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Jeffrey E. Shuren, M.D., J.D.
Director, Center for Devices and Radiological Health
Food and Drug Administration
Department of Health and Human Services
WO 66, Room 5442
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Shuren:

These comments from Public Citizen's Health Research Group are being submitted in follow-up to our testimony[1] presented at the October 9, 2013, meeting of the Food and Drug Administration's (FDA's) Circulatory System Devices Panel of the Medical Devices Advisory Committee regarding Premarket Approval (PMA) application P100045 for the CardioMEMS Champion Heart Failure Monitoring System (the CardioMEMS System).

As previously stated in our testimony, we strongly oppose FDA approval of the CardioMEMS System for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in patients with New York Heart Association (NYHA) class III heart failure who have been hospitalized for heart failure in the previous year because:

(1) The design and conduct of the single pivotal clinical trial evaluating the CardioMEMS System had multiple features creating readily apparent sources of bias, explicitly acknowledged by the FDA, with respect to the effectiveness endpoints in favor of the experimental group. This prevents any valid conclusions from being drawn regarding the effectiveness of the device.

(2) Every ancillary analysis had serious limitations and flaws that prevent valid conclusions from being drawn about the effectiveness of the CardioMEMS system.

(3) As a result of (1) and (2), there are insufficient data to provide a reasonable assurance that the device is effective for the proposed indication or that the benefits of using the device outweigh the risks related to the implantation procedure.

[1] Carome MA, Wolfe S. Testimony to the FDA's Circulatory System Devices Panel on the Premarket Approval (PMA) Application P100045 for the CardioMEMS Champion HF Monitoring System. October 9, 2013. http://www.citizen.org/hrg2164. Accessed November 20, 2013.

A majority of the members of the Circulatory System Devices Panel agreed with our overall assessment. In particular, on the question of whether there is a reasonable assurance that the CardioMEMS System is effective for use in patients who meet the criteria specified in the proposed indication — which was the most important question addressed by the committee — seven members voted no, and four voted yes.[2] This outcome was nearly identical to the committee's vote on the same question when it met to consider approval of the PMA application for the CardioMEMS system on December 8, 2011. (At that meeting, seven members voted no, and three voted yes.)

A. Problems with the single, randomized pivotal trial

For the single randomized pivotal trial of the CardioMEMS System, the primary effectiveness endpoint was the rate of heart-failure-related hospitalizations through six months.[3] Secondary effectiveness endpoints included the following:[4]

(1) Change from baseline in pulmonary (PA) mean pressures

(2) Proportion of subjects hospitalized for heart failure

(3) Days alive outside of the hospital

(4) Total quality-of-life score on the Minnesota Living with Heart Failure Questionnaire

While statistically significant differences were seen in each of the pre-specified primary and secondary effectiveness endpoints, as well as many other supplementary endpoints, the absolute differences between the treatment and control groups for several endpoints — such as days alive without heart failure hospitalization — were relatively small.[5]

More important, several features of the design and conduct of the study created readily apparent bias in favor of the treatment group. Thus, it is highly plausible that the differences seen in the effectiveness endpoints were due in large part or even entirely to bias, rather than use of the device itself. The most prominent and egregious source of bias in the pivotal trial was found in the subject-specific treatment recommendations provided to individual site clinical investigators by nurses employed by the sponsor for treatment group subjects only.[6] However, other important sources of bias included the following:

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[2] Food and Drug Administration. Brief summary of the circulatory system devices panel meeting — October 9, 2013. Page 3. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM370995.pdf. Accessed November 20, 2013.

[3] Food and Drug Administration. FDA executive summary for the December 8, 2011, meeting of the Circulatory System Devices Panel. Page 14. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM282098.pdf. Accessed November 20, 2013.

[4] *Ibid*. Page 16.

[5] *Ibid*. Pages 12-26.

[6] Food and Drug Administration. FDA executive summary – addendum, prepared for the December 8, 2011, meeting of the Circulatory System Devices Panel. Pages 2-4.

(1) Single-blinded study design: This is one feature of the study design that unavoidably contributed to study bias. Nevertheless, clinical investigators' awareness of each subject's study group assignment may have influenced decisions regarding both medical therapy and whether to hospitalize a subject, both of which would directly affect the primary and secondary effectiveness endpoints.

(2) Consultation with the national principal investigators (PIs) regarding medical management of treatment group subjects only: Per the study protocol, clinical investigators at each of the study sites were encouraged to consult with the national PIs — who likely were nationally recognized experts in the management of congestive heart failure — "to optimize the success of medical management of PA pressures."[7] Apparently, no such encouragement for consultation was provided with respect to the medical management of control subjects, whose care might have been enhanced had the site clinical investigators consulted with the national PIs with the same frequency as for treatment group subjects.

(3) Unbalanced content and frequency of telephone contacts between investigators and treatment group subjects versus control group subjects: The protocol included scripts for telephone contact with subjects in both study groups. The scripts were identical except for subject-specific medication adjustments that occurred in the treatment group in response to PA pressure data.[8] Whenever a telephone contact occurred with a treatment group subject, a control group subject was randomly selected to receive a matching phone contact.[9] These were not comparable study interventions because treatment subjects received telephone contacts that were based on contemporaneous, subject-specific clinical information (i.e., PA pressure information) and included medication changes. Control subjects, on the other hand, received random, generically scripted calls unrelated to any pertinent contemporaneous contextual clinical information that may have warranted medication changes.

During the first advisory committee review of the CardioMEMS System PMA application on December 8, 2011, the FDA staff made several critical points that clearly supported the decision by the agency to disapprove the PMA application for the CardioMEMS System, including the following:

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http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM282272.pdf. Accessed November 20, 2013.

[7] Food and Drug Administration. FDA executive summary for the December 8, 2011, meeting of the Circulatory System Devices Panel. Page 52. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM282098.pdf. Accessed November 20, 2013.

[8] CardioMEMS, Inc. CardioMEMS Heart Failure Monitoring System briefing document, prepared for the December 8, 2011, meeting of the Circulatory System Devices Panel. Page 38. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM281523.pdf. Accessed November 20, 2013.

[9] *Ibid*. Pages 38-39.

(1) Statistical review:

Dr. Yonghong Gao, a statistical reviewer from the Center for Devices and Radiological Health's (CDRH's) Office of Surveillance and Biometrics, noted the following regarding the robustness of the data for the primary effectiveness endpoint from the single pivotal clinical trial evaluating the CardioMEMS System based on the FDA's sensitivity and tipping point analyses:[10]

- The sponsor's analysis of the primary effectiveness endpoint is **not robust** with respect to the methods used to estimate the parameters of the negative binomial model [emphasis added].
- In the sponsor's analysis, if 13 more [heart-failure related] hospitalizations (from [84] to [97]) are added at random to the patients in the Treatment arm [i.e., the group managed using PA pressure data from the implanted CardioMEMS System sensor], the result is no longer statistically significant at 0.048.
- For the bootstrap [nonparametric] model[,] if only two hospitalizations are added to the Treatment arm[,] the p-value exceeds 0.1.

Dr. Gao also stated the following regarding the robustness of the data for the second of four secondary endpoints (i.e., the proportion of subjects hospitalized with heart failure):[11]

- If the number of [hospitalized] patients in the Treatment arm is increased by only 3 (from 55 to 58 out of 270 versus 80 out of 280), the p-value is no longer significant at 0.05.

(2) Medical officer review of the conduct of the pivotal clinical trial:

Dr. Randall Brockman, the primary clinical reviewer for the CardioMEMS System PMA application, expressed the following concerns regarding the conduct of the single pivotal clinical trial evaluating this device:[12]

- Sponsor [and] National [principal investigators] made specific treatment recommendations for [the] Treatment group only.
- Level of interaction between sponsor and clinical investigators [was] inconsistent with FDA's expectations.
- FDA [is] concerned these actions may bias results.
- FDA believes measures taken by sponsor would not be duplicated in [the] post-market setting.

[10] Food and Drug Administration. Slide presentation for the CardioMEMS Champion HF Monitoring System: FDA review of P100045. December 8, 2011. Slide number 20. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM284020.pdf. Accessed November 20, 2013.
[11] *Ibid*. Slide number 22.
[12] *Ibid*. Slide numbers 96-97.

- Substantial therapy recommendations were made only for the treatment group subjects.
- FDA is concerned that the observed treatment effect may not be due solely to the device.
- Given the potential bias introduced by study conduct, FDA is concerned that **we cannot make an accurate risk: benefit determination** for this device [emphasis added].

(3) Presentation of overarching statistical considerations:

Dr. Gregory Campbell, director of the CDRH's Division of Biostatistics, ended the FDA's presentation at the Circulatory System Devices Panel meeting with the following overarching observations regarding the potential for bias in the CardioMEMS System pivotal clinical trial:[13]

- If the two arms [in a randomized trial] are treated differently this can introduce a **potentially large bias** [emphasis added]. (In [the CardioMEMS System pivotal trial], the two arms are treated very differently by recommendations by entities outside the clinical site.)
- In general, failure to mask (blind) the subjects, the investigators or the third-party evaluators introduces a bias.
- Only subjects were blinded in this study.
- [It is] [i]mpossible to mask the treating physicians from the output of the diagnostic device. However, patient-specific recommendations that the sponsor provided to the clinical sites are problematic. In addition, the sponsor has not remained masked (blinded) and has made differential patient-specific recommendations in only one of the two arms.
- [It is] [d]esirable to have an endpoint that cannot be directly and easily influenced by knowledge of which group a subject is in. That is not the case for this PMA, where the primary effectiveness endpoint is [heart-failure related] hospitalizations.
- The [d]ilemma [given the conduct of the pivotal clinical trial:]
  - The effect of [the device in] this study is confounded.
  - It is the confounding of the diagnostic information and the "[e]xtra [i]nterventions."
  - The possible bias from this confounding is of **serious concern** here and, given the sensitivity analyses presented earlier, this bias could have produced **some or all** of the significant effectiveness results seen in this trial [emphasis added].

Dr. Campbell made the following conclusions:[14]

- Confounding of planned intervention (use of CardioMEMS information by the physician) and "extra interventions" (differential patient-specific treatment recommendations) [render] interpretation of this trial problematic.

[13] *Ibid*. Slide numbers 103, 104, and 108.
[14] *Ibid*. Slide number 111.

  - Which intervention caused the observed outcome?
- The [CardioMEMS System] trial does not provide an unbiased estimate of the effect of the device. It is not clear what if any effect in the study is due to the device itself. Further, the effect of the device in a real-world setting (if this device were to be approved) is unknown.

The FDA clearly recognizes that bias is very insidious and can influence investigators' actions and judgments in subtle and not-so-subtle ways. Once a study is completed, it is impossible to prove how much of any difference between study group outcomes resulted from bias and how much was from an actual difference between the interventions being tested. In this case, multiple features of the pivotal study design and conduct created readily apparent bias and prevented any valid conclusions from being drawn about the effectiveness of the CardioMEMS System.

B. Problems with the new ancillary analyses conducted by the sponsor

In January 2012, the FDA issued a "not approvable" letter to the sponsor, requesting additional data to demonstrate that there is a reasonable assurance of effectiveness of the device.[15] The agency appropriately recommended that a new, prospective clinical trial be conducted to assess the effectiveness of the CardioMEMS system.

CardioMEMS — unfortunately with FDA agreement — instead conducted multiple ancillary analyses of longitudinal follow-up data from subjects who had been enrolled in the randomized pivotal trial (Part 1) and had survived and not dropped out. During this follow-up study (Part 2), pressure data from the CardioMEMS implanted device were made available to the physicians for all subjects. A number of comparisons were made to assess effectiveness, including the following, among others:[16]

(1) Comparison of heart failure (HF) hospitalization rate in former control group subjects (n=170) to the rate seen in control group subjects during the randomized trial (n=280)

(2) Comparison of the HF hospitalization rate in former treatment group subjects (n=177) to the rate seen in treatment group subjects during the randomized trial (n=270)

(3) Comparison of the HF hospitalization rate in former control group subjects to the rate seen in former treatment group subjects

(4) Comparison of the change in HF hospitalization rate between the randomized study and the follow-up study for the control subjects versus the treatment subjects

Although the results of these analyses consistently suggest that access to the CardioMEMS pressure data reduced the HF hospitalization rate, several factors highlighted by the FDA

[15] Food and Drug Administration. FDA executive summary for the October 9, 2013, meeting of the Circulatory Systems Devices Panel. Pages 9. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM370689.pdf. Accessed November 20, 2013.

[16] *Ibid*. Pages 15-19.

seriously undermine the validity of these analyses. In particular, FDA reviewers noted the following:

(1) These analyses "are considered ancillary [not primary] analyses because no study success criteria could be defined a-priori and because the study was not originally designed with these analyses in mind… Caution should be used when interpreting the results because the study is not powered for these analyses, multiple analyses were conducted on the same data, and preservation of Type I error was not attempted."[17]

(2) 93 of 270 (34%) treatment group subjects and 110 of 280 (39%) control group subjects randomized into the pivotal clinical trial did not enter the follow-up study (Part 2). Bias in the ancillary analyses may have been "introduced due to the non-random exiting of subjects prior to onset of Part 2. It appears that the subjects who exited in the Control group were similar to those who exited in the Treatment group with respect to their baseline characteristics (as measured at the start of Part 1). However, the clinically important covariates were not collected at the beginning of Part 2, which started a mean time of approximately 525 days after the baseline covariates were measured. It is possible that the values of some important covariates changed from Part 1 to Part 2. Using Part 1 baseline values for those covariates in the proposed combined data analysis approach may not be appropriate. Furthermore, because of the lack of the covariates at baseline of Part 2 study, FDA was not able the evaluate:

1. if the subjects in Part 1 and Part 2 were comparable after subjects exited from the duration of Part 1;
2. if important covariates between the comparison arms remained balanced in Part 2; and
3. if subjects in Part 2 study still met the trial inclusion/exclusion criteria."[18]

(3) "It is not possible to evaluate…whether the difference in clinical outcome [in the ancillary analyses] may be confounded with differences in the subject populations."[19]

(4) "The mortality in Treatment groups changed from 18.5% in Part 1 to 17.5% in Part 2. This similarity in mortality is expected since the Former Treatment group continued to have access to PA pressures. The mortality in the Control groups decreased from 22.9% in Part 1 to 12.4% in Part 2. Although a decrease in mortality was expected in the Control groups due to PA data availability in the Former Control group, one would have expected the rate to be similar to that of the Treatment group in Parts 1 and 2, approximately 18%. The fact that the mortality rates in the Former Control group is 12.4% versus 17.5% in the Former Treatment may suggest a difference in the patient populations in Part 2 of the study."[20]

[17] *Ibid*. Page 15.
[18] *Ibid*. Pages 24-25.
[19] *Ibid*. Page 41.
[20] *Ibid*. Page 25.

On this last point, it is inappropriate of the FDA to suggest that a decrease in mortality was expected in the former control group subjects due to PA data availability in light of data from the pivotal trial showing no evidence of a mortality benefit in subjects in the treatment group.

Even if these ancillary analyses were valid, we agree with the FDA's stated view that "the clinical significance [of any reduction in heart failure hospitalization] is less clear."[21] This is particularly true given the absence of any survival advantage and the apparent lack of a sustained quality-of-life benefit at 12 months in the treatment group in the randomized pivotal clinical trial.

C. Key observations by members of the advisory committee

As previously noted, the majority of the advisory committee members concluded at the October 2013 meeting that based on the data presented by the sponsor there was not a reasonable assurance that the CardioMEMS System is effective for use in patients who meet the criteria specified in the proposed indication. Members who reached this conclusion made the following important and insightful comments that argue against approval of this device:

(1) Dr. Brent Blumenstein, Biostatistician:

- "Well, it seems like what we have here is a hoist it on your own petard moment. The randomized clinical trial has been shown to have an effect, and part of the effect results in patients not going on to Part 2. And so therefore you, by definition, are defining the groups in Part 2 as being different. And so how can we feel confident that we're comparing interventions when we have something that defines a different sample of patients in the various arms that we're comparing. Have you -- I guess the lack of measurement of covariate on entering Part 2 is a big problem. And has there been any effort at all to try to figure out whether you're comparing kumquats and potatoes or whether you're comparing apples and pears?"[22]

- "But the real issue is the patients coming into it and the fact that you have groups of patients that are being compared that aren't comparable, and they're not, and they're not comparable because you treated them differently, and you can show me covariates and try to convince me that the distribution of baseline covariates at the time they transition from Part 1 to Part 2 are comparable. And I looked at them, and I don't know. I would want to see some more -- something more convincing than a list of p-values, or whatever.

  "But the fact is that the patients get into Part 2 because they've been treated in Part 1, and because they've been treated in Part 1, they're different if they survived that. Now, you could make an argument that, well, the patients that survived that and get into Part 2 are comparable, but there's already more deaths in part -- in the control

[21] *Ibid*. Page 41.
[22] The Food and Drug Administration. Transcript of the October 9, 2013, meeting of the Circulatory System Devices Panel of the Medical Devices Advisory. Page 150. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM373578.pdf. Accessed November 21, 2013.

arm in Part 1. And so there's a really confusing and nonrandomized comparisons that are being done here, and that's the crux of the matter."[23]

- "[T]he randomized clinical trial is what you would call Level I evidence, that is, level Roman numeral I evidence, because it's based on a randomized clinical trial comparing the use of the device with the supplemental nurse against… So you have this Level I [evidence]. And then what is going on is that what we're asked to comment on is really Level III [with respect to the ancillary analyses]. And the reason it's Level III is because it's not a designed study. It's a convenience sample. It's observational. And it has no real control over the biasing factors. That is, specifically the patients going into Part B are different, and it's what I referred to before as hoisted on your own petard. If you have a result, that significant result from Part A, then by definition, you're going to end up with different populations in Part B.

  "And so for that reason, I tend to think that this -- that these are problems. They're real. And they inform us as to the value of the data…

  "I don't know what to make of [the ancillary analyses] because the [the problems with the] selection factors that went into the makeup of the patients entered into those analyses are **serious and structural**. They come from the design of the trial, and there's nothing much that can be done about it. And covariate adjustment, while it's sometimes useful in situations like this, **it's seldom useful**."[24] [Emphasis added]

- "So I voted… no for the two efficacy-related questions. I didn't feel that the additional analyses clearly demonstrated that the device could be used without nurse assistance, based on the fact that there was a lack of experimental structure in the data analyzed."[25]

(2) Dr. Richard Lange, Interventional Cardiologist and Vice Chairman of the Department of Medicine at the University of Texas, San Antonio:

- "[I]t's hard for me to figure out whether it's, in fact, the monitor itself or they just trigger someone to pick up the phone and call every day and say how are you feeling. And when someone describes shortness of breath, they'd treat them before they got to the hospital stay.

  "And the issue about the patients being very different, apropos to the covariates, remember that to get in the trial, you had to have New York Heart Association Class III symptoms… But you also had to have a hospitalization within one year. So by virtue of the fact that if you have the device and were followed for a year and you didn't have a hospitalization, you wouldn't even have been enrolled in the trial. So it is a different group, and I'm not quite sure how to deal with that."[26]

[23] *Ibid*. Page 195
[24] *Ibid*. Pages 246-247.
[25] *Ibid*. Paged 306-307.
[26] *Ibid*. Page 218.

(3) Dr. Valluvan Jeevanandam, Chief of Cardiac Surgery at the University of Chicago:

- "So if we're looking at the Part 2, you would say that you wouldn't approve this device because you didn't have any effectiveness in decreasing hospitalization over control. So it's only by combining it with the first part [the randomized trial with nurse communications with site investigators] that you can come up with some indication of efficacy."[27]

- "I think that the sobering thing here is that it's not really taking care of heart failure, right, because your PA pressure is still up, you have incidence of mortality that's significant, you have instance of transplants and LVADs and everything else that doesn't seem to change between control and treated patients. So as a monitoring device, it's fine. Is it affecting heart failure? Other than just admissions, we don't have any functional improvement in these patients, and we don't have really any long-term outcome improvements. But as a monitoring device, I think it's effective in monitoring PA pressure."[28]

(4) Dr. John Somberg, Professor of Medicine and Pharmacology at Rush University Medical College:

- "[The CardioMEMS System is] a diagnostic test. But is it a diagnostic test alone -- and that's why they have the second panel, the second discussion -- or is it the diagnostic test plus the advice from a panel of nurses in constant calls. And Dr. Lange, I think, said it, you know, very succinctly. Is it because there are just a lot of calls and heightened surveillance, and therefore, people are being identified who all of the sudden have a change in symptoms? Because if the pulmonary pressures are up in all of these people -- what was it, 4,000 or something -- and we only have 1 in 4, 1 in 5 of those acted upon, there's something else there. And how is Dr. Zuckerman going to draft a label for that when that's an unknown factor?

  "And, you know, I hate to keep raising the unknowns…but there are a tremendous amount of unknowns. So I feel the feeling is not that there is lack of a mortality effect. The question is if this was a clear-cut guidance on how to use this data, then I would be very happy to support it. But I think there's a lot of danger here."[29]

- "I think [the ancillary analyses are] very problematic, and because of… the difference in mortality of the groups [i.e., former treatment versus former control subjects], I think that severely questions the validity. It's convenient to say things are going in the right direction, looks good, these are good guesses. And that may be the case. But there are a lot of pieces of data that don't fit in here, such as a large number of elevated pressures, et cetera. So, therefore, because things are not going in the right direction, it might be that there are biases pushing them in that direction. And that's

[27] *Ibid*. Page 219.
[28] *Ibid*. Page 259.
[29] *Ibid*. Pages 237-238.

why we do randomized controlled studies. And I'm not sure how I'm voting at this point, but this Panel question is really very important, and it's very troubling."[30]

- "I thought there was certainly a consistent trend to support its efficacy, but there were really a lot of unknown questions. And I couldn't say the data was valid to support that. So I voted no for 2. I abstained on the third on because -- and my vote would be changeable if the -- if some time in the future we would have data in sets with a controlled trial. But without a controlled trial, just a registry, we will never have it, so therefore, I could not vote affirmatively."[31]

(5) Dr. Kristen Patton, Cardiac Electrophysiologist at the University of Washington:

- "But I'm still trying to figure out how a device that had 44,000 transmissions, 32,000 of which were alerts that resulted in 1,400 medication changes, was the reason why we see this enormous clinical change. And so I'm still not quite sure how to make sense of that data."[32]

(6) Dr. David Milan, Cardiac Electrophysiologist at Massachusetts General Hospital:

- "And what I have to say about that longitudinal analyses is that I still have serious issues with the validity of those analyses mostly because of the 39% dropout – I'm talking about just comparison number 1 -- a 39% dropout in the patients entering Part 1 versus Part 2, which makes it very difficult for me to draw any meaningful conclusions about how those patients did in those two parts of the study."[33]

- "So, finally, my only other point I want to make is that many people are saying, oh, the data are pointing in the right direction and it's plausible and we should just let the totality of the evidence push us in that direction, and I want to return to the Lange/Patton argument, which is there were a lot of alerts, very few of which seem to have been acted on, and how do we know that it was really that -- the PA data alerts that made those patients better or whether it was some other aspect of this clinical intervention that made the patients better."[34]

- "So I voted that… there was not a reasonable assurance of its effectiveness. And I believe that the ancillary data presented here were not valid or convincing, and I think that the appropriate approach is what the FDA originally recommended, which is a properly performed randomized trial."[35]

(7) Dr. Joaquin Cigarroa, Clinical Professor of Medicine at Oregon Health & Science University:

[30] *Ibid*. Page 248.
[31] *Ibid*. Page 308.
[32] *Ibid*. Page 257.
[33] *Ibid*. Page 272.
[34] *Ibid*. Page 273.
[35] *Ibid*. Page 306.

- "With regards to Question No. 2, is there reasonable assurance, I voted no, and I have been conflicted about the meaning of reasonable with regards to the scientific evidence given that I am unable to resolve what I believe are the substantial probability of differences in patients at the outset of Part 2 of the study."[36]

Finally, two committee members who concluded that there was *not* a reasonable assurance that the CardioMEMS System is effective for use in patients surprisingly concluded that the benefits of the device outweigh the risks for use in patients who meet the criteria specified in the proposed indication. However, the following explanations given by these two members for their votes on this final question assumed an indication for use different from that proposed by the sponsor:

(1) Dr. Patton: "But my third vote, which was a yes, was because I felt like the device was very effective in doing what it was intended to do as a diagnostic device, and the risk profile was so low that I felt like there was a good chance that this could be clinically useful."[37]

(2) Dr. Jeevanandam: "However, the safety profile was good enough, and I think it's an excellent diagnostic tool. And, you know, even if it's not used in this particular indication, there are an innumerable number of heart failure patients that I take care of that I'd love to put this thing and know what their PA pressures are. For LVAD [left ventricular assist device] patients, you know, you can actually make a big difference in the PA pressures just by turning that LVAD up. And I think that's why, you know, from a selfish point of view, I'd love to be able to put this in one of my patients and measure their PA pressures. I just got paged for two people who need right-heart caths tomorrow who won't need them if you had this sensor in, so that's why I voted yes for Question 3."[38]

In light of these explanations, the "yes" votes by Drs. Patton and Jeevanandam on the final question of whether the benefits of the CardioMEMS system outweigh its risks *for the proposed indication* should be given little weight by the FDA because their votes reflect a desire for a different indication not presented to the advisory committee.

D. Conclusions

In summary, the ancillary analyses performed by the sponsor had numerous limitations and flaws that undermine their validity, and they are not adequate to support approval in the absence of a well-designed, prospective randomized clinical trial. The combined data from the biased randomized clinical trial and the subsequent ancillary analyses conducted by the sponsor fail to provide sufficient evidence to conclude that there is reasonable assurance that this first-in-class, permanently implanted medical device is effective. A significant majority of the advisory committee reached this same conclusion.

[36] *Ibid*. Page 309.
[37] *Ibid*. Page 307.
[38] *Ibid*. Pages 309-310.

Therefore, we again strongly urge the FDA to disapprove the PMA application for the CardioMEMS System. The signal to the device industry that would emanate from FDA approval of the CardioMems System, given the multiple problems noted by the agency as well as a majority of the advisory committee, would be that the FDA is not really serious about implementation of the medical device laws and regulations.

Thank you for taking our comments into account when considering action on the PMA application for the CardioMEMS System.

Sincerely,

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cc: Dr. Margaret A. Hamburg, Commissioner, Food and Drug Administration
Dr. Bram D. Zuckerman, Director, Division of Cardiovascular Devices, Office of Device Evaluation, CDRH, FDA