

FDA Executive Summary

*General Issues: Meeting to Discuss the Evaluation of
Safety and Effectiveness of Endovascular Medical
Devices Intended to Treat Intracranial Aneurysms*

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Neurological Devices Advisory Panel
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1 Introduction and Purpose of Advisory Panel Meeting

The Center for Devices and Radiological Health (CDRH) is responsible for protecting and promoting the public health. We assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products. We provide consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee. We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the United States (U.S.). Towards these goals, this panel meeting is intended to support FDA's mission to ensuring U.S. patients have access to high-quality, safe, and effective medical devices of public health importance first in the world, including medical devices indicated for aneurysm treatment.

A cerebral aneurysm (also known as an intracranial or intracerebral aneurysm) is a weak or thin spot on a blood vessel in the brain that balloons out and fills with blood. The bulging aneurysm can put pressure on nerves, meninges, and/or surrounding brain tissue. It may also leak or rupture, spilling blood into the surrounding tissue (referred to as an intracranial hemorrhage). Some cerebral aneurysms, particularly those that are very small, may never bleed or cause clinical sequelae. Cerebral aneurysms have been reported in the literature for several decades (Housepian and Pool 1958; Chason and Hindman 1958; Jellinger 1976) and it is estimated that on average five percent of the population is afflicted with this disease (Jellinger 1976).

Originally, open direct surgery was the most common to treat aneurysms by placing a clip across the neck of the aneurysm to eliminate flow from the parent artery into the aneurysm sac. In recent years, there have been several advancements in the treatment of aneurysms through endovascular means (Johnston et al. 1999; Roy, Milot, and Raymond 2001; Starke et al. 2012) such as using neurovascular embolization coils alone, with stent assisted coiling, and flow diversion technology (Berge et al. 2012; Byrne and Szikora 2012; Wakhloo et al. 2015; D'Urso et al. 2011). Understanding the safety and effectiveness for many of these novel interventional aneurysm treatments is an evolving, innovative product area and crucial for the Food and Drug Administration (FDA) from a regulatory perspective. Therefore, the FDA is convening this Advisory Committee meeting to seek expert opinion on scientific and clinical considerations relating to the determination and evaluation of the safety and effectiveness of novel endovascular aneurysm treatment devices for marketing approval in the United States (US).

2 Cerebral Aneurysm Overview: Diagnosis and Characteristics

2.1 Morphology and Size of Aneurysms

Cerebral aneurysms are often classified by their morphology. Aneurysms may be described as saccular, fusiform, pseudoaneurysm (resulting from trauma to the blood vessel wall), or dissecting. The most common types of cerebral aneurysms are saccular (sometimes referred to as berry aneurysms) which protrude from the side of the vessel; fusiform aneurysms which is a dilation of a particular segment of a vessel, and dissecting aneurysms which results from a tear between the inner (intima) and outer vessel wall causing blood to collect between layers of the vessel wall. Neck size, the size of the opening that connects the parent artery to the aneurysm body, is also an important descriptor for aneurysms and can dictate treatment options. Aneurysms with a neck ≥ 4 mm in diameter or dome to neck ratio < 2 are typically classified as wide-neck (Biondi et al. 2007; Sedat et al. 2009; Huang et al. 2009; Standhardt et al. 2008; Wiebers 2003). A study conducted by Roy et al. on 125 unruptured aneurysms determined 37.6% of those aneurysms to be wide-neck (Roy, Milot, and Raymond 2001). Such aneurysms can be

difficult to treat and are less amenable to coiling alone or surgical clipping in comparison to aneurysms with smaller necks (O.K. Kwon et al. 2005).

Aneurysm size is also another factor that can affect the type of treatment prescribed. Although some disagreement exists on the precise size classifications of naturally occurring aneurysms, a general trend can be seen and most studies have defined aneurysm sizes (based on the maximum diameter of the dome) as follows: small ≤ 5 mm, medium 6-10 mm, large 11-25 mm, and giant ≥ 25 mm (Molyneux et al. 2009). The International Study of Unruptured Intracranial Aneurysms (ISUIA) retrospectively studied 1449 patients with angiographically confirmed aneurysms and identified the size distribution of aneurysms to be 47%, 27%, 12%, and 14% for small, medium, large, and giant aneurysms, respectively (Wiebers 1998). The predominant occurrence of small and medium aneurysms has also been confirmed in additional studies (Standhardt et al. 2008).

2.2 Anatomical Locations

Intracranial aneurysms typically occur at vessel branch points as illustrated in Figure 1. Aneurysms of the anterior neurovasculature can be located at the following locations: cavernous internal carotid artery (ICA), ophthalmic artery, superior hypophyseal artery, posterior communicating artery (PComm), anterior choroidal, ICA terminus, anterior communicating artery (AComm), anterior cerebral artery (ACA), or middle cerebral artery (MCA). Aneurysms of the posterior circulation can be located at the posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery (AICA), superior cerebellar artery (SCA), basilar apex, or posterior cerebral artery (PCA) (Greenberg 2010; Winn 2011). The initial ISUIA study data referenced above determined that of the 1449 aneurysms included in the trial, only 207 (14%) were located in the posterior circulation (Wiebers 1998). In a 2003 follow-up study, 12% of the 4060 participating patients had aneurysms located in the posterior circulation (Wiebers 2003). The relative occurrence rates between the different locations is also shown in Figure 1.

Most common sites of intracranial saccular aneurysms

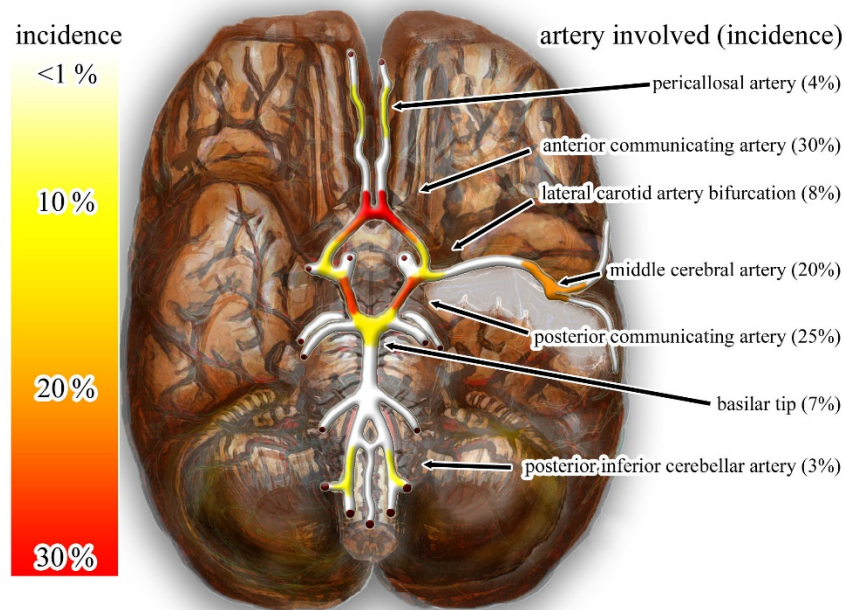


Figure 1. Illustration of saccular aneurysms occurring throughout the neurovasculature. The percentages are the relative occurrence rates based on the different locations

The distinction between anatomical locations is noteworthy because the posterior vasculature has been shown to be an indicator of poor clinical outcome for both open surgery and endovascular treatment of unruptured aneurysms, primarily due to the increased risk of rupture (Wiebers 2003). This difference in patient outcomes based on anatomical location was primarily based on the safety and effectiveness of the treatment modality, and was supported by subsequent studies which determined that the advantages of endovascular versus open surgical treatment can depend greatly on the aneurysm location in part due to the accessibility of the aneurysm through endovascular means (Molyneux et al. 2005). This investigation was a randomized, prospective study where 1070 patients were selected for surgical clipping and 1063 were treated using endovascular approaches. The primary outcome was measured by death or dependence at 1 year (modified Rankin Scale (mRS) of 3-6). The investigators determined that the risk ratio more strongly favored endovascular treatment in the posterior circulation (risk ratio of 0.39) as compared to the anterior circulation (risk ratio of 0.89), although the risks of treatment were lower in both locations of the neurovasculature in favor of endovascular treatment (Molyneux et al. 2005).

2.2.1 Perforating Arteries

One of the contributors of worse clinical outcomes for patients with cerebral aneurysms located in the posterior circulation of the neurovasculature may also be due to the presence of perforating arteries. Perforating arteries are small branches that emerge from larger vessels that are responsible for supplying blood to various portions of the brain. While perforators are present in both the anterior and posterior circulations, perforator vessels in the posterior circulation are at particularly high risk for occlusions causing infarction relative to those in the anterior circulation. This discrepancy is likely because of the delicate perfusion and lack of collateral blood supply to brainstem structures. During endosaccular treatment such as using traditional coiling alone, perforators typically are unaffected. However, techniques such as stent-assisted coiling, flow diversion, and even surgical clipping can potentially impact the perforators by occluding or damaging these branches (Molyneux et al. 2005) with clinical outcomes dependent on the type of treatment used. For example, it has been estimated that based on the flow diverter mesh size and the size of the perforator, a flow diverter could reduce the perforator orifice area by 55% (Kulcsár et al. 2010). Perforator (and also small named arteries such as the ophthalmic) occlusion has also been discussed in the clinical literature for both flow diverters as well as stent assisted coiling (SAC) devices and has raised concern regarding the safety of such devices (Lopes et al. 2003; Masuo et al. 2005; D’Urso et al. 2011; Kulcsár et al. 2010). Conversely, several literature sources de-emphasize the concern for perforator occlusion. A series of in vitro studies have stated that because flow through perforators is driven by pressure, even with 90% coverage of the perforator inlet area, the resulting perforator blood flow may only be reduced by < 10% (Seong, Wakhloo, and Lieber 2007; Appanaboyina et al. 2008; D’Urso et al. 2011).

2.3 Risk Factors for Aneurysm Rupture

Most aneurysm treatments are performed electively on unruptured aneurysms. Treating unruptured aneurysms helps to prevent the risk of aneurysm rupture, which can result in a subarachnoid hemorrhage (SAH). Subarachnoid hemorrhage can lead to mortality and serious morbidity and thus treatment is performed prophylactically. Ruptured aneurysms are also commonly treated as there is a high risk of recurrent SAH with untreated ruptured aneurysms. Based on natural history, it has been suggested that aneurysms have an average rupture rate of around 1% per year in patients with a diagnosed aneurysm, although that number can vary based on the study (Ishibashi et al. 2009; “The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort” 2012; Juvela et al. 2013). Of the 1449 patients enrolled in the ISUIA trial, 32 had a confirmed aneurysm rupture (2.2% of the total number of patients), with 28 of those in the first 7.5 years of follow-up (rupture rate of 0.3% per year) (Wiebers 1998). For the small number of patients in this study who did progress to a ruptured aneurysm, there was a 66% overall mortality rate and aneurysm rupture was the leading cause of death for patients in the study. In a later

study comparing conservative management to intervention, 51 patients in the unoperated cohort (3% of the patients) experienced a confirmed aneurysm rupture during follow-up with 49 of those occurring within the first 5 years of diagnosis (rupture rate of 0.5% per year) (Wiebers 2003) while Juvela et al. (2013) followed patients for more than 20 years and found an annual incidence rupture rate of 1.1%.

In summary, it is difficult to predict the risk of aneurysm rupture because the rupture risk can be affected by many factors such as a history of prior SAH, location of the aneurysm in the neurovasculature (e.g., posterior vs. anterior circulation), aneurysm morphology, as well as the overall size of the aneurysm (Ishibashi et al. 2009). For example, the published literature suggests that the rupture rate for patients without a prior history of SAH (Type 1) can be as low as 0.05% in the first year, which is 10 times lower than those with a previous SAH (Type 2) (0.5%) (Wiebers 1998). Additional studies have confirmed the correlation between increased rupture rates and a prior history of SAH (“The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort” 2012).

Size and location of the cerebral aneurysm in the neurovasculature can also affect the risk of rupture. In the article by Wiebers (2003), aneurysms in the ICA, AComm, ACA, or MCA that were < 7 mm, 7-12 mm, 13-24 mm, and \geq 25 mm had rupture rates of 0%, 2.6%, 14.5%, and 40%, respectively, at 5 years. In addition, from this same study, rupture rates of 2.5%, 14.5%, 18.4%, and 50% were seen, for the same distribution of sizes, for aneurysms located in the posterior circulation and posterior communicating artery. Aneurysms in the posterior circulation have a rupture rate almost three times that of an aneurysm located in the ICA (Ishibashi et al. 2009; Wermer et al. 2007). Several additional studies have suggested that smaller aneurysms (< 7 mm) rarely rupture, with a rupture rate reported at 0.7%, and therefore, may inform an opinion that these aneurysms be best treated conservatively (“The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort” 2012; Rinkel et al. 1998; Komotar, Mocco, and Solomon 2008). For patients with an unruptured aneurysm without a history of SAH (Type 1), the risk of rupture rate drops to 0.1% for aneurysms < 7 mm in diameter (Ishibashi et al. 2009; Wiebers 2003). Conversely, larger aneurysms are at a greater risk for rupture; i.e., the rupture rate for aneurysms \geq 25 mm have a reported 6% rupture rate in the first year (Wiebers 1998) with other studies reporting an annual rupture rate as high as 43.1% (Ishibashi et al. 2009).

FDA Comment: Aneurysm anatomical location, size, and morphological characteristics can impact both the safety (e.g., rupture risk, perforator occlusion) and effectiveness (e.g., rate of complete occlusion) of a treatment device. Regarding safety, accounting for these different factors when evaluating the clinical evidence is important to ensuring a complete understanding of new medical devices. Please see FDA questions 1, 2, and 3.

3 Aneurysm Treatment Methods

3.1 Surgical Clipping

Aneurysms, both ruptured and unruptured, may be treated via craniotomy by surgical clip ligation and microsurgical clip(s) placed on the aneurysm neck to remove the aneurysm from the circulation and prevent possible rupture (or if the aneurysm had already ruptured, to stop bleeding and prevent re-rupture). Surgical clips are regulated as Class II (low to moderate risk) medical devices under 21 Code of Federal Regulations (CFR) 882.5200, Aneurysm Clip, product code HCH. New devices or modifications

to a legally marketed device are submitted to FDA through the premarket notification [510(k)]¹ regulatory pathway to establish substantial equivalence to another legally marketed device with the same intended use and technological characteristics (or if different technological characteristics, performance data that demonstrates substantial equivalence). For marketing clearance in the US, surgical clips typically only require performance standards (in vitro and/or in vivo testing) to establish substantial equivalence and human clinical data is not required.

The clinical evidence from open surgical clipping has primarily been found through studies published in the literature. For example, one of the advantages with this technique is that it can provide immediate aneurysm occlusion and has been shown to provide positive results for patients with large and giant aneurysms (Cantore et al. 2008; Steklacova et al. 2016). As part of the International Subarachnoid Aneurysm Trial (ISAT) that compared open surgery to endovascular coiling, surgical clipping was shown to have a lower annual risk of re-bleeding in previously ruptured aneurysms, 3.6% and 4.2% for clipping and coiling respectively, at 7 year follow up (Molyneux et al. 2005). It has also been shown that clipped aneurysms are 4 times less likely to be retreated than with endovascular treatment (Campi et al. 2007). It is important to note however, that clipped aneurysms are much less likely to have follow-up imaging.

Based on the published literature, with respect to safety events, there was a higher mortality rate reported with open surgery, i.e., 13.8% vs. 10.7% for surgical clipping and traditional coiling, respectively (Molyneux et al. 2009). Patient age has been shown to be a strong indicator of poor surgical outcome (Wiebers 2003). It has also been shown that surgical clipping carries an increased risk of seizures both in short and long term follow up where Molyneux et al. (2005) showed that 4.1% of open surgical patients (compared to 2.5% of the endovascular treated patients) had seizures associated with re-bleeding after receiving treatment for their aneurysm. Furthermore, as previously discussed in Section 2.2, open surgical clipping may be limited with respect to accessibility to treat certain aneurysms based on their location in the neurovasculature (e.g., posterior circulation aneurysms in perforator rich regions).

3.2 Neurovascular Embolization Coiling

Endovascular treatment methods offer an alternative method for the treatment of intracranial aneurysms. Neurovascular embolization coils have been used since the 1970s and were the first type of medical device to be used via an endovascular approach to treat intracranial aneurysms. For traditional neurovascular embolization coiling, a catheter is inserted through entry in the femoral artery and tracked through the vasculature to the cerebral aneurysm. Coils are delivered through this catheter to fill the sac of the aneurysm and promote occlusion. From a regulatory perspective, neurovascular embolization coils were “pre-amendment devices” meaning that they were legally marketed in the US prior to May 28, 1976. These devices were initially regulated as Class III (highest risk) devices requiring a premarket approval (PMA) application. In 2004, FDA reclassified these devices to Class II with special controls², meaning these devices could now be cleared for market under the 510(k) regulatory pathway (21 CFR 882.5950, Neurovascular Embolization Device, product code HCG). Because embolization coils were legally marketed in the US prior to the amendment of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to regulate and provide for the safety and effectiveness of medical devices intended for human use in 1976, there have not been many well controlled clinical trials to establish the safety and effectiveness of these

¹ Premarket Notification [510(k)] regulatory process information can be found on the FDA website at: <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm>.

² The special controls guidance document for embolization coils can be found on FDA’s website at <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072055>.

devices. The cleared Indications for Use (IFU) for neurovascular embolization coils states that these devices are indicated for the embolization of intracranial aneurysms and other neurovascular abnormalities such as arteriovenous malformations and arteriovenous fistulae, without any specification on the specific types or locations of intracranial aneurysms indicated for treatment.

Studies published in the literature consist of an early trial that included 15 patients all of which showed significant benefit from the procedure (Guglielmi et al. 1991). Subsequent to this first trial, several larger studies have investigated the benefit of coiling for aneurysm repair (Campi et al. 2007; Standhardt et al. 2008; Cognard et al. 1999). The largest of these investigations was the ISAT which studied 2143 patients treated with either surgical clipping or coiling (Molyneux et al. 2002, 2005, 2009). This study found that while there was a small increased risk of recurrent bleeding from coiling (i.e., 1.0% and 0.3% for coiling and clipping, respectively), a decreased risk of death was observed at 5 years for patients treated endovascularly, i.e., 10.7% and 13.8% for coiling and clipping, respectively (Molyneux et al. 2009). Standhardt et al. (2008) retrospectively investigated the treatment of 173 patients with unruptured aneurysms (202 total aneurysms) over a 12 year period, all treated with traditional coiling alone. Aneurysms in this study were primarily small (< 7 mm) and medium (7-12 mm) in size, 43.5% and 37.1% respectively, and were most frequently found in the ICA (i.e., 43.1%). Of the 202 aneurysms treated, 57.5% demonstrated complete (100%) occlusion following the procedure. This outcome was significantly higher for small sized aneurysms (71.6%). Giant aneurysms (> 25 mm) resulted in the poorest initial occlusion rate at 10.5% rising only slightly to 11.8% at follow up. Morbidity and mortality rates for the 173 patients were relatively low, 3.5% and 0.5%, respectively. The most common complication found in this study was thromboembolic events with 3% of these patients suffering a stroke. This study also noted a strong dependence on neck size and occlusion rate. Aneurysms with narrow necks had an average rate of complete occlusion of 77.1% while the rate for wide-neck aneurysms was 35.8% (Standhardt et al. 2008).

Cognard et al. (1999) performed a prospective study investigating the use of detachable coils in 169 aneurysms. This study focused almost exclusively on smaller aneurysms (< 8 mm) with aneurysms most frequently occurring in the ICA (35%). Immediate complete occlusion was seen in 56% of the aneurysms treated with that number rising to 79% at follow up. Of the 148 aneurysms that reached complete occlusion, 20 (14%) required retreatment within the first 3-40 months after treatment. This study showed almost no connection between retreatment rate and anatomical location but did show a slight dependence on neck size, with wide-neck aneurysms having a higher probability of requiring retreatment. Although traditional coiling is less invasive than surgical clipping, the possible need for retreatment is another important factor when deciding on a treatment method. In addition, these results suggest that not all aneurysms types may be best suited for treatment with traditional coiling alone.

3.3 Balloon Assisted Coiling

Embolization coiling alone has been widely used as a treatment approach for intracranial aneurysms; however, one of the risks associated with coiling alone is the possibility of coils protruding into the arterial lumen and occluding flow in the parent artery or causing increased risk of thromboembolic events due to the presence of a coil mass within the parent artery. To help mitigate this risk, an endovascular surgical technique referred to as balloon assisted coiling (BAC) was developed (Moret et al. 1997). During this technique, a balloon catheter is inflated inside the parent artery after a microcatheter that will be used to deliver the coils, is placed inside the neck and sac of the aneurysms. The coils are then individually detached while the balloon remains inflated to allow the clinician to more tightly pack the aneurysm without the risk of coils protruding into the parent artery lumen (Nelson and Levy 2001). The balloon catheters used in BAC are cleared under the 510(k) regulatory pathway as Class II medical devices requiring special controls in the same regulation as neurovascular embolization coils (21 CFR 882.5950, Neurovascular Embolization Device) but with a different device product code of MZQ

(Balloon, Detachable, for Neurovascular Occlusion). The balloon catheters used for BAC are cleared usually with no or limited clinical data and are indicated for use in the embolization of intracranial aneurysms typically with no specification on aneurysm characteristics that will result in the most favorable clinical outcomes using this technique and device, similar to neurovascular embolization coils.

Primarily, the clinical experience with BAC has been through clinical studies published in the literature. With regard to safety and effectiveness using this procedure, Pierot et al. (2008) investigated BAC as part of the “Analysis of Treatment by Endovascular Approach of Non-Ruptured Aneurysms (ATENA Trial),” which was a prospective trial that included 649 patients harboring 739 unruptured aneurysms. The majority of these aneurysms (54.5%) were treated with traditional coiling alone, while 37.3% were treated using BAC. Of the 739 unruptured aneurysms, 91.9% were located in the anterior circulation with only 60 (8.1%) aneurysms in the posterior circulation. Aneurysm size was classified using the following groupings: 1-3 mm (17.7%), 4-6 mm (41.1%), 7-10 mm (29.1%), and 11-15 mm (12.0%). Aneurysms greater than 15 mm were listed as part of the exclusion criteria for the study. Postoperative evaluation of aneurysm occlusion (evaluated by a core laboratory) showed that 59.0% had complete occlusion, 21.7% had some neck remnant (i.e., flow still present in a portion of the aneurysm neck), and 19.3% had aneurysm remnant (i.e., flow still present in the dome of the aneurysm). When comparing the number of complications between traditional coiling alone and BAC, this study showed an increased percentage of patients had thromboembolic complications with coiling alone as compared to BAC (7.3% compared to 5.5%, respectively).

A recent review article discussed some of the differing opinions on the safety and effectiveness of BAC, such as complication rates and thromboembolic events as well as the treatment of wide-neck aneurysms (Pierot, Cognard, et al. 2012). One of the studies included in this review article indicated that there was increased risk of procedure related complications with BAC, 14.1% as opposed to 3.0% seen with traditional coiling alone (Sluzewski et al. 2006). A more recent study has shown that complication rates are similar between BAC and traditional coiling alone, 10.8% and 11.7%, respectively (Pierot et al. 2009). Another study documented the rate of thrombus events with these two treatment techniques of 14% and 9% for BAC and traditional coiling alone, respectively (Layton et al. 2007).

3.4 Stent Assisted Coiling (SAC)

In conjunction with detachable neurovascular embolization coil technology, stent assisted coiling (SAC) is another endovascular surgical technique developed mainly to treat wide-neck cerebral aneurysms by placing a neurovascular self-expanding nitinol stent across the neck of the aneurysm and implanted in the parent artery to support neurovascular embolization coils from herniating out of the aneurysm sac (see Figure 1A). Patients implanted with a neurovascular stent typically are prescribed with antiplatelet medication(s) pre- and post-procedure to reduce the risk of thromboembolic events due to the stent placed in the parent artery. All commercially available neurovascular stents indicated for SAC in the US are classified as Class III medical devices and were approved through the Humanitarian Device Exemption (HDE) regulatory pathway, which was created for products intended for diseases or conditions that affect small (rare) populations where it may be difficult to gather enough clinical evidence to meet the FDA standard of reasonable assurance of safety and effectiveness. For a medical device to be eligible for the HDE pathway, the manufacturer must first obtain a Humanitarian Use Device (HUD) designation noting that the medical device is intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the US per year. HDE marketing applications are only supported by performance data (e.g., in vitro, in vivo, human clinical) that demonstrates that the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness

from its use of the medical device for the proposed patient population for treatment and is exempt from the effectiveness requirements of the FD&C Act³.

The first neurovascular stent for SAC approved in the US was the Stryker Neurovascular Neuroform Microdelivery Stent System (HDE H020002, 2002)⁴, followed by the Codman & Shurtleff, Inc. Enterprise Vascular Reconstruction Device (H060001, 2007)⁵, MicroVention, Inc. Low-Profile Visualized Intraluminal Support (LVIS) Device (H130005, 2014)⁶, and the Pulsar Vascular, Inc. PulseRider Aneurysm Neck Reconstruction Device (H160002, 2017)⁷. The first 3 approved neurovascular stents were indicated generally for the treatment of wide-neck aneurysms with neurovascular embolization coils, with no consistent specification of the type, size, rupture status, or location of cerebral aneurysm, or patient characteristics (e.g., age), that should be treated. The PulseRider Aneurysm Reconstruction Device was approved with an IFU to be used with neurovascular embolization coils in patients ≥ 18 years of age with an unruptured wide-neck intracranial aneurysm originating on or near a vessel bifurcation of the basilar tip or carotid terminus. The IFU for the PulseRider Aneurysm Neck Reconstruction Device identified more specific anatomical and aneurysm characteristics because the device design (T- or Y-shaped) was specifically designed to be implanted at a vessel bifurcation location and these aneurysms were what was studied in the clinical trial supporting the HDE application. The clinical studies used to support approval of the HDEs for intracranial aneurysm treatment devices historically have been based on data collected from approximately 30 patients, and were typically not designed with pre-specified hypothesis testing or study success criteria.

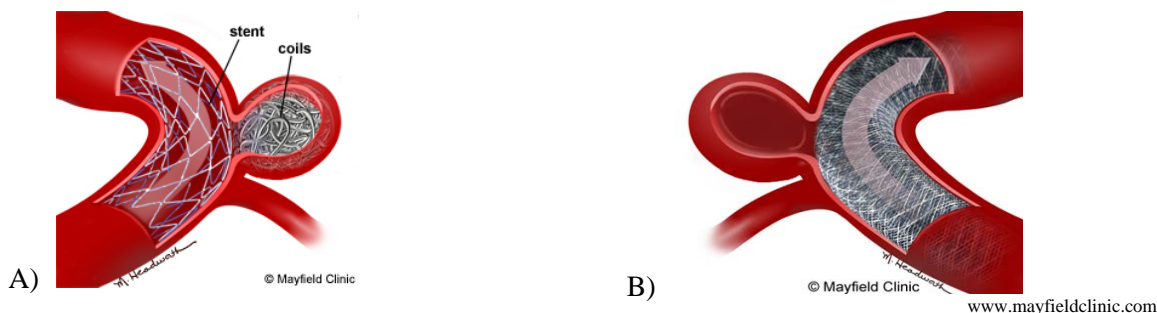


Figure 2. Illustration of (A) stent assisted coiling (combination of endosaccular and endoluminal treatment) and (B) flow diversion (solely endoluminal).

³ Additionally information regarding the Humanitarian Device Exemption regulatory pathway can be found on FDA's website at <https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/humanitariandevicexemption/default.htm>.

⁴ The approval information for the Neuroform Microdelivery Stent from Stryker Neurovascular can be found on FDA's website at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H020002>.

⁵ The approval information for the Enterprise Vascular Reconstruction Device from Codman & Shurtleff, Inc. can be found on FDA's website at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H060001>.

⁶ The approval information for the LVIS Device from Micro Vention, Inc. can be found on FDA's website at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H130005>.

⁷ The approval information for the PulseRider Aneurysm Neck Reconstruction Device from Pulsar Vascular, Inc. can be found on FDA's website at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=388322>.

Based on the published literature, one of the first studies to investigate the use of SAC for the treatment of intracranial aneurysms was Lanzino et al. (1999), which utilized coronary balloon expandable stents in sections of the ICA, vertebral, and basilar arteries. Of the 10 patients treated in this study, there were no periprocedural complications that resulted in permanent injury. Greater than 90% occlusion was seen in all 8 of the patients treated with both a stent and detachable coils (2 patients were treated with stenting alone). In-stent stenosis was noted on follow-up angiography for at least one of the patients. Benitez et al. (2004) demonstrated the use of the Neuroform Stent for use with both ruptured and unruptured wide-neck intracranial aneurysms. This study included 48 patients with 49 aneurysms (32 of which were unruptured). Eight of the stent deployments failed. Forty-one aneurysms were stented then coiled, six were treated with stent only, and one aneurysm was coiled and then stented. The mortality rate for this trial was 8.9%, with four patients (7%) experiencing a thromboembolic event with an overall complication rate of 10.7%. Complete occlusion was reported in 35 (66%) of the patients treated.

Lee et al. (2005) also performed one of the first studies that investigated the use of SAC specifically for wide-neck intracranial aneurysms. Twenty-two patients harboring 23 aneurysms (16 unruptured) were treated with SAC. These aneurysms were primarily located in the ICA (60%). Immediate occlusion was reported in 43% of the aneurysms studied in this trial. Interestingly, this study reported infrequent in-stent thrombosis even when patients were not given anti-thrombotics due to the presence of SAH. The authors also reported no evidence of stent-related thromboembolic complications during the follow up period.

As this technology has been further developed, SAC has been shown to have a lower recurrence rate (i.e., flow returning to the aneurysm dome) compared to coiling alone (Piotin et al. 2010). Clinical outcomes of 1137 patients with 1325 aneurysms were retrospectively analyzed between 2002 and 2009. Of these aneurysms, 206 (16.5%) were treated with stents while the remaining aneurysms (1109) were treated with coiling alone. A significantly higher recurrence rate was seen in the patients treated with coiling alone versus those treated with stents, 33.5% and 14.9%, respectively. The authors suggested that one factor reducing aneurysm recurrence rates with SAC could be caused by improvements to arterial wall reconstruction at the aneurysm neck. In summary from the literature, in comparison to treatment using embolization coils alone, follow-up results show SAC to have a better long term occlusion rate (Piotin et al. 2010; Biondi et al. 2007; Sedat et al. 2009; Lubicz et al. 2009). In comparison to BAC for the treatment of wide-neck cerebral aneurysms, a retrospective study by Chalouhi et al. (2013) found that SAC had higher occlusion rate than BAC, 75.4% versus 50% respectively, as well as a lower retreatment rate, 4.3% and 15.6%, respectively. From a regulatory perspective, one of the limitations of SAC is that the effectiveness of this technique has not been established in well-controlled clinical studies and it remains unclear which patient population may be best indicated for treatment with SAC in comparison to alternative treatment modalities.

3.5 Flow Diversion

Another rapidly developing treatment method for cerebral aneurysms has been flow diversion technology. The mechanism of action of a flow diverter is to divert the blood flow from entering into an aneurysm sac from the parent artery (see Figure 2B). This reduction in blood flow into the aneurysm sac is designed to promote blood stasis, endothelial growth across the neck, and occlusion of the aneurysm. While flow diverters are intended to be used by themselves as a stand-alone medical device, some clinicians choose to use the device similar to SAC; but implanting fewer neurovascular embolization coils within the aneurysm sac. In comparison to endosaccular devices implanted within the sac of the aneurysm that are intended to promote complete blood stasis immediately post-procedure, Pierot et al. (2011) observed complete occlusion in only 49% of patients with a flow diverter at 3 months and 95% of patients at 6 months post- procedure, indicating a delayed occlusion effect. Although the slower occlusion may be attributed to the dual antiplatelet therapy (DAPT) regimen that is required to be prescribed to patients

with a flow diverter to reduce the risk of thromboembolic complications, aneurysm occlusion appears to be slower in patients with a flow diverter where the aneurysm sac is left completely empty. This latent occlusion has been cited as a potential major safety risk because of the possibility for aneurysm rupture during this time (D'Urso et al. 2011).

The only flow diverter that is available in the US and has received FDA approval through the PMA regulatory pathway is the Micro Therapeutics, Inc. d/b/a ev3 Neurovascular Pipeline Embolization Device (PED) (PMA P100018, 2011)⁸. The PED was approved with the IFU for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms in the ICA from the petrous to the superior hypophyseal segments. While a device approved under an HDE may be exempt from the effectiveness requirements of a PMA, PMA medical devices must demonstrate a reasonable assurance that the device is safe and effective for its conditions of use to obtain marketing approval. The data supporting a PMA must be valid scientific evidence. Per 21CFR860.7(c)(2), “valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.” The PMA approval of the PED was supported by a single arm, prospective, multicenter clinical trial titled “Pipeline for Uncoilable or Failed Aneurysms (PUFS)” conducted in the US (8 sites) and outside the US (OUS) (8 sites) with 111 enrolled subjects (108/111 subjects were attempted device treatment) under Investigational Device Exemption (IDE) G080093. An approved IDE permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations on that device⁹. The results of the PUFS study to support the PMA approval of the PED showed 6/108 subjects (5.6%) exhibited primary safety events of neurological death or major stroke and 77/110 subjects (70.7%) had complete aneurysm occlusion without re-treatment of the target aneurysm and ≤ 50% stenosis of the parent artery evaluated at 1 year post-procedure/follow up.

Additional studies published in the literature on the PED include many that involve treatment of aneurysms considered off-label from the FDA approved IFU. One of these studies was conducted by Lylyk et al. (2009) that presented results on 53 patients harboring 63 wide-neck aneurysms who were enrolled in this multicenter trial. Most the aneurysms included in this study were in the anterior circulation (87%). Immediate occlusion was only seen in 5 aneurysms (8%), all of which were < 10 mm in their maximum dimension. At 6-months of follow-up, 93% (26 of the 28 available aneurysms, not all patients were available at follow up) had complete occlusion with this percentage rising slightly at 12 months to 94.4% (17 of the 18 available aneurysms). A second study titled “Pipeline Embolization Device for the Intracranial Treatment of Aneurysm Trial (PITA)” (Nelson et al. 2011) investigated 31 patients harboring 31 aneurysms with all but two located in the anterior circulation. These aneurysms were primarily small and medium sized, < 10 mm (64.5%), and only 2 aneurysms (6.5%) were ≥ 25 mm. While PED is intended to be used without adjunctive coiling, 16 of 31 aneurysms included in this trial used coils in addition to the PED. At follow-up (180 days), 93.3% of the aneurysms had been fully occluded with no reported device migrations. Mild in-stent stenosis (25%-50%) was reported in one case.

⁸ The approval information for the Pipeline Embolization Device from Micro Therapeutics, Inc. d/b/a ev3 Neurovascular can be found on FDA's website at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P100018>.

⁹ Additional information regarding the Investigational Device Exemption (IDE) process is provided on FDA's website at <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm162453.htm>.

A meta-analysis of the literature was performed that included 29 studies with a total of 1654 aneurysms treated with flow diverters (Brinjikji et al. 2013). This analysis showed that 76% of these aneurysms achieved complete occlusion at 6 months with procedure related morbidity and mortality as low as 5% and 4%, respectively. One of the major concerns with flow diverters is the risk of rupture due to the latency of occlusion. It has been estimated that the risk for SAH after treatment with a flow diverter could be between 2 and 4% (D'Urso et al. 2011; Brinjikji et al. 2013; Briganti et al. 2012), and the rate of SAH and intraparenchymal hemorrhage decreases after the first 30 days post-treatment (Brinjikji et al. 2013).

Although flow diverters are becoming more prevalent in clinical practice and in the literature, the available safety and effectiveness data is primarily limited to only the approved IFU of the PED (i.e., large or giant wide-necked intracranial aneurysms in the ICA from the petrous to the superior hypophyseal segments). In addition, the risk of occluding perforator arteries is one of the concerns with flow diverters due to its dense mesh design. Specifically, occlusion of perforating vessels by the flow diverter can lead to infarcts, which can significantly impact patient function as presented in a study by Phillips et al. (2012) that investigated 32 posterior aneurysms. The authors noted that higher clinical perforator infarction in the basilar artery compared to the carotid may be seen with the PED. In this study, perforator occlusion was seen in 3 patients (14%). While no deaths or poor neurological outcomes were reported, this study highlights that flow diverters can produce varying results based on the target aneurysm location and aneurysm location may be a factor in deciding the best course of treatment.

3.6 Endosaccular Flow Disruption

One of the newest developments reported in the literature for the treatment of aneurysms has been endosaccular flow disruption devices, sometimes referred to as “mesh balls” (Klisch et al. 2011; S. C. Kwon et al. 2011). These endosaccular devices are typically constructed from a tightly woven wire mesh that has been wrapped to form a semi-spherical shape. These devices are implanted within the aneurysm sac and the mechanism of action is that the mesh design covers the aneurysm neck and obstructs blood flow from entering the sac of the aneurysm, creating blood stasis in the sac, and promoting endothelial growth across the neck of the aneurysm. Based on the design and shape of these devices, the need for adjunctive devices within the aneurysm sac and in the parent artery should not be needed and these devices are optimally designed for the treatment of wide-necked bifurcation aneurysms¹⁰ (Papagiannaki et al. 2014; Pierot et al. 2016). Additionally, because these devices are designed to fill the sac of the aneurysms, typically a single device is used to treat an aneurysm, which may reduce procedure times, the amount of patient exposure to ionizing radiations, and the quantity of metal/foreign material implanted into the patient (Mine, Pierot, and Lubicz 2014).

Currently, none of these endosaccular flow disruption devices are approved for use in the US. Due to the novelty of these devices, there is limited clinical information available in the literature, with most clinical experiences associated with the Woven Endo Bridge (WEB) device (Sequent Medical, Inc.) that has received Certification Marking (CE) and is available in the European Union (EU). In an early prospective multicenter trial conducted in France, 77 patients with 79 aneurysms, 73 of which had a neck width > 4 mm, were treated using the WEB device (Papagiannaki et al. 2014). With an average follow up of 5.3 months, it was shown that 37 patients (56.9%) had complete occlusion, 23 patients (35.4%) had a neck remnant, and 5 patients (7.7%) had a residual aneurysm. This study also indicated a low occurrence of safety events with 71 patients (94.7%) having an mRS score of 0 at one month post-procedure. This study did note that there can be difficulty in navigating the device in more tortuous anatomy due to the use with

¹⁰ There are currently no endosaccular devices approved by the FDA. The Woven Endo Bridge (WEB) device (Sequent Medical, Inc.), Luna Aneurysm Embolization System (Covidien Neurovascular, Inc.), and Contour Neurovascular System (Cerus Endovascular, Ltd.) have received CE mark and are available for use in Europe.

a larger delivery microcatheter in comparison to those used with traditional neurovascular embolization coils (Papagiannaki et al. 2014). More recently, 51 patients were treated as part of a prospective multicenter European clinical trial, investigating the use of the WEB device in the treatment of wide-neck bifurcation aneurysms (Pierot et al. 2016). In this study, 94.1% of the aneurysms treated were unruptured occurring at bifurcations at the basilar apex, MCA, AComm, and ICA terminus. The authors noted that at 6 months, 23 patients (56.1%) had complete aneurysmal occlusion while 12 (29.3%) patients and 6 (14.6%) had a neck remnant and aneurysm remnant, respectively. While these occlusion results are lower than typically seen with other wide-neck aneurysm treatment devices such as SAC or flow diversion, the difficulty of the aneurysms being treated (i.e., wide-neck bifurcation aneurysms) should also be considered. Regarding safety events, the authors reported only one patient suffered a safety event (thromboembolic event), which resulted in a change in the mRS score (i.e., from 0 to 1). However, this study did document technical problems in 8 patients (15.7%) that included prolonged detachment (n=3) and device protrusion (n=5) (Pierot et al. 2016). While endosaccular flow disruption devices provide an alternative treatment approach for difficult to treat aneurysms (i.e., wide-neck bifurcation), additional clinical evidence is needed to evaluate the safety and effectiveness of these devices, long-term follow-up data, and the patient population that is best indicated for this treatment modality in comparison to alternative treatment methods.

3.7 Other Treatment Approaches

Additional treatments for cerebral aneurysms, although less common, include pharmacotherapy in which drugs are prescribed to lower blood pressure or reduce the impact of the heart's contraction in order to minimize the risk of an aneurysm rupture, and/or ongoing observations, and periodic assessment to track the aneurysm status. Additional approaches reported in the literature include the development and use of precipitates, second generation stents of various designs, aneurysm liners, liquid polymers, hydrogels, aneurysm neck protection, and micro-anastomoses, bioactive manipulations to endovascular devices (Szikora et al. 1996; Jeffree et al. 1999; Kallmes and Fujiwara 2002).

FDA Comment: The current understanding of the safety and effectiveness of different treatment options is a major focus of this Advisory Committee meeting. Because different treatment approaches can have different results and depends on the specific aneurysm characteristics being treated, it is important for FDA to understand how to utilize effectiveness data and evidence from prior studies to evaluate new devices in the US. Please see FDA questions 4, 5, 6, 7, and 8.

4 Evaluating the Safety and Effectiveness of Aneurysm Treatments

The treatment methods available for the treatment of intracranial aneurysms have been the subject of controversy for a number of years (Ishibashi et al. 2009; Hetts et al. 2014; Chalouhi et al. 2014; “The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort” 2012; Komotar, Mocco, and Solomon 2008). Based on the background information presented in this Executive Summary, there are limitations to the available clinical evidence in determining which aneurysms are best treated with each different treatment modality. In addition, with the advent of the less invasive endovascular treatments, there has been an increase in the number of unruptured aneurysms that are being treated rather than followed (Wiebers 2003; Komotar, Mocco, and Solomon 2008; Ishibashi et al. 2009; “The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort” 2012; Hetts et al. 2014; Chalouhi et al. 2014). There remains uncertainty from the clinical community as to whether certain aneurysms should be treated or simply routinely followed by observation only. One of the primary purposes of the March 1, 2018 Advisory Committee meeting is to seek expert recommendations regarding how FDA should evaluate the safety and effectiveness of new endovascular aneurysm treatment devices under the PMA regulatory pathway, and taking into consideration various factors including, but not limited to, the device

design, limitations of the clinical study data, patient population that should be indicated for treatment with each device technology, follow-up duration, safety and effectiveness outcome measures, and acceptable rates of safety events and aneurysm occlusion.

4.1 Clinical Trial Design

There are various types of clinical trial designs used to evaluate the safety and effectiveness of medical devices, which can include a randomized controlled trial (RCT) when an appropriate concurrent comparator device or control group can be identified, partially controlled studies, a single-arm study where the investigational device is compared to a performance goal (PG) developed from historical data from prior studies or published literature data, or retrospective review of clinical data sets. The most rigorous clinical trial design is a double blind, placebo controlled, RCT, but under medical device regulation RCT studies are only one type of valid scientific evidence. Further, RCTs may not always be feasible if a control group is not available, and clinical equipoise may not exist. An RCT may also require an increased number of study subjects because subjects are needed for both arms of the study, although more recent statistical approaches may reduce the patient size.

In contrast, a main advantage of RCT studies is that the investigational product is concurrently or directly compared to a control arm, using the same patient selection criteria and study test conditions, minimizing bias or confounding factors that may affect the final study results. For example, with an RCT, because patients are randomized to treatment groups, their individual characteristics are probabilistically balanced across groups. That is, a patient with a specific characteristic is equally likely to be in either group. The result is that patient characteristics tend to be balanced across groups, so that patient characteristics are less likely to cause one treatment group to perform better or worse than the other. The only systematic difference between groups should be the treatment received.

In a single-arm study design, there may be limitations to understanding the safety and effectiveness of the investigational product due to temporal bias as a result of changes in the comparator device(s) since the prior trial or the studies published in the literature may be outdated, improvements in standards of care over time, experience and technique over the intervening years, as well as differences in study populations. In addition, a single-arm PG based trial is subject to selection bias. Furthermore, the clinical outcome of aneurysm treatment likely depends on multiple factors such as demographics, concomitant diseases and treatments, aneurysm characteristics, location of aneurysm, and bias in assessments of disease and outcomes that may be difficult to capture in a PG based single arm clinical study. The clinical trial design of cerebral aneurysm treatment devices, in particular flow diverters and SAC systems, was the subject of an Advisory Committee meeting in April 2015 in which the panel recommendation was that RCT trials be performed when feasible. Additionally, the panel provided specific anatomical and morphological characteristics, such as aneurysm location and size, that should be considered when constructing clinical trials¹¹. In contrast, the use of PG studies may be valuable to evaluating medical devices due to the potential for lower costs, resource investments, and a more rapid development of clinical data as the basis for submission to FDA.

From a regulatory perspective, FDA accepts all valid scientific evidence to determine whether there is reasonable assurance that the medical device is safe and effective for its proposed conditions of use. As of July 9, 2012, the FDA Safety and Innovation Act (FDASIA) specified that IDE clinical studies cannot be

¹¹ FDA received input from an Advisory Committee meeting regarding trial design for aneurysm treatment devices on April 17, 2015. Additional information regarding this prior meeting can be found at <https://wayback.archive-it.org/7993/20170114022911/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm440392.htm>.

disapproved because the investigation may not support a marketing application or because another investigation may be needed. Since FDASIA was enacted, FDA has been conveying concerns related to the trial design as “Study Design Considerations” as an attachment to IDE decision letters, which are optional for the sponsor of the study to address or not within the course of study conduct. If the sponsor completes their proposed study even though there were outstanding FDA concerns regarding the study design, the FDA will still review the data generated from the clinical study, considering the previously conveyed study design considerations, and decide as to whether the data supports a reasonable assurance of safety and effectiveness for the medical device and whether the PMA marketing application can be approved for the proposed indications for use.

4.2 Primary Endpoints for Safety and Effectiveness

As discussed above, each of the different cerebral aneurysm treatment methods have certain associated risks that can result in adverse events with varying severity and different effectiveness (aneurysm occlusion) results based on the type of aneurysm being treated. In coordination with the chosen trial design (e.g., RCT, single arm PG, historically controlled, nonrandomized concurrently controlled), trial endpoints and success criteria must be pre-defined prior to study initiation to create a hypothesis driven study for the investigational device. The primary safety and effectiveness endpoints are very important elements in terms of review of a marketing application; however, the totality of the evidence is considered as part of the benefit-risk assessment of the investigational device.

Based on results reported in the literature studies for aneurysm treatment devices and the prior FDA reviewed PUFs trial for the PED in PMA P100018, the primary safety endpoints or events have been focused on neurological deaths and major ipsilateral strokes (defined as an increase ≥ 4 points in the National Institutes of Health Stroke Scale (NIHSS) score during the stroke event) within 6 months to 1 year of treatment. In addition to these primary safety events, FDA has recently begun to consider whether additional neurological adverse events (AEs) (e.g., minor strokes, transient ischemic attacks (TIAs), seizures, hemorrhages) and all serious adverse events (SAEs) should be considered in the overall assessment of device safety. Furthermore, the FDA is considering whether the change in the mRS score at 1 year post-treatment compared to pre-procedure (patients’ baseline status) may be a better indicator of patient disability as a result of treatment in assessing device safety, since this clinical outcome measure will be able to assess overall functional independence of the patient including the severity and long-term effects of any neurological AEs. The mRS assessment is typically being collected in all aneurysm clinical trials as a secondary endpoint and usually administered pre-procedure, at hospital discharge, and at 3 months, 6 months, and 12 months follow-up. FDA has considered identifying any change in mRS as clinically significant, especially for the treatment of smaller (< 5 mm) unruptured aneurysms, which has been shown to have a low risk of rupture, absent any additional patient risk factors (Molyneux et al. 2002, 2005). Thus, any change in mRS after treatment compared to the patients’ baseline status should be considered significant in assessing the benefit/risk of the device and treatment procedure.

With respect to the primary effectiveness endpoint, FDA has used a composite endpoint defined as the percent of subjects demonstrating a Raymond I classification for complete occlusion (i.e., 100% aneurysmal occlusion) without retreatment of the target aneurysm or significant parent artery stenosis ($\geq 50\%$) evaluated within 1 year post-procedure. Due to the increased risk of aneurysm recanalization with aneurysms that are not 100% occluded, FDA has taken the more conservative approach when considering the effectiveness of an investigational device. Published literature has discussed the possibility of “adequate occlusion” for aneurysms, which is typically defined as either complete occlusion or neck remnant (i.e., Raymond I or II classification) (Sprengers et al. 2008; Pierot et al. 2011; Pierot, Liebig, et al. 2012). While clinicians may have different approaches to care for patients if there is an aneurysm neck remnant after treatment such as observation only of those aneurysms that are otherwise stable or to retreat immediately, from a regulatory perspective, Raymond II classifications for aneurysm occlusion is a

challenging result to determine whether the investigational device is considered effective in treating the aneurysm. Also, if a target aneurysm requires retreatment, this is not only an effectiveness concern but also tied to patient safety because there are risks with retreatment related to having another permanently implanted device and the patients being subjected to another procedure.

4.3 Follow-Up Duration (Pre-/Post-Market Balance)

From a regulatory perspective, the FDA has previously made a premarket decision as to whether an investigational device should be legally marketed in the US for the proposed conditions of use using 1 year patient follow-up data for PMA and 6 months of follow-up clinical data for HDE applications, respectively. The difference in the follow-up durations is largely based on whether effectiveness or probable benefit needs to be demonstrated based on the regulatory pathways. In addition, the follow-up durations used to make a premarket regulatory decision is based on obtaining sufficient clinical data to be able to assess the safety and effectiveness (or probable benefit) of an investigational device while balancing the public health needs to have available treatment options and taking a least burdensome approach with the sponsors conducting the trials (e.g., time, resources, and cost of conducting studies). The IDE clinical trial patients are usually consented for up to 5 years when they agree to participate in the study and the follow-up data from > 1 year to ≤ 5 years can be used as to collect post-market data to determine whether there are any delayed safety events or change in effectiveness of the initial treatment.

From the published literature, the optimal time of follow-up is largely unknown. For patients treated with traditional coiling alone, Raymond et al. (2003) found a strong correlation of initial incomplete treatment, initial aneurysm dome or neck size and rupture status on the subsequent risk of recurrence, and the need for retreatment. The authors also reported that only 46.9% of recurrences were detected at 6 months after treatment. Recurrences were still being detected as long as 3 years after surgery. Additional studies have even suggested that recurrence of clinical symptoms for patients treated with surgical clipping may take up to 10 years to present (Ebina et al. 1982; Sakaki et al. 1994). In a study looking at long-term follow-up for SAC, 8.3% of patients required retreatment for their original aneurysm (Fargen et al. 2012). This study also showed an increased frequency of retreatment in patients previously diagnosed with a SAH. Long term follow up has also shown that 3.6% of patients treated with SAC suffered a TIA or stroke in the region around the stent (Shapiro et al. 2012).

FDA Comment: FDA requests the Advisory Committee to provide recommendations on overall safety and effectiveness endpoints, the follow up duration to support a marketing application, retreatment outcomes, alternative types of assessments, and the follow-up duration in post-market studies. Please see FDA questions 7, 8, 9, and 10.

4.4 Labeling

Labeling is an important consideration for ensuring safe and effective use of medical devices. The purpose of labeling is to provide information about the product, including the indicated patient population and how the end user should use the device to achieve the intended use of the product in the indicated patient population, for which the device was deemed safe and effective.

Intracranial aneurysm medical devices can be used to treat a variety of aneurysm types, sizes, morphologies, and locations. Adequate labeling is needed to appropriately guide the safe and effective use of novel endovascular aneurysm treatment devices in the United States.

FDA Comment: FDA is interested in the recommendations on the extent of labeling for intracranial aneurysm occlusion devices. FDA requests the Advisory Committee to provide recommendations on the types of content to be included in the Indications for Use for intracranial aneurysm occlusion medical devices. Please see FDA question 11.

5 Summary

In summary, cerebral aneurysms are a complex neurological disease with multiple factors that can affect the final clinical outcome (e.g., aneurysm size, morphology, rupture status, location in the neurovasculature, patient risk factors for treatment, and device design). This makes designing clinical trials of new investigational medical devices challenging in the treatment of this disease and evaluating the clinical data once the trial is completed can be an even more challenging task.

Therefore, FDA is convening this Advisory Committee meeting on March 1, 2018 to seek panel feedback on several questions related to how the safety and effectiveness of new investigational devices should be reviewed to make a final regulatory decision on whether these devices should be legally marketed in the U.S. and the exact patient population that should be indicated for treatment in the device labeling. One of the main challenges is understanding which aneurysm treatment technology will result in the most favorable clinical outcomes based on the patient cerebral aneurysm characteristics and the clinical data set available. Another main topic of discussion in which FDA requests the panel's guidance is to determine how aneurysms with a Raymond II classification or small neck remnant should be assessed with respect to effectiveness of the investigational device. For example, one consideration may be that if there is a significant rate of Raymond II classifications in a given trial, should longer-term follow-up (for example, 2 years) be required premarket to assess whether these aneurysms are stable or increased recanalization is observed requiring the need for retreatment. In addition, another important topic of discussion with the panel is to help guide FDA regarding the evaluation of the primary safety and effectiveness endpoint rates obtained with the investigational device in the absence of a concurrent comparator group in the trial and how we should be comparing the safety and effectiveness of different investigational devices treating the same patient populations. For example, if there are two investigational devices both intending to treat small to medium sized bifurcation aneurysms, FDA needs panel input as to how a final decision should be rendered if one investigational device is determined to have inferior effectiveness or safety compared to the current clinically accepted standards, based on the single arm design. The questions for the panel's consideration are included in the following Section 6.

CDRH's mission is to protect and promote the public health, and to assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices, striving to ensure that medical devices reach the marketplace in as an efficient regulatory process as possible.

6 Panel Questions

Safety

Adverse Events & Endpoints

1. Typically, aneurysm device trial primary safety endpoints have focused on death and major ipsilateral stroke (defined as an increase in the National Institutes of Health Stroke Scale (NIHSS) by 4 points at the time of stroke event within 1 year after treatment). Additional safety events (adverse events or AEs) that are considered in our safety assessment of new devices include:

Adverse Events
Access Site Issues (e.g., Dissections, Hematomas)
Aneurysm Leak, Rupture, or Contrast Extravasation
Distal Embolic Phenomenon
Dual Antiplatelet Therapy (DAPT) Related AEs
Mechanical Device Failures and/or Acute or Delayed Device Migration or Embolization
Minor Ipsilateral Strokes (NIHSS Change < 4)
Transient Ischemic Attacks (TIAs)

Please address the following:

- a. Is the AE list above complete? If not, what AE(s) should be added?
 - b. Are there specific rates of AEs that would raise serious concerns about the safety of any specific device?
2. The modified Rankin Scale (mRS) has often been incorporated as a secondary endpoint. Can the mRS at 1 year also be a potential primary safety outcome measure for all endovascular device trials? If yes, what magnitude of decline in the mRS and for what percentage of treated subjects with a decline in the mRS at 1 year follow-up would raise serious concerns

about the safety of the device? If no, what alternative primary safety outcomes are possible and for what duration of time.

Safety & Patient Demographics

3. Considering the AE list above and any additional AEs specified in response to question #1.a., what patient characteristics (e.g., malignancy, advanced age, aneurysm size) justify foregoing treatment for an aneurysm that would otherwise be considered for treatment?

Effectiveness

Effectiveness Measures

4. Typically, intracranial aneurysm device trial primary effectiveness endpoints have focused on the percentage of subjects who achieve a Raymond Classification I (complete 100% occlusion) without significant parent artery stenosis ($\geq 50\%$) or re-treatment at 1 year post-procedure. Please address the following:
 - a. Do you consider the Raymond Classification Scale to be the standard to assess effectiveness for ALL endovascular intracranial aneurysm treatment devices? If you do not consider the Raymond Classification Scale to be standard, please identify an alternative well accepted assessment(s) to adequately assess effectiveness for ALL endovascular intracranial aneurysm treatment devices.
 - b. Many studies have used the Raymond Classification Scale. If the Raymond Classification scale is used, is Raymond II (or higher) classification a satisfactory outcome for aneurysm patients with unruptured aneurysms? And is Raymond II (or higher) classification a satisfactory outcome for aneurysm patients with ruptured aneurysms?

Aneurysm Occlusion

5. For device effectiveness, what percent of morphological occlusion is acceptable and in what percent of patients should this result be achieved?
6. Do your aneurysm occlusion assessment recommendations using Raymond (or another system if identified in question #4.a.) differ for endosaccular devices (e.g., neurovascular embolization coils, balloon assisted coiling (BAC), stent-assisted coiling (SAC), saccular obturation devices)? Intraluminal flow diversion devices? If so, how?

Follow Up

7. What length of follow-up is recommended to assess effectiveness for endovascular aneurysm treatment devices? Please discuss how your recommendation is impacted if the aneurysm status of the patient at 1 year is a Raymond II or III classification.

Retreatment

8. Some initial interventions result in a clinically unacceptable outcome and retreatment is considered. Does a worsening in the Raymond scale at follow-up imaging warrant retreatment and should FDA consider a worsening of the Raymond scale during 1 year follow-up to represent a failure of treatment?

Alternative Imaging Assessments

9. We consider digital subtraction angiography (DSA) to be the gold standard to assess aneurysm occlusion at follow-up. Can magnetic resonance angiography (MRA) or computed tomography angiography (CTA) serve as a surrogate follow-up examination and when should this take place?

Post Approval Studies

10. In some cases, a post-approval study may be warranted, for example when limited follow up exists for patients. What is a sufficient long term follow-up period for a post-approval study where the majority of patients have the following outcomes for ruptured or unruptured aneurysms?
 - a. Raymond I
 - b. Raymond II
 - c. Raymond III

Labeling

11. What patient characteristics should be specified in the Indications for Use (IFU) (i.e., age, aneurysm morphology, location, size, Type 1 or Type 2 status, ruptured vs. unruptured)? For intraluminal flow diverters? And for endosaccular devices?

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