SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES

ADVISORY PANEL

MEETING

March 2, 2007

Hilton Washington D.C. North
Gaithersburg, Maryland

Circulatory System Devices Advisory Panel Meeting

March 2, 2007

Attendees

Chairperson
William H. Maisel, M.D., M.P.H.
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Voting Members
Sharon-Lise Normand, Ph.D.
Harvard School of Public Health
Boston, Massachusetts

John C. Somberg, M.D.
Rush University Medical Center
Lake Bluff, Illinois

Clyde W. Yancy, M.D.
Baylor University Medical Center Dallas
Dallas, Texas

Consultants
Gary M. Abrams, M.D.
Neurorehabilitation Clinic
UCSF Medical Center, California

Philip B. Gorelick, M.D.
University of Illinois at Chicago
Chicago, Illinois

David C. Good, M.D.
Penn State College of Medicine
Hershey, Pennsylvania

John W. Hirshfeld, M.D.
The Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Richard A. Jonas, M.D.
Children's National Medical Center
Washington, D.C.

Norman S. Kato, M.D.
Cardiac Care Medical Group
Encino, California

Warren K. Laskey, M.D.
School of Medicine
Albuquerque, New Mexico

Richard E. Ringel, M.D.
The Johns Hopkins University
Baltimore, Maryland

Industry Representative
Marcia S. Yaross, Ph.D.
Biosense Webster, Inc.
Diamond Bar, California

Consumer Representative
Mike Fleming, D.D.S., P.A.
Dentist
Durham, North Carolina

Executive Secretary
James P. Swink
Food and Drug Administration
Rockville, Maryland

FDA Participants
Bram Zuckerman, M.D.
Director, Division of Cardiovascular Devices

Ashley Boam

Donna Buckley, M.D., M.S.
Interventional Cardiology Devices Branch

Billy Dunn, M.D.
Division of Neurology Products

Julie Swain, M.D.
Consultant to Division of Cardiovascular Devices

CALL TO ORDER AND INTRODUCTORY REMARKS

Chairperson William H. Maisel, M.D, M.P.H., called the meeting to order at 8:01 a.m. He noted that the voting members present constitute a quorum. He asked the panel members to introduce themselves.

Panel Executive Secretary James P. Swink read the conflict of interest statement. A full waiver has been granted to Philip B. Gorelick, M.D. He noted that Michael J. Domanski, M.D. was unable to attend and that Warren K. Laskey, M.D. would be participating during the afternoon via telephone.

FDA PRESENTATION

Donna Buckley, M.D., M.S., Interventional Cardiology Devices Branch, CDRH/ODE/DCD, began the FDA's presentation on trial design issues for patent foramen ovale (PFO) closure devices, specifically those intended to treat stroke. She provided an overview and some regulatory background. There is currently no device approved for a PFO indication. Two applications under the Humanitarian Device Exemption (HDE) program were recently withdrawn; the indication was for patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO who also failed conventional drug therapy. They were withdrawn after FDA concluded that the eligible patient population is over 4,000 patients per year.

Dr. Buckley described previous recommendations made by the panel and said that enrollment in the randomized trials has been critically slow. The meeting is intended to reevaluate whether randomized control trials are really essential and, if so, to identify potential changes that may increase patient enrollment or, if not, to identify critical trial design elements for non-randomized trials.

Billy Dunn, M.D., Division of Neurology Products, CDER, provided background on PFO. The relationship between stroke and PFO is uncertain, and there is conflicting data in the literature. There is even a wide range of data on the actual prevalence of PFO.

Julie Swain, M.D., Consultant to the Division of Cardiovascular Devices, discussed trial design recommendations made by the agency and concluded that the weight of the data seems to support the need for randomized control trials with this particular diagnosis.

Dr. Buckley said FDA has recommended randomized control trials for the purposes of establishing proof of principle and establishing reasonable assurance of safety and effectiveness. She said enrollment issues are jeopardizing completion of the trials and described some of the design modifications that have already been made.

Dr. Somberg asked about the possibility of various sponsors pooling resources for several different devices. Ms. Boam said the possibility has been explored but they were not successful in bringing about a joint effort. Dr. Maisel asked what a sponsor would have to do to obtain approval for their device if proof of principle had already been proven. Ms. Boam said that an individual hypothesis around device safety and effectiveness from a closure perspective would have to be assessed for each device.

Dr. Somberg said there is not proof of principle that surgical closure of cryptogenic stroke prevents future cryptogenic stroke. Dr. Normand asked about confounders predictive of PFO. Ms. Boam was unaware of any predictive factors and said that 25 to 30 percent of the general population appears to have a PFO, and many apparently have no related symptoms. Dr. Swain said confounders about who has a PFO have not been identified but said that in various studies many covariates have been shown to be over-represented among those with a PFO.

Dr. Yancy asked about the apparent dichotomy between not being able to identify enough patients to enroll in trials and the withdrawal of HDE status because there are more than 4,000 patients per year. Dr. Buckley said the HDE indication was for patients who had at least two strokes in spite of medical therapy while the patient population under discussion is those who had a single stroke or TIA event. Dr. Yancy asked about the number of these devise being placed, including off-label. Dr. Buckley said he does not know the number of patients and that FDA knows how many devices were distributed but not whether they were implanted under the HDE indication or off-label.

Dr. Jonas asked if there was data from the WARSS database on the risk of stroke using these devices in a non-high risk population. Dr. Buckley did not have any information. Dr. Jonas asked whether there had been strokes reported in the ASD population where the devices have been used for elimination of a left-to-right shunt, and Dr. Buckley said yes.

Dr. Hirshfeld asked whether relaxing endpoint criteria by using TIAs or lacunar strokes would introduce more noise into the data due to the heterogeneity of endpoints and the ambiguity of their relationship to the pathophysiology being targeted. Dr. Dunn said it could create more noise and that the key is making sure it is an ischemic event.

Dr. Abrams asked if data pooling had been done frequently and whether there was a good model. Dr. Zuckerman said it has been done very infrequently, generally due to the reluctance of sponsors. He said the most successful use of pooling involved a breast imaging randomized trial involving four sponsors. Dr. Abrams said there would be safety issues for each device, and Dr. Zuckerman said the Data Safety Monitoring Board as well as the agency would need to carefully follow the progress of the trial.

Dr. Ringel stated that only control data would have to be pooled. He then asked if the FDA has a target sample size for the sponsors to reach a meaningful endpoint. Ms. Boam said sample sizes are largely driven by the wide range of reported rates of recurrent embolic events and how conservative one wants to be in powering the trial sufficiently. She said the agency has been unable to determine which estimated rates are more or less valid. Ms. Boam explained that even with the same assumption about the reduction in event rates, there will be different sample sizes based on what particular rates are assumed.

Dr. Normand suggested that FDA should be able to come up with the baseline rate in the control group. Dr. Swain said the covariates, both known and unknown, essentially make every institution a different population. Dr. Zuckerman said there are multiple ongoing trials with different assumptions which FDA believes are supportable enough such that sponsors can take the risk of trying to develop adequate clinical data. Dr. Zuckerman urged caution regarding any specific discussion regarding proprietary trial protocols provided to the panel. Dr. Maisel said that control rates for a given inclusion and exclusion criteria will vary as those criteria vary.

Dr. Gorelick asked which of the factors limiting enrollment are more significant. Dr. Buckley said the individual sponsors would be in a better position to respond. Dr. Maisel asked if the agency's position is that off-label use is interfering with enrollment efforts. Ms. Boam said they do not have an official position

but that patients present wanting their hole closed and knowing there are physicians who will use a device off-label.

Dr. Somberg returned to the issue of pooling and wondered if it would be possible to keep the results for each particular device proprietary. Ms. Boam said that would be reasonable but that the sponsors would likely need to agree on an independent third party to hold onto the data.

Dr. Ringel wondered about the controls already obtained by the various sponsors. Dr. Zuckerman noted that data from an ongoing IDE belongs to the sponsor, so that sort of aggregate analysis could not be legally performed without concurrence of the sponsors. Dr. Maisel wondered if individual sponsors would be able to adjust the control estimate from pooled control data for the patient population captured by the sponsor's inclusion and exclusion criteria. Dr. Normand said if the patient populations were approximately the same one could develop a method to determine the right control rare for each particular device, but she noted that the studies themselves would be observational and not randomized because of the pooling. She compared it to a meta-analysis which she described as an observational study of randomized trials.

Dr. Maisel then asked about the possibility of pooling device and control groups to look at proof of principle. Ms. Boam said the agency would be open to that discussion.

Dr. Gorelick asked whether cardiologists or neurologists were driving these trials. Dr. Buckley said they started as primarily cardiologist driven since it is a cardiology treatment but that sponsors acknowledged the role of neurologists in preventing recurrence of stroke so they were included as co-investigators and eventually provided a more balanced perspective of other treatment options. Dr. Gorelick asked if all the cardiology societies had bought into the concept of the trials. Ms. Boam said a representative from the American Heart Association (AHA) would speak later and that the American College of Cardiology (ACC) had provided a written statement. She said position statements have thus far come primarily from the neurology community.

Dr. Ringel thought it would be difficult to pool devices due to the possibility that some devices may have a higher recurrence rate due to provoking clot formation on the device itself. Dr. Yancy was uncomfortable with the idea of a meta-analysis as proof of principle given that the question remains

fundamentally unanswered. Dr. Somberg urged the panel to be realistic and thought a pooled study looking at proof of concept is the way to go. Dr. Normand clarified that they are not really talking about a meta-analysis and described it instead as a large stratified analysis.

Dr. Jonas asked about the potential size of the market for these devices and about market dominance where there are multiple devices. Dr. Maisel said the panel is generally not to discuss issues of cost and economics. Ms. Boam said FDA has not conducted an economic analysis but said the potential market is substantial. Dr. Jonas suggested use of the devices off-label as a way to become seen as the dominant provider could be another factor leading to the difficulties in enrollment. Dr. Yaross agreed there is an incentive to being first to market but said there may be many reasons why sponsors would hesitate to collaborate with one another. She emphasized the importance of patient willingness to be randomized.

Dr. Hirshfeld hoped there could be a broader approach, involving the major professional societies and NIH, to solving the core clinical question. Dr. Somberg suggested a proof of concept trial with some proprietary aspects maintained could be sponsored by NIH. Dr. Zuckerman said it has been informally discussed with NHLBI but it is not one their most critical problems. Dr. Maisel said that if many years of additional trials are required the answer may never be reached because the devices may end up on the market for other indications such as migraine.

Dr. Maisel asked if designs other than superiority such as noninferiority or equivalence would be acceptable to the panel. Dr. Somberg was not in favor of such approaches since we don't know what the best therapy is. Dr. Good noted that the current designs are somewhat contaminated in that they compare medical therapy plus closure to medical therapy. Dr. Maisel said at least some of the devices endothelize so there is potential to stop medical therapy after some duration of time. Dr. Jonas noted the difference between surgical closure and closure with a device and the risk of thromboembolic stroke from putting prosthetic material in the left side circulation.

Dr. Normand said the design must be superiority. Dr. Abrams agreed given that we don't even know the cause of the disease. Dr. Good and Dr. Kato agreed as well. Dr. Kato urged caution in letting the device drive the pathophysiology of the disease.

Dr. Maisel asked about the appropriate endpoints. Dr. Abrams said adding TIA would be messy. Dr. Somberg said adding TIA, particularly in a pooled study, might help answer whether those with PFOs and repeated TIAs need the closure as well. Dr. Good said there would be additional noise since not every event that looks like a TIA is one, and he suggested possibly having an MRI indicator following a transient event. Dr. Somberg proposed only taking very severe TIAs with neurologic sequelae or evaluating the TIA in some other way.

OPEN PUBLIC HEARING

Steven K. Kittner, M.D., M.P.H., American Academy of Neurology, said it was highly plausible that patients choosing or guided toward device closure could be a lower-risk group, so non-randomized designs would not be valid. Noting that cryptogenic stroke patients are very heterogeneous, he said it would be preferable to maintain stratified analysis within randomized designs rather than pooling control groups. Dr. Kittner stated that off-label use is the main obstacle to enrollment, and he suggested limiting CMS reimbursement to randomized patients or very limited medical exceptions. He endorsed the idea of establishing proof of principle by pooling data to get an answer sooner and suggested ensuring treatment effects are homogenous before combining the trials.

John C. Ring, M.D., American Heart Association/American Stroke Association, described the development of the association's guidelines. He said the guidelines should continue to inform and guide practice with any revisions being based on the best available data; the knowledge gap regarding management of these patients can only be filled by randomized controlled trials; and that important clinical and economic adverse consequences must be discussed. He said that although the research is challenging it is not impossible. He said the association would be willing to provide suggestions regarding study design.

Larry Latson, M.D., Director, Pediatric and Congenital Cardiac Catheterization Laboratory, Cleveland Clinic Foundation, said there are often problems in doing trials comparing two very different types of treatment. He said catheter closure is an outpatient procedure. There is no consensus on what constitutes best medical management. He suggested variations of randomized trials such as leveraging geographical variations in practice and allowing sites to enroll patients in only one arm. He stated that only

patients very likely to have had a real embolus preferably with MRI findings should be included and recommended emphasizing reduction in permanent damage rather than TIAs. Dr. Latson said ultimate proof of principle will not come from any single trial conducted now.

Dr. Maisel read part of a statement in support of randomized trials from Dr. Tuzco at the Cleveland Clinic submitted on behalf of the ACC.

PANEL DELIBERATIONS

Dr. Somberg said pooling data is important to proof of concept but acknowledged there may be other possibilities. Dr. Yancy said a registry could help collect data on background noise and event rates; there has been sufficient application of the technology worldwide that there could have been adequate post-marketing data collected; and that off-label is compromising the science.

Dr. Maisel asked about the current standard of care. Dr. Yancy noted that percutaneous closure of a PFO is a class 2B AHA recommendation with a C level of evidence. Dr. Kato said we will only know we should close the PFO when we can say that something is no longer a cryptogenic stroke but a PFO-related stroke. Dr. Ringel urged the panel not to overly condemn off-label device use given the number of pediatric cardiology therapies that never have and presumable never will be studied in randomized controlled trials and given that there are patients who either do not qualify or refuse to participate in a trial.

Dr. Maisel stated that the position of the panel is that PFO closure is not the standard of care because we lack the evidence. Dr. Yaross noted that the medical device regulations allow for forms of scientific evidence other than from randomized controlled trials.

Dr. Ringel said standard of care is what is actually happening and that we do not know what it is. Dr. Kato noted that Dr. Maisel's statement should pertain to both surgical and device closure. Dr. Normand expressed her frustration regarding the lack of data on the magnitude of off-label use.

Dr. Maisel asked hypothetically how the panel would feel about pooling data for the control group. Dr. Somberg said it would be useful for the control group and restated his assertion that it would be a valid approach for a proof of concept study for the device. Dr. Normand said we would have to first determine if control groups are poolable and said that since patients all want the device it would be a way to get an

adequately sized control group for all the devices. She said the control and treated data would need to be collected around the same time and that there would be lots of corrections involved in the analysis.

Dr. Laskey asked how we would address the issue of the unblinded assessment of the endpoint. Dr. Normand said that issue would exist even if the data were not pooled. Dr. Laskey said there could be blinded observers, but Dr. Normand said the patient would still know whether or nor they got the device.

Dr. Good explained his belief that the only way to answer the question is through some form of randomized clinical trial. Confining the discussion to patients with PFO and a first cryptogenic stroke, Dr. Maisel asked if the panel agreed with Dr. Good. Dr. Abrams agreed that randomized controlled trials are probably the only way to get good answers. He also suggested that much information could be gleaned from pooling the device data collected thus far. Dr. Maisel noted there would be a potential major penalty if their trial weren't entirely ruined. Dr. Somberg said they could simply look at what happened when a PFO was closed without knowing which particular device was used. Once we know there is benefit to closing the hole, there may be approaches other than randomized trials that could provide data on performance of individual devices. Dr. Yancy agreed that we could learn something but still did not feel it appropriate to pool the device data.

Dr. Zuckerman urged the panel to consider other options as well given that industry generally does not agree to pool data. He said there would considerable effort involved in pooling the data, and he asked for comments on Dr. Somberg's point that if proof of principle were shown there could be reduced requirements for each individual device manufacturer. Dr. Gorelick suggested they may need to conduct the trials separately to decide if the devices work and then do an overview analysis to look at just how well it works. Dr. Normand said that if pooling data at the beginning is not useful then it won't be at the end either. Regarding pooling device data she said she was less sure about the exchangeability of the devices than of the patients.

Dr. Normand proposed a delayed strategy as an alternative whereby patients assigned to medical therapy could, after some period of time, get the device. Dr. Yaross cautioned not to pool device data on an intention-to-treat basis because of potential differences in effectiveness and suggested looking at confirmed

closure rather than mere use of the device if that sort of pooling is used. Dr. Jonas was opposed to pooling device data due to varied thromboembolic risks.

Dr. Hirshfeld said the trials could be enrolled fully if off-label use was stopped so that the trials were the only way to get the devices. Dr. Gorelick talked about the financial pressures for clinicians to do the procedures. Dr. Maisel noted that CMS will not pay for a PFO closure device since none has been approved but it is difficult to sort out off-label uses of other devices put into PFOs. He stated that off-label use is not the sole impediment to enrollment, eliminating it would not be easy, and doing so likely would not cause a huge immediate spike in enrollment.

Dr. Somberg said off-label use can be very useful in certain situations where regulation has fallen behind. He acknowledged the concerns regarding pooling different devices but said there are ways to deal with the problems.

Dr. Maisel asked if there are high-risk patient subsets in which randomized controlled trials would be either unnecessary or inappropriate. Dr. Abrams stated that a patient with a large PFO, atrial septal aneurysm, and recurrent stroke will likely automatically get a closure, but he noted that even in such a patient there is no evidence of effectiveness. Dr. Yancy said surgical closure would also be an option for high-risk patients. Dr. Norman wondered why we should let a closure happen in certain patients when we don't know if it will do anything.

Dr. Somberg believed there is no subset that should not be randomized but suggested there may be some who one may not initially enroll due to resistance to studying them. Dr. Maisel suggested an IDE registry for those who will not or can not be randomized. Dr. Zuckerman noted that since there is not proof of principle such registries could not by themselves have enough data to provide reasonable assurance of safety and effectiveness. Dr. Hirshfeld agreed and said the registry patients might not be representative of the overall population of patients with the disorder.

Dr. Yancy said if the goal is identifying patients not suitable for the clinical trial, then a registry concurrent with the trial would seem to be appropriate, but if the purpose is to understand the universe of patients, then the registry would not necessarily have to be in line with the trial. Dr. Ringel said it is

important for effectiveness to be demonstrated in lower-risk patients before the devices are approved for the higher-risk population and that registries for high-risk patients may provide useful adjunctive information. Dr. Yaross said that each sponsor has the right to identify the population they intend to treat with their device. Dr. Kato said it is difficult to condone something other than the traditional randomized prospective trial and acknowledged that it may well take quite some time to complete the trials.

Dr. Somberg said that registries siphon patients from the intended study because the urgency given to each individual patient can make one feel that a less sick patient is really very sick.

Dr. Fleming brought up ongoing research implicating periodontal pathogens in thromboembolic events and said it offers an additional confounder. He stated that he does not think a patient undergoing active therapy for periodontal disease would be a good candidate for an implanted device. He also was concerned about the materials used in the devices with regard to patient sensitivity. Dr. Maisel noted that FDA requires extensive biocompatibility testing.

FDA QUESTIONS

1. Please identify and discuss the barriers to enrollment in the current randomized trials.

Dr. Maisel said the panel's general feeling is that off-label use is likely the biggest barrier. There is also physician and patient bias, and some inclusion and exclusion criteria could be broadened. One panel member noted there are also barriers related to insurance.

2. Given the answer to number one, what, if any, changes do you suggest in order to facilitate enrollment? Please comment on the following:

a. investigational plan (patient selection criteria, statistical plan, follow-up, medical therapy arm)

b. recruitment method (referral patterns, patient educational materials, direct patient incentives, advertising).

One panel member suggested a website to provide unbiased information and urge patients enroll in a trial. Dr. Zuckerman suggested a consistent true message on the websites of the major professional societies. Another member suggested that the sponsors and their investigators also work to get the message out.

One member said that legitimate TIA could be included and suggested getting neurologists involved in the initial recruitment process. One member suggested strengthening the requirement of the data to support the hypothesis. Another member said there are statistical methods for adaptive allocation of sample size that will penalize you for an interim analysis but thought it would be better to select a different design from the beginning. Another thought it would be beneficial to somehow facilitate reaching proof of principle.

One member felt that relaxing eligibility or endpoint criteria might reduce the likelihood of a positive finding. Another possibility is pooling of the medical therapy arms. Regarding patient incentives, one member suggested things like travel money and flexible hours. Dr. Maisel said the biggest incentive should be the chance to help answer a question that could save the patient's life. Another member suggested offering patients the cost of the procedure. Dr. Maisel agreed that patients in a trial should not have to pay for their procedure but noted that many of the patients fall below the Medicare age. A member suggested that sponsors look at increasing the number of sites.

3. For alternate trial designs, please provide your recommendations for critical trial design elements such as overall design, control group, patient selection criteria, endpoints, statistical methods, and methods to reduce bias.

Dr. Maisel stated that for the group of PFO and first cryptogenic stroke randomized trials are needed but that a complementary registry for higher risk groups would be acceptable. Some members felt that a registry could potentially siphon patients away from the trials and that the critical question should be answered before doing a registry. Dr. Maisel admitted there may be ways to game the system but stated that there will be patients not eligible for enrollment whose physicians want to close their PFO. Dr. Zuckerman agreed and said that adjunctive registries can be designed.

Dr. Maisel repeated his belief that physicians will not randomize patients who have already had two strokes to medical therapy. A member noted that just as we do not know how to treat patients with first

cryptogenic stroke we also do not know how to treat those with more than one. He stated that we will never find the answer for these patients from registry data. One member agreed. Another disagreed and thought it would be backtracking from the precedent established with the HDE indication.

One member did not think whatever is decided for the HDE population will have a major impact on successful completion but thought it reasonable to enroll them in a registry. Two members agreed that they would not be enrolled and that it would better not to lose their data entirely. Another also agreed with putting them in a registry. Another member disagreed with the use of a registry. Another was unsure of what the HDE group is at high risk of but thought it reasonable to put them in a registry.

One member suggested they could be enrolled in a different randomized trial, perhaps with more stringent medical therapy or with a surgical arm. Two members felt that a randomized trial should be the first choice but failing that a registry would be acceptable.

The industry representative noted that inclusion is up to the individual sponsors and that the particular devices granted HDEs were found by FDA to be reasonably safe and have probable benefit. One member stated that if some of the protocols allow those randomized to medical therapy to cross over if they have another event, then we should allow those who have already had a second event to get the device and be put into a registry.

Dr. Maisel said selection criteria had already been discussed. He said the consensus is that death and stroke are good endpoints, particularly when strokes are blindly adjudicated or demonstrated by hard radiographic evidence. One member wondered whether the main endpoint should be at less than two years. Another stated that the early time period is high-risk for recurrence following TIA and ischemic stroke but that risk remains fairly high out four or five years. One member noted that estimates of recurrent stroke rates are not necessarily reliable.

Ms. Boam said that FDA had recommended a short period of time, 90 days, between first event and enrollment in a trial in order to capture early recurrence, but they found it to be a barrier to enrollment because patients could not qualify for the trial within that time period. One member encouraged the investigators to do as comprehensive a workup as possible to ensure that the strokes are actually cryptogenic.

Dr. Zuckerman asked proposed an alternative design consisting of two trials, one an equivalence trial comparing to medical therapy with an agreed upon delta, followed by a single arm registry of device use id the sponsor was able to show non-inferiority in the first trial. Dr. Normand said the first would have to show equivalence and not simply non-inferiority and that there would be much debate regarding the range of equivalence. She would be comfortable then using a well-designed observational study to learn more about superiority of the device. A member was concerned in that we don't know which if any medical therapy works but thought an observational study would be reasonable once we establish that closing the hole works.

Another member said to make a case for the device one would have to show it is superior, not equivalent, to antiplatelet therapy since antiplatelets are not a big deal. Another suggested the alternative of a three-arm study showin warfarin was superior to dual antiplatelet therapy and the device was even just noninferior to warfarin.

4. Given the discussion for numbers 1 through 3 above, is randomization of device closure to medical therapy (in patients with cryptogenic stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramen ovale) essential to generate interpretable data for the evaluation of device safety and effectiveness to support approval of a PMA application?

5. Please provide any other recommendations you believe would facilitate enrollment and completion of these clinical trials.

Dr. Maisel said his sense is that the panel feels randomization is necessary for patients with PFO and first cryptogenic stroke but there may be a subset of patients who fit the former HDE criteria that may be appropriate for enrollment in a registry. The panel agreed that randomization is necessary. Some urged consideration of pooling control data, and one emphasized that it be a contemporaneous control population. The industry representative urged the panel to be open to alternative designs which may provide valid scientific evidence.

ADJOURNMENT

Dr. Maisel adjourned the meeting at 3:56 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel on March 2, 2007, and that these minutes accurately reflect what transpired.

James P. Swink
Executive Secretary

I approve the minutes of the March 2, 2007, meeting as recorded in this summary.

William H. Maisel, M.D., M.P.H.
Chairperson

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