy of the lung and how that impacts the lung re-expansion I think also can be different and knowing how they were done per given patient and comparing patient to patient, comparing patients in one group compared to the other, and then translating that into chest x-ray review, I think without a prospective plan for which data is collected and a way of assessing it, so that we have some kind of way to normalize the data to have it on a common base line, I think presents an analytical dimension that I think we don't know how to address right at this point.

So we're always welcome to look at all sorts of analysis, but I think that should be considered, as to what the clinical meaning of that is and the clinical translation of that into the chest x-ray reports.

CHAIR BIRNBACH: While you're there, I have a quick follow up question to that. I'm sure I misunderstood something this morning from the sponsor, but when you go back to slide 32 of yours, there is no difference in, albeit by surrogate measures, how sick the patients were in any other group or whether they had had previous surgery, thoracic surgery, correct?

DR. HORBOWYJ: I'm sorry, can you say that again?

CHAIR BIRNBACH: When you look at your slide 32 --

DR. HORBOWYJ: Yes, which is directly from the PMA.

CHAIR BIRNBACH: Correct, there is no difference between the two groups in the

previous number of surgeries that had occurred or how sick the patients were in either group.

DR. HORBOWYJ: Previous thoracic surgery is listed five from below.

CHAIR BIRNBACH: Fourteen(point)six percent versus 17.2 percent.

DR. HORBOWYJ: So it's 14.7 percent versus 17.2 percent, it's three percent, however you wish to interpret that.

CHAIR BIRNBACH: And not statistically?

DR. HORBOWYJ: Correct, none of these were statistically different, including COPD, including chemotherapy use. There's a little bit of a difference for steroid use and clinically judging, they seem to be comparable to my assessment.

CHAIR BIRNBACH: Are there any other questions? Dr. Stoller.

DR. STOLLER: My question regards the independent radiologic assessment at one month, I guess slide 64.

Two questions, one, were there any statistics on these ratios, suggesting that there is an 11 percent excess of non-complete lung expansion in the sealant group compared to the other?

DR. HORBOWYJ: I can get that information for you.

DR. STOLLER: Okay.

DR. HORBOWYJ: Again, however, because these studies are not powered --

DR. STOLLER: I understand, right.

DR. HORBOWYJ: -- we tend not to --

DR. STOLLER: Fair enough. The second question is, obviously, a decision was made about doing an incomplete sample of the independent radiologic assessment. This end is 149 as opposed to 161, and I guess I'm wondering, in the remaining 12 patients, is there any other reason to think that those 12 patients not included are somehow different in characteristics than the 149 that were evaluated?

In other words, if we had a complete independent radiologic assessment of the 161, would that look different? Is there some reason to think it would look different than the assessment that we're looking at here?

DR. HORBOWYJ: I don't know that we know. We tried to arrange the studies so that the sample would be representative of the cohort, so we chose very carefully with the sponsor, sites that were largely -- could have a representative sample and not just one center. So we went across three centers.

We really -- we know the burden that this presents to a sponsor, so we tried very much to be reasonable and we tried to make up for the small amount of the partial patients, by being very careful in how assessments were made.

There did seem to be a disparity in this group of patients with right upper lobe resection, compared to the overall cohort.

Now, whether or not that then -- how much of this translates to the overall cohort isn't really clear.

However, in the overall cohort, there was no real difference between those rates, so then you would think that perhaps the finding that was in the overall cohort was the same or maybe even would have been larger if we had done this assessment this way.

So unfortunately, even though we tried to answer this question, to lay this to rest, it didn't answer the question and the question, so far, remains this way.

CHAIR BIRNBACH: Dr. Jeevanandam.

DR. JEEVANANDAM: I just want to refer to, again, slide 71. Interesting, the study shows that the sealant stops the air leaks early, and that's why you have the big difference early on, in terms of the disappearance of the air leaks.

But then, I guess this is following up over 30 days and there are two things.

First of all, although the pneumothorax incidence was the same, more people with the sealants required therapy for their pneumothorax and then if you look at incomplete lung expansion, there were more patients in the sealant group that had incomplete lung expansion.

Do you think that could be an effect of the sealant itself, since the sealant, at least in pigs, seems to disappear in 14 days, do we think we have an initial effect and then, the sealant is disappearing and perhaps, these pneumothoraces that need to be treated or these incomplete lung expansions are occurring in the sealant group?

DR. HORBOWYJ: If I may, I think this is why we would like to have you discuss these issues.

DR. JEEVANANDAM: Okay.

DR. HORBOWYJ: I don't know if it's appropriate for me to give a comment this way or if it's more appropriate for you to discuss

--

DR. JEEVANANDAM: Do we discuss this now or do we discuss this later when we have our --

CHAIR BIRNBACH: We discuss this later. Are there any other questions for the FDA at this point? Dr. Domino.

DR. DOMINO: On slide 69, we were discussing deaths, and you mentioned that there are -- or pointed out that there are three cases of ARDS, multi-organ system failure, at least in two of them in the sealant group and no cases of ARDS in the other group.

Is there a physiologic mechanism for why there might be the difference, other than patient differences? Is there something that the sealant could do, set up a hypersensitivity response or anything that might contribute to this, from what we heard before, there were all kind of patient problems, unrelated to the sealant.

DR. HORBOWYJ: Okay, I'm not sure that it's appropriate for me to answer. I think this is part of why we have the questions to you, to discuss amongst yourself and amongst the questions that we were asking.

CHAIR BIRNBACH: Dr. Normand.

DR. NORMAND: Yes, I had a question regarding to where patients went after they were discharged. So were all patients discharged home or did some patients get discharged to another facility?

DR. HORBOWYJ: It is my understanding -- I can go back to the PMA and see if we have that level of detail, but most patients went home. But I don't know that -- I'd have to see if that level of detail, we actually have in the PMA.

DR. NORMAND: Because it would be important if someone was trying to -- you know, if let's say, length of stay was reduced, then we really want to know the whole period of care. You wouldn't want to

discharge them to another facility and not count that. So that's why I'm asking.

DR. HORBOWYJ: Okay, we can try to see if we have that level of detail.

CHAIR BIRNBACH: Dr. Stoller.

DR. STOLLER: One question, again, in follow up regarding the ARDS attribution, and I'm looking at the sponsor's slide 77 versus the FDA slide 69, and if I'm reading this right, in the review of control deaths, ARDS is listed actually in three of the four control deaths and yet, in the FDA's attribution of death, there is no mention of ARDS in the control group.

So I wonder where the truth lies, with regard to the prevalence of ARDS.

DR. HORBOWYJ: We listed the etiologies as they were presented to us and these were the causes of death that were considered to be the prime causes of death and that's how they were listed.

DR. STOLLER: So I guess my follow

up question really regards whether it happened or not and how we would know that, as a committee, because I'm looking at the scored reporting of the prevalence of ARDS. So I need some help in clarifying that.

MR. MELKERSON: May I suggest the sponsor identify where, in the PMA, their information was? I believe Dr. Horbowyj was describing, this is the information that we're aware of. If there's other information that we're not, I think that would answer the question.

DR. HORBOWYJ: It's also the case that how people presented the prime etiology of what was considered death and the composition.

I understand your concern. I'll try to confirm that afterwards.

DR. STOLLER: So a follow up question. Is there any independent review of charts, independent of the sponsor, with regard to the occurrence of ARDS cause of

death, death review committee, that sort of thing? I gather that was not part of the study design and therefore, independently assessed attribution of death is not available, is that correct?

DR. HORBOWYJ: Independent assessment of death, I don't believe there was independent assessment of death, but there were summaries of -- describing the patients who died.

CHAIR BIRNBACH: Are there any other Panel questions? Yes, Dr. Loeb.

DR. LOEB: I'd like to follow up on a point that was brought up earlier and it sort of pertains also to what Dr. Stoller was just speaking about, and that is, I just want to make sure I understanding comparing your slide 64 to 65, one, showing the incidents of incomplete or complete or incomplete lung expansion, as submitted by the investigators for 149 patients, which I assume is a reading of a chest radiograph, that there was in the

control group, 22 percent incomplete expansion and in the treatment group, 33 percent incomplete expansion, as compared with your independent radiologic survey of 59 patients, where there were zero, no incomplete expansions in the control group and 17 percent in the sealant group. Am I reading that correctly?

DR. HORBOWYJ: If I could just summarize your comments, you're comparing the incomplete chest x-ray expansion at one month from slide 64, the 11 percent difference being higher at -- for the sealant group and 22 percent occurring in the control group, compared to zero occurring in the sample of 59 patients?

You're comparing basically 22 percent and zero percent? That's a function of the sample selection and that is part of the quandary, the question that had been posed, is how well does this sample represent the other, if we looked at the whole group,

would we find different answers? Potentially, you would because there is this discordance.

DR. LOEB: Just as a follow up, did -- in your group, you knew which patient -- is there any way to know that your radiologists were getting basically the same answers? It's just very confusing.

DR. HORBOWYJ: I should --

DR. LOEB: It's very confusing to me that 22 percent, that 12 patients in the control group, 12 out of 149, have incomplete expansion in all of the patients versus zero out of -- well, I don't know the sizes of the two different groups.

But anyway, that you had no patients with incomplete re-expansion by your radiographic readings versus --

DR. HORBOWYJ: These were not our radiographic reasons. The sponsor conducted this study. We simply worked with the sponsor, as to the design. The sponsor chose the patients, the sponsor chose the

radiologist, the sponsor actually progressed with this --- designed the case report forms in conjunction with us. We spoke.

The sponsor carried out the study. The sponsor analyzed the data and presented the data to us.

DR. NORMAND: Which slide are you referring to, just so I could follow along?

DR. LOEB: Slide 64 and 65 of this last presentation. So there were 20 patients in the -- there were 53 control patients initially, 12 of whom had an incomplete re-expansion and in the subsequent analysis, there were 20 patients, none of whom had an incomplete re-expansion.

DR. HORBOWYJ: Right, and as you see, they didn't define chest x-rays, perhaps for all patients. So that's why the data is presented that way. They did the best they could, as far as we understand, to find all x-rays for all patients.

So the data is presented very

straight with numbers for that reason.

DR. LOEB: Thank you.

DR. HORBOWYJ: And it's understood that 17 percent is a large percentage, but on a small number of patients.

DR. JEEVANANDAM: Again, going back to slide 64 and 65, it seems like 64 is on all patients and 65 is on a randomly selected group of only 59 out of 161 patients.

Did they do that sub-analysis because you -- why did they do that sub-analysis?

DR. HORBOWYJ: In the initial review, the PMA --

DR. JEFFANANDAM: Were they requested to do it or were they just worried about the data?

DR. HORBOWYJ: In the initial review of the PMA, we came across this finding of 33 percent sealant group and 22 percent control patients have an incomplete lung expansion. That raised a question to us, as to why this

difference and in an attempt to try to understand this difference, to understand its impact, does it go across cohort and what kind of adverse events may be associated with it, we asked -- and potentially, if there could be bias.

We asked that we have -- that an independent assessment be re-done to try to reconfirm the results or maybe find that they weren't that way, so since review of all of the chest x-rays seemed to be burdensome and that all x-rays seemed even to be accessible for such review, the agreement was to review 60 of the total cohort.

DR. JEEANANDAM: And then the numbers got even worse.

CHAIR BIRNBACH: Are there any other comments for the FDA?

(No audible response.)

CHAIR BIRNBACH: Thank you. Given that there are no more comments, it's currently about 12:10 p.m. We will now break

for lunch. We will reconvene in this room in one hour at 1:10 p.m.

Please take any personal belongings you may want with you at this time. The ballroom will be secured by FDA staff during the lunch break. You will not be allowed back into this room until we reconvene in one hour.

I'd like to again remind the Panel members there should be no discussion of the PMA during the break among yourselves, with the sponsor, the FDA or with the public. We'll see you in one hour.

(Whereupon, the above-entitled matter went off the record at 12:10 p.m. and resumed at 1:18 p.m.)

DR. BIRNBACH: Welcome back. We're going to get started now. Before we proceed with the panel of discussion, I would like to ask the sponsor to come forward and address any of the detailed issues raised during the morning session that the sponsor has been asked to address after the lunch break.

MR. MELKERSON: Panel chair?

DR. WALSH: Thank you for the opportunity to come back and say a few things after the discussion this morning. It still seems an issue in trying to understand for the panel the difference between a completely expanded lung, incompletely expanded lung and other.

In the original report, in the original report in 3M, and as it was designed, the investigators had three boxes that you could tick off: fully expanded, lung partially expanded within normal limits for post operative thoracotomy, and other.

So the second category, which is the one that's confusion -- confusing for everyone is the one that is really where the thoracic surgeon judgment comes into play.

If you've had a lobectomy, and there's no air leak, there's an expectation in virtually all lobectomy patients that you're going to have a residual pleural space. So on

this form, when that was deemed to be appropriate by the thoracic surgeon, that part was clicked off.

When it came to analyzing the reports by the FDA, this report raised a concern by the FDA because you can see 33 percent of the patients in the sealant group, and 22.6 percent in the control group were listed as partial, although that would be normal partial expansion based on that -- on our study.

Nevertheless, this prompted a review of partial, and what does partial mean? And we can see of the 32 partial sealant patients versus the 12 partial control patients, when we look at the AEs related to incomplete lung expansion, again this is a radiographic appearance, you can see in fact that the complication rate was less in the sealant group than the control group, again pointing to the clinical acumen of the thoracic surgeons that we know when you have a

residual pleural space with no air in the chest tube, that is of no clinical significance.

And again, when we looked at these patients' length of stay, versus controlled partial length of stay, again the sealant partial expansion did not result in a longer hospital stay versus control. The sealant partial expansion did not result in a lower rate of air leak free one-month analysis versus control.

When the FDA then asked for a independent review of 60 patients, these were pulled out, 40 in the sealant group, 20 in the control group. We see that there were six patients identified with partial lung expansion on the 40 patients in the sealant group.

Of those, all of them at the one-month follow up had in fact shrinking residual airspaces as we would expect the normal post-operative expansion of these lungs. Only

therefore one patient of the 40 randomly selected actually had an increasing airspace. And this was in a patient who had had a bilobectomy, right upper and right middle lobe.

We also see in the selection of these 40 patients that we are -- that they were -- it just happened that they picked out more patients who had right upper lobe resections in the sealant group. So that even compounds it a little bit more.

But the bottom line is only one out of the 40 sealant patients ended up having to require treatment for an expanding residual pleural space.

So again, in summary, there is a clinical benefit to this product. Air leaks make a big difference. We cannot solely rely on chest tube output, or chest tube length of stay of the chest tube as the end point, because that is not how this study was powered. There are a lot of other things that

come out of the chest tube: pleural fluid, chyle, lymphatic drainage.

So even if you had a completely sealed air leak at day one would not necessarily imply that the chest tube would be removed. We know as well that even with a sealant across the centers, there was a decrease in length of hospital stay, and in fact when we look at it, the incidence of adverse events as far as pneumonia as compared to controlled, and quite frankly deaths in the sealant group were less.

This is a product that we desperately need as thoracic surgeons to help us take care of these patients. Thank you.

There's more slides? Okay, more slides. Again, length of stay, as you can see, median, mean, both significant reductions in the sealant group. And again, one of the problems when doing studies is that you're dependent on who fills out the death certificate, because this is a point that was

raised.

And clearly when we look at the deaths in the sealant group, there were -- the percentage of deaths because of the larger number of patients were less. When you look at the control group deaths, we can see that there was ARDS obviously listed and pulmonary complications in the sealants. But when we do a better analysis and look at the deaths in the control group, you can see that three out of the four patients also had a pulmonary complication associated with the deaths.

There's only one patient in the control who looks like they had a predominately cardiac death. But everyone throughout the study, they were dying of the usual sort of things that these patients die of after major pulmonary receptions: multi-system organ failure, death. Thank you.

DR. BIRNBACH: Thank you. Mr. Melkerson?

MR. MELKERSON: Just FDA has a

couple clarifications first from Dr. Chang, and then a follow up. You had asked about the deaths, and I think Dr. Horbowyj has a clarification on where that information we've posted was from.

DR. BIRNBACH: Thank you.

DR. LAO: I want to clarify my answer to Dr. Normand's question. I'm very sorry, I misunderstood your question. Question is at the ratio of chest tubal, poor, is that you're a Kaplan-Meier survivor and it's time to event. But the primary efficacy end point purely was based on the binary outcome, proportion of the post operative air leak sealed or not sealed in the binary article. Not related to the time after air leak sealed.

So I made my review the time to event Kaplan-Meier analysis for the primary efficacy end point. Did I answer your question?

DR. BIRNBACH: Yes, go.

DR. NORMAND: Yes and no. And I probably was the one who was confusing and not you, but here's the question. I understand one was a time to -- one was an event time analysis and one wasn't. One was a binary. But I think I want to make sure I understand that the outcome is exactly the same.

In other words, in one it's called no -- air leak free, and the other one is chest tube removal. Is -- are those two equivalent is the question? Because if that was the case, I just want to know what would be the equivalent of the time to event analysis on the primary outcome? That's what I had wanted to know.

DR. LAO: Yes, I didn't recall the link between the chest tube removal and the primary efficacy end point. And I clearly see the analysis.

DR. NORMAND: Okay.

DR. LAO: Try to link the two outcome together.

DR. NORMAND: Okay, okay. So thank you.

DR. LAO: Thank you.

DR. WALSH: Just want -- can I address that issue?

MR. MELKERSON: Yes, go ahead.

DR. WALSH: I think this is really important, that when an air leak is stopped is not equal to the same day as the chest tube comes out. And so the -- and the management of chest tubes is different, depending on the patient, different on the center, different about the amount of pleural drainage. You may have one patient who had a fairly bloody dissection, and the chest tube is sill draining fairly bloody fluid.

You do not pull out the chest tube until it turns into a nice serosanguinous output. So just because the air leak is over does not mean the chest tubes come out. Tubes are put for two reasons: one for air, one for fluid. And both of those depend on the

surgical judgment that the air leak is absolutely stopped, and the fluid drainage is at a level that we find acceptable.

DR. NORMAND: So I just -- I ,because it's a primary end point, I just sort of feel like I need to understand how it's measured. And so does that mean that your number of -- you count -- your primary efficacy end point is 01, whether all air leaks were stopped by a certain time point. My concern is the time points varying. It's not at 30 -- it's not one month for everybody.

But my question really is it's a 01 for whether the air leak -- all air leaks -- the patient is air leak free?

DR. WALSH: Correct.

DR. NORMAND: And it sounds to me like you are using multiple ways to determine that outcome. It's not just the fact how you determine that. Is it the chest tube is pulled, and therefore it's met? That's what I want to get a sense of.

DR. WALSH: No, no. Every morning, we were consistent. Every morning, the staff surgeon or their research nurse looked at the tubes and made an assessment whether there was an air leak. The patients are asked to perform standard maneuvers" valsalva maneuvers, cough, make sure that the tube tidals well, and make sure the system is patent.

And after repeated coughing, valsalvas, there's no air bubbling out of the chest tube, and the air leak is stopped. And that's the time of air leak stop.

DR. NORMAND: So that means -- if I could -- I'll say one more thing, and I know you're getting tired of me. So that means at -- in theory, this didn't happen because of follow up times differing a bit. But in theory, once that happened, you would say therefore the patient -- let's say -- suppose that happened at day 12 post surgery.

You say, "Okay, it's done." That

means therefore the outcome for that patient is a success, as defined by within -- by 30 days?

DR. WALSH: No, no.

DR. NORMAND: So that's the --

DR. WALSH: No, this is the remarkable thing about this product that you can see. Even with the best surgeons in the country doing these procedures, with attention to meticulous dissection of the hilum, only 14 percent of the time can we have a patient who actually makes it to the recovery room with a no air leaks.

So over 80 percent of the patients will have an air leak. What is remarkable here is 35 percent of the patients from the recovery room to one month have no issues with air leak, which is extraordinary.

DR. NORMAND: Thank you.

DR. BIRNBACH: We're now going to proceed to the panel discussion. I believe we already have, actually, so, I'm going to open

the floor to the panel members for questions either to the sponsor or the FDA. But first, Mr. Melkerson has a comment.

MR. MELKERSON: There was one more clarification. There was a question related to one of the tables related to death, and Dr. Horbowyj went back to find out where that information that we pulled --

DR. BIRNBACH: Great. Let's do that.

DR. HORBOWYJ: Dr. Durfor and I went back to our records in the PMA file to find the source of the death ideologies, which we presented to you. And we find them in amendment 6, the details on pages -- appendix 1 of amendment 6, pages 43 and 44. And the causes of death are as listed in our presentation.

We do not find for the control group any etiology of death being attributed to ARDS. There is, however, one contributing factor the way this table is set up, is that

it lists the patient number, the age, gender, day of death, device related cause of death contributing factors by reviewing investigator.

So what we listed was the cause of death. In the control group, there is under the contributing factors, our reviewing investigators one time listed ARDS. There is no listing in our -- in this presentation in the PMA of ARDS as a contributing factor etiology or cause of death itself.

And as cause of death in the sealant group, we do have three instances of ARDS reported, and we do have two instances of ARDS being reported with multi-system failure as a cause of death, not in the contributing factors by reviewing investigators.

Now, how those are mixed and matched I think can probably vary by opinion, but that's the way we were listing them in any case. For control, we do not have ARDS other than in the one contributing by the -- excuse

me. We do not have other patients listed, though. We do not have three control patients being listed in with ARDS.

DR. BIRNBACH: Thank you. Now, we'll open the floor to the panel members for questions either for the sponsor or for the FDA. Dr. Stoller?

DR. STOLLER: So this is in follow up to the slide Dr. Walsh showed, which may avail a little bit more clarity from my point of view. You made the statement that the slide you showed validated the thoracic surgeon's impression about air leak, and maybe I could ask you to revisit that. I'm still stuck on this.

I understand the difference. As a pulmonologist, I understand the difference between air leak and residual air. See it all the time. But I need clarification as to how your impression of that slide -- I just don't -- it went by too fast, validates the notion that a -- an unblinded review at one month

with regard to air leak secures the efficacy.

DR. WALSH: I think the big concern is, okay, you know you've applied the sealant and the patient does well. The -- you identified through your usual maneuvers every morning under the water seal component of the atrium drain that there's no bubbles.

We generally even wait another 24 hours after identifying there's no air leak and then pull the tube out. And you do an x-ray, and the lung is -- there's residual air space. So although that was on the original tick off form, which was developed for this study, it was a tick off to show that the lung was not completely -- there was still this residual space.

So that group is the partial, although that would be viewed as a normal patient for us, a normal finding. But if you look at the 20 patient -- I'm sorry, the 32 patients in the sealant group with partial lung expansion, let's say, we can see if we

dropped down and see if there's subsequent problems with adverse pulmonary vents identified in these patients: subcutaneous emphysema, pneumonia, dyspnea, pleural effusions, pneumothorax, compared to the partial lung expansion in the control group, that there's really no difference between the sealant and the control group.

Most of the complications that we see that develop are the usual pneumonias. Some people develop surgical emphysema, but that sometimes implies that the lung has stuck, and there may be some subcutaneous spread.

DR. STOLLER: And again, how are those -- in the column, the second from the left column, how are those ascertained? By the surgeon assessing the presence of a pneumothorax? How are they ascertained?

DR. WALSH: I believe that these are adverse events identified in that patient after, you know, the chest x-rays showing an

incomplete expansion, or a complete expansion, after the chest tube --

DR. STOLLER: So the definition of a pneumothorax would've been based on the surgeon's assessment of the presence or absence of a pneumothorax, assuming that there was an assessment of growth or non-growth of the residual air at the one-month follow up?

DR. WALSH: Correct, correct.

DR. STOLLER: That was not the independent radiologist's review of the subset?

DR. WALSH: No, that --

DR. STOLLER: At least by shown on the slide, correct?

DR. WALSH: No, this is our hard data. So, you know, once the chest tube is out, then the only way that we -- the ways that we have to assess the patient are obviously clinical assessment. How are they doing? Have they developed a cough? Have they developed fever? Have they developed a

new air fluid level in that residual space? And then at the follow up one-month, as that residual space increased in size, or have they developed a cough? Do they look unwell as you'd expect someone who is developing the affects of a bronchopleural fistula, or a, or an --

DR. STOLLER: So I'm imagining you're assessment of pneumothorax, for example, would be based on finding the surgeon's reviewing the x-ray at the one-month visit, assessing growth of the air space, and/or the presence of subcuemphysema or something of that sort? Is that how that pneumothorax gets classified that way on this table?

DR. WALSH: I believe so.

DR. STOLLER: Okay.

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

DR. LOCICERO: Two questions. Dr. Walsh, back to the slide before this, the

definition, and this goes to the FDA as well. The -- number two. This is a fact and a qualification. That was acceptable to the FDA?

DR. WALSH: Well, I believe that the original study, and someone from the 3M can correct me, but the original study was done in concert with the FDA. So this was part of the original tick off list.

DR. LOCICERO: This was a measurable event as an adverse event, with a qualifier?

DR. WALSH: No, it wasn't meant to be an adverse event. It was basically this is the assessment after the patient has had the tube removed. Lung completely expanded at the time of discharge or follow up, lung partially expanded. But felt to be the normal residual airspace that one might see after a right upper lobectomy, or bilobectomy, in the other.

So the other category would be the ones that really would be the ones that needed

to be investigated. But when this chart was -- came out and was reviewed by the FDA, obviously it raises a flag because of the partial group, which 33 percent in the sealant group, and 22.6 percent in the control.

So they say, "Well, you've got a problem there with partial expansion, although the complete and partial we would view that as 51 percent plus 33 percent; we would view that as over 84 percent normal post operative x-ray appearance of the patients." But because of that concern, that's why the company had to go back and do again independent x-ray evaluation.

But it was really designed to simply be a tick off box that we'd accept that this is normal post operative right upper lobectomy residual space that is going to take another six weeks to improve.

DR. LOCICERO: Okay, so it's not listed on your adverse event sheet?

DR. WALSH: No.

DR. LOCICERO: Okay. And to the death slide, am I interpreting this right that essentially 60 percent, between 50 and 60 percent of all of the partial expansions occurred in upper lobectomy patients?

DR. WALSH: Correct. And again, those of us thoracic surgeons know particularly the problems of right upper lobectomy and left -- specifically right upper lobe seem more difficult than left upper lobes, because the middle lobe and the lower lobe, it takes a while for the superior segment of the lower lobe to rotate to come up to fill the space, and for the middle lobe to expand.

You always have that little triangular residual air deficit or residual pleural space deficit after a right upper lobectomy.

DR. LOCICERO: Do you mean the horizontal fissure as opposed to the left side, which does not have a --

DR. WALSH: Correct, correct.

DR. LOCICERO: Okay, what other patients fit into this category? Do you know? Do you have any information on that?

DR. WALSH: In the partial -- do you have a list? Certainly we could get it but --

DR. LOCICERO: Thanks.

DR. BIRNBACH: Since the FDA has respond --

DR. WALSH: So it's basically all of the anatomic recessions are in the partial, not the wedges and segments. So it's the ones that were taking out a sizeable portion of lung in an anatomic setting. So it's going to take a while for the fissures to reorient.

DR. BIRNBACH: Does the sponsor have any comments to the FDA responses? Is there anything the sponsor would like to address as regards the FDA comments? There being none, we'll go back to the panel discussion. So does anyone on the panel have

any comments? Dr. Topoleski.

DR. TOPOLESKI: So my understanding of this material is that it really has no biological function. In other words, it doesn't have anything to speed wound healing, and it's sole biological function is to be non-toxic and not elicit an immune response, and to go away after some designed time. Therefore, its sole function is mechanical, right?

And so my question is maybe to both the FDA and to the sponsor, and to my clinical colleagues here on the panel: Would it change the way you manage the patient if you knew for example what the probability of failure or success, and let's call it success because that sounds better, if you knew the time evolution of the probability of success?

In other words, after one day it's 95 percent successful, or it has 95 percent of its ultimate strength; 90 percent after two days; 80 percent after three days. Or, are

you satisfied with just knowing that at time zero, as Dr. Cerofolio passionately said, "You know you can close the leak right away, but you don't care what happens afterwards."

DR. DURFOR: I don't mean to be rude, because I think it's an excellent question, but I think it's one of the reasons we assembled this group of experts here to give us that insight. And I think that with the number of well talented surgeons here, I think it's a great point for this panel to discuss.

DR. PARKS. Well, let me see. The original design specifications were to make it a mechanical sealant. It does nothing, according to our experiments, to delay healing. It does nothing to reduce healing in that regard. It does nothing to elicit immune response, but meets the design specifications.

As far as predictability, I'll let it to the clinicians. But I will add one comment that what we're looking at in this

setting is a dynamic situation. What we're looking at is the, on the one hand, the in growth of healing elements contributing a mechanical strength, and in addition to the sealant itself, and the process by which the sealant undergoes the solution.

And so it became difficult for us experimentally to do the type of experiment that you suggest, which is to find predictability as a function of time.

DR. CERFOLIO: And I can just say from a clinical standpoint that it'd be nice information, but it wouldn't change my management, which was your question. My management is going to be based on that patient's air leak on the chest tube.

So whether I'd say, "Oh, he maybe has a ten percent more likelihood having that leak sealed the next day, I'm going to manage him the same; I'm going to remove the tube as soon as I can when there's no air leak."

DR. WALSH: I'd say, you know, in

an ideal world if you had a product that worked 100 percent of the time and allowed sufficient time for the underlying lung parenchyma to heal to allow the lung to expand into the residual space, that would be perfect. But, you know, whatever air leaks we can control with these products is going to help us a lot more towards getting the tubes out, getting the tubes out faster.

So, I'd echo was Dr. Cerfolio said. This is -- any little help we can get is going to be important in managing these patients, especially in difficult to seal areas like the hilum, which it's difficult for that area to rotate, and sometimes contact the chest wall. That's how most lung leaks seal is with contact of the autogenous pulmonary tissue with other autogenous tissue: pericardium, diaphragm, pleura.

DR. LOEB: I would offer a different opinion about what was just said, in that I think it's going to be safer for your

patients if you have an air leak and watch it disappear, than to not have an air leak and manage the patient as if there's no potential for an air leak, and then have an air leak appear.

So I think from a clinical standpoint, it's a very important question, and the thing that I'm most concerned with in this whole package is the potential for late pneumothorax or late air leaks. To me, that's the crux of the matter. Does this potentially give the appearance that there's no problem, and then a problem appears later?

DR. TOPOLESKI: I just wanted to explain why I am -- or motivate that question. It's because we pretty much know the time strength relationship in resorbable sutures, for example. We can follow their strength as a function of time as they are dissolving in solution. So I was wondering if there was an analog with this particular material.

DR. BIRNBACH: Dr. Jeevanandam?

DR. JEEVANANDAM: You know, we come back to the chest tubes, and you say you want -- air leak cause the prolongation of chest tube placement. Well, your data has -- in terms of chest tubes has the same time duration of chest tubes. It's not different between control and patients who are treated. Then, you know, you have length of stay. Of course the length of stay is there, but you also have ten patients on a Heimlich valve who probably could've been discharged earlier because they had a Heimlich valve on the control -- on the treated group.

So I guess -- and we always talk about these air leaks being really bad. I think what you've shown is that with this device you can stop an air leak faster, or you maybe come out of the operating room, or the recovery room without an air leak, but the control patients remarkably stopped it early as well.

And these maybe take a little while

longer, but ultimately the chest tubes are coming out at the same time, so --

DR. SPINDELL: Just one -- I thought I saw a slide earlier where if you took the Heimlich patients out of the equation, the length of hospitalization was still shorter. And I -- do we have that slide, or was -- that was in the packet? I understand the concern, but I thought I saw a slide earlier --

DR. MILLER: And that is correct. When you took out the ten percent of patients who had a Heimlich valve, the hospital stay was still shorter than the control group. So it made no difference.

DR. BIRNBACH: Actually, Mr. Melkerson, do you want to comment now?

MR. MELKERSON: I believe that's the information that was not submitted as part of the PMA. So like I said, we haven't had a chance to evaluate it. So questions related to it should be directed in terms of what's the interpretation mean clinically, you know,

would help. But in terms of our evaluation, we had not seen that data presented that way.

DR. BIRNBACH: Thank you. Dr. Ries?

DR. RIES: My impression is very similar to Dr. Jeevanandam said about, you know the crux of issues and I think were actually very nicely summarized on the tables on the FDA handout, page 30, slides 59 and 60. Looking at the time of air leak and the time of chest tube removal, I'm convinced that the product does control air leaks in the operating room and in the immediate post-operative period. But the issue is what does that mean clinically?

And it seems to me the interpretation of the -- all the results is that the time to the cessation of the air leak, slide 59, is really no different in the early periods between the two groups. And in fact, if anything, the sealant patients actually there's a subset of actually wind up

with a prolonged air leak, and a prolonged chest tube related to whether it's an air leak or, I'm inclined to call it response.

I mean, basically what you have is a product that causes no difference in the clinical outcome when the chest tube comes out, or how long the air leak persists when the chest tube comes out. But those result in some prolonged chest tube insertion in a subset of patients.

Maybe I'm interpreting it wrong, but it seems to me this is the crux of the matter.

DR. CERFOLIO: I think I can answer that. One of the reasons that that's true is because you had ten patients who got the sealant get a Heimlich valve, and only one control that got it.

One of the reasons for that may be that the sealant made the leak small enough that the patient could get a Heimlich valve and go home, as opposed to in the control

group where the air leak maybe was too large. You put a Heimlich valve on, we all know you watch for a day. If the lung comes down you say, "You can't go home." You go back to suction.

So that may be one of the reasons for that. That's why we did an analysis without the Heimlich valves and showed a difference.

Finally, I got to drive home and come back to the point that the study was not designed to look at chest tube removal, because you have ten different surgeons that manage the chest tubes differently.

The end point of the study was specifically look at this freedom for air leak, and the study was positive in favor of the sealant.

DR. RIES: I would just go back to slide 59, where it looks like within this first six to eight days of surgery, about 85 percent of control patients had no air leak,

and 75 percent of the sealant patients had no air leak. So it seems to me that they're really not having a significant impact in that early post operative period in terms of cessation of the air leak or the removal of the chest tube.

DR. BIRNBACH: Dr. Normand?

DR. NORMAND: This goes back to the how you actually did your analysis for your primary efficacy end point. And I had asked for the distribution of the time at which the one month follow up was actually obtained. I didn't get that information.

I'm assuming that wasn't 30 -- 31 days for everybody. And as a consequence, using a binary endpoint would be inappropriate if that failure time, which we are seeing a pattern in -- well, let me call it survival, no air leak is differing as the panel members are pointing out.

And so I really need to see an analysis that uses or takes into account the

different durations of when a patient had their measurement taken. And so far, no one has told me the distribution of when the measurement was taken.

So was everybody assessed at 30 days? I doubt it. Were some people assessed at 25 days? So I just -- that's really important because you don't do a Cochran-Mantel-Haenszel test on that type of statistic, which would respond to Dr. Ries' comments about the distribution of time to air leak free freedom.

DR. CERFOLIO: Well, I think Dr. Walsh sort of showed that when he looked at -- if I can find the correct slide right here. Look at the bottom bullet of this. I think that this answers your question.

So the average time to the "one-month" follow up was shorter in the sealant group. What does that mean? It seems confusing. I understand. I was confused when I saw it, too, because one month is 30 days.

What we're saying there is --

DR. NORMAND: I'm not confused. I understand that. But go ahead.

DR. CERFOLIO: I was confused.

DR. NORMAND: Okay.

DR. CERFOLIO: To me, one month is 30 days. I don't care what group you're in. But the average time to one month follow up is shorter. That's probably because some of those patients went home on a Heimlich valve, and then they came back.

And so if you look at the actual follow up, you see it's significantly shorter in the sealant group, and that's probably why they had more space problems. Because we said it takes maybe six weeks for those space problems to go away, but we're seeing them a little sooner.

DR. NORMAND: Thank you. So this just is proving my point.

DR. BIRNBACH: Now you've got me confused.

DR. NORMAND: Yes.

DR. BIRNBACH: So patients 30 days are not necessarily seen 30 calendar days --

DR. NORMAND: No.

DR. BIRNBACH: -- after they leave the hospital? It could be --

DR. NORMAND: There's differential follow up.

DR. BIRNBACH: -- 42.8 days, is that correct?

DR. WALSH: Well, I can tell you when we were designing the study we made every effort to get it within the four to six week time frame. A lot of the centers, Mayo Clinic, M.D. Anderson, a lot of our patient population are from -- you travel long ways.

So sometimes, we have to see them at three weeks if they're traveling, and some of them at five weeks. So although we really try to get it and be consistent at the 30 days, you know, there's a slight variation there.

DR. NORMAND: So just to finish my question --

DR. HORBOWYJ: This slide represents the random cohort, not the whole cohort. So that follow up time is most likely calculated on either of these six patients, or part of the random cohort, and may not be really representative of the whole study population.

DR. NORMAND: So the -- sort of in terms of what the statistical community would strongly recommend when you have differential follow up time on patients is not to use a 01 end point at 30 days, because of differential follow up. And so I had just wanted to see for the intention treat cohort what that distribution was.

Now, apparently that's not it. But whatever it is, we need to see an analysis of the results for the intention to treat cohort to look at a time to use it, sort of as a survival analysis, because you have

differential follow ups. And so short of -- if I, sort of, see on average it being shorter for one group than another, then that's a bad thing. So that's just my concern in terms of the primary efficacy end point.

DR. LOCICERO: Okay, now I'm confused. All right, so you say one-month follow up. Is that from the time of operation, or the time from discharge?

DR. WALSH: From surgery.

DR. LOCICERO: Okay, we're saying a whole bunch of different things, because I just heard one of your investigators say 30 days after discharge.

DR. WALSH: Actually I --

DR. LOCICERO: Could you --

DR. WALSH: We do have the table here, table 4. We've found of the 103 sealant groups, the mean follow up was 41.5 days, plus or minus 14.4. The control group was 39.1 days, plus or minus 14.6, measured from the day of surgery. So usual length of stay is

approximately five to seven days, seven minus 41. So that's when that --

DR. LOCICERO: So it's one month after discharge?

DR. WALSH: No.

DR. LOCICERO: Thirty-nine days minus seven is close to 30. So what's your length of stay?

DR. WALSH: Your average length of stay is seven days -- six days.

DR. LOCICERO: Six to eight days, yes.

DR. WALSH: So it's 30 days from discharge. It looks -- the mean is 41.5 and 39.5 so it does look like it's 30 days if you take the five to seven day -- the median follow up for the sealant group is 41 days, 36 days for control. So plus or minus six days. So it's pretty close to the 30 days.

DR. BIRNBACH: Following up on Dr. Normand's question. I'll just ask a quick question. When the FDA asked you to look at

that subset group, and you picked 60 patients, how did you pick those? One person said that they were randomized. One person suggested they might not have been. So how did you get those patients?

DR. METZGER: Is that for the FDA or the sponsor?

DR. BIRNBACH: That's for you, the sponsor.

DR. METZGER: As I understand it, what happened is when FDA looked at the discrepancy or the difference between the sealant and the control group with regard to partial and complete lung expansion, they asked for a further analysis in part to answer the question, "Is there any investigator bias in the reading of the x-rays?"

And so went back to the sponsor. The sponsor went back to the investigational sites. What we found was of the five sites, three sites had digital x-rays, two head analog.

And so it was agreed for the sake of expediency and getting that study done, that the study, this subgroup analysis would be done at these three sites that had digital x-rays that could be forwarded to one blinded radiologist. And what they boiled it down to is they could find a pretty complete set of x-rays for 60 patients out of these three sites, 40 sealant, 20 control.

DR. BIRNBACH: But how did they pick those? Those were not all of the cases from those sites.

DR. METZGER: They were randomly --

DR. BIRNBACH: So was there some kind of randomization?

DR. METZGER: They were randomly picked out of those sites.

DR. BIRNBACH: And do you have any idea how they were randomly chosen? Just whichever files happened to be around, or?

DR. METZGER: Well, no. You know, at that point in time, it wasn't easy to get a

full set of x-rays for all of these patients, and they did the best job they could to come up with a complete set of x-rays for as many patients as they could. And what they settled on was 60 so that they could maintain a 2 to 1 randomized subset.

DR. BIRNBACH: Okay. Are there any -- go ahead.

DR. JEEVANANDAM: When you guys looked at that data, and then the 11 percent difference became 17 percent difference, did you think about trying to get all the x-rays re-analyzed? I mean it's -- the digital x-rays should be easy to retrieve, and the analog x-rays, yes, I know they're difficult, but they're not impossible to get. It's only another 40 patients.

DR. METZGER: Well, all right, again, the one point I meant to make was the purpose, the primary purpose of that subgroup analysis of these x-rays by the independent radiologist was to determine if there's any

bias by the investigator in the reading of the x-rays for or against the sealant of the control group.

The end result of that analysis was there was no bias by the investigator for or against either treatment group. It was only after an -- further analysis of some of that data, some of these other things popped up, and we started drilling down a little bit deeper and deeper into fewer and fewer patients, and this was what we wound up with.

DR. LOEB: But to follow up on that, how is that assessment made that there was no bias, given that the control group had a better outcome than was initially decided upon, you know, initially ranked, and the sealant group had a worse outcome? So if anything, that would confirm bias as far as I'm concerned. Yes, eleven percent -- I forget the numbers, but 11 percent went to zero percent in the control group, and 70-some percent went to 50-some percent in the sealant

group. DR. WALSH: Right. I think it was a little bit of a selection bias after that that it actually selected out as you see here a lot of the patients who had had the more anatomic recessions, the right upper lobes, the bilobectomies.

And also, in continuing to answer Dr. LoCicero's question as well, going back to the original study design, the follow up was four to six weeks post. So that's -- we try to give a little bit of leeway to deal with the travel schedules of patients, and, you know, those sort of things.

DR. NORMAND: Can I just -- it was planned four to six weeks. I just want to know the observed -- it's the observed actual assessments, the time of the observed assessments that really count, because of issues in --

DR. OST: Censoring. I just would be -- I would emphasize though, remember that these are normal readings, meaning in the

original, you know, six of 20 in this subset analysis, which is, you know, of the available x-rays. But remember the initial reading is lung partially expanded within normal limits.

So these are really not air leaks. They are not necessarily clinically significant. The primary outcome agreed on was air leaks. We do not have the Kaplan-Meier analysis. But remember that at the end of the day, 35 percent of the patients who got the sealant never developed an air leak from the moment of the recovery room.

And we do know that at the best, the group which had the control, if you look, started with 33 percent. So the survival curves, if you did survival analysis, don't cross.

Okay, so we know that one, the partially expanded is a normal thing as judged by thoracic surgeons; that partially expanded on this table is not associated with any higher incidence of respiratory adverse events

than fully expanded. That's what we know. And for the primary outcome of air leaks, there's a 21 percent difference at the binary at 30 days.

DR. BIRNBACH: Thank you. We're now going to focus our discussion on the FDA questions, and there'll be plenty of opportunity while doing that to discuss all the other issues that we have on the panel. So can we start with that process, please?

DR. DURFOR: Thank you. We'll go ahead and project the first question. As that's occurring, I just want to give you an oversight of our intention in these questions. The first two are our specific issues that have been discussed, and are focused.

Questions three and four, the language is a little stilted, but their intent is the following: They are an opportunity -- questions 3 and 4 will offer you an opportunity to comment on the overall safety and effectiveness profile of the product, and

the languages reflects the regulations that we operate under.

So the first two questions are specific questions about concerns. The first question states, "Pre-clinical data suggests that ProGEL Surgical Sealant clears rapidly from rats and pigs. For example, over 50 percent of a carbon 14 labeled device was excreted in 24 hours, and virtually all radioactivity was recovered from rats in 14 days after implantation."

"Sealant was also largely absent at four days with only isolated fragments of sealant apparent at seven days, after implantation in pig lungs."

"In the randomized 2 to 1 ratio controlled multi-center study, in which 103 patients were treated with ProGEL Surgical Sealant and 58 received control treatment, 32 or 33 percent of the ProGEL Lung Sealant, and 22 percent of the control patients had partial lung expansion at 30 days post surgery."

"In an independent radiologist assessment of chest x-rays from a subset of study subjects", and now this is not the entire subject, studies population, "the incidence of complete lung expansion in the recovery room was similar for both treatment groups: 72 percent for the sealant group, and 70 percent for control in this subset of patients."

"The incidence of complete lung expansion was 51 percent for ProGEL Surgical Sealant, compared to 40 percent for control patients on the day of chest tube removal. And 30 days post surgery, 100 percent of the control patients achieved complete lung expansion, compared to 30 of 36, or 83 percent of the sealant patient, plus the incidence of incomplete lung expansion in the sealant cohort was about 16 percent, 16.7 percent."

Now, in this sub-cohort, in this cohort, once again we show you the data in terms of what their readings were for these

six of 36 subjects in the cohort.

So we ask you as a committee to discuss the clinical significance of these pre-clinical and clinical findings, and their impact on the clinical safety and effectiveness of the device as an adjunct to standard care, compared to controlled. Thank you.

DR. BIRNBACH: So I'd like to open the discussion of the first question, which is regarding the clinical significance of the pre-clinical and clinical findings, and their impact on the clinical safety and effectiveness as compared to control. Anyone on the panel have any comments?

DR. JEEVANANDAM: Well, one of the things -- could you go to the slide before this, please? Okay, so if you looked at this group of patients, you had -- at 30-day follow up, I think the slide before this showed that 100 percent of the control group patients were expanded, and there were these six patients in

the sealant group that were not expanded, right?

So -- yes, if you can -- I guess my question is yes, it's normal to have some space after a lobectomy, but why is it that the control group is expanded and the treated group is not expanded? Is it possible that the treated group has some inflammatory response, or something that's preventing the lung from expanding completely? Because in the control group, they were expanded. It's a question. Who am I asking the question to? Us?

DR. BIRNBACH: Actually, the conversation is for us at this point --

DR. JEEVANANDAM: Okay, okay.

DR. BIRNBACH: -- rather than --

DR. JEEVANANDAM: Okay, I guess -- so, you know, is there an inflammatory reaction that's preventing this thing from expanding, number one, and I guess then we get back to the crux of the clinical realty of

this compound in that yes, if you have patients who have no air leaks, there's a statistically increased number of those patients who have been treated.

But, if you look at time to no air leak, again, this is the FDA's slide 59. Within four days, whether you're treated with sealant for control, there's the same number of people who don't have an air leak.

So I think this device works initially. The control group catches up within four days. And then potentially, you have some disturbing data that, at least in the control group, they have expanded and you don't have residuals at least in the slide we just saw, whereas we do have some residual space with the slide that's been treated, so.

DR. BIRNBACH: Dr. Loeb, how does that fit in with your question before about the late pneumorathoraxes, and whether you think that that's something that we should be worried about? Are the two related, do you

think?

DR. LOEB: Yes, I definitely think they're related, and it is interesting. We never saw any graph. We saw graphs for length of stay and chest tube, I think. We never saw a time graph of days versus percent of the people with this tie in to no air leak. It seems like we haven't seen all of the data there. But yes, I'm -- I absolutely agree, and I think that's -- it's troubling.

DR. BIRNBACH: So once again, since we're looking at "clinical safety and effectiveness," are there any comments about whether based on this preclinical and clinical data, we believe that there is in fact evidence of clinical safety and effectiveness? Dr. Wilcox?

DR. WILCOX: Not all. I was not going to address that. I was just going to address his question, and I believe, I won't put words in anyone's mouth. But I believe it was postulated that one reason might be that

because in the sealant group, the air leak quit sooner, that tubes may have been pulled sooner before there was full resolution of the air space or the space.

And so that might be an explanation as to this apparent difference in the two groups. Does that make sense?

DR. JEEVANANDAM: Although if you look at the next slide, FDA slide 60, time to chest tube removal is similar between both groups. So the chest tubes were pulled at the same time, or similar times. Although 12.6 percent of the sealant group had greater than 11 days because of the Heimlich valve. So maybe the Heimlich valve is causing the air space to exist as opposed to a chest tube with negative pressure.

DR. WILCOX: Possibly. And the fact that they were pulled at the same time in aggregate, but not in -- on the individual, and the individual case is --

DR. BIRNBACH: Can I take a chair's

prerogative and ask the FDA when you say that you want us to address the safety and effectiveness, would you be defining that based on the primary end point, or based on clinical practice?

Because as we heard this morning from several comments, if you stop an air leak on hour one, but at three weeks it's irrelevant or maybe even there's an increased risk of pneumothorax, that might define our discussion about effectiveness. So effectiveness as termed how?

DR. DURFOR: Thank you. It seems to me that it would be appropriate to ask you to comment on both. And I appreciate you being alert to that they may not be the same in terms of a primary end point, versus clinical practice. And I think that comment on the primary end point is appropriate, but one of the strengths of having a panel such as this is to draw upon your clinical practice.

DR. BIRNBACH: Dr. Spindell?

DR. SPINDELL: I just maybe the FDA can help clarify this. If my understanding is correct, the -- this safety and effectiveness, they're both part of this, but they're really separate discussions. And to my understanding the burden is to prove efficacy against its intended use and then safety. All right?

So if I read the intended use, the intended use is an adjunct to sealing or reducing air leaks. So my understanding would be that the burden on the manufacturer would be to prove efficacy in sealing and reducing air leaks as the efficacy part of it. And then some of the discussions we're having here really, to me, talk to the safety aspect, and how it's used in clinical practice.

MR. MELKERSON: The issue of safety and effectiveness, in other words, the FDA charged this to determine the relative safety and effectiveness for its intended use. So we don't separate safety and effectiveness into two categories. You have a primary end point:

the study met its primary end point.

The question -- since the study was powered for effectiveness, not for safety, these are issues that came up in what was studied. So the question of clinical significance here is are those clinical adverse event findings when you're looking at a risk benefit ration for this product, is it relatively safe and effective is looked at in total, and not as separate entities.

DR. BIRNBACH: Dr. Normand?

DR. NORMAND: I just wanted to follow up on Dr. Wilcox's last question, which was a while ago now. But in fact when you did do -- when FDA slide 51 actually shows that -- sort of the probability of chest tube removal by time is no different between the two groups. Not looking at the mean time, but looking -- doing a survival analysis, which actually shows there's no difference, and that would have included the Heimlich valve people that would've been censored appropriately.

And then I just want to -- again, this is related to the clinical effectiveness. I think at least in my mind, and perhaps I've also heard a little bit around the table, is to -- in order to sort of assess the validity or the clinical efficacy end point, I really think we needed to see a Kaplan-Meier analysis done of the time to air leak free because of the differential follow up time.

So at least in my mind, I'm not -- it's not necessarily clear to me that the end point was met. It was in the binary analysis. It's not necessarily true with the differential follow up time. So just so that everybody knows what it is, because although some people might've been measured on average 30 days, some were measured 14 days. Some were measured 44 days, and that's very, very important.

DR. RIES: I would just say we don't have the Kaplan-Meier, but table 59 has a pretty close approximation of the Kaplan-

Meier, and it looks like they're pretty equivalent in terms of time to no air leak.

DR. BIRNBACH: Can we move maybe a little off to get back to the safety? Are there any issues on the panel regarding safety? And Dr. Loeb, I'm not sure if you're answering that, or?

DR. LOEB: I actually noticed something. I've heard two hypotheses about why the residual space seems to be less of an issue, or it seems to resolve faster in the control group. And one was that there's some sort of inflammation from the, or irritation from the compound. The other being the chest tube placement management might've been different given that the air leaks were not as apparent from the get go.

And I don't know enough about this. I'm going to ask the thoracic surgeons, especially that it's apparent that in the recovery room, there were -- these was less residual space. There was more complete

filling of the chest in the recovery room, and then that got worse.

And so I assume that has to do because the chest tubes in the recovery room are on suction, and then they were not on suction later on. And so I'm wondering if maybe we're being -- maybe that's affecting what we're seeing later with the maybe the earlier placement of Heimlich valves, which don't have the chest on suction, which might slow the -- the re-expansion of the lung.

That might all be due to just chest tube management and not just the presence of the chest tube, but how much suction is on the chest tube. And it might be that it's sort of a red herring. Because what we're really interested in is not necessarily how quickly the lung re-expands, but how much that's going to end up being a problem for the patient and be a late complication.

And so I'm interested in what the thoracic surgeons think about how this product

might have changed the management of chest tubes, especially air seal versus suction, and how that might have impacted the rate of lung re-expansion.

DR. BIRNBACH: Gentlemen?

DR. WILCOX: It'd be my guess that they were on suction on the ward as well. I think throughout the post operative period as long as they were in, they were on suction. But I think that's a point: the chest tube management might've impacted this, and maybe it is a red herring as you suggested.

DR. JEEVANANDAM: Perhaps, but I mean there is a real bias towards putting Heimlich valves in patients who've had treatment or who have the sealant. All right, so clearly the sealant might have masked a very, very small air leak. I mean who knows? But it was -- it's pretty striking. I mean it's either that, or the surgeon is biased and says, "Well, I'll put sealant in this patient. It must not have an air leak." And then go

ahead and put a Heimlich valve.

So perhaps it's also true that as the sealant -- that it could be constricting the lung and preventing it from expanding as well. But I think it has a lot to do with the chest tube management, and you're right, but it's the chest tube management being masked by the sealant.

Because there was an amazing amount of -- a big discrepancy in who got Heimlich valves. And why did that occur? I don't know, it occurred because they thought there was no leak, but there was like a small sub-clinical leak.

DR. BIRNBACH: Dr. Loeb, the comment that you made about the potential risk of a delayed pneumothorax, do you believe that that indeed is a safety issue that we should be discussing now?

DR. LOEB: Certainly if it occurs outside of the hospital, then definitely. If it occurs within the hospital, I mean one of

the things that I've thought about in -- in this is that these patients are being managed by a thoracic surgery service, who is -- who are just by their nature very comfortable with following, treating, managing pneumothorax.

So of the type of complication that is basically going to be -- they're being cared for by a team who is used to, and going to be observant, and know how to deal with that, it makes it a somewhat less important complication compared to, for instance, cardiac problems or renal problems, and patients on a thoracic surgery service.

DR. BIRNBACH: Did you have another one? Do you believe that there are any safety issues from a thoracic surgical perspective that we need to discuss as related to question 1?

DR. JEEVANANDAM: I think I'm pretty convinced that this thing stops air leaks in the immediate post operative period. Now, whether that led to different management

styles in terms of keeping these lungs expanded, one doesn't know. But I would assume that if it became clinically available, that people would maybe keep the chest tubes on a little bit longer, and perhaps not have that residual space.

I think from a toxicity point of view, the only thing that really gets my attention a little bit is this renal adverse events where there was 9.5 percent with the sealant and 3.8 percent with the control. And I think that is probably one of the toxicities or safety issues that may be more important than even the residual space that's left.

DR. BIRNBACH: And I think we're going to discuss that in a little more detail in question 2. But are there any --

DR. SPINDELL: Addressing Dr. Loeb's concern: can we ask the sponsor? I don't know, were any of the complications with pneumothorax or whatever occur between hospital discharge and one-month follow up

that required treatment?

DR. BIRNBACH: Dr. Locicero, you had a question too, or no?

DR. WALSH: There was one patient, and it was my patient actually, who had a problem. It was a 28-year-old female with sarcoma, who had had I think four thoracotomies, and had had radiation therapy where the apex of the chest had been radiated.

She underwent radio-thoracotomy, had obviously multiple air leaks and getting into resect the sarcomas. When the sealant was applied, she did well, and was discharged, and three weeks later did develop a pneumothorax.

I was the one who raised the concern, "Could this have something temporarily related to the -- to the absorption of the polymer?" Although to be fair, this was not a normal lung. This was a radiated lung that really has characteristics of dry balsa wood, and probably I wasn't

necessarily given the sealant the full, normal lung to adhere to.

So that was -- that was one of the patients who raised that flag.

DR. JEEVANANDAM: Actually, that's very well summarized in FDA slide 71, where it says, "Six percent more sealant patients had late onset air leaks." And out of those patients, it said five out of nine sealant patients actually required invasive intervention. I assume that's putting in an extra chest tube. So those are I think patients who had late leaks.

DR. CERFOLIO: I'm glad you brought that up because that's sort of a misnomer. Four of those five patients were Heimlich valves, and I think some people think that the Heimlich valve is a procedure. I mean you put the Heimlich valve on the chest tube, but that's not a delayed pneumothorax.

So one of the concerns, Dr. Loeb, that you've mentioned is these delayed

pneumothorax. There aren't, though. There's one patient, one patient, that had a delayed pneumothorax with the sealant. There's -- in my opinion, there's really -- I'm not worried about this thing masking pneumothorax and sending people home, and then they come back.

I don't think we've found that. We had only one patient. These other four patients were Heimlich valves. They somehow got put in there as delayed pneumothorax.

DR. DOMINO: I guess it would be more convincing to me if I would see literature suggesting risk factors for these things happening, and people without -- you know, control group patients since your numbers are so small.

Is this something that happens, as you were saying, with radiation therapy? And you could say, "Yes, it occurs in one out of 200 patients?" Then we'd say, "Okay, it's a risk of the procedure." But here, the numbers are so small, it's hard to get a feel is it