FDA EXECUTIVE SUMMARY MEMORANDUM

Transcatheter ASD Occluders: Clinical Update and Review of Events

Prepared for the May 24, 2012 meeting of the
Circulatory System Devices Advisory Panel
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I. Introduction

Surgical closure was previously the standard of care treatment for atrial septal defect (ASD). However, there has been over one decade of U.S. clinical experience with use of transcatheter ASD occlusion devices to close ostium secundum defects (the most common type of ASDs), and transcatheter closure has now become the standard of care at many clinical centers. The AGA/St. Jude AMPLATZER® Septal Occluder (ASO) device was the first device approved for the U.S. market in 2001, followed by the Gore HELEX® Septal Occluder (HSO) device in 2006. (The AMPLATZER® and HELEX® devices are hereinafter referred to as the ASO and HSO devices, respectively.) With widespread use of these devices, more information has become available regarding adverse events. These events range from rare life-threatening complications (such as tissue erosion) to more common events that generally have less severe clinical sequelae (such as device embolization). Although most types of adverse events were seen in the premarket studies, rare serious events such as erosion were not observed.

FDA believes that in keeping with its public health protection mission, it is appropriate to conduct a clinical/scientific review of adverse events associated with transcatheter ASD closure and provide a greater understanding of the benefit-risk profile of these devices. The objectives of this Circulatory System Devices Advisory Panel meeting are: (1) to discuss the significance of important adverse events; (2) to discuss whether additional measures should be taken to improve protection of the public health (e.g., additional clinical studies, data analyses, or labeling changes); and (3) to discuss how best to communicate to patients and physicians what is and is not known about transcatheter closure of ASDs.

FDA is not advocating that there should be restrictions on the use of ASD closure devices in the U.S. Rather, our goal is to be proactive in seeking expert advice on whether our regulatory actions to date have been sufficient or whether additional action (e.g., additional clinical studies, labeling changes, and/or patient/physician communication) would be beneficial. Expert guidance in the form of an FDA Advisory Panel meeting is sought for the following reasons:

- ASD closure devices are permanent cardiac implants (and would be expected to remain in place for many decades for most patients), yet our clinical experience consists largely of relatively short-term use;
- Device use may involve vulnerable pediatric patients, thus increasing our responsibility for scrupulous monitoring;
- Assessment of the etiology and public health significance of rare adverse events (e.g., erosion) is controversial;
- Multiple medical specialties (e.g., clinical cardiology, cardiothoracic surgery, and interventional cardiology) are involved in the assessment and treatment of the condition; and
- A public meeting setting provides full transparency and open communication among experts.

This Advisory Panel meeting is not intended to: (1) reassess the original market entry data for ASD closure devices; (2) substantively discuss off-label device use (e.g., device use for patent foramen ovale (PFO) closure); or (3) suggest that one treatment modality (i.e., surgery versus transcatheter closure) or device model (i.e., the AMPLATZER ASO versus HELEX Occluder) is preferred.

II. Clinical Background

A. Background

ASD Incidence and Types: Ostium secundum ASDs are the most common type of ASD. They account for approximately 75% of all ASDs, and represent approximately 7% of all congenital cardiac defects and 30-40% of all forms of congenital heart disease found in patients older than 40 years. Due to their position and location in the midportion of the atrial septum, secundum ASDs are uniquely suited for attempted percutaneous device closure. Other types of ASDs not currently amenable to catheter-based closure are Ostium Primum Defects (15-20% of ASDs, part of the spectrum of AV canal defects), Sinus Venosus ASDs (5-10% of ASDs) and Coronary Sinus ASDs (rare).

Physiology: ASDs are a family of congenital anomalies characterized by a defect in the interatrial septum allowing pulmonary venous return from the left atrium to pass directly to the right atrium (left-to-right shunt). The magnitude of the left-to-right shunt across the ASD depends on the defect size, the relative compliance of the ventricles, and the relative vascular resistances in both the pulmonary and systemic circulations. A chronic left-to-right shunt results in increased pulmonary blood flow and diastolic volume overload of the right ventricle. Compliance of the right ventricle and vascular resistance in the pulmonary vascular bed is commonly normal in children with ASD, and the volume load is usually well tolerated even though pulmonary blood flow may be more than two times systemic blood flow. Altered ventricular compliance that occurs with aging can result in an increased left-to-right shunt contributing to symptoms. A chronic significant left-to right shunt can alter the pulmonary vascular resistance leading to pulmonary arterial hypertension (PAH), even reversal of shunt to a predominant right-to-left shunt, and the development of the Eisenmenger syndrome.

Gender: Secundum ASD occurs with a female-to-male ratio of approximately 2:1. Because of an increase in plasma volume during pregnancy, shunt volume can increase leading to symptoms in previously asymptomatic patients.

Age at Diagnosis and Treatment: Patients with ASD can be asymptomatic during infancy and childhood, though the timing of clinical presentation depends on the degree of left-to-right shunt. Symptoms become more common with advancing age. By the age of 40 years, 90% of untreated patients have symptoms of exertional dyspnea, fatigue, palpitations, sustained arrhythmia (primarily atrial arrhythmias, especially atrial fibrillation), or evidence of heart failure. Most symptomatic adults older than 40 years have mild-to-moderate PAH in the presence of a large left-to-right shunt resulting in both pressure and volume overload of the aging right ventricle.

The age at diagnosis is bimodal with the majority of patients diagnosed from 0-4 years of age and in the 3-4th decade of life when symptoms develop. Data from the Nationwide Inpatient Sample for the annual number of ASD closures of all types (surgical or percutaneous) are summarized in Figure 1[1], and show the bimodal distribution of ASD closure procedures.

Figure 1: Nationwide Inpatient Sample – ASD/PFO Closures Over Time (1988-2005) as Function of Age and Year[1]

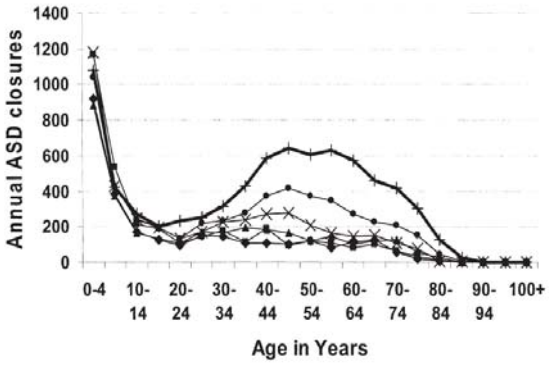


Fig 2. Annual average number of atrial septal defect (ASD) and patent foramen ovale (PFO) closures as a function of patient age. A dramatic rise in the annual number of ASD closures per capita is seen among patients aged more than 40 years in the most recent year sextile. (Diamonds = 1988–1990; squares = 1991–1993; triangles = 1994–1996; crosses = 1997–1999; circles = 2000–2002; vertical slash = 2003–2005.)

B. Therapeutic Alternatives

Treatment: Considering the presence of symptoms, right ventricle remodelling, and increased pulmonary artery pressure with increasing age, closure of an uncomplicated ASD in children is usually recommended for large shunts (Qp/Qs ≥ 2.0), especially when evidence of RV volume overload is present. Long-term prevention of death and complications is best achieved when the ASD is closed before 40 years of age, before symptoms develop. However, even in older patients, the development of symptoms (e.g., embolization, pulmonary artery systolic (PAS) hypertension (PASP ≥ 40 mm Hg), atrial arrhythmias) is a specific indication for closure of the ASD, though long term results are not as favorable.

Alternative Therapies: Both surgery and device closure may be appropriate for treatment of isolated Secundum ASDs.

- Surgery is the historical standard of care for ASD treatment. Direct closure of the defect is achieved using an open approach with extracorporeal support and pharmacologic cardiac arrest. The edges of the defect may be approximated (small defect with sufficient bordering tissue), or native pericardium or synthetic patch materials can be sewn circumferentially at the borders to close the defect. Minimally

[1] Karamlou et al. The Rush to Atrial Septal Defect Closure: Is the Introduction of Percutaneous Closure Driving Utilization Ann Thor Surg 2008; 86:1584-91.

invasive surgical approaches (non-sternotomy, 5-10 cm incision) are now routinely used in experienced centers. All types and sizes of ASD can be treated, and rim insufficiency is not an impediment to successful surgical ASD closure.

- Transcatheter closure of secundum ASDs is now established practice at most cardiac centers. The ASO (and AMPLATZER® Cribriform Devices for fenestrated secundum ASDs) and the HSO are currently approved in the U.S. for this indication. Devices from both manufacturers are percutaneously placed via the femoral vein in a catheterization laboratory setting. Septal occluders are also commonly used "off-label" to close patent foramen ovale (PFO) in patients with cryptogenic stroke, medication-resistant migraine, or other conditions such as orthodeoxia-platypnea.

No large scale, prospective randomized trials comparing open surgery versus transcatheter device closure for the treatment of secundum ASD have been performed. Both the ASO and the HSO devices established a reasonable assurance of safety and effectiveness through trials comparing device closure to non-randomized surgical comparator groups (See Section III below). In these premarket controlled studies, avoidance of surgery, lower incidence of in-hospital adverse events, and reduced length of hospital stay and anesthesia times were the primary benefits attributed to device closure. No mortality advantage was observed for either approach (mortality rates < 0.2% for both surgical and device ASD closure). Clinically significant residual leaks occurred in 2-5% of device closure patients and <1% of surgical patients, while bleeding (resulting in the need for reoperation and wound infections) were more common for surgical patients.

Atrial arrhythmias may occur late after surgical ASD closure, but long-term follow-up is generally not required in surgical patients. Atrial arrhythmias, heart block, thrombus formation, stroke, endocarditis, nitinol allergy, pericardial effusion, embolization, and erosion have been reported as both early and late complications after implantation of an ASD device raising the question whether long term surveillance of ASD device closure patients is warranted.

Changes in Treatment Patterns: Using data from the Nationwide Inpatient Sample, Karamlou et al[1] identified a total of 15,482 secundum ASD/PFO closures between 1988 and 2005, yielding a national estimate of 79,841 ± 2,526 procedures. Of these, 5,495 (national estimate 27,554 ± 2,526) were percutaneous, 10,278 (national estimate 53,710 ± 1,451) were surgical, and 1,196 (national estimate 6,348 ± 235) were unspecified or undetermined type. As shown in Figure 2[1] there has been a substantial increase in the number of ASD closures after 2002, increasing from a prior stable level of approximately 1.08 per 100,000 patients in 1988 to 2.59 per 100,000 patients in 2005, an increase of 139%. This increase in the ASD repair rate has been largely, if not totally, driven by the availability of transcatheter devices approved for the non-surgical closure of secundum ASDs.

Figure 2: Nationwide Inpatient Sample; (a) left – ASD/PFO Closures Over Time (1988-2005) as Function of Age and Closure Type; (b) right -- ASD/PFO Closures Over Time (1988-2005) as Function of Closure Type[1]

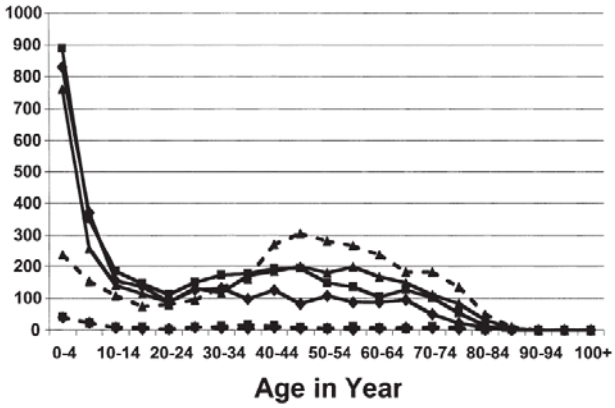


Fig 4. Number of atrial septal defect (ASD) and patent foramen ovale (PFO) repairs per closure type per year as a function of patient age. In earlier years, surgical closure (SC) type was dominated by patients under the age of 10 years. Over time, the proportion of percutaneous closures (PC) exceeded surgical closures, largely as a result of closure among patients aged more than 40 years. Note the increasing number of older patients undergoing surgical closure as well. (Diamonds/dashed line = PC 1988–1993; squares/dashed line = PC 1994–1999; triangles/dashed line = PC 2000–2005; diamonds/solid line = SC 1988–1993; squares/solid line = SC 1994–1999; triangles/solid line = SC 2000–2005.)

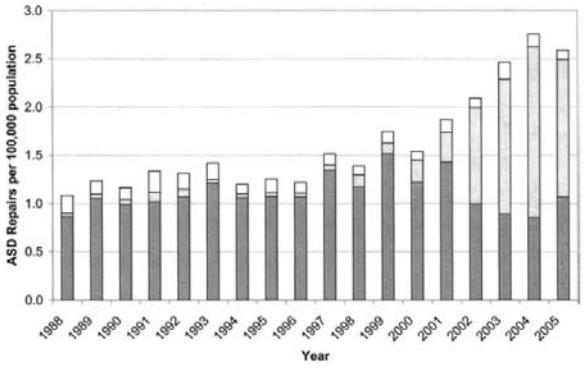


Fig 1. Proportion of each atrial septal defect (ASD) and patent foramen ovale (PFO) closure type normalized to population growth over an 18-year period. Percutaneous closure began to increase in 2001, and supplanted surgical closure as the dominant method of ASD/PFO closure by 2003. (Dark gray area = surgical repair; light gray area = catheterization repair; open area = unknown type of repair.)

Note: As described by Karamlou et al, *"The Nationwide Inpatient Sample (NIS) is a stratified, cross-sectional database that includes approximately 20% of all community (nonfederal) hospital discharges in the United States. The NIS is not a self-selecting, and potentially growing, set of hospitals reporting their data. Rather, it is a national sample of hospitals representing 20% of all national discharges. The fixed structure of the NIS makes it an ideal database to study national trends over time because the influence of increased participation is dramatically reduced. The NIS is managed under the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality. To ensure the representative nature of the database, the NIS is stratified by geographical region, urban versus rural location, teaching status, hospital ownership, and hospital bed size."*

FDA Commentary: Overall, regulatory and historical data suggest that acute and chronic results of surgical and percutaneous repairs have balanced benefits and risks.

The absolute number and normalized rate of ASD closure has more than doubled since the introduction of transcatheter ASD occluders to the U.S. market in 2002. As of 2005, surgery remained the dominant method of ASD repair in the pediatric age range especially under the age of 10, while percutaneous closure was the most common ASD repair procedure overall and is dominant in adults (Figure 2).[1]

C. Approval Decision

The ASO device was FDA-approved via a premarket approval application (PMA) on December 5, 2001 (P000039). Prior to approval, the application was reviewed by the Circulatory System Devices Panel, and the Panel voted 10-0 that the application be found approvable with conditions. The Panel's conditions included recommendations for a Post Approval Study (PAS), wherein the sponsor was to continue to follow the pivotal clinical trial population for a period of

5 years. However, the sponsor was unable to complete the initial PAS and a new PAS of 1,000 patients was initiated; subjects are still being evaluated in this trial. Additional information regarding the PAS is included in Section IV.A.1 below.

The HSO device was reviewed under a PMA application (P050006) and was approved for marketing in the United States on August 11, 2006, approximately 6 years after the approval of the ASO device. The HSO device was not subject to panel review since it was not considered a first-of-a-kind device. In addition, during its regulatory review of study data (see Section III.B.2), FDA considered knowledge gained from the ASO device as well as information from another device (NMT Medical's CardioSeal® Device, which was placed in patients with ventricular septal defect; this device is no longer marketed). Similar to the ASO, the HSO was approved with a PAS requirement as a condition of approval. Subjects are still being evaluated in the PAS which is further detailed in Section IV.B.1.

III. Regulatory History of Transcatheter ASD Device Closure & Pre-Market Approval Data

A. ASO Device – AGA Medical/St. Jude Medical

1. Device Description and Regulatory History

The ASO device, depicted in Figure 3, is indicated for "the occlusion of atrial septal defects (ASD) in secundum position" and is also indicated for "those patients who have undergone a fenestrated Fontan procedure and who now require closure of the fenestration."

The ASO device is delivered percutaneously and is a self-expanding, repositionable, double-disk device comprised of nitinol metal braid. Eighteen device sizes are available ranging from 4 mm to 38 mm corresponding to the device "waist" size. The left atrial disk is slightly larger than the right atrial disk, and the maximum left atrial disk diameter is 54 mm. Polyester patches are sewn into the disks and waist to promote defect closure and tissue growth. The device is designed to be placed via a 6-12F femoral vein sheath. Note that subsequent to approval of the ASO device, the sponsor obtained approval of an additional device model with a smaller waist and equal disk sizes intended for the closure of multi-fenestrated (Cribriform) ASDs, referred to as the Cribriform Occluder. A distinction between the ASO and Cribriform devices is not made in the remainder of this document.

Figure 3: AGA Medical/St. Jude ASO Device [2]

2. Market Entry Trial

The ASO device was studied under an Investigational Device Exemption (IDE) application. There were 423 patients who received 433 devices and 154 patients who underwent surgical closure (a concurrent control group) in a multi-center, non-randomized pivotal study. Enrolled subjects had echocardiographic evidence of an ostium secundum ASD (device group defect size <38 mm) and clinical evidence of right ventricular volume overload or symptoms. The trial was intended to evaluate safety (incidence of major complications) and effectiveness (closure of the defect defined as a <2 mm residual shunt) for marketing in the U.S. The average patient age was 18.1 years (±19.3 years, range 0.6-82.0 years) and average follow-up was >2 years (25.6 months, range 0-38.9 months). The principle safety and effectiveness results (as reported in the Summary of Safety and Effectiveness Data (SSED)[3]) are shown in Table 1 and Major Complications are summarized in Table 2.

[2] Images From: Johri AM, Rojas CA. Imaging of atrial septal defects: echocardiography and CT correlation. Heart 2011; 97: 1441-1453.

[3] ASO SSED may be found at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3790b1_03_sponsorss&e.pdf

Table 1: ASO Market-Entry Trial Principal Effectiveness and Safety Results

	ASO Patients[1]	Surgical Control Patients	90% Confidence Interval
Technical Success	423/442 (95.7%)	154/154 (100.0%)	(-0.084,-0.010)
Procedure Success	413/423 (97.6%)	154/154 (100.0%)	(-0.059, +0.008)
Early (<30 days) Composite Success	401/442 (90.7%)	148/154 (96.1%)	(-0.111, -0.005)
12-month Composite Success	331/362 (91.4%)	146/154 (94.8%)	(-0.153, -0.033)
24-hour Closure Success	404/418 (96.7%)	154/154 (100%)	(-0.073, -0.001)
6-month Closure Success	376/387 (97.2%)	154/154 (100%)	(-0.068, +0.003)
12-month Closure Success	326/331 (98.5%)	149/149 (100%)	(-1.052, 0.017)
Principal Safety Measures			
Major Complications 12-months	7/442 (1.6%)	8/154 (5.2%)	(-0.090, -0.002)
Minor Complications 12-months	27/442 (6.1%)	29/154 (18.8%)	(-0.200, -0.070)
12-month Composite Success (K-M)	0.934	0.938	[-0.101, +0.003]
Survival at 30 days (K-M)	0.939	0.956	[-0.091, -0.003]
Survival at 180 days (K-M)	0.936	0.947	[-0.092, +0.002]

[1]Unit of analysis = Patient. Although 10 patients had 2 defects each treated with an ASO; all patients with multiple ASO implants were successfully treated.
Technical Success: successful deployment of the device, or the successful completion of the surgical procedure.
Procedure Success: successful closure of the defect as measured immediately following the procedure (<2 mm residual shunt)
Composite Success: All device placement attempts without a major complication, surgical reintervention, embolization, technical failure or major shunt (defined as >2 mm).
Closure Success: Among patients that were technical successes, closure of the atrial septal defect (defined as a shunt <2mm) without the need for surgical repair.
Major Complications: Events that are life threatening, prolong hospitalization or have long-term consequences or need for ongoing therapy. These include but are not limited to cerebral embolism, cardiac perforation with tamponade, endocarditis, pericardial effusion with tamponade, repeat surgery, death, cardiac arrhythmias requiring permanent pacemaker placement or long term anti-arrhythmic medication and device embolizations requiring immediate surgical removal.
Minor Complications: Device embolization with percutaneous retrieval, cardiac arrhythmia with treatment, phrenic nerve injury, hematoma, other vascular access site complications, retroperitoneal hematoma, surgical wound complications, other procedural complications, pericardial effusion requiring medical management, evidence of device associated thrombus formation without embolization (with or without treatment) and marker band embolization without known sequelae.

Table 2: ASO Market-Entry Trial Major Complications Through 12-Month Follow-Up

Major Complication	ASO Patients	Surgical Control Patients	p-value
Cardiac Arrhythmia requiring major treatment	2/442 (0.5%)	0/154 (0.0%)	1.00
Device Embolization with surgical removal	3/442 (0.7%)	na	---
Device Embolization with percutaneous removal	1/442 (0.2%)	na	---
Delivery System Failure	1/442 (0.2%)	na	---
Pericardial Effusion with tamponade	0/442 (0.0%)	3/154 (1.9%)	0.017
Pulmonary Edema	0/442 (0.0%)	1/154 (0.6%)	0.26
Repeat Surgery	na	2/154 (1.3%)	---
Surgical Wound Complication	na	2/154 (1.3%)	---
Total Major Complications Patients	7/442 (1.6%)	8/154 (5.2%)	0.030

Additional minor complications were reported for both groups with cardiac arrhythmias requiring treatment being the most common event in both groups (3.4% device; 5.8% control). Pericardial effusion in the surgical group (3.9%) and thrombus deposition on the device group (0.7%) were the second most common minor complications.

FDA approved continued use of the ASO for an additional 475 subjects that were enrolled under a Continued Access protocol, and at least 465 ASO implants were performed prior to PMA approval. Initial results in the Continued Access study were consistent with early safety and effectiveness results seen in the pivotal trial.

FDA Commentary: Major adverse events such as embolization (requiring percutaneous or surgical removal) and arrhythmia were noted in the ASO premarket studies; however, erosion events were not observed.

The market entry study data served as the basis for the establishment of reasonable assurance of device safety and effectiveness for initial device marketing and are presented for reference only. During the Advisory Panel meeting, it is not FDA's intention to discuss the market entry data for the purposes of revisiting the ASO safety and effectiveness approval decision.

B. HSO Device – W. L. Gore

1. Device Description and Regulatory History

The HSO device, depicted in Figure 4, is also indicated for "the percutaneous, transcatheter closure of ostium secundum atrial septal defects (ASDs)."

The HSO device assumes a double disk configuration following deployment of a helical nitinol wire frame covered with expanded polytetrafluoroethylene (ePTFE). A maneuver is performed to "lock" the two disks together prior to release from the delivery system/catheter. The device is designed to be placed via a 9-13F femoral vein sheath. Five device sizes are available and are designed to close defects ranging from ≤18 mm in diameter corresponding to nominal disk diameters ranging from 15 mm to 35 mm.

Figure 4: Gore HSO Device[2]

2. Market Entry Trial

The HSO was studied under an IDE application that consisted of a feasibility study (two-center, single arm study, 51 subjects), a pivotal study (multi-center, controlled study utilizing a non-randomized surgical control, 271 subjects), and a continued access study (multicenter, single arm study, 156 subjects) prior to marketing approval. For the pivotal study cohort, there were 119 non-training subjects treated with the device and 128 subjects treated with surgical closure. Principal Effectiveness and Safety Results (as reported in the Summary of Safety and Effectiveness Data (SSED)[4]) for the Pivotal and Continued Access studies are shown in Table 3 and Major Complications for the Feasibility, Pivotal, and Continued Access studies are summarized in Table 4.

[4] HSO SSED may be found at: http://www.accessdata.fda.gov/cdrh_docs/pdf5/P050006b.pdf

Table 3: GORE HSO Market-Entry Trial Principal Effectiveness and Safety Results Through 12-Month Follow-Up

Study Outcomes	Pivotal Study			Continued Access Study
	Device Arm	Surgery Arm	Difference (95% CI)[4]	
Technical Success[1]	119/135 (88.1%)	na	na	113/132 (85.6%)
Clinical Closure Success[2]				
Pre-Discharge	115/118 (97.5%)	123/123 (100%)	-2.5% (-5.4%, 0.3%)	110/112 (98.2%)
Month 6	99/101 (98.0%)	na	na	80/80 (100%)
Month 12	103/105 (98.1%)	82/82 (100%)	-1.9% (-4.5%, 0.7%)	50/51 (98.0%)
Principal Safety Measures				
Major Adverse Events 12 Months	7/119 (5.9%)	141128 (10.9%)	-5.1% (-11.9%, 1.8%)	3/77 (3.9%)
Minor Adverse Events 12 Months	34/119 (28.6%)	36/128 (28.1%)	0.4% (-10.8%, 11.7%)	21/77 (27.3%)
Survival at 365 Days (K-M)	100%	99.1%		100%
Composite Clinical Success 12 Months[3]	100/109 (91.7%)	72/86 (83.7%)	8.0% (-1.3%, 17.4%)	50/54 (92.6%)

NOTE: Analysis includes all nontraining Pivotal subjects and Continued Access subjects enrolled and evaluated through 12 month followup as of database closure on 12/15/05

1. Technical Success defined as successful delivery of the device in subjects with a delivery attempted.
2. Clinical Closure Success defined as residual defect that is either Completely Occluded or Clinically Insignificant Leak. Leak status was evaluated by the investigational sites at pre-discharge and 6 months and by the echocardiography core laboratory at 12 months
3. Composite Clinical Success defined as no major adverse event or repeated procedure and clinical closure success at 12 months
4. Differences between Pivotal device and surgery groups and associated 95% confidence intervals.

Table 4: GORE HSO Market-Entry Trial Major Complications Through 12-Month Follow-Up

		Pivotal Study			
	Feasibility Study	Device Arm	Surgery Arm	Difference (95%CI)'	Continued Access Study
Subjects Evaluable for Safety	51	119	128		77
Deaths (Any Cause)	0	0	1 (0.8%)	·0.8% (-2.4%, 0.8%)	0
Subjects With One or More Major Adverse Events	2 (3.9%)	7 (5.9%)	14 (10.9%)	-5.1% {-12.1%, 1.9%)	3 (3.9%)
Cardiac	1 (2.0%)	2 (1.7%)	10 (7.8%)	-6.1% (-11.5%, -0.8%)	2 (2.6%)
Arrhythmia	1 (2.0%)	0	0		0
Bleeding (treatment required)	0	0	1 (0.8%)	-0.8% {-2.4%, 0.8%)	0
Device Embolization (post- procedure)*	0	2 (1.7%)	na	na	2 (2.6%)
Pulmonary Edema	0	0	1 (0.8%)	-0.8% (-2.4%, 0.8%)	0
Post-Pericardiotomy Syndrome	na	na	8 (6.3%)	na	na
Integument (Skin)	0	1 (0.8%)	0	0.8% (-0.8%, 2.4%)	0
Allergic reaction	0	1 (0.8%)	0	0.8% (-0.8%, 2.4%)	0
Neurologic	1 (2.0%)	2 (1.7%)	0	1.7% (-0.6%, 3.9%)	0
Migraine (new)	0	2 (1.7%)	0	1.7% (0.6%, 3.9%)	0
Paresthesia	0	1 (0.8%)	0	0.8% (0.8%, 2.4%)	0
Seizure	1 (2.0%)	0	0		0
Pulmonary (Respiratory)	0	0	1 (0.8%)	-0.8% (-2.4%, 0.8%)	0
Stridor	0	0	1 (0.8%)	0.8% (2.4%, 0.8%)	0
Vascular	0	1 (0.8%)	1 (0.8%)	0.1% (-2.2%, 2.3%)	0
Hemorrhage (treatment or intervention required)	0	1 (0.8%)	1 (0.8%)	0.1% (2.2%, 2.3%)	0
Wound	0	0	2 (1.6%)	-1.6% (-3.8%, 0.7%)	0
Hernia	0	0	1 (0.8%)	0.8% (2.4%, 0.8%)	0
Scarring or scar related	0	0	1 (0.8%)	-0.8% (-2.4%, 0.8%)	0
Device (HELEX Septal Occluder)	0	3 (2.5%)	na	na	1 (1.3%)
Allergic reaction	0	1 (0.8%)	na	na	0
Device size inappropriate	0	2 (1.7%)	na	na	0
Device removal due to fracture	0	0	na	na	1 (1.3%)
Other	0	0	1 (0.8%)	-0.8% (-2.4%, 0.8%)	0
Anemia	0	0	1 (0.8%)	0.8% (-2.4%, 0.8%)	0

NOTE: Analysis includes all Feasibility subjects, nontraining Pivotal subjects and Continued Access subjects enrolled and evaluated through 12 month follow-up as of database closure on 12/15/05
na - not applicable
NOTE: Gore's MAE definition: Major Adverse Event – an event potentially or definitely related to device and/or procedure that resulted in hospitalization and/or permanent damage or deficit, e.g., any post-procedural device embolization, post-procedure device removal, etc.
Differences between Pivotal device and surgery groups and associated 95% confidence intervals
* The 4 embolized devices were removed by transcatheter technique

Minor Complications were also reported for both groups, with the most common complication categorized as "cardiac" (device ~12-14%; control ~20%). Post-pericardiotomy syndrome was the second most common minor surgical complication (7.8%) and minor arrhythmia was the second most common minor device complication (~6-8%). Wire frame fractures were reported in all device groups with an overall rate of ~5-6.5% with an increased frequency of device fracture associated with larger diameter devices.

FDA Commentary: The market entry study data served as the basis for the establishment of reasonable assurance of device safety and effectiveness for initial device marketing and are presented for reference only. During the Advisory Panel meeting, it is not FDA's intention to discuss the market entry data for the purposes of revisiting the HSO safety and effectiveness approval decision.

IV. Information Obtained Since PMA Approval

FDA has been monitoring adverse events that have occurred with ASD devices since their approval. This monitoring has included assessment of PAS interim results, analysis of the Manufacturer and User Facility Device Experience Database (MAUDE), and literature reviews. More data and clinical experience is available for assessment of the ASO device (compared to the HSO device) given its substantially longer marketing experience and larger market share.

A. ASO Device

1. ASO Post-Approval Study (PAS)

The original conditions of PMA approval specify that AGA/St. Jude would continue to follow the pivotal clinical trial population (IDE G960209) for a period of 5 years post-device implantation.[5] However, AGA/St. Jude was not able to collect adequate follow-up data to fulfill the condition of approval obligation as patients were originally consented for only one-year follow-up when they enrolled in the clinical trial. FDA, therefore, mandated that the sponsor conduct a new PAS to meet their condition of approval requirements. FDA approved the new PAS protocol on August 16, 2007. Subject accrual began on March 30, 2008. FDA approved a revised study protocol on January 4, 2011, and the most recent PAS status report was received on February 16, 2012.

Protocol

The currently enrolling ASO Post Market Study is a prospective, non-randomized, multi-site, single arm clinical study. The purpose of this study is to prospectively evaluate the incidence of hemodynamic compromise and to obtain long-term survival data on patients implanted with the ASO through two years post-device implantation. Hemodynamic compromise is defined as any condition that results in shortness of breath and a decrease in systemic blood pressure that may result in patient collapse and/or death (e.g., pericardial tamponade). Hemodynamic compromise is a composite of multiple events with erosion being one of the event components. There is no control group in the post-market study.

There will be a maximum of 1,000 patients recruited in the post-market study. Assuming that 85% of these patients will be available throughout the 2 year follow-up period, approximately 850 patients will be assessed for adverse events related to hemodynamic compromise. The

[5] ASO Approval Order may be found at: http://www.accessdata.fda.gov/cdrh_docs/pdf/P000039a.pdf

adverse event rate will be determined by the number of patients with at least one event, with exact methods used to provide the corresponding 95% confidence interval.

Endpoints

The primary endpoint of the study is considered met if a patient has one or more adverse events classified by the AGA/St. Jude Erosion Board as event(s) that likely were a result of hemodynamic compromise caused by or likely caused by the implantation or presence of the ASO device. The co-primary endpoints include: (1) safety, defined as the incidence of system-related (i.e., resulting from any component of the device or device system) adverse events per patient; and (2) effectiveness, defined as the percentage of patients for whom Closure Success was achieved. Closure Success is defined as among patients that were technical successes, closure of the atrial septal defect (defined as a shunt < 2mm) without the need for surgical repair. Technical Success is defined as successful deployment of the device percutaneously.

In addition, the study will evaluate the association of device sizing with the incidence of hemodynamic compromise. Device sizing will be determined by evaluation of the size of the atrial septal defect, the location of the atrial septal defect, and the size of the device. Classification of device sizing will be made using guidelines specified in the Instructions for Use (IFU).

Finally, the study will evaluate the association of highly experienced versus less experienced implanting physicians with regard to the incidence of hemodynamic compromise.

Follow-up

Patients enrolled in the study will be evaluated pre-procedure, at implant post device deployment, pre-discharge, and at one month, one year, and two years post-implant. Patient data will be obtained at the time of visit and/or if appropriate through a telephone interview.

Statistical Plan

The primary aim of the statistical analysis of this study is to determine the rate of patients who have hemodynamic compromise caused by the device or implant procedure. The rate will be an estimate with a corresponding precision, but no formal hypotheses will be tested with respect to this rate and no specified time period is outlined in the protocol for how this rate is captured. In addition, analyses will be conducted to determine procedural differences between historically highly experienced versus less experienced implanting physicians.

In the ASD PMA trial, there were no adverse events in the device arm that were classified as hemodynamic compromise. Thus, the observed rate of patients with hemodynamic compromise in this trial was 0%. In 2004, Amin et al.[6] published an incidence rate of 0.16% of reported events among patients using the ASD device since the device was approved in December 2001. After allowing for the possibility that there may be unreported hemodynamic compromise events

[6] Amin Z, Hijazi ZM, Bass JL, Cheatham JP, Hellenbrand WE, Kleinman CS. Erosion of Amplatzer septal occluder device after closure of secundum atrial septal defects: review of registry of complications and recommendations to minimize future risk. Catheter Cardiovasc Interv. 2004 Dec;63(4):496-502.

among these patients and for the fact that not all of the patients in the Amin paper may have had the device for two years, the sponsor is using a 0.5% rate as a conservative *a priori* estimate for the post-market study.

Timeline
There have been 876 patients enrolled as of the database lock on January 13, 2012. At this time, subject enrollment is on pace with the enrollment timeline detailed in the study timeline submitted to FDA. The sponsor reports the 24-month follow-up rate as being 87%. The study is projected to be completed in September 2014.

Interim Results
At the time of the last interim report, the sponsor reports three patients with events resulting in hemodynamic compromise that was related to the implantation or presence of the ASO device. The three events were a device embolization, sinus bradycardia, and atrial fibrillation.

The sponsor reports 30 adverse events as device-related and four adverse events as related to the delivery system. No erosion events were observed. However, subsequent to the submission of this most recent report, the sponsor indicated in their materials for the current Panel Meeting that two events have been adjudicated by the Erosion Board as erosion events. Details regarding the cases have not been submitted to FDA under the PAS application; however, information regarding these cases has been submitted to MAUDE. Based on the number of patients enrolled as of the last interim report, the erosion incidence rate is 0.2% (2/876) since the start of the study.

FDA Commentary: There have been two confirmed erosions in the ASD PMS II Post Approval Study to date. Otherwise, data from the PAS does not raise any new safety or effectiveness concerns compared to the premarket data.

2. Overview of ASO FDA MAUDE Analysis Results

A total of 705 medical device reports (MDRs) on ASO devices received in the past 10 years were identified for events associated with device on-label use and off-label use in PFO closure. The analysis included assessment of the ASO device, Cribriform device and ASO accessory devices. Most types of events were known prior to device marketing; however, FDA received MDRs describing "erosion" after the device was marketed. The reported adverse events for all ASO devices and more details regarding FDA's analysis of the MAUDE data are provided in Section V.E.1 below.

B. HSO Device

1. HSO Post-Approval Study (PAS)

1.1 Gore HSO Post-Approval Studies

The Gore HSO device was approved on August 11, 2006. The conditions of approval from the approval order[7] are:

- The long-term safety and effectiveness of the Gore HSO will be further characterized by following for 5 years the first 50 subjects enrolled in your continued access study, as the data from the first 50 subjects were provided in the premarket application to support approval of device modifications.[8] At least 80% of these subjects should be available for follow-up out to 2 years.

- The long-term safety and effectiveness of the device will be further characterized by following for 5 years at least 200 subjects that do not include the first 50 subjects enrolled in your continued access study. At least 80% of these subjects should be available for follow-up out to 2 years.

The protocol was approved by the Agency in December 13, 2006. The 6-year report was received by FDA on July 18, 2011.

The primary objective of this study is to provide long-term safety and effectiveness data on the GORE HSO device.

Study Population
This study population consists of two cohorts:

(1) 50 subjects from IDE Continued Access Study who have been successfully implanted

(2) 90 subjects subsequently enrolled in the IDE Continued Access Study combined with approximately 125 subjects that were to be enrolled in the Post-Approval Study, with the goal of attaining 110 subjects with a successful implant. This part of the PAS study will enroll subjects until a combined cohort of approximately 200 subjects with 2 years of follow-up data has been obtained.

Endpoints
The primary endpoint is Composite Clinical Success evaluated at 12 months and is defined as a subject with the targeted defect assessed by TTE as being either completely occluded or the residual shunt is clinically insignificant, with an absence of repeat procedure to the target ASD,

[7] HSO Approval Order may be found at: http://www.accessdata.fda.gov/cdrh_docs/pdf5/P050006a.pdf
[8] Gore implemented certain device modifications during enrollment of the pivotal clinical study. To confirm the results of in vitro bench studies suggesting no adverse impact on device performance, the sponsor enrolled 50 subjects in a continued access study and submitted their outcomes in the PMA to support the applicability of the pivotal study data to the modified device design.

and absence of any major complication.

The primary safety analysis is the calculation, with 95 percent confidence, of the proportion of successfully implanted subjects experiencing one or more major device- or procedure-related adverse events through the 12-month follow-up visit. All adverse event data collected will be included and classified by time interval of occurrence: early, 30 days or less from procedure, and within the first year postprocedure.

Follow-up
The endpoints will be evaluated annually through 5 years post procedure.

Statistical Plan
The primary safety analysis is the calculation, with 95 percent confidence, of the proportion of successfully implanted subjects experiencing one or more major device- or procedure-related adverse events through the 12-month follow-up visit. All adverse event data collected will be included and classified by time interval of occurrence: early, 30 days or less from procedure, and within the first year postprocedure.

Timeline
The study is expected to be completed in August 2014.

Interim Results – Cohort (1)

The database closing date for this report is June 10, 2011.

Thirty-four (34) subjects were available for the 60-month follow-up evaluation, of which 32 subjects (94.1%) completed the evaluation.

Major adverse events occurred in 6.0% (3/50) of subjects and minor adverse events were reported in 32% of subjects. There were three major adverse events, and all were device-related, with 2 embolizations occurring within 24 hours and 1 fracture occurring at 37 days leading to removal. Fractures only occurred in devices >25 mm in diameter. No unanticipated adverse events have been reported to date.

Of the 28 echo core lab reviews available at 60 months post procedure, clinically successful defect closure was observed in 100% of subjects. Clinical Success was achieved in 87.0% (20/23) of subjects evaluated at 60 months. Three subjects were considered clinical failures. These are the same three subjects identified at the 12 month post procedure interval. However, 27 subjects were not evaluated, and of these, 15 were lost to follow-up and 12 have not completed or are missing the Echo Core Lab information regarding residual shunt status. Overall, the observed clinical success rates have been relatively high over the course of the study; however, there is considerable missing data. Follow-up on this cohort, originally consented to one year, is currently ongoing.

Interim results – Cohort (2)

The database closing date for this report is June 10, 2011.

Subject enrollment in the Post-Approval Study of the HSO began May 15, 2007. The study enrolled 128 subjects with successful device implantation and was closed to enrollment as of October 17, 2008. Eighty seven (87) subjects enrolled under the Continued Access IDE study have been combined with the 128 subjects enrolled in the Post-Approval Study for a total of 215 subjects, at 21 sites. These 215 subjects implanted will be followed under the approved protocol dated October 10, 2006.

Sixty-two (62) subjects were available for 60 month follow-up, of which 50 (80%) completed the evaluation.

The median age of enrolled subjects was 6.5 years (range: 0.8 to 88.5 years), median estimated ASD size 10 mm (range: 1.7 to 21.0 mm), 60.5% female, and 65.6% Caucasian.

No unanticipated adverse events have been reported to date. Two subject deaths have been reported during the study, and both deaths were determined as unrelated to the device/procedure by the study DSMB.

Major adverse events were reported in 4.7% (10/215) of subjects through the 60 month follow-up period. Device embolization was reported in 2 subjects (0.9%), both within the first 30 days post-procedure. Device removal (non-embolization) was reported in 4 subjects (1.9%), all of whom had device fractures:

- One (1) subject with an identified fracture at day 43 was determined to have a significant residual shunt and mitral leaflet damage caused by a device fracture of the left atrial arm of the HSO device. The fracture was on the inferior aspect of the left atrial device side and appeared to have caused trauma to the mitral valve resulting in significant mitral insufficiency. The 35 mm occluder was removed. The ASD and mitral valve were repaired surgically.

- One (1) subject with an identified fracture at the 6 month follow-up subsequently had the 25 mm device removed after device migration was observed at the 3 year follow up evaluation. The occluder device was removed at day 1175, and the ASD was closed by surgical patch repair.

- One (1) subject had multiple (3) device fractures reported at the 1 month follow up evaluation. Due to the unstable condition of the 35 mm device and a small residual shunt between the anterior rim of the device and the aortic valve, the physician decided to remove the device at day 94 and repair the ASD surgically.

- One (1) subject had multiple fractures and malposition of the right atrial disc. There was no residual ASD. Approximately 40 percent of mitral valve annulus was covered by the

disc. The physician elected to remove the 35 mm device at day 320 and repair the defect surgically.

The proportion of patients with fractures increased with device size. There are no fractures reported in the 15 mm and 20 mm diameter devices. However, the proportion of patients with fractures with larger size devices, identified on fluoroscopy, are as follows: 25 mm (1.8%), 30 mm (15.1%), and 35 mm (50.0%).

The purpose of the primary safety analysis was to evaluate and describe the proportion of successfully implanted subjects experiencing one or more major device- or procedure-related adverse events through the 12-month follow-up visit. Clinical Success was achieved in 95.0% (170/179) of subjects evaluated at 12-months, 89.3% (75/84) of the subjects evaluated at 36-months, and 97.8% (44/45) of the subjects evaluated at 60 months. Of the clinical failures, only 1 significant leak was reported at 12 months (0.6%). Clinical success remains consistent and relatively high.

2. Overview of HSO FDA MAUDE Analysis Results

A total of 150 MDRs for the HSO device were identified for events associated with device on-label use and off-label use in PFO closure. The analysis included assessment of the HSO device only, as accessory devices are not separately sold. Most types of events were known prior to device marketing. The reported adverse events for the HSO device and more details regarding FDA's analysis of the MAUDE data are provided in Section V.E.2 below.

V. FDA Analysis of MAUDE

A. Overview of FDA MAUDE Database

Medical Device Reports (MDRs) received and entered into the MAUDE database provide adverse event information involving marketed medical devices. MAUDE is comprised of MDRs received from varied sources, including voluntary reports since June 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August 1996.

FDA medical device adverse event reporting is a passive surveillance system. The strengths of MDRs are that they provide for:

- A qualitative snapshot of adverse events for a specific device or device type
- Detection of Signals for
    - device problems in "real users" in "real world" settings/environment
    - rare serious adverse events
    - unexpected adverse events
    - long-term adverse events
    - vulnerable population
    - off-label use
    - use error

However, MDRs also have the typical limitations of a passive surveillance system including:

- under-reporting of events
- incomplete information
- causality not confirmed
- reporting bias: reporting practice, media effect, regulatory actions
- inability to estimate rate of adverse events (no "denominator" data)
- interpretation of "trends" in numbers is limited and should be interpreted cautiously

B. Initial FDA MAUDE Search

As part of ongoing monitoring of adverse event reporting associated with this device type, a preliminary manual search of the Public MAUDE database was performed in 2010 in which each MAUDE report for any marketed atrial septal occluders [Product Code MLV (AGA/St. Jude ASO, Gore HSO, NMT CardioSeal)] from 2000 to August 2010 was read and manually tallied with an initial focus on erosion events, perforation and pericardial effusion events, 30 day death or sudden death events, and events resulting in valvular injury or interference requiring surgical intervention. For this initial manual review and tally, events citing surgeon identification of an erosion at the time of surgery, specific imaging findings of atrial or aortic erosion, or an autopsy report identifying an erosion were counted as erosion events. This initial manual review included all devices placed in the atrial septum (for closure of secundum ASD and PFO only) and generated the results summarized in Table 5.

Table 5: Initial MDR Review Results for all ASD Occluders

Event	AGA/St. Jude AGO	Gore HSO	NMT
Erosion (OR or Autopsy)	79	0	0
Perforation/Effusion	13	4	13
Sudden Death	7	0	1
Valve repair/Replacement	7	2	0

As a result of this initial review, a large apparent discrepancy in reported erosion events between the various septal occluders was noted. Specifically, no erosion events were detected for either the Gore HSO or NMT CardioSeal Devices, and all reports of device erosion were limited to the AGA/St. Jude ASO/Cribriform device. After this initial manual review of the publicly available MAUDE database, an automated search of the FDA internal CDRH MAUDE database[9] was performed, duplicate reports were identified, and all erosion events and deaths were successfully reconciled between the manual and automated searches.

In October 2010, FDA notified AGA/ St. Jude of the results of our preliminary review, including the specific MAUDE report numbers of all Agency-identified erosion events and deaths. Through ongoing discussions in meetings and teleconferences, FDA and the sponsor limited the subsequent analysis of erosion events to on-label use and reconciled the number/adjudication of

[9] At any given time, the internal CDRH MAUDE database may contain records not yet released in the publicly accessible MAUDE database; additionally, the internal database may also contain further details in the event narrative (such as institution) that are not included in the public database. Hence, for regulatory purposes, the internal database is used for analysis of MDR reporting.

all erosion events reported on or before November 29, 2011. The number of agreed upon erosions as of that date was identified as 92.

In preparation for this discussion of a broader range of adverse events beyond reported erosion events, FDA conducted a more thorough analysis of the internal CDRH MAUDE database.

C. FDA MAUDE Search Methodology

The following searches and steps were conducted to query the CDRH MAUDE database on January 25, 2012 for all MDRs associated with the ASO and HSO devices.

- First, searches of Device Brand Name containing the words "Amplatzer" or "ASO" or "Helex" or "Helix Septal" were performed and resulted in identification of 51 variants (spelling) of Amplatzer and 7 variants of HSO devices.
- Next, a search using the aforementioned variants of ASO and HSO brand names and Date Report Received between January 1, 2002 and December 31, 2011 (data locked date) yielded 1175 MDRs.
- Then, the 1175 MDRs were grouped into several categories by device name or catalog/model numbers (where device name was not provided in the MDR).
- As a result of the device categorization, 181 MDRs were excluded from the dataset as those MDRs were for non-ASO devices manufactured by AGA/St. Jude including the Duct Occluder (81 MDRs), VSD Occluder (39), PFO Occluder (27) and the Vascular Plug (34).
- The remaining **994 MDRs** on ASO, Cribriform, and HSO devices were subsequently processed as follows:
    1. Duplicate reports (e.g. reports from different sources involving the same event, or a reported event from one patient with ≥ 2 devices from more than one manufacturer) were identified and excluded based on the MDRs with the same Implant Date and the same Reporting City, or same Patient Age/Gender.
    2. Time to Event Occurred (TTEO) for each MDR was calculated for the MDRs where both the Implant Date and Event Date were provided.
- An extensive report review was conducted using an adjudication process to assure that duplicate reports were removed and events were adequately categorized, according to the different indications for use, types of AE events and outcome of the patients. The CDRH MDR adjudication process is described in the following Section.

D. FDA CDRH MDR Adjudication Process

MDR reports submitted to FDA typically consist of certain preselected descriptive fields (device problem, patient problem, etc.), a narrative about the event, and in some cases, further information from the manufacturer's analysis (especially in cases where the device was explanted and returned). In order to categorize adverse events as consistently and accurately as possible across MDR reports and across devices, FDA developed and implemented an adjudication process specifically for this Panel review and discussion.

2.1 Summary of Overall FDA Adjudication Process

Using the CDRH MAUDE data generated from the queries described above, spreadsheets were developed to categorize each adverse event for each MAUDE report as completely and accurately as possible using the following procedures:

- Independent manual review of each set of Event and Manufacturer reports for all devices by at least two FDA physicians (cardiothoracic surgeon, interventional radiologist, cardiology fellow) for initial categorization of all adverse event(s) and their sequelae (explant, death, surgery, type of device retrieval, drainage, etc.) for each patient MDR. The events were adjudicated and categorized as follows:
  1. Device on-label or off-label Use
  2. Reported Adverse Event
     - Erosion
     - Perforation/Tamponade (no erosion)
     - Pericardial Effusion (no erosion)
     - Embolization
     - Malposition
     - Residual/recurrent Shunt
     - Neurological Event
     - Device Thrombus
     - Device Fracture
     - Device Malfunction
     - Valve Malfunction
     - Endocarditis/Infection
     - Arrhythmia
     - Allergy
     - Others
  3. Device Explant and Patient Outcome (Death)

- All discrepancies in adverse event determinations between the physicians performing the manual reviews were resolved and reconciled.
- Adverse event "buckets" (erosion, embolization, thrombus, fracture, etc.) were developed to allow separate classification of each patient record by its primary adverse event(s) and sequelae where appropriate.
- A final consolidated list of individual records was generated to allow categorization and automated counts of all adverse event records sorted by their primary adverse events.

This final list of individual MAUDE report numbers categorized by their primary adverse event resulted in a complete and robust classification of all adverse event reports received by the Manufacturers and FDA for both currently marketed septal occluder devices and for both on-label and off-label (PFO only) use. The primary results of this review were then shared with both AGA/St. Jude (ASO and Cribriform devices) and Gore (HSO device) on April 3, 2012. The

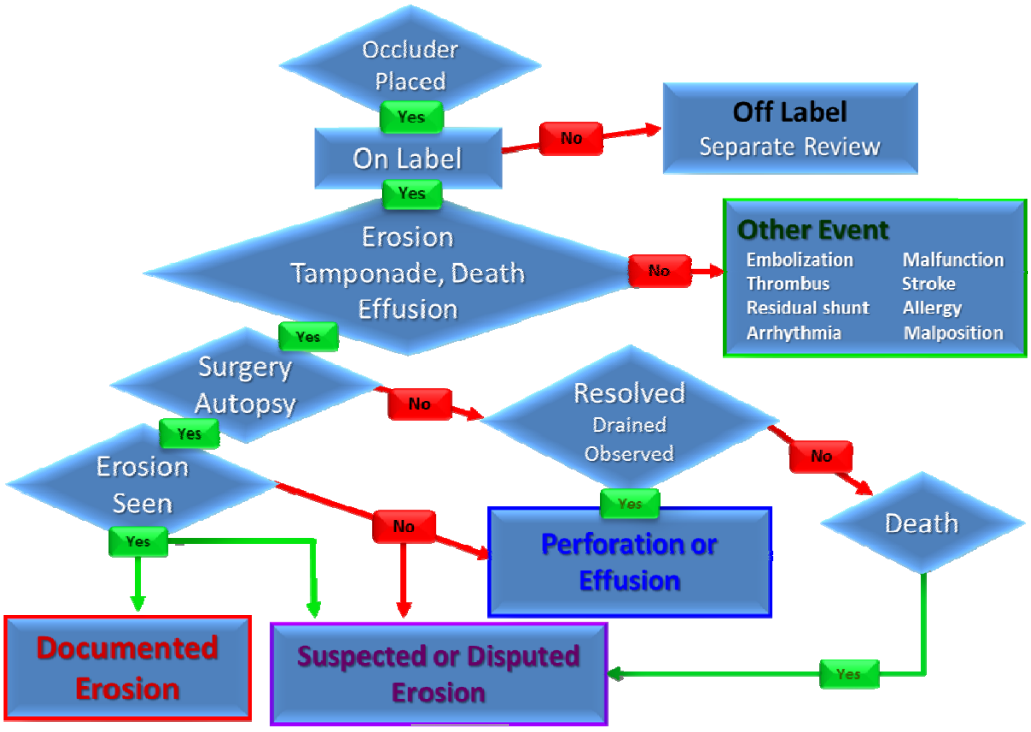
sponsors were given an opportunity to comment on and to dispute event categorization and FDA reconciled some of those events. Specifically, several erosion events were added or re-categorized based upon the findings of the AGA/St. Jude Erosion Board who had benefit of more detailed information regarding most cases (e.g., patient records, imaging). (Although FDA did not review the same source information, FDA agreed with the sponsor's characterization/results as documented in their comments regarding disputed documented cases.) In those circumstances, FDA accepted the Erosion Board's findings for re-categorizing "suspected" erosions as "definite" erosions." This resulted in the addition of 4 documented on-label erosions to the total, the elimination of 6 suspected/disputed erosion events, the re-categorization of a suspected/disputed on-label erosion to a documented off-label erosion, the re-categorization of a suspected/disputed off-label erosion to an off-label erosion, and the re-categorization of an on-label erosion to an off-label erosion. Also included in Appendix A are 5 events that occurred with the HSO device that AGA/St. Jude reviewed (using their methodology as outlined in Appendix B) and determined that these events should be categorized as suspected erosion events. These events were not re-categorized by FDA and are noted as discrepancies/disputes in Appendix A.

Some new reports of events not captured in our internal CDRH MAUDE search were identified (occurring before 12/31/11, but not being reported or entered into the MAUDE database prior to the MDR search was conducted on 1/25/12), and these were adjudicated and categorized accordingly. Additional discrepant non-erosion events were noted by both sponsors, but these were a minority of the total overall events and, for the vast majority, reflected differences between the sponsor's and FDA's adjudication and interpretation of the primary event responsible for generating the report. These discrepancies did not affect the overall analysis in any substantial way, and did not warrant event by event reconciliation with each sponsor. As a result, these non-erosion events were not re-categorized by FDA. Events that were not incorporated in FDA's final analysis and remain as "discrepancies" are listed in Appendix A as "All Other Events." FDA does not believe that these "discrepancies" substantively affect the broader issues to be discussed at the Panel Meeting.

2.2 Details Regarding Erosion Event Adjudication Process

The final process used by FDA for initial and subsequent MAUDE reviews for determination and categorization of adverse events is summarized in Figure 5.

Figure 5: Summary of Final FDA MAUDE Analysis Review Scheme



Yes* = Suspected/Disputed erosion event

Erosion Events

Adjudicated or suspected/disputed erosion events typically result in tissue perforation at the right and/or left atrial domes and/or in the wall of the adjacent aortic root (non-coronary sinus), or the formation of an aortic-to-atrial fistula between the aforementioned sites. Due to their adjacent locations, which are separated only by the free pericardial space, erosions of the atrial domes and/or the adjacent aortic root usually result in either pericardial effusion or tamponade, and usually present with the acute onset of symptoms including chest pain and hemodynamic compromise.

Perforation or Effusion Events

Patients undergoing surgical or percutaneous drainage of a periprocedural pericardial effusion with or without tamponade, where a definite erosion event was not identified due to a) treatment by percutaneous drainage, or b) a surgeon noting no injury or an injury atypical for erosion at the time of surgical drainage (e.g. where atrial holes were located apart from areas typically associated with erosion atrial appendage or pulmonary veins), were generally labeled perforation/effusion events. In addition, events undergoing percutaneous or surgical drainage of an acute peri-procedural effusion where the report indicated that cardiac or great vessel injury was the result of a procedural manipulation

(malplacement or injury due to a guidewire, retrieval device, or the occluder device) were also categorized as perforation/effusion events.

As discussed above, FDA and AGA/St. Jude had reached agreement on the number of 92 erosion events (as of November 2011) based on FDA's initial review and analysis of the Public MAUDE database. The final list of 95 events presented here and agreed upon with AGA/St-Jude (as of April 2012) are events defined as "definite erosion events" and their original adjudication was not revisited for the CDRH MAUDE review since agreement with the Sponsor had already been reached.

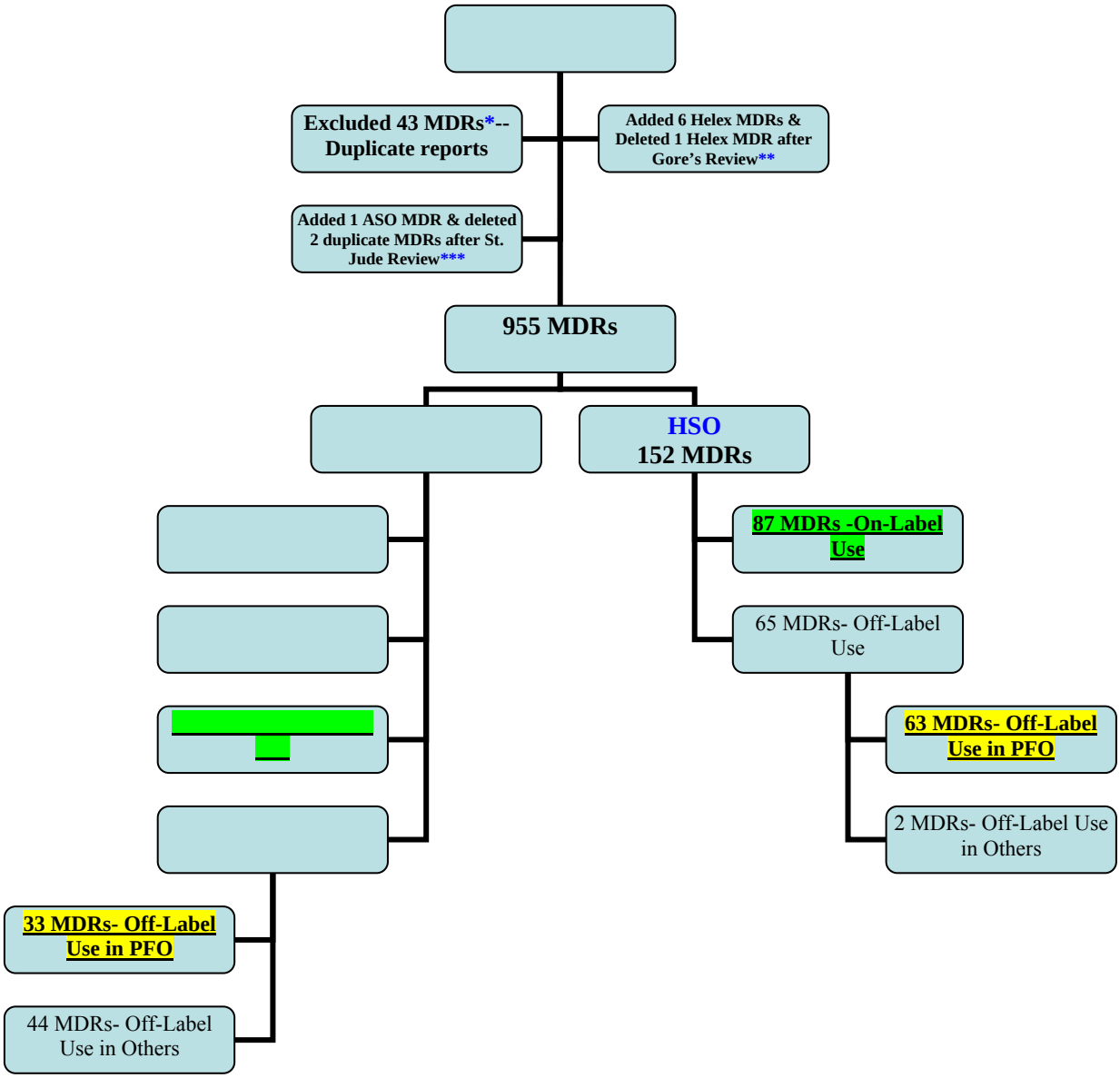
However, during FDA final manual re-review of all Internal CDRH MAUDE MDR records (detailed above) an additional 8 ASO cases were identified where the Agency felt that there was a substantial likelihood that an on-label use erosion event had occurred. These additional events are labeled "suspected or disputed erosions." In all of these, either sudden death without other cause, erosion, or a clinical scenario highly suspicious for erosion was documented; however, these reports were either identified too late for joint FDA-sponsor adjudication (after November 29, 2011; suspected), or were re-identified as suspected events where final agreement had not been reached with AGA/St. Jude or their Erosion Board regarding whether or not an erosion had occurred (disputed). Off label Erosion events (PFO closure only) were also evaluated for both St. Jude and Gore devices. The only erosion events identified were for St. Jude devices (ASO or Cribriform). A total of 5 documented off-label erosions were identified with one additional suspected/disputed off-label erosion event.

FDA Commentary: All devices from both manufacturers were evaluated by FDA using the same procedures and rigor for each review step. Due to the detection of documented erosion events for only the ASO device, additional interaction with the manufacturer of those devices occurred to allow characterization and quantification of those events as fully as possible. It is recognized by the Agency that MAUDE MDR adverse event reports have numerous shortcomings such as under-reporting. As a result, data regarding adverse event reports cannot be used to calculate either the true or relative incidence of events. Data generated from MAUDE is most reliably used as a signal to identify adverse events and/or trends that require a) more specific and rigorous evaluation, and b) rational dissemination of pertinent information to the medical and patient communities at large.

E. FDA MAUDE Analysis Results

As a result of the adjudication process on the 994 MDRs, four groups of the MDRs were determined to be the focus of FDA review, since these resulted in placement of the occluder devices in the atrial septum. These groups include on-label use (secundum ASD closure, highlighted in Green in the MDR Flow Chart) and off-label use (off-label use is limited to PFO closure only, highlighted in Yellow in the MDR Flow Chart) for both ASO and HELEX devices. The MDR Flow Chart also incorporates the results of reconciliations on the event adjudications between CDRH and two sponsors in April 2012. The MAUDE analysis results are detailed in the following Section E1 for ASO and Cribriform devices and Section E2, HSO device.

Figure 6: FDA MDR Analysis Adjudication Process



The 43 duplicate MDRs include 6 duplicate MDRs identified by St. Jude in April, 2012.
***** Six HSO MDRs were added in April 2012 as Gore identified 6 additional MDRs which were not captured in FDA original MDR data set due to different search methods or the time delay of MDR being entered in MAUDE database. One MDR was deleted as FDA agreed that the event should not have been reported as an MDR, as there was no patient injury, nor device malfunction.***
******One ASO MDR was added and 2 duplicate ASO MDRs were deleted in April 2012 as a result of St. Jude's review (Please note that the added MDR event occurred in 2010, but was not reported until Jan. 2012.)***
*******For the purposes of reporting the MAUDE analysis, ASO devices will be used to include both AmplatzerAtrial Septal Occluder and Amplatzer Cribriform devices.***

1. ASO Device

1.1 Summary of MAUDE Analysis results following FDA adjudication

A total of 705 MDRs on ASO devices received in the past 10 years were identified for events associated with device on-label use (672 MDRs) and off-label use in PFO closure (33 MDRs). The patient gender information is provided in 526 MDRs, 326 females and 200 males (ratio: 1.6:1). The age of the patients ranged from 5 months to 87 years of age. The average age of the patients was 28.5 years (S.D: 22.5).

The most commonly reported problem, device embolization, comprises about 47% of all the MDRs (329 of 705) received by CDRH for ASO devices. The second commonly reported event was erosion (15%, 109 MDRs; 100 documented and 9 suspected), followed by device malfunction (8%, 59 MDRs), device malposition (8%, 55), and arrhythmia (5%, 36). Other reported events include non-erosion perforation/effusion (defined in Section V. D above), residual/recurrent shunt, valve dysfunction, device fracture, neurological events, device thrombus, infection/endocarditis, air embolism, allergy and others.

The MDR counts and the numbers of deaths and explants associated with each of the reported problems are listed in Table 6 below.

Table 6: Reported Events, Death and Explant in ASO and Cribriform MDRs

ASO & Amplatzer Cribriform	On-Label Use			Off-Label Use for PFO			Total		
	MDR Count N= 672	*Patient Death n=24*	*Explant n=505*	*MDR Count N=33*	*Patient Death n=2*	*Explant n= 24*	*MDR Count (%)* N=705*	*Patient Death n=26*	*Explant n=529*
Erosion	103	13	74	6	0	6	109 (15)	13	80
Documented	*95*	*8*	*71*	*5*	*0*	*5*	*100*	*8*	*76*
Suspected	*8*	*5*	*3*	*1*	*0*	*1*	*9*	*5*	*4*
Perforation/Effusion (No erosion)	26	2	2	4	2	1	30 (4)	4	3
Device Embolization	318	3	315	11	0	10	329 (47)	3	325
Malposition	55	0	46	0	0	0	55 (8)	0	46
Residual/recurrent Shunt	0	0	0	2	0	2	2 (0.3)	0	2
Valve Dysfunction	8	0	7	0	0	0	8 (1)	0	7
Fracture**	1	0	0	0	0	0	1 (0.1)	0	0
Device Malfunction***	57	0	27	2	0	1	59 (8)	0	28
Neurological Events	14	0	4	1	0	1	15 (2)	0	5
Stroke	*7*	*0*	*4*	*0*	*0*	*0*	*7*	*0*	*4*
Other	*7*	*0*	*0*	*1*	*0*	*1*	*8*	*0*	*1*
Device Thrombus****	14	1	2	4	0	2	18 (2.5)	1	4
Infection/Endocarditis	6	0	6	0	0	0	6 (0.8)	0	6
Air Embolism	6	2	1	0	0	0	6 (0.8)	2	1
Arrhythmia	35	0	9	1	0	0	36 (5)	0	9
Allergy	9	0	5	1	0	1	10 (1.4)	0	6
Others*****	20	3	7	1	0	0	21 (3)	3	7

* MDR %: The percentage in the ( ) represents the proportion of the MDR of the reported problem over the total of all ASO MDRs (N=705)

** The fracture event was reported, but investigation did not confirm that it actually occurred.

***Three MDRs categorized in "Device malfunction" were also reported with device embolization.

**** Five MDRs categorized in "Device thrombus" were also reported with stroke.

***** Others: include events such as headache, effusion after CPR, non-device-related stroke, aborted procedure, femoral access site fistula, septal tear to inferior vena cava, guidewire extraction difficulties, respiratory failure, and death (cause unknown).

1.2 Death associated with ASO

Among the 705 MDRs for ASO devices, there were 26 death reports, 24 associated with on-label use of the device and 2 with off-label use in PFO. The reported problems associated with the 26 fatal events are listed below.

Erosion (n=13 deaths): Thirteen of the 26 death reports (50%) have been adjudicated as device erosion or suspected erosion (8 documented and 5 suspected erosions). Nine of these erosion events occurred in the US and four outside the US. Some patients developed sudden onset of signs and symptoms and required emergency interventions. The signs and symptoms include cardiac tamponade (9 of the 13 erosion death events), pericardial effusion, hemodynamic compromise, chest pain, shortness of breath, syncope, and sudden cardiac death. The time to erosion reported in the 13 deaths ranged from 1 day to 821 days (2.2 years) post implant. Patient gender, as reported in the 13 erosion death MDRs, was 10 females and 3 males (ratio 3.3:1). For the details of the 13 death events, please refer to Appendix C.

Perforation/Effusion, not erosion related (n=4 deaths): Four deaths were reported as non-erosion cardiac perforation/effusion, two associated with on-label use of ASO devices and the other 2 with off-label use in PFO. All of the non-erosion perforation/effusion occurred during implant procedure or within 1 day post implant.

Embolization (n=3 deaths): Three death MDRs occurred within 24 hours post implant following device embolization. One patient expired and the device was not explanted. Attempts of percutaneous device retrieval were not successful in 2 patients and resulted in cardiac perforation in one of the patients. Both of these patients expired after attempted surgery.

Air embolism (n=2 deaths): There were 2 deaths associated with air embolism during the implant procedure, likely procedure-related.

Device Thrombus (n=1 death): A patient with history of small strokes and atrial fibrillation developed two serious strokes and a transesophageal echocardiogram showed device thrombosis. The patient subsequently expired.

Others (n=3 deaths): One patient died during implant procedure after extraction of a guidewire. Difficulties of guidewire extraction were noted prior to the guidewire extraction. Another patient developed respiratory failure, possibly not device-related. The other one patient expired 12 hours post-implant. The cause of the death is unknown.

1.3 Explants Associated with ASO

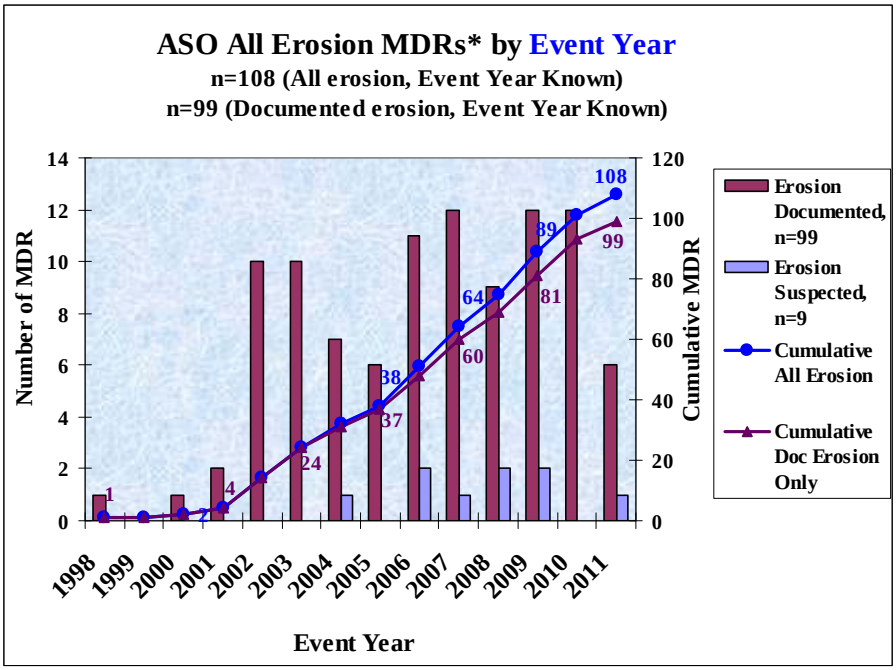
Of the 705 ASO Device MDRs, 529 noted device removal/explant. The top 5 reported problems associated with device explant are listed in order as follows:

1. Device embolization: 325 of 329 MDRs (99% explanted)
2. Erosion: 81 of 109 MDRs (74% explanted)
3. Device malposition: 46 of 55 MDRs (84% explanted)
4. Device malfunction: 28 of 59 MDRs (47% explanted)
5. Arrhythmia: 9 of 36 MDRs (25% explanted)

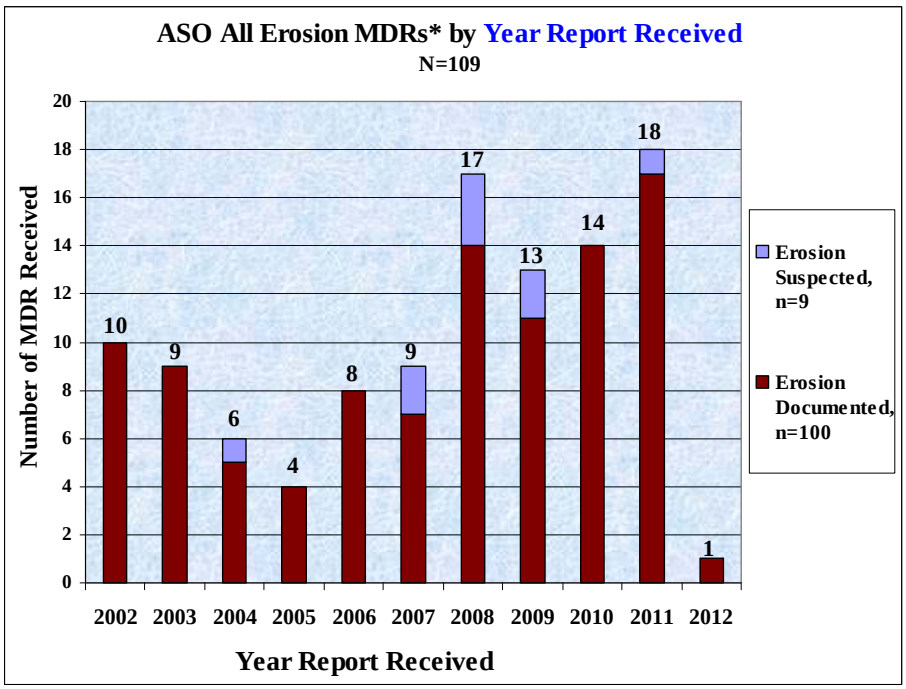
1.4 ASO Device Erosion MDR Trend

Given the seriousness of the erosion events in particular, erosion MDRs for all ASO devices were further analyzed. The 109 erosion MDRs comprise 15% of all the MDRs received by CDRH for ASO devices. Of the 109 erosion MDRs/events, 103 were associated with on-label use of ASO device and 6 with off-label use. Figure 7a below provides MDR counts by event year on the left axis and the cumulative MDR counts (blue line for all erosion and red line for documented erosion only, right axis). Please note that the Event Date information was not provided in one of the documented erosion MDRs. Therefore the Event Date is available in 108 of the 109 documented and suspected erosion MDRs; 99 of the 100 documented erosion MDRs. Despite a decrease in 2004 and 2005 (6 to 7 MDRs per year, documented erosion), the number of erosion events occurring per year slightly increased after 2005, ranging from 9 to 12 MDRs per year between 2006 and 2010. The increase may reflect an increase in the cumulative number of patients implanted with the ASO device, or an increase in the number of events reported due to increased awareness of these issues given the labeling changes implemented in 2005 and discussion in associated publications. For 2011, the reasons for the decrease in number of erosion MDRs are not clear; it may reflect the time delay between event occurrence and reporting to FDA, which could be days to months, or occasionally year(s) (see Figures 7a and b). For example, several erosion events occurred between 1998 and 2005 were not reported until 2011.

Figure 7: ASO Erosion Events as a Function of Year; (a) top – Reported according to Date of Event Occurrence; (b) bottom – Reported According to Date Report Received



*** MDRs include documented and suspected erosion events on ASO in On-Label Use and Off-Label Use in PFO.**

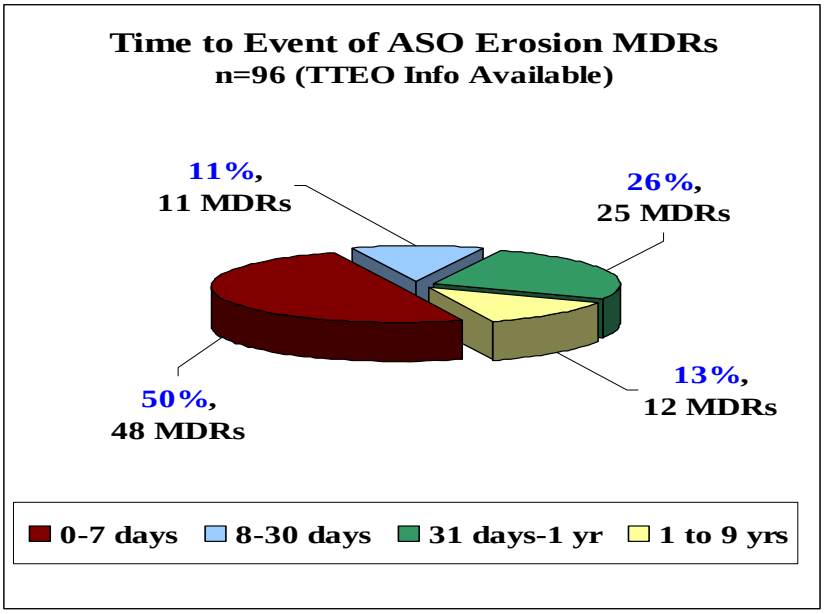


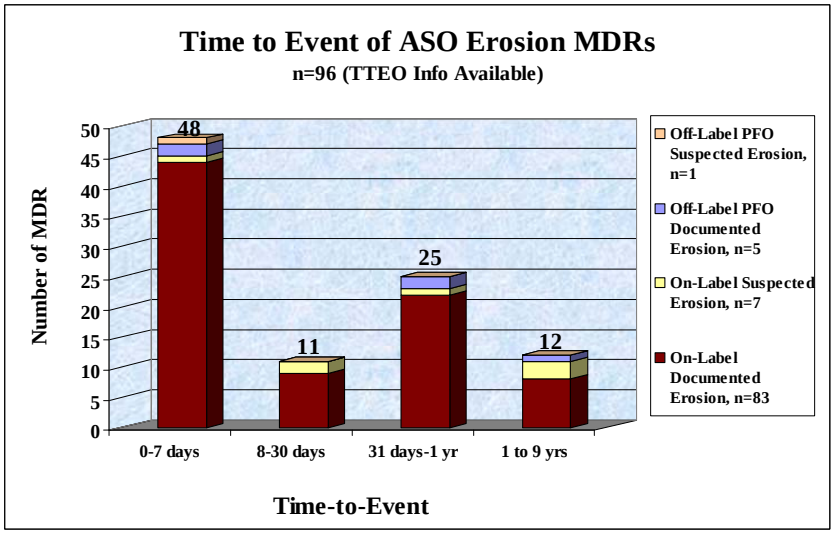
*** MDRs include documented and suspected erosion events on ASO in On-Label Use and Off-Label Use in PFO.**

The time from ASO implant to identification of erosion varied widely, and ranged from 0 to 3,139 days (8.6 years), for the reports providing both implant and event dates (96 of the 109

MDRs). About 50% of the erosion occurred in the first week, 61% in the first month (50% + 11%), and 87 % in the first year after implant as shown in the Figure 8. FDA has noted that 12 erosion events (13%) occurred beyond one year post implant, including 4 documented erosions between 5.3 and 8.6 years post implant.

Figure 8: Time to Erosion Event; (a) top – as Percentage of MDR Reports; (b) bottom – as Function of On-Label/Off-Label (PFO) Event and Documented/Suspected Events





Clinical Rationale for Focused Assessment of Erosion

Whatever their cause, erosions typically cause immediate hemodynamic compromise due to pericardial effusion and/or tamponade since all effected areas communicate directly with the free pericardial space. As a result, these events may present as pericarditic chest pain, clinical instability with hypotension, or even sudden death. If the process is chronic, and fibrosis develops as erosion progresses, an atrial-to-aortic fistula may alternatively develop.[10]

The overwhelming majority of the reported erosion events require the need for emergency open heart surgery to relieve the tamponade, correct the erosion(s) and/or fistula, remove the device, and surgically close the underlying ASD. Mortality for on-label adjudicated erosion events is high (8/95, 8.4%). The denominator (total ASO devices implanted) for these events remains unknown but is estimated to be 35,000 US and 15,000 OUS by AGA/St. Jude Medical. Therefore, the estimate for the incidence of erosion events ranges from ~0.1 – 0.2% (97/50,000). Due to under reporting within the MAUDE passive surveillance system, the estimate is likely to represent the lowest range of erosion events.

FDA Commentary: There are no known clinical or imaging predictors of patients at risk that have been identified as warnings or precursors which occur prior to the acute onset of symptoms due to erosion.

2. HSO Device

2.1 Summary of MAUDE Analysis results following FDA adjudication

A total of 150 MDRs for the HSO device were identified for events associated with device on-label use (87 MDRs) and off-label use in PFO closure (63 MDRs). The patient gender information is available in 147 MDRs, 86 females and 61 males (1.4:1). The age of the patient ranged from 1 year to 84 years of age (mean age = 31.9, SD = 2.5).

Of the 150 HSO MDRs, the most frequently reported problem is device embolization. Device embolization reports comprise 38% of all the MDRs (57 of 150) received by CDRH for HSO devices. The second most commonly reported event was residual/recurrent shunt (15%, 23 MDRs), followed by device malposition (13%, 20 MDRs), arrhythmia (9%, 13 MDRs) and device fracture (5%, 8 MDRs). Other reported events include device thrombus (5%), malfunctions (5%), non-erosion perforation/effusion (5%), neurological events (3%), air embolism (0.7%, 1 MDR) and others (1.4%, 2 MDRs), including one event of femoral access site hematoma/fistula and one event of percutaneous device removal secondary to chest pain.

[10] Mello, DM et al. Repair of Aortic–Left Atrial Fistula Following the Transcatheter Closure of an Atrial Septal Defect. Ann Thorac Surg 2005;80:1495-1498.

The MDR counts and the numbers of deaths and explants associated with each of the reported problems are listed in the Table 7.

Table 7: Reported Events, Death and Explant in HSO MDRs

HSO	On-Label Use			Off-Label Use for PFO			Total		
Reported Problem	*MDR Count N=87*	*Patient Death n=1*	*Explant n=71*	*MDR Count N= 63*	*Patient Death n=0*	*Explant n= 29*	*MDR Count (%)* N=150*	*Patient Death n=1*	*Explant n=100*
Erosion	**0**	**0**	**0**	**0**	0	**0**	**0**	**0**	**0**
Documented	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
Suspected	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
Perforation/Effusion (No erosion)	**2**	**0**	**0**	**5**	**0**	**2**	**7 (5)**	**0**	**2**
Device Embolization	**40**	**0**	**39**	**17**	**0**	**16**	**57 (38)**	**0**	**55**
Malposition	**15**	**0**	**13**	**5**	**0**	**3**	**20 (13)**	**0**	**16**
Residual/recurrent Shunt	**9**	**0**	**6**	**14**	**0**	**0**	**23 (15)**	**0**	**6**
Valve Dysfunction	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Fracture	**6**	**0**	**5**	**2**	**0**	**0**	**8 (5)**	**0**	**5**
Device Malfunction	**3**	**1*****	**1**	**4**	**0**	**3**	**7 (5)**	**1**	**4**
Neurological Events	**0**	**0**	**0**	**5**	**0**	**1**	**5 (3)**	**0**	**1**
Stroke	*0*	*0*	*0*	*2*	*0*	*0*	*2*	*0*	*0*
Other	*0*	*0*	*0*	*3*	*0*	*1*	*3*	*0*	*1*
Device Thrombus	**4**	**0**	**3**	**3**	**0**	**2**	**7 (5)**	**0**	**5**
Infection/Endocarditis	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Air Embolism	**0**	**0**	**0**	**1**	**0**	**0**	**1 (0.7)**	**0**	**0**
Arrhythmia	**7**	**0**	**4**	**6**	**0**	**1**	**13 (9)**	**0**	**5**
Allergy	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Others**	**1**	**0**	**0**	**1**	**0**	**1**	**2 (1.3)**	**0**	**1**

* MDR %: The percentage in the ( ) represents the proportion of the MDR of the reported problem over the total of HSO MDRs (N=150)

** Others: include one event of femoral access site hematoma/fistula and one event of percutaneous device removal secondary to chest pain.

***The reported information suggests this death is not related to a device malfunction but may be more accurately characterized as a procedural perforation/effusion, as noted below in section 2.2.

2.2. Death associated with HSO

Among 150 MDRs for the HSO, there was one death report. A patient underwent aortic valvuloplasty to treat valve stenosis and an ASO implantation for ASD. An HSO device was deployed over the ASO for treating the PFO shunt. The HSO device was not adequately covering the secundum. A retrieval cord broke during the retrieval of the HSO device. A procedural perforation was noted during the case. The patient developed pericardial effusion and expired during 4 hours of pericardial effusion treatment. The images were not available for event evaluation. Gore asserts that the retrieval cord break was incidental to the case and is not believed to have caused the perforation or patient death.

2.3. Device Explant of HSO

Of the 150 HSO MDRs, 100 reports noted device explant. The explants include both surgical and percutaneous device removal. The top 5 reported problems associated with device explant are listed in the following order:

1. Device embolization: 55 of 57 MDRs (97% explanted)
2. Device malposition: 16 of 20 MDRs (80% explanted)
3. Residual/Recurrent shunt: 6 of 23 MDRs (26% explanted)
4. Arrhythmia: 5 of 13 MDRs (38% explanted)
5. Device Fracture: 5 of 8 MDRs (63% explanted)

Note that other than device embolization, issues related to device position and structural integrity of the device (i.e., malposition, residual/recurrent shunt, fracture) account for events reported to the MDR with the highest frequency. A large proportion of these events are also associated with a decision to explant the device either by transcatheter or surgical technique.

VI. Summary of Current Atrial Septal Occluder Literature (ASO and HSO)

Introduction

The purpose of this literature review is to provide a summary of the known data available in the current peer-reviewed literature on atrial septal occluders. The review provides information on safety and effectiveness outcomes for closure of atrial septal defects.

Methods

A literature search was conducted through PubMed and included literature published through March 22, 2012. The following search criteria were used:

"septal" AND "occluder" AND (erosion OR perforation OR embolization OR fracture OR arrhythmia OR thrombus) AND (English[lang]) AND ("Amplatzer" OR "HELEX")

This search yielded 334 papers. These papers were reviewed, and those reporting on PFO or VSD closure, reporting on the Amplatzer vascular plug, without any original data or otherwise not including adverse event data associated with septal occluder devices, were removed (n=244). Ninety (90) references are included in this review of the literature (Appendix C). The results published below focus on papers that provide an estimate of the rate of adverse events.

Results

Overview of Published Literature

Table 1 in Appendix C provides a summary of the papers reviewed. During the literature review, emphasis was placed on extracting information on adverse events and the suspected cause of the adverse event. The majority of papers were case reports (n=40) or case series (n=18). There were also several prospective cohort studies in which the authors were interested in following a cohort of subjects to observe their outcomes (n=29). Of the papers reviewed, 82 included data on the

ASO, six on the HSO and 1 had data on both the ASO and HSO device. These studies were limited by the fact that they most often did not have a control group and, more importantly, were not powered to detect low frequency adverse events. In addition, there is a substantial range of variability in the incidence estimates of various adverse events.

Erosion

Due to the seriousness of associated clinical outcomes, most erosion reports are presented as case reports or case series and were not often found in the prospective cohort studies. The **erosion rate range is estimated to be 0.1-0.2%.**[i,ii,iii] These published erosions all occurred less than 48 hours after device implant. These rates are based on case series of events reported to the manufacturer, a MAUDE review and an operator survey. The rate estimate is not based on evaluation of a prospective cohort hence there is limited information on time to event. **All of the erosion events were reported for the ASO device, and there are no published reports of erosions occurring with the HSO device** [ix, iv,v].

Embolization

Based on the 7 cohort studies reporting, it is our **best estimate that the embolization rate is in the 0.3 – 3.5% range.** [vi,vii,viii,ix,x,xi, xii,xiii] with the mean value being reported as 1.4% and the median rate in the 0.55-0.7% range. The follow-up times vary widely between these studies, ranging from periprocedural outcomes out to 3 year follow-up. Majunke et al.[ix] followed a cohort of patients for 36 months and estimated an embolization rate of 0.5% associated with the ASO device. Everett et al.[x] included follow-up only for 24 hours and reported an embolization rate of 1.1% associated with the ASO. Omeish et al.[xii] reported a rate of 0.39% at 3 years associated with the ASO.

Fracture

An adverse event unique to the HSO device is **wire fracture which occurs in the 6.4-8% range**[xiv,xv] through 12 month follow-up. Fagan et al. provided data from all HSO implants over a 12 month period[xiv] Latson et al. reported data from the pivotal trial supporting the HSO market approval.[xv] There are rarely, if ever, any clinical sequelae associated with wire fracture events in the literature.

Other Adverse Events

There are other adverse events also reported in the literature. Arrythmias in the range of 2-5% were reported between 1.8 and 2.5 years of follow-up,[xvi] perforation of 0.05% was observed through two years follow-up[xii] and thrombosis formation on the device in the 0.8-10% range in patients followed for 6-14 months.[xvii,xviii] Most of these studies were performed on the ASO device. There is limited data in the published literature on the HSO device.

Discussion of Strengths and Limitations

The strengths of the literature include the fact that many case reports have been published that give extensive detail about patients with serious outcomes. This includes information on patient history, imaging that was performed and extensive discussion on root cause.

The most significant limitations of the published literature on septal occluders are the small sample sizes and the lack of control groups in most studies. With events such as erosion in the 0.1-0.2% range, a large sample size would be needed to detect events with adequate precision.

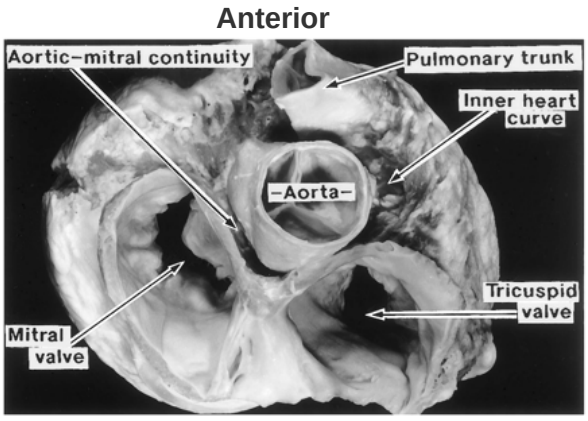
Conclusion
The currently available literature does not provide robust estimates for the incidence of adverse events associated with atrial septal occluders. In addition, the cohort studies that do provide estimates are generally not powered to detect very low frequency events. The case reports do not provide definitive information on the causes of adverse events, particularly embolization and erosion, and the literature does not provide adequate data on precise estimates of the incidence of such events.

VII. Erosion Events - Root Cause Analysis

Given the seriousness of the clinical sequelae associated with device erosion, FDA and AGA/St. Jude have conducted root cause analyses in an attempt to determine the etiology of this adverse event, and/or identify patients or septal anatomies at higher risk for erosion events. The original and recent root cause analyses commissioned by the manufacturer have focused on anatomic factors as being the primary cause of acute tissue erosion, specifically citing the importance of an absent aortic rim, which may or may not be exacerbated by device over-sizing. Although these factors can be documented as being associated with the occurrence of erosion, it is FDA's observation that these anatomic associations are only part of a complex set of interactions between factors including, but not limited to, the aforementioned underlying anatomic substrate, the dynamic hemodynamic counter-motion between the atrium and pressurized aorta, and device specific characteristics designed to provide enhanced structural integrity and stability in this dynamic environment. Since erosion has only been observed following use of the AGA/St. Jude ASO device, all of the following FDA comments regarding device erosion and its proposed mechanisms have been derived primarily from the description of events related to this device.

Device Positioning and Clinical Sequelae:
The normal anatomic relations of the inter-atrial septum and atrial domes to the non-coronary sinus of the aortic root are shown in the Figure 9 below. Free intrapericardial space separates the structures. (Note: No ASD is depicted.)

Figure 9: This dissection of the cardiac short axis, seen from its atrial aspect, reveals the relationships of the cardiac valves, interatrial septum and aortic root.[11]

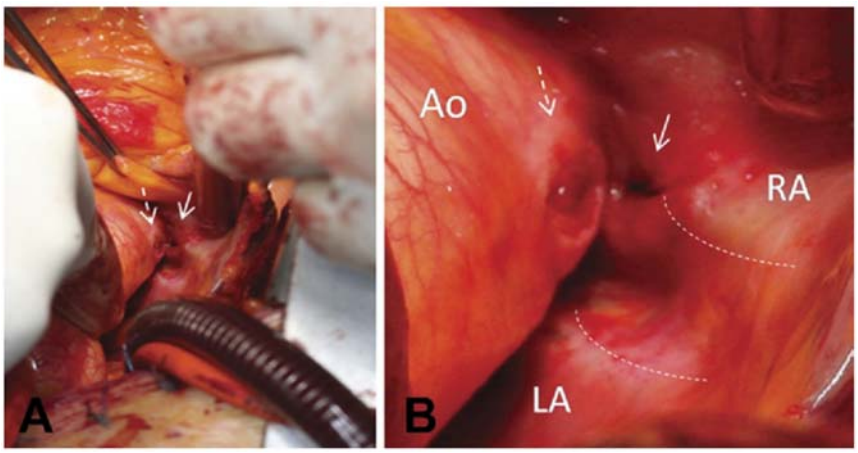


* = Site of Occluder Device

The available information suggests that erosion occurs when an ASO device comes in direct contact with the atrial dome tissue, and due to pressure and/or friction on the atrial roof tissue, erodes through the right or left atrial dome into the free pericardial space. Whether this erosion occurs due to pressure necrosis (ischemia), friction between the device and atrial tissue, or a combination of the above two factors is unknown. The same forces, when exerted by the device on the opposing pressurized and beating aorta may cause erosion of the aortic root at the level of the non-coronary sinus which lies directly across the free pericardial space from the atrial domes. In particular, the pressure/friction forces for both atrial and aortic tissues may be exacerbated by the counter-movements of the "stented" atrial domes and pressurized and pulsatile aorta that occur as a natural result of the cardiac cycle. Over-sizing of the device, and/or the absence or deficiency of the aortic rim of the secundum defect may potentiate these factors by placing the device in closer apposition to both the atrial domes and the aorta. The typical intraoperative appearance of an ASO erosion event is seen in Figure 10 below.

[11] Image From: Online edition of Cardiac Surgery in the Adult. Lawrence Cohn, Editor. http://cardiacsurgery.ctsnetbooks.org/cgi/content/full/2/2003/31/F4?ck=nck

Figure 10: Intraoperative Photograph taken from the head of the operating table following relief of tamponade, evacuation of pericardial blood, and institution of full cardiopulmonary bypass. Images are from the same patient whose imaging studies are shown in Figure 11. Erosions of the right atrial dome (solid arrow) and adjacent aortic root (interrupted arrow) are clearly seen, as are the left and right disc edges of the ASO device (curved dashed lines in panel B).[12]



Over time, several etiologies for erosion have been proposed, including device over- or under-sizing, device configuration against the aortic root and free atrial wall (straight vs. splayed), and deficient (<5 mm) anterior-superior aortic rim. Device over-sizing was implicated in early publications[6], but subsequent peer-review articles have suggested alternatively over-sizing and under-sizing as culprits. Whether there is an optimal final configuration of the ASO device disc orientation (straight or splayed) is unknown and also the subject of debate.[13] More recent analyses have identified deficient aortic rim as a primary anatomic factor in erosion development, in which the device is displaced closer to both the atrial domes and aortic root. However, it is notable that 5 cases (4 documented, 1 suspected/disputed) of device erosion in cases of PFO closure have been reported and it is unclear how this proposed etiology alone would explain these events.

It may be that a device design with more robust structural integrity that resists the failure mode of device fracture is more likely to impart greater pressure on the free atrial wall and pressurized aortic root. This may further contribute to a propensity for erosion due to local tissue ischemia or friction. However, given the available information, it is unclear whether device design is a primary factor, a contributing factor, or increases the likelihood of an erosion in the presence of certain anatomic substrate and dynamic hemodynamic conditions.

FDA has also evaluated the incidence and timing of erosion in adult versus pediatric (≤18 years) patients. In general, erosions occurred in both pediatric and adult patients; device over-sizing

[12] Image from: Santini, F et al. Life-Threatening Isometric-Exertion Related Cardiac Perforation 5 Years After Amplatzer Atrial Septal Defect Closure: Should Isometric Activity Be Limited in Septal Occluder Holders? Ann Thorac Surg 2012;93:671

[13] El-Said H, Moore J. Erosion by the Amplatzer Septal Occluder: Experienced Operator Opinions at Odds With Manufacturer Recommendations? Catheterization and Cardiovascular Interventions 2009; 73:925–930.

was more highly correlated with erosion in pediatric patients; and erosion events tended to present early (i.e., within 72 hours of implant) in pediatric patients. Although these trends are interesting, it is important to note that the same characteristics seen in patients with erosion are seen with much higher frequency in patients without erosion, suggesting that these factors are correlative, but not necessarily causative.

Figure 11: CT scan (left, A) and Transesophageal Echocardiographic (right, B) images of ASO Device (right disc edge at arrow) and adjacent anatomic structures. (device outline is hyperlucent and hyperechoic structure in septum between RA and LA with straight right disc edge protruding into the aortic root - Ao). This CT scan and TEE image are from the same patient depicted in Figure 10 above.[14]

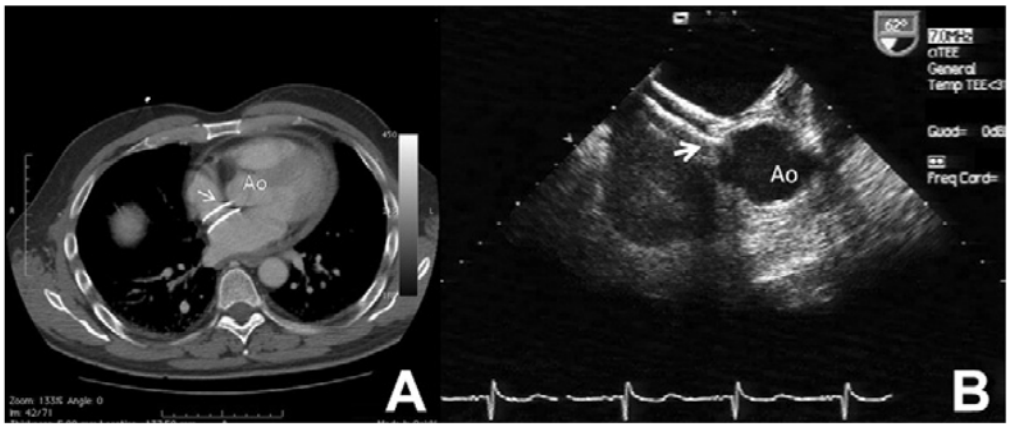
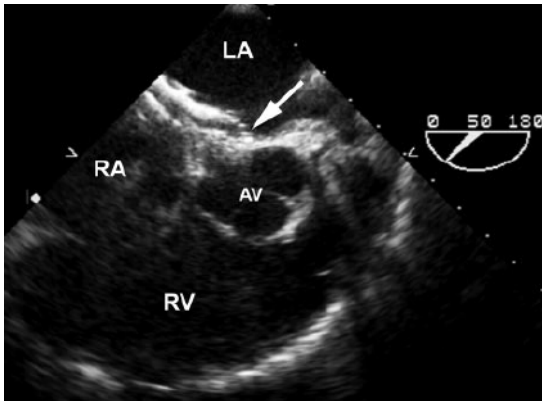


Figure 12: Transesophageal Echocardiographic image of ASO Device (Left disc edge at arrow) and adjacent anatomic structures. (device outline is hyperechoic structure in septum between RA and LA with edges splayed over aortic root - AV).[15]



[14] Images From: Santini, F et al. Life-Threatening Isometric-Exertion Related Cardiac Perforation 5 Years After Amplatzer Atrial Septal Defect Closure: Should Isometric Activity Be Limited in Septal Occluder Holders? Ann Thorac Surg 2012;93:671.

[15] Image From: Yared, K et al. Echocardiographic Assessment of Percutaneous Patent Foramen Ovale and Atrial Septal Defect Closure Complications. Circ Cardiovasc Imaging 2009;2;141-149.

Manufacturer identified contributors to erosion:

The PMA for the ASO device was approved in 2001. The first report submitted to the MAUDE database of an erosion event occurring as a complication of the ASO device was received on February 27, 2002. Following the receipt of numerous additional reports of erosion, AGA/St. Jude commissioned an in-depth root cause analysis, identifying device over-sizing as the likely cause (2004)[5]. Publication of these findings, labeling changes, and widespread distribution of warnings related to revised sizing recommendations were undertaken and are reproduced below (Figure 13).

Figure 13: Reproduction of recommendations from AGA commissioned root cause analysis – 2004[6].

TABLE II. Recommendations

Follow instructions for use when performing balloon sizing
Avoid overstretching the balloon when balloon sizing the defect
Use stop-flow technique for maximum inflation of sizing balloon
Be gentle with to and fro of the device (Minnesota wiggle) while the device is attached to the delivery cable
Identify patients who may be at higher risk and will require closer follow-up
Patients who require significantly larger ASO (> 1.5 times) than the native diameter of the ASD
Patients with development of small pericardial effusion at 24-hr follow-up
Patients with deformation of the ASO at the aortic root (significant splaying of the device edges by the aorta)
Patients with high defects (minimal aortic and superior rims)
Mandatory 24-hr follow-up in all patients
Educate patients about the risk and need for echocardiography with symptoms

Although the authors of this review recognized the obvious need for the presence of a device and device contact with tissue in the production of erosions, the primary root cause was attributed generally to anatomic factors (deficient aortic rim recognized in 89%) and specifically to device over-sizing.

Despite the above findings and widespread dissemination and acceptance of the sponsor's recommendations, the reports of early and late erosion events have continued to be submitted to FDA prompting the current review (see Figure 7).

In response to the results of the current review, AGA/St. Jude has commissioned a second root cause analysis. This analysis will be presented in detail as part of the AGA/St. Jude Medical Executive Summary, and will only be summarized briefly here. This analysis has identified deficient (<5 mm) aortic rim as the proposed primary factor in erosion development, and device over-sizing and erosion, though potentially a contributing factor, is no longer felt to be a primary root cause for the production of erosion. The sponsor's current analysis suggests aortic rim deficiency is the primary anatomic contributor to erosion, exerting its influence by displacing the device closer to the atrial domes and aortic root. However, it is notable that 6 cases (5

documented, 1 suspected/disputed) of device erosion in cases of PFO closure have been reported and it is unclear how the proposed etiology would explain these events.

No documented or suspected on-label erosions have been reported for the HSO device. This was true whether the FDA MAUDE adjudication process (Figure 5) or the AGA/St. Jude MAUDE adjudication process was used (Appendix D). Although the HSO device is implanted in the same anatomical location, differences in device design and materials, as well as the tendency for the largest devices to fracture under certain physiological conditions, lessening the force applied against the aortic root, may partially explain the lack of erosion events.

Note: *A case of early post procedure tamponade treated by pericardiocentesis without recurrence following HSO insertion for a PFO (off-label) has been reported (report 2010-00166). Using FDA criteria, this event is classified as an off-label event, perforation/effusion with drainage or explant and a non-erosion event since no erosion was observed or suggested by the clinical events and course. It is not regarded as a documented or suspected off-label erosion event by FDA analysis, and this judgment is consistent with procedures used for evaluation of all on and off-label erosion events for all reports on both devices. (See Section 3.2).*

FDA Commentary: The root cause analysis and conclusions regarding etiology conducted by AGA/St. Jude may identify an important factor leading to erosion, but they do not explain erosion events that occur in patients with "sufficient" rims, or those occurring following off-label PFO closure. Furthermore, although it is generally recognized that a device and device contact with the eroded tissue is a necessary prerequisite for erosion, the extent to which device characteristics (e.g., design, materials) contribute to a synergistic effect when placed in a dynamic environment is unknown.

VIII. Actions Implemented by Manufacturers

A. ASO Device

In order to address the issue of erosion, St, Jude Medical has recently instituted additional labeling changes (January 2012) in an attempt to further mitigate the incidence of erosion events. The changes as they compare to prior labeling (as revised in 2005) are summarized below:

- Replaced Patient Selection Precaution:
  - Certain patients may be at higher risk for complications such as tissue erosion and device embolization. …Patients with high defects (minimal aortic and superior rims)..."
- With Contraindication as follows:
  - Any patient with echocardiographic evidence of absent or deficient anterior-superior rim (sufficient rim is defined as presence of at least 5mm rim in multiple AND sequential short-axis views confirmed by ICE or TEE).

- Added Contraindication as follows:
  - Any patient in whom the device would interfere with or contact other intracardiac or intravascular structures, e.g., atrial roof, cardiac valves, pulmonary veins, coronary sinus, or aorta.
- Note that the following Contraindication was included in the prior and revised labeling:
  - Any patient where the margins of the defect are less than 5 mm to the coronary sinus, AV valves, or right upper lobe pulmonary vein.

- Observed Adverse Events reworded from:
  - Tissue erosion/perforation is understood to be caused by cardiac function in circumstances when the implanted device is oversized in relation to the ASD diameter. The risk is mitigated when the sizing recommendations and device size selection instructions are followed.
- To:
  - "…Tissue erosion is understood to be caused by absence of sufficient anterior-superior rim and/or device oversizing, enabling device distal edge contact with adjacent cardiac structures. The risk is mitigated through echocardiographic guidance and sizing recommendations…."

FDA Commentary: AGA/St. Jude Medical has proposed and implemented labeling changes to reflect their most recent analysis. They have also made exhaustive efforts to capture available data on suspected erosion events and to subject those events to independent clinical review (i.e., Erosion Board). They have conducted additional analyses of their PAS data and conducted physician surveys to capture additional events as well as obtain feedback regarding root cause. In association with their new labeling recommendations, they have also initiated an additional physician training program.

B. HSO Device

In order to address the issue of fracture, the sponsor provided revised labeling with the following language added to the "Frame Fractures" section of the IFU (December 2010):

"Although an association of frame fractures with serious adverse events is rare, clinical event reports have described events in which frame fractures have results in a second surgical or interventional procedure. For example, frame fractures have been observed in cases of residual shunts, excessive motion/improper apposition of the device, device displacement, separation of the right disc from left disc, and mitral valve damage. The frequency of these events, based on voluntary reports, is estimated at < 0.1% of devices sold.**"**

"The mechanism for frame fractures is related to fatigue, and has been hypothesized as stemming from the repeated ovalization[16] of the device within the atrial chamber. No clinical sequelae were

[16] Device ovalization is defined as compression of the device with unequal force around the circumference leading to a slightly oval configuration instead of the intended circular configuration.

observed in these trials as a result of a wire frame fracture. Only one fracture was associated with device instability. This device was removed surgically. The remaining fractures were detectable only by careful radiographic examination. No special treatment was recommended for incidentally detected asymptomatic fractures in stable devices.

"It is recommended that patients should have TTE exams prior to discharge, and at 1, 6, and 12 months after occluder placement to assess, in addition to residual leak status, the stability of the device, as a lack of device stability may be indicative of wire frame fractures. In instances where device stability is questionable, fluoroscopic examination without contrast is recommended in order to identify and assess wire frame fractures. Routine fluoroscopic evaluation is not felt to be necessary in patients who are asymptomatic with stable devices by TTE."

Note that since the addition of this change to the Instructions for Use, there have been more events observed, as previously discussed, whereby device fracture has been associated with a clinical decision to explant the device.

IX. Additional Regulatory Action Considerations

A. Prospective Collection of Additional Data – 522 Study

FDA is asking the Panel to consider whether, given the available information presented by FDA and each sponsor, additional regulatory actions are needed. If the Panel believes that additional regulatory actions are needed, possible actions FDA could pursue are described in more detail below.

Postmarket surveillance under section 522 of the FD&C Act is one means by which the FDA can obtain additional safety and/or effectiveness data for a device after it has been cleared through the 510(k) process or approved through a PMA, humanitarian device exemption (HDE), or product development plan (PDP) process. Additional information can be found in Appendix E).

There is limited data available on rare adverse events available to the FDA from the mandated post-approval studies for these devices. Studies in this device area have been very difficult to enroll, therefore we do not think a large scale study is necessary or feasible. A registry may be the most reasonable/feasible approach to further evaluate adverse events associated with these devices. Patient characteristics, in particular echocardiographic (and/or other imaging) criteria, are expected to be the most instructive in identifying patients with increased risk for erosion in particular. If 522 orders are issued to address the issues of concern, FDA would recommend a prospective registry and possibly a retrospective analysis of events.

B. Reanalysis of Data Already Collected

If specific patient or technical issues are identified that may be further instructive, re-analysis of data collected from the pre-market or post-market studies may be warranted.

C. Communication to Physicians/Patients

If deemed necessary, FDA may issue a Public Health Advisory to patients in whom devices have been implanted regarding the signs and symptoms of events that warrant immediate medical attention (e.g., severe chest pain for erosion; arrhythmia for embolization). Alternatively, FDA may issue a physician communication regarding topics such as implant considerations, patient follow-up, or important issues to consider for discussion during the informed consent process. If such communication is considered useful, we would seek input from the Advisory Panel regarding suggested content of that communication such that it would facilitate a responsible and meaningful message to patients and/or physicians without either minimizing events or creating unnecessary concern for patients.

D. Labeling Changes

Labeling changes have been previously instituted for the ASO in response to erosion events and for the HSO device to include updated information about device fracture. Additional labeling changes may be instituted in response to adverse events for either/both the ASO and HSO devices and feedback is sought whether any additional action is necessary in this regard or whether current labeling is sufficient. Additional guidance regarding labeling definitions may be found in Appendix F.

E. Tracking

FDA plans to initiate "tracking" of ASD devices (under a new product code, OZG - transcatheter septal occluder (atrial)) as permitted under Section 519(e) of the FD&C Act. Devices eligible for tracking include those for which:

> (A) the failure of which would be reasonably likely to have serious adverse health consequences; or
> (B) which is:
>> (i) intended to be implanted in the human body for more than one year, or;
>> (ii) a life sustaining or life supporting device used outside a device user facility.

The Medical Device Tracking Regulation requires manufacturers to track certain devices from their manufacture through distribution for the life of the product. The purpose of device tracking is to ensure that manufacturers of certain devices establish tracking systems that will enable them to promptly locate devices in commercial distribution. Tracking information may be used to facilitate notifications and recalls ordered by FDA in the case of serious risks to health presented by the devices. FDA's decision to institute tracking was informed by prior interactions with AGA/St. Jude, feedback from their clinical consultants and input from FDA advisory panel members (during the prior panel "homework assignment").

X. Conclusions

For most medical products, additional information about device safety becomes available with increased experience and more widespread use. Transcatheter ASD closure devices are no exception. Postmarket surveillance data has provided insights into the adverse event profile for both ASO and HSO devices.

For the ASO device, erosion events were not apparent in the market entry trial nor have they been observed in the ongoing post approval study. Erosion rate estimates from the literature and MAUDE system are similar (~0.1-0.2%); however, these estimates are limited given the rarity of event and methodology used to capture data. Data from the MAUDE database and preliminary data reported to the FDA by AGA/St. Jude show most erosions (60%) occur after discharge from the hospital, and 1 in 8 erosions (12%) occur beyond the one year post-implant with a single event reported as late as 8 years post implant (2003-2011). Although this type of event appears to be quite rare, the associated morbidity is considerable.

Embolization rates experienced in the clinical trials (~1-3%) are similar to those reported in the literature (~0.3-3.5%) and constitute the majority of adverse events reported to the MAUDE system. These events are not consistently associated with life-threatening sequela; however, they nonetheless require an additional procedure, percutaneous or surgical, for retrieval.

Fracture events with the HSO device were noted in the market entry clinical data (~6-7%) and are similar to literature estimates (6-8%). Prior trends of associated adverse clinical sequelae have not been reported; however, ~2% of post-approval study patients have undergone device explant due to device fracture.

FDA appreciates the Panel's consideration of this information and feedback on the Questions in Tab 2 of the Panel Pack.

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