FDA Panel Summary

Date: January 31, 2007

To: Circulatory System Devices Panel Members
From: Division of Cardiovascular Devices PFO Review Team
Re: PFO Trial Design Issues

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I. INTRODUCTION

The concept of percutaneous closure of a Patent Foramen Ovale (PFO) in patients with cryptogenic stroke has been under various forms of clinical evaluation in the United States for approximately ten years, yet no prospective trial has been completed and no device has been approved under the Premarket Approval (PMA) process. Although limited marketing applications (i.e., Humanitarian Device Exemptions (HDE) applications) were approved for “high risk” populations, these applications have been recently withdrawn secondary to an increasing patient population, beyond the limit eligible for the special Humanitarian Use Designation (HUD), thus rendering them ineligible for continued marketing under HDE applications.

For numerous reasons, FDA has required sponsors to design randomized controlled trials that would allow for the assessment of safety and effectiveness. FDA’s requirement has been supported by the Circulatory System Devices Panel on two occasions. Currently, the standard therapy for patients with cryptogenic stroke due to presumed paradoxical embolism is medical treatment, although septal occlusion devices approved under PMA applications for other indications are also used in some patients “off-label.” Despite efforts to develop trials that have lower sample sizes, broader patient populations, multiple control options and increasingly novel statistical methods, enrollment in these trials has been slow and sponsors who have made efforts to complete randomized trials have suggested that a randomized study is simply not feasible and will not be completed. The purpose of this meeting is to reevaluate whether randomized trials are essential. If so, we hope to identify potential changes that may improve patient recruitment and, if not, we hope to identify critical trial design elements for nonrandomized trials.

II. HISTORY OF PFO OCCLUDERS

A. Device Descriptions

AMPLATZER PFO Occluder
The AMPLATZER PFO Occluder is a self-expandable, double disc device made from a Nitinol wire mesh. The two discs are linked together by a short connecting waist allowing free motion of each disc. Both discs are covered with a polyester fabric to enhance its closing ability. The polyester fabric is securely sewn onto the device by a polyester thread. Platinum maker bands are attached to the wire ends and laser welded. A microscrew attachment on the proximal disk connects the device to a microscrew attachment welded on the distal end of the delivery cable. A pin vise attached to the proximal end of the delivery cable is used to unscrew the PFO device from the delivery cable following deployment. The device is available in the following sizes (corresponding to the left and right atrial disc diameters, respectively): 18/18mm, 18/25mm, and 25/35mm.

The AMPLATZER PFO Occluder is only available in the U.S. under IDE.
**NMT STARFlex® Septal Closure System**

The STARFlex® Septal Closure System includes a device that has two opposed disc-like occluders each having an umbrella shape and constructed of a metal framework (MP35N) to which polyester is attached. At the center of the occluders is an inter-connecting point, which allows the product to be placed within the defect and opened such that one umbrella is on either side of the defect. Nitinol microsprings are attached between the distal end of each arm to its opposing arm to provide a flexible, adjusting centering system. The device consists of eight wire spring arms covered with two pieces of knitted polyester fabric. The device incorporates a self-centering mechanism which assists to centrally locate the implant within the defect. The device is available in three sizes: 23 mm, 28 mm, and 33 mm.

The NMT CardioSEAL Septal Closure System, a previous generation device, is also available under PMA P000049 for closure of muscular ventricular septal defects (VSDs), approved December 5, 2001 (see [http://www.fda.gov/cdrh/pdf/P000049.html](http://www.fda.gov/cdrh/pdf/P000049.html)).
**St. Jude Medical PREMERE PFO Closure System**

The PREMERE PFO Closure System includes a self-expanding dual-anchor (left atrium anchor—LAA and right atrium anchor—RAA) arm occlusion device; the anchors are made of Nitinol. While the LAA is fixed to the distal termination of the tether, the RAA is attached by a flexible tether and is free to move along the tether to allow for variable length between the anchor arms and is secured by a lock on the proximal side of the RAA. The right anchor is sandwiched between two knitted polyester fabrics. A flexible polyester braided tether running through the center of the anchor holds the two anchors together. The anchors are locked together after delivery and the tether is cut. The distance between the two anchors are variable depending on the length of the PFO track. The Implant Assembly is shipped preloaded into the Loading Tube and assembled together with the Delivery Catheter Assembly. A retrieval basket assembly allows for the retrieval of the device before the tether is cut. The implant device is supplied in the following sizes: 20mm, 25mm, & 30mm.

The PREMERE PFO Closure System is only available in the U.S. under IDE.
**Cardia PFO Closure Device**

The Cardia PFO closure device consists of two sails of white, polyvinyl alcohol foam sutured to a Nitinol and platinum-iridium frame. Attached to the frame are Nitinol struts, each with a small titanium endcap, which serve to anchor the device. The Nitinol struts secure the device in place in vivo by holding each PVA sail on its respective side of the interatrial septum. The struts range in length from 15-45 mm and the center post lengths range from 1.25 to 5 mm. The PVA sails close the patent foramen ovale by holding the septum primum and septum secundum together in a “closed” position, by obstructing the through-flow of blood, and by providing scaffolding on which endothelial in-growth will occur. At the right atrial side of the device’s platinum-iridium center post is a grasping knob, where the delivery forceps used during implantation holds the device. These forceps allow for retrieval of the device prior to release (an in some embolization events) in the case that the device is unable to be properly seated in the defect; the device can be re-grasped at any of the nitinol strut end caps, or grasping knob, withdrawn into the delivery catheter and removed. The device and forceps are transported using a loading sheath.

The Cardia PFO Closure Device is only available in the U.S. under IDE.
The GORE HELEX Septal Occluder implantable device is comprised of a hydrophilic, expanded Polytetrafluoroethylene (ePTFE) material supported by a nickel-titanium (nitinol) super-elastic supporting wire frame. The ePTFE leaflet is supported by the nitinol frame and spaced by distal (left atrial), central, and proximal (right atrial) nitinol eyelets. The ePTFE material is bonded to the nitinol support wire by Fluoronated Ethylene Propylene (FEP). The nitinol wire frame is pre-formed into a helical shape then stretched and supported as it is loaded into the delivery system. When fully deployed it resumes a low profile double disc, circular shape in the heart. Once the occluder covers the defect, the porous ePTFE material allows tissue attachment that ultimately produces a stable, permanent defect closure.

The GORE HELEX Septal Occluder (implantable device) is supplied in five sizes sufficient to give the deployed, double disc nominal diameters of 15 mm, 20 mm, 25 mm, 30 mm, or 35 mm. The GORE HELEX Septal Occluder is deployed from a 10 French (Fr) outer diameter delivery system.
The GORE HELEX Septal Occluder is also available under PMA P050006 for the closure of ostium secundum atrial septal defects (ASDs), approved August 11, 2006 (see http://www.fda.gov/cdrh/pdf5/P050006.html).

B. Anatomy/Physiology of PFO and Cryptogenic Stroke

PFO is a congenital cardiac lesion that persists into adulthood in approximately 25-30% of individuals. A PFO is a flap-like opening between the atrial septum primum and secundum at the location of the fossa ovalis (see Figure 1 below). During fetal development, oxygenated blood from the inferior vena cava crosses through the foramen ovale to provide oxygenated blood for the systemic circulation. At birth, establishment of the pulmonary circulation increases the left atrial pressure, pressing the flap against the septum and closing the communication. Complete closure occurs in 70-75% of individuals by age 2; it is unknown why closure fails to occur in the remainder. PFO may be associated with an atrial septal aneurysm (ASA), which is present when redundant tissue in the region of the fossa ovalis results in excessive septal wall motion during respiration. Many patients with ASA also have a right-to-left shunt, and in

patients with a PFO, the presence of an ASA has been associated with a larger separation between the septum primum and secundum and a larger right-to-left shunt.4

Figure 1 – PFO with shunting

Strokes may be ischemic or hemorrhagic in nature, with the majority of ischemic strokes due to cardioembolism, large vessel atherothromboembolism, small vessel occlusive disease or other mechanisms. However, in patients under 55 years of age, an estimated 30-40% of ischemic strokes have no identifiable cause, and are labeled as cryptogenic.5

The prevalence of a PFO with or without ASA has been shown to be higher in individuals with cryptogenic stroke than in individuals with a stroke of known cause. These findings have suggested a causal relationship between atrial septal abnormalities and stroke, with the mechanism posited to be a paradoxical embolus. Although this is the most frequently cited mechanism, some evidence has been presented to support other suggested etiologies such as cardiac embolism secondary to aortic atheromatous disease, hypercoagulable states, preclinical or subclinical cerebrovascular disease, and inflammatory disease.

Among patients with cryptogenic stroke and a PFO, recurrence rates have been estimated to be 1 to 2% per year6,7 and as high as 4.0% per year in patients with a PFO and ASA.8

However, stroke patients with PFO did not have a significantly increased risk of recurrent stroke or death at 2 years compared to stroke patients without a PFO in the PICSS trial. Additionally, a recent prospective population-based study found that, after correction for age and comorbidity, PFO was not an independent risk factor for future cerebrovascular events in the general population.

C. Current Therapies

Therapeutic options for patients with ischemic, cryptogenic stroke and PFO include medical therapy, surgical closure, or percutaneous device closure. Medical therapy includes antiplatelet medications such as aspirin, clopidogrel (Plavix), and dipyridamole (Aggrenox). Anticoagulation therapy, mostly warfarin (Coumadin) has also been used to prevent recurrence of stroke, although continuous monitoring to maintain an appropriate international normalized ratio (INR) is critical to prevent an increased risk of bleeding complications. The Seventh ACCP (American College of Chest Physicians) Conference on Antithrombotic and Thrombolytic Therapy resulted in the publication of evidence-based recommendations for medical therapy for the prevention of stroke. For patients with PFO and cryptogenic ischemic stroke, the ACCP recommends use of antiplatelet therapy over no therapy as well as over warfarin. For patients with deep venous thrombosis, the group recommends the use of anticoagulation. The American Heart Association/American Stroke Association (AHA/ASA) practice guideline also finds the use of antiplatelet therapy reasonable to prevent a recurrent event in patients with PFO and stroke or TIA. The AHA/ASA also recommends warfarin for high-risk patients who have other indications for oral anticoagulation such as those with an underlying hypercoagulable state or evidence of venous thrombosis.

PFO closure can be achieved through surgical closure or placement of a device. Surgical closure attains high rates of defect closure, but the reported efficacy in reducing recurrent stroke and transient ischemic attack (TIA) in patients with prior ischemic events has been variable (ranging from 0-14% recurrence over 5-13 months follow-up).13,14

Closure of a PFO can also be accomplished through percutaneous placement of an occluder device. The effectiveness of percutaneous device closure of PFO for the prevention of recurrent stroke or TIA has not been established in a randomized, controlled trial setting compared to medical therapy. A systematic review of 10 studies of device closure reported that the rate of recurrent neurologic embolic events at one year ranged from 0% to 4.9%. Major complications such as death, hemorrhage requiring transfusion, cardiac tamponade, need for surgical intervention and fatal pulmonary embolus occurred in 1.5%, with minor complications occurring in 7.9%.15

In 2000 and 2002, FDA approved Humanitarian Device Exemptions (HDEs), for two devices intended for the non-surgical closure of a patent foramen ovale (PFO) in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy. Note that this indication required that the patient have been unsuccessfully treated with drug therapy following an initial cryptogenic stroke. HDEs are a form of marketing approval established for devices intended to treat diseases or conditions that occur in patient populations of fewer than 4000 individuals in the US per year. HDEs are exempted from the effectiveness requirements for a Premarket Approval Application (PMA), for which a manufacturer must demonstrate a reasonable assurance of both safety and effectiveness. In granting these approvals, FDA concluded that the each manufacturer had demonstrated that its device, when used according to the proposed indication, provided safety and probable benefit.

D. HDE Approvals/Withdrawals

FDA recently notified two manufacturers, AGA Medical and NMT Medical, of its intent to formally propose to withdraw the HDE marketing approvals for two patent foramen ovale (PFO) occluders previously approved for the treatment of patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO and who have failed conventional drug therapy; that is, patients who have had at least one additional stroke despite treatment with appropriate medications. As a result, the sponsors agreed to voluntarily withdraw their HDEs, effective October 31, 2006. Although these devices are no longer available for marketing under the HDEs, FDA has worked with the sponsors to

develop Investigational Device Exemption (IDE) studies to continue access of the device
to eligible patients. Because Humanitarian Device Exemptions (HDEs) are a special type
of marketing approval granted for devices intended to treat fewer than 4,000 people a
year in the U.S., HDEs are a mechanism to encourage development of medical devices
for rare conditions. These regulations authorize FDA to withdraw an HDE approval if a
device no longer meets the eligibility requirements. After FDA’s most recent review,
FDA concluded that the patient population described by the approved indication (patients
with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO
and who have failed conventional drug therapy) is significantly in excess of 4,000
patients in the U.S. per year (see http://www.fda.gov/cdrh/ode/h000007-
h990011withdraw.html for more information).

III. PREVIOUS PANEL RECOMMENDATIONS

PFO trial design issues have been discussed during two prior meetings of the
Circulatory System Devices Panel held on October 24, 1997 and September 10,
2002. The October 24, 1997 meeting was held specifically to discuss trial design
issues for transcatheter devices intended to treat Atrial Septal Defect (ASD),
PFO and Patent Ductus Arteriousus (PDA). Although, the majority of the
discussion considered ASD and PDA trial design issues, the panel offered the following
conclusions regarding PFO trials:

- randomized controlled trials are essential
- assessment measure should be freedom from recurrent stroke and perhaps
  reduced need for anticoagulation.

The September 10, 2002 meeting was held in order to discuss PMA approval for a limited
PFO indication. The proposal included a retrospective evaluation of “high risk” patients
and was unanimously considered “not approvable.” Furthermore, the Panel made the
following general recommendations regarding PFO trial design during that meeting:

- randomized controlled trials are essential
- primary endpoint should be stroke and death evaluated at two years
- patient population should be limited to patients who have suffered a
  permanent neurological deficit (i.e., stroke)
- medical therapy administered to both control and device patients should be
  given according to pre-specified regimens

IV. CURRENT FDA TRIAL DESIGN RECOMMENDATIONS

FDA’s most recent recommendations regarding PFO trial design include many
suggestions offered during the September 10, 2002 Panel Meeting. Although a guidance
document specific to PFO closure for the prevention of recurrent stroke is not available,
FDA has been consistent in its recommendations to study sponsors since the most recent Panel meeting. In particular, for the treatment of patients who have a history of cryptogenic stroke or transient ischemic attack due to presumed paradoxical embolism through a PFO, FDA has recommended prospective, multi-center, randomized controlled superiority trials comparing stroke and TIA reduction in patients treated with "best medical therapy" plus device versus patients treated with "best medical therapy" alone. (Note that TIA was included, despite the Panel’s suggestion of its exclusion, in order to promote patient recruitment.) FDA suggested that the trials should be conducted under the guidance of a Data Safety Monitoring Board and incorporate Core Lab Review. The following additional recommendations were made regarding: (1) primary endpoint; (2) patient selection criteria; and (3) follow-up:

1. **Primary Endpoint**: combined endpoint with the following components:
   a. **neurological death**: all cause mortality within 30 days of procedure or until hospital discharge (whichever is greater) and neurological death after 30 days
   b. **stroke**: acute focal neurological deficit that is MR imaging positive, regardless of the duration of symptoms (or neurological deficit persistent for over 24 hrs if no imaging performed)
   c. **TIA**: acute focal neurological event (defined as focal motor deficit, aphasia, difficulty walking, hemisensory deficit, amaurosis fugax, blindness, or focal visual deficit) lasting at least 5 minutes that is MR imaging negative

2. **Patient Selection Criteria**:
   a. demonstration of R→L shunt with a transesophageal echocardiogram (TEE)
   b. history of stroke or TIA within the past 90 days (study sponsors have extended this time period to ≥180 days promote enrollment)
   c. no other apparent source of stroke (exclude patients with carotid stenosis, mitral/aortic stenosis, history of atrial fibrillation, coagulopathies, etc.)

3. **Follow-up**:
   a. History, physical exam, chest x-ray, EKG
   b. TEE versus transthoracic echocardiogram (TTE) to assess shunting (6 months and every 6 months thereafter until closure or “trivial” shunt)
   c. neurological evaluation (baseline, 30 days, 6 months, 12 months and yearly thereafter)
   d. DWMRI with any neurological event

V. **DATA INTERPRETATION PROBLEMS WITH NON-RCT**

In general, randomized controlled trials are the gold standard for the evaluation of new drugs and devices. They reduce the likelihood of bias (e.g., patient selection bias), enhance the likelihood that comparable groups of subjects are actually compared (balances unknown and known covariates) and support use of common statistical tests. Although FDA does not require randomized clinical trials for all new technologies,
randomization becomes increasingly important when: (1) the method of diagnosis is variable and the disease state is poorly understood; (2) there is no single agreed upon standard of care; (3) there are likely covariates that may impact data interpretation; and (4) there are reasons to believe that bias may be a significant problem.

Unfortunately, the treatment of patients with cryptogenic stroke who have a PFO appears to have these limitations; therefore, making this condition an ideal and necessary candidate for study under a randomized controlled trial.

(1) The principle assumption that there is a direct causal relationship between PFO and increased risk for stroke is debated. In fact, the description of the patient population highlights this uncertainty, i.e., cryptogenic stroke patients with presumed paradoxical embolism. The diagnosis is one of exclusion and highly dependent upon the ability to effectively and thoroughly exclude alternative stroke etiologies (e.g., cerebral ischemia related to occult paroxysmal atrial fibrillation). As advances continue to be made in diagnostic testing (e.g., vascular imaging, markers for hypercoagulable states), more strokes that were previously classified as cryptogenic, will have an identifiable etiology and treatment that has no relationship to PFO closure. The lack of certainty regarding stroke etiology in some patients who happen to have a PFO increases the need that well-controlled trials be performed to avoid providing an arguably unnecessary treatment to some patients with all of its attendant costs and risks. Although some argue that PFO closure may be justified on the basis of eliminating a risk factor for stroke in a patient with known stroke, there are others who argue that this position is based on the faulty assumptions that there is a certain and predictable relationship between the presence of PFO and the risk of stroke and that the procedure is perfectly efficacious (i.e., device placement will not increase the patient’s risk for an embolic stroke, for example, due to thrombus on the device.)

Therefore, rigorous randomized trials have been consistently recommended given the basic lack of certainty regarding the causal relationship between PFO and stroke and, further, the difficulty in definitively identifying those patients in whom the presence of a PFO has been established to have “caused” the stroke by excluding other etiologies.

(2) Currently, no optimal medical therapy has been clearly identified. Nonrandomized trials rely on the certainty that comes with the repeatable, predictable and comprehensive outcomes of patients who are treated with an agreed-upon standard of care therapy in order to establish a plausible control group. The choice of treatment for the prevention of stroke in this subject group of patients varies tremendously. The medical agent chosen may be based on the treating physician’s familiarity with the drug, their belief that one agent is more efficacious than another, their fear of adverse events associated with a particular agent as well as individual patient characteristics (e.g., overall medical condition, age, prior bleeding events). Even if a single agent is chosen, there is variance in terms of the agreed upon dose (or goal INR) and how patients should be followed for recurrent disease. The variability in individual practice is likely a reflection of the conclusions of clinical trials that have not consistently established one agent as superior over another.
Therefore, prospective, randomized trials comparing devices to medical therapy have been consistently recommended because of the inadequacy of a clear control group from which to define outcome measures for comparison.

(3) Even if one were to accept that there is a clear relationship between PFO and stroke and that there is a clearly definable and accepted medical therapy to develop a control group, a nonrandomized trial cannot control for known and unknown covariates. There have been studies to suggest that there are several factors that may also influence stroke recurrence in these patients. For example, many would argue that the presence of an atrial septal aneurysm is an independent risk factor for stroke and will influence outcome. Other factors may include patient age, comorbid medical conditions, defect size/configuration, and thrombophilic disorders among other plausible covariates, as well as those covariates that are unknown.

Randomized trials have been recommended because they increase the likelihood that comparable groups will actually be compared by balancing unknown and known covariates.

(4) Multiple forms of bias may be expected to influence the conduction of a nonrandomized trial. Patient selection bias is expected given the variability in treatment modalities and the differences in institutional/investigator beliefs and approaches. Patients will be expected to be chosen for entry into a nonrandomized device trial, not based on their eligibility with regard to the trial’s selection criteria, but rather if the investigator has already reached the conclusion that device closure will be the patient’s “best” treatment option. Perhaps more significantly, patients will certainly self-select their preferred treatment based on the information they have gathered from the internet, sponsor advertising, and the physicians to whom they have been exposed. Investigator bias is another form of bias that may influence the evaluation of patients on follow-up (e.g., neurological exam) and, as a result, influence results in the direction of the investigator’s predicted outcome.

Randomized trials have been recommended because they were considered necessary to minimize the expected introduction of bias into the trial.

VI. PUBLISHED PROFESSIONAL SOCIETY POSITIONS

At this time FDA does not consider the information available on the broader use of device closure of PFO as valid scientific evidence sufficient to support the approval of a premarket approval (PMA) application. The available data, whether presented in the literature or at scientific meetings, have significant limitations, having been derived from mostly retrospective, single-arm studies with generally small series of patients and in some instances, limited follow-up.
The American Academy of Neurology has issued a practice parameter that is consistent with this position, stating, “For patients who have had a cryptogenic stroke and have a PFO...There is insufficient evidence regarding the effectiveness of either surgical or endovascular closure of PFO.” The American Heart Association/American Stroke Association has reached a similar conclusion in its most recent guidelines, stating, “PFO closure may be considered for patients with recurrent cryptogenic stroke despite medical therapy” but concluding that “Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO.”

FDA has strongly recommended that prospective, randomized clinical trials are needed to support the safety and effectiveness of PFO closure devices for patients with first stroke or TIA. The Stroke Council of the American Heart Association, the American Academy of Neurology and several authors have echoed this call for randomized trials to be completed.

VII. CONCLUSIONS

FDA has previously recommended to study sponsors that randomized, concurrently-controlled trials comparing device closure to medical therapy are necessary to both establish proof of principle (i.e., closure of a PFO reduces the risk for recurrent embolic events) and to establish a reasonable assurance of safety and effectiveness to support a PMA application. Both the American Academy of Neurology and the American Heart Association/American Stroke Association have concluded in their publications that insufficient evidence exists to support device closure for patients with PFO and stroke or TIA. However, ongoing trials are facing significant enrollment difficulties, leading some manufacturers to urge FDA to consider non-randomized trial designs in the hopes of collecting adequate data more efficiently. In light of the real difficulties that manufacturers are currently facing, we are requesting that this Advisory Panel fully explore all possible relevant options to obtain necessary data.

A table with sample size estimates for a randomized, concurrently controlled trial is included in Attachment 1, for your reference only. A selection of relevant literature is included in Attachment 2.

FDA welcomes the Panel’s expert opinion on the issues raised above; specific questions for your consideration are included in Section 4 of this binder.