DR. BIRNBACH: It has been moved that the PMA be approved with conditions and seconded.

Please refer to the yellow portion of the voting procedure flowchart in your folder. Remember, we're voting on the conditions of approval for this PMA application as it stands. We must first recommend the condition. The condition must then be seconded. There will be discussion regarding the recommended condition as it was worded. Then there will be a vote on that condition.

If that condition is approved, it will be the first condition to the main motion approvable with conditions. We will then move onto a new condition and repeat this process until there are no new conditions.

Finally, we will vote on the motion to approve the Zephyr Endobronchial Valve System with all of the conditions we have just approved by a majority vote.

Having said that, does anyone wish to recommend a condition? Dr. Marcus.

DR. MARCUS: I would recommend that the post-approval study as outlined in number 6 in the questions for the Panel be a condition of approval.

DR. BIRNBACH: So the condition recommended

was that there be a postmarket study that is mandated based on question number 6?

DR. MARCUS: Correct. And with the provisions of the discussion that we've had with the concerns that it may not be exactly as that, that is there needs to be evaluation of quality of life as well.

DR. BIRNBACH: Is there a second for that?

UNIDENTIFIED SPEAKER: Second.

DR. BIRNBACH: Okay. Is there discussion of the first condition? Dr. Dominik, is that you?

DR. DOMINIK: Yes.

DR. BIRNBACH: I couldn't tell if you were having a seizure or --

DR. DOMINIK: It's a seizure. We've talked about one sort of study for a postmarketing study. If this were approved with conditions, I would have to see a randomized trial, you know, done immediately as well.

DR. BIRNBACH: Are you moving that a new condition be a randomized trial or are you responding to --

DR. DOMINIK: Well, I don't know how we --

DR. BIRNBACH: We need to --

DR. DOMINIK: So in addition to --

DR. BIRNBACH: -- come up with all the conditions and then we need to vote. So if you're suggesting that you would rather not vote for approval with conditions, you will have that opportunity when this is voted on with all of the conditions.

On the other hand, at this point, we need to figure out what those conditions should be, should the vote be positive for going ahead with approval with conditions.

DR. DOMINIK: I mean should the vote be positive for approval with conditions? I am proposing that one of those conditions be that a randomized trial of the device --

DR. BIRNBACH: We vote on each condition separately. So we now have a motion on the table, and we're going to vote on that one, and then we're going to open it up to new conditions, and that would be the time to add the new conditions. Dr. Li.

DR. LI: I just have a mechanics question that maybe either you or someone from the FDA can answer. If we approve with conditions, does that mean the device is essentially approved and they can start selling it on day one, but they have to promise to do whatever it is we specify as a condition, or

can we say that they have to do the condition first before it's approved?

Let me try to reask the question in a more straightforward way. If we add conditions, those are conditions that happen essentially after approval. Is that correct?

DR. LIN: Yes. Uh-huh. When you say approvable with conditions, that means that the Sponsor has to conduct the study when we approve that the study, you know, that's -- post-approval study.

DR. LI: Okay. So we basically approve it with just whatever it is that we've got right now, whatever --

DR. LIN: Yes.

DR. LI: Okay.

DR. TILLMAN: Good afternoon. I'm Donna Bea Tillman. I'm the Director of the Office of Device Evaluation. I just want to clarify because this is a very complicated issue.

So what the Panel needs to decide, in determining whether the PMA should be approved or approved with conditions, is whether or not the Sponsor has the data right now that demonstrates a reasonable assurance of safety and effectiveness.

So you have to first find that they have

demonstrated a reasonable assurance of safety and effectiveness, and then if you think that there are conditions that need to be applied, including a post-approval study to answer other important questions, then you can recommend that that study be conducted.

But it's really important to remember that it's not appropriate to request the Sponsor to do a post-approval study that would give you the data that you would need to have to show a reasonable assurance of safety and effectiveness. You have to make that finding first. Is that clear?

DR. BIRNBACH: Dr. Dominik, I think that's for you. So we need to vote --

DR. DOMINIK: I think it's for all of us actually.

DR. BIRNBACH: We need to vote on the first condition if there's no more discussion about the condition, and the first condition was that we require a post-approval study based on question number 6.

All of those in favor of condition number 1?

DR. MARCUS: Do we not vote for all of the conditions?

DR. BIRNBACH: One at a time. We vote on

one condition at a time, put all the conditions in, and then we vote on a decision.

DR. MARCUS: Got you. Okay.

DR. BIRNBACH: So condition number 1 is that we mandate a post-approval study and that we make it a little bit more intense than originally suggested.

All those in favor of condition 1?

(Show of hands.)

DR. BIRNBACH: So for the record, Dr. Marcus votes yes, Dr. Ries votes yes, Dr. Loeb votes yes, and Dr. Domino votes yes.

All of those against condition 1?

(Show of hands.)

DR. BIRNBACH: Okay. Dr. Dominik votes no, Dr. Halabi votes no, Dr. Willsie votes no, Dr. Li votes no, Dr. Cassiere votes no, Dr. Wilcox votes no, Dr. Vassiliades votes no, Dr. Wiswell votes no, and Dr. Brunson votes no.

Are there any other conditions at this point that anyone would like to propose? Dr. Loeb.

DR. LOEB: I would like to propose changing the labeling dramatically to very specifically to identify the appropriate patient use and the early evaluation of effectiveness to create a decrease in

the size of the --

DR. BIRNBACH: Hold on. Early evaluation of effectiveness has nothing to do with labels. So is that a second condition or third condition?

DR. LOEB: Well, I don't know where else you'd put evaluating the effectiveness except in the labeling. Would that be -- I guess the other place would be in the education of users perhaps.

DR. WILCOX: It's my understanding that we can't put a condition on to evaluate effectiveness. We have to be satisfied that it is an effective device.

DR. LOEB: I'm not saying effectiveness in that way. I'm saying to -- that the placement is achieving the goal of decreasing the size of the diseased lobe, that the diseased lobe is atelectatic. I would think that would go in the labeling, but maybe I'm wrong.

DR. BIRNBACH: Okay. So I have a motion to change the labeling to specify which patients and to also somehow specify a way to evaluate the effectiveness from the practitioners.

DR. LOEB: The effective placement, yes.

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

UNIDENTIFIED SPEAKER: Second.

DR. BIRNBACH: Is there any discussion of this motion? Dr. Ries.

DR. RIES: It sounds like to me that's two conditions. One is a condition over the selection of patients, which has to do with characteristics of the lung or radiographic characteristics. And the second is actually a condition on the procedure which is lobar, you know, just trying to effect lobar exclusion. So I might suggest as an amendment that we consider this as two conditions.

DR. BIRNBACH: Do you accede to that request?

DR. LOEB: Yes.

DR. BIRNBACH: All right. So we have one condition, and it's been seconded, which is that we change the label. Is there any discussion on changing the label? Dr. Li.

DR. LI: I'll just reiterate, I didn't see who said it at the end, but I'll just reiterate not so much the comment on your condition, but the idea that the labeling will control the use at all I think is not a reasonable supposition.

DR. BIRNBACH: Okay. Any other discussion? Are we ready to vote on condition number 2, condition

number 2 being changing of the labeling? All in favor of changing of the labeling?

(Show of hands.)

DR. BIRNBACH: Okay. Dr. Marcus votes yes, Dr. Ries votes yes, Dr. Loeb votes yes, Dr. Domino votes yes.

All those against changing the labeling?

(Show of hands.)

DR. BIRNBACH: Dr. Dominik votes no, Dr. Halabi votes no, Dr. Willsie votes no, Dr. Li votes no, Dr. Cassiere votes no, Dr. Wilcox votes no. Dr. --

DR. VASSILIADES: V.

DR. BIRNBACH: Thank you. Why didn't I think of that all day? Dr. V says no, Dr. Wiswell says no, and Dr. Brunson votes no.

I believe we have a motion for a third change. You originally had two, and you tabled your second one to be a separate --

DR. LOEB: Well, I guess my third one then will relate to education and training of the people who will be using the device to include patient selection, how to perform the procedure the best way, and how to evaluate proper placement of the device, that the placement has been effective and the

appropriate indications for removing the device.

DR. BIRNBACH: So this condition would be a part of education.

DR. LOEB: I think that's where it would go. I can't envision that this would be done without rigorous education that would include all of those four components.

DR. BIRNBACH: All right. So there is a motion on the table to have a rigorous educational program associated with this device after approval, and that would include information such as proper placement, how many you have to do before you're capable of doing them and when to remove the device.

Is there a second for this --

DR. LIN: Can I may a comment?

DR. BIRNBACH: Yes.

DR. LIN: As Dr. Tillman just mentioned, before you consider any approval with condition, I think first the Panel need to decide whether this PMA provide enough data to show a reasonable assurance of safety and effectiveness. Then you probably can start to discuss any conditions.

DR. BIRNBACH: I believe that when we vote on this, that will become germane, if not obvious.

So is there a second for that motion?

UNIDENTIFIED SPEAKER: I'll second it.

DR. BIRNBACH: There is a second for the motion. Is there any discussion about having rigorous education after approval?

DR. VASSILIADES: Well, I'll just make a comment to Dr. Lin. It seems to me that is sort of the critical question because, you know, if we don't accept the fact that there's reasonable assurance of safety and effectiveness, then I don't know why we're making further conditions.

DR. BIRNBACH: So at some point, since you guys were the ones who moved and seconded that this be approved with conditions --

DR. VASSILIADES: We believe it is.

DR. BIRNBACH: -- the way that this reads is we have to see if we can come up with conditions and the entire Panel has to decide whether they agree with that. If at that point, the Panel agrees or if there is opinion that with or without conditions that the majority do not, then another motion can be made, and I believe that's the way this has to play out.

UNIDENTIFIED SPEAKER: That's the way I read it.

DR. BIRNBACH: Okay. So are there any -- oh, we need to vote on this. So it has been moved

and seconded that there be a rigorous educational program if this is approved. All of those in favor of a rigorous educational program as part of the approval, if it is approved?

(Show of hands.)

DR. BIRNBACH: Okay. So keep your hands up. We've got Dr. Marcus, Dr. Ries, Dr. Li, Dr. Wilcox, Dr. Loeb, Dr. Brunson, and Dr. Domino saying yes.

All those against having a rigorous educational program?

(Show of hands.)

DR. BIRNBACH: Okay. Dr. Dominik, Dr. Halabi, Dr. Willsie, and Dr. V, oh, no, and Dr. Wiswell and Dr. Cassiere say no. And the numbers are 7 for, 6 against.

Okay. So we have condition number 1.

Are there any other conditions that anyone would like to propose or make a motion?

(No response.)

DR. BIRNBACH: Okay. Based on that, I believe that we are ready for the main motion vote. My understanding is that we are voting for approval with conditions, and the condition that we have amended to this is that there be a rigorous

educational program that is required after release.

Okay. So that being said, time to vote. Will all of those in favor of the motion show your hands?

(Show of hands.)

DR. BIRNBACH: Okay. So Dr. Marcus and Dr. Ries vote to approve with the condition.

All those against the motion to approve with the condition?

(Show of hands.)

DR. BIRNBACH: Dr. Dominik, Dr. Halabi, Dr. Willsie, Dr. Li, Dr. Cassiere, Dr. Wilcox, Dr. V, Dr. Loeb, Dr. Wiswell, Dr. Brunson and Dr. Domino vote no.

The motion fails. The vote fails. Is there another motion?

DR. VASSILIADES: I have another motion.

DR. BIRNBACH: Okay. So we'll go in order. Dr. V's motion.

DR. VASSILIADES: I would motion that the device not be approvable.

UNIDENTIFIED SPEAKER: Second.

DR. BIRNBACH: Okay. We have a motion that the device not be approved and a second.

Is there discussion?

DR. VASSILIADES: I'd like to say that personally I'm very sympathetic to the patients that this device is trying to treat. A lot of time, money, effort, blood, sweat, and tears have gone into this trial on the way of the Sponsor, and I'm not unsympathetic to that either. I think they've advanced the field tremendously, and I would hope there's some way they can find to continue this, but again, for reasons I stated earlier, I don't think that we should be approving and playing around with the labeling to try to continue to do clinical research, that we have to have a controlled study through a PMA process that specifically looks at the group that we're wanting to treat.

And so, I would much rather approve a device and have it out there, but based on the data, I cannot in good conscience go to my patients and ask them to participate in this trial given the data.

DR. BIRNBACH: It has been moved and seconded that the PMA P070025 for the Zephyr Endobronchial Valve System from Emphasys Medical, Incorporated, be found not approvable.

With a show of hands, please indicate if you concur with the recommendation that the above-named PMA be found not approvable?

(Show of hands.)

DR. BIRNBACH: The voting members who are raising their hands indicating that they concur with the recommendation, that the above-stated PMA is not approvable, are Dr. Dominik, Dr. Halabi, Dr. Willsie, Dr. Li, Dr. Cassiere, Dr. Wilcox, Dr. V, Dr. Loeb, Dr. Wiswell, Dr. Brunson and Dr. Domino.

Please raise your hands if you are disagreeing with that?

(Show of hands.)

DR. BIRNBACH: Dr. Marcus and Dr. Ries oppose the recommendation, that PMA P070025 be found not approvable.

And please raise your hands if anyone is abstaining from the vote.

Since everyone has voted already, I think that's unlikely.

It is the recommendation of this Panel to the FDA that the PMA P070025 for the Zephyr Endobronchial Valve System from Emphasys Medical be found not approvable.

This motion was carried 11 to 2, and there were not abstentions.

I would like to ask each Panel member to explain why he or she voted. Also, I would like to

ask the non-voting industry and consumer representatives for their comments. So, we'll start with Dr. Domino. I'd like for you to state the reasons why you voted the way you did.

DR. DOMINO: Well, I thought looking at the risk benefit ratio, I see potential benefit in a subcategory of patients that weren't well defined, and certainly the data that we were presented, we do not have specific data in a large number of those patients, with looking at fairly limited effectiveness, with some procedure that is invasive; yes, the risks are not terrible, but it just didn't add up to me in this category for all comer type patients.

DR. BIRNBACH: Dr. Domino, and for each of you that follows, could you please tell the Sponsor what you believe must be done to make the PMA approvable.

DR. DOMINO: Yes, I'd like to see your data on the heterogeneous, you know, the CT scanning and picking in that population who might have a greater benefit of effect, and looking more specifically at their -- and I would also like to see perhaps follow-up safety data for more than one year.

DR. BIRNBACH: Dr. Brunson.

DR. BRUNSON: I agree with what Dr. Domino has said. I think that there is promise for this, and I think there is a subcategory of patients that you will find benefit in. And I think what you need to do is tighten up selecting that group, and you may have already got a good start on that. But based on what I see, even though the risk seemed to be fairly small, I still don't see the benefit of it right now in an approvable manner for me to say that the device ought to be approved. I think it's headed in that direction, and I think you need to do a little bit more work to show us that subcategory of patients that it will benefit.

I would like to see more long-term data about the sustainability when you select the subset of patients that you find benefit in.

DR. BIRNBACH: Dr. Wiswell.

DR. WISWELL: Similar to my colleagues, I didn't see enough clinical effectiveness for approving. I would have loved to have approved it with a number of conditions, but I have to say to myself, from what Mr. Patel put out, we have to have substantial clinical effectiveness, and it just wasn't there. Another randomized control trial, and I think all of us are sympathetic to these economic

times, and when I think all of us here see something that is really promising and would really like to see something out there that's helping a part of this population, right now we can't justify its use. And, the other thing I'd like to see besides narrowing down, perhaps again the same highly heterogeneous population, similar randomized control trial, that long-term safety data upwards of three years or so.

DR. BIRNBACH: Dr. Loeb.

DR. LOEB: I'm less concerned with long-term safety. I just don't believe that's going to be a real big problem. I think long-term, I can envision patients who would have devices like this would have, you know, need for long-term follow-up, repeated hospitalizations, repeated procedures as part of what they expect but not in terms of long-term safety. I don't think that's particularly going to be the problem.

I think that the data presented did not show an adequate benefit risk ratio but that another trial, probably more limited in scope with better patient selection and earlier evaluation that the devices are placed properly, would have an adequate risk benefit, but the data's not there. If it were presented today, I certainly would have voted for it,

and as much as I emotionally would like to believe that that's how it would work, you can't believe what's going to happen until you have the data. So I couldn't in good faith vote for approvable with conditions.

DR. BIRNBACH: Dr. Vassiliades.

DR. VASSILIADES: I think my comments from earlier pretty much sum up my feeling. I don't need to reiterate.

DR. BIRNBACH: And do you want to suggest what you think needs to be done to give approval?

DR. VASSILIADES: Yeah. I think with the data that has been acquired now in terms of further defining the subgroups to try to do something with that, whether it's reworking the data, following those patients longer, or having to do another clinical trial, which I realize probably financially is just not doable. That's all I would suggest.

DR. BIRNBACH: Dr. Wilcox.

DR. WILCOX: I voted for non-approval, although I believe the Sponsors have addressed an important clinical problem in a creative and responsible manner. Unfortunately, the clinical problem and the proposed treatment are so complex that no clear-cut resolution of the issues was

achieved by this clinical trial. I do not believe they have provided reasonable assurance that the use of this device is broadly applicable clinically.

I don't have a lot to add or anything to add to suggestions except in terms of tightening it up, perhaps fewer centers. That must have been really hard, with the large number of centers to control patient selection and follow-up. So --

DR. BIRNBACH: Dr. Cassiere.

DR. CASSIERE: I voted non-approval. I think what needs to be done is there needs to be niche patient population clearly defined, and then looking at the outcomes of those patients after a year, especially given the infectious complications and the fact that you're decompressing a lung in a patient who is at increased risk for pneumonia and COPD exacerbations.

DR. BIRNBACH: Dr. Li.

DR. LI: It's probably of little consequence or consolation to you, but I thought the study actually was very clever, and I was most impressed actually by the dedication and honesty and actually the compassion of the presenters. So it actually kind of breaks my heart to actually vote against this. But for the reasons that we just

specified for, I voted against it.

I'll just speak from the device side. The thing that seemed to be missing for me was really kind of the underpinning of why this is working. You know, the original hypothesis appeared to be volume reduction, but the correlation of volume reduction to FEV_1 and the six-minute walk were poor at best. And there was a hypothesis proposed, it's maybe volume redistribution. Well, that's fine, but that's now yet another hypothesis.

So to me the no vote was really a combination of clinical results that really could have been a lot better but that was actually reinforced by the kind of lack of understanding of how these devices are actually performing. And then superimposed upon that, I learned from several of you today that, you know, the correlation of even FEV_1 with actual patient activity may not be as strong as we would like it to be, and the FEV_1 was probably your best clinical results. So all of that really kind of left me personally with kind of nowhere to go but to vote the way I did.

DR. BIRNBACH: Dr. Willsie.

DR. WILLSIE: I voted no also for the reasons that have been identified, and what I would

like to see is a new study looking at newly defined population that's most likely to respond using lessons that you've learned regarding the fissure, regarding the lobe selection, and particularly looking at clinical significance for your outcome, and if anyway to abolish the placebo effect, I think that would be valid as well.

DR. BIRNBACH: Dr. Ries.

DR. RIES: Well, I voted against not approval. I agree with the other Panel members that the data presented today, in terms of effectiveness and the balance of effectiveness and safety are not compelling, but I think I was focused more on the term reasonable, and I think there is a signal there. I think the Sponsors are really well on their way into finding the appropriate use of this in terms of the heterogeneity and the lobar exclusion, and I think there clearly is a modest effect here that I think outweighs the potential, very limited safety concerns. So I voted against non-approval at this point.

DR. BIRNBACH: Dr. Marcus.

DR. MARCUS: I agree with Dr. Ries. I voted against non-approval, and I think that we have lots of things we do that we have a certain degree of

uncertainty. I still don't know why pulmonary rehabilitation works and improves many outcomes despite the fact that it doesn't improve pulmonary function. And I think there was enough evidence to show that there was improvement, albeit perhaps in a select group of patients, and that the safety did not seem to be a major concern. So I think there still is a future for this, and perhaps more studies need to be done, if that's something that can be accomplished financially.

DR. BIRNBACH: Dr. Halabi.

DR. HALABI: I voted for the device not to be approved. As a statistician, I do appreciate the challenges in the conduct and analysis of a trial using that specific endpoint, but nevertheless, because of issues of a large proportion of missing data, post-hoc window extension, multiplicity of analysis, because of all these issues that really threatened the validity and reliability of the results, and I would have liked to see perhaps a larger trial with smaller number of missing data.

DR. BIRNBACH: Dr. Dominik.

DR. DOMINIK: Obviously I voted to not approve the device, but I think that perhaps if you are right, that the high heterogeneity subgroup is

more likely to have the benefit, and if there are some changes that could be made in the procedures for how the device is placed and followed up immediately that might also help to improve the effectiveness, then it may not take as large of a study to demonstrate the effect in that group if that has truly a greater effect. And a new trial showing effectiveness more definitively in that subgroup plus safety data from the current trial, I think together would contribute to the overall evaluation of safety and effectiveness. So I don't think you would necessarily need to study as many patients if you really do have a group that has a higher chance of benefiting if that's any consolation.

DR. BIRNBACH: I'd like to ask your non-voting industry and consumer representatives for their comments. Ms. Petersen.

MS. PETERSEN: It's true I did not vote. I think this afternoon there was general consensus that the risks and benefits were not in alignment, and I appreciate your voting this afternoon not to approve, resisting the temptation to use the approval process to facilitate the research that I think everyone would like to see and the positive results to help patients. In the long-term, getting the additional

research we need to understand who we can help and what the benefits are, I think, is in the public's best interest. Thank you.

DR. BIRNBACH: Mr. Osborn.

MR. OSBORN: Thank you, Mr. Chairman. It would seem that there was a consensus on the Panel that there was adequate safety. I personally would have liked to have seen an analysis of the data breaking apart at the six-month point, those patients that had leakage from those that didn't, because I think that might have correlated with those that had an effect and didn't, but that wasn't part of the data that was presented to us.

Clearly in terms of conducting further trials, it's very important to focus on the right patient, the proper placement of the valve, and perhaps most importantly the complete blockage of the desired lobe. I think there was also consensus that the labeling needed work and that a training module would need to be created to reflect some of that.

For all of those seriously ill COPD patients, clearly this is a disappointment because they have very few treatment options, and I'm sure that those patients would have liked to have seen a device that was safe and effective to give them some

chance of a better short-term outlook on life.

Thank you.

DR. BIRNBACH: I'd like to thank the Panel, the FDA and the Sponsor. Dr. Lin, do you wish to say anything?

DR. LIN: Yeah, on behalf of FDA, I want to thank the Panel for this hard work. I know this is a very difficult PMA to discuss, and I also wanted to thank the Sponsor for working very -- with the Sponsor, and I'm sure we will still have a lot of opportunity to work together. Thank you.

DR. BIRNBACH: The December 5, 2008 meeting of the Anesthesiology and Respiratory Therapy Device Panel is now adjourned. Thank you.

(Whereupon, at 4:30 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

ANESTHESIOLOGY AND RESPIRATORY THERAPY DEVICES PANEL

December 5, 2008

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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