Summary of Safety and Probable Benefit

cPAX Aneurysm Treatment System

I. GENERAL INFORMATION

Device Generic Name:	NeuroVascular Embolization Device
Device Trade Name:	cPAX Aneurysm Treatment System
Applicant's Name and Address:	NeuroVasx, Inc
	7351 Kirkwood Lane North, Suite 112
	Maple Grove, MN 55369

Humanitarian Device Exemption (HDE) Number:	H100002
Humanitarian Use Device (HUD) Designation Number:	#09-0218
Date of Humanitarian Use Device (HUD) Designation:	February 12, 2010
Date(s) of panel Recommendation:	None
Date of Good Manufacturing Practice Inspection:	October 2010
Date of Notice of Approval to Applicant:	April 1, 2011

II. Indications for Use

The cPAX Aneurysm Treatment System is indicated for use in the adult population (22 years of age and older) for the treatment of wide-necked large and giant-sized cerebral aneurysms (> 10) mm that require use of adjunctive assist-devices such as stents or balloons.

III. Contraindications

Use is contraindicated in:

Patients with active bacterial infection

Patients in whom anticoagulation and antiplatelet therapy is contraindicated

IV. Warnings and Precautions

Warnings

1. The safety and performance of this system have not been evaluated in patients with ruptured aneurysms.
2. Verify repeatedly that the distal shaft of the Microcatheter is not under stress before detaching the cPAX. Axial compression or tension forces could be stored in the Microcatheter, causing the tip to move during cPAX delivery. Microcatheter tip movement could cause the Aneurysm to perforate or rupture.
3. At no time should the tip of the D3 be shaped by the user.
4. Advancement of the D3 outside the distal tip of the cPAX involves risk of aneurysm or vessel rupture.
5. Advancing the D3 proximal end of the marker beyond the proximal marker of microcatheter after detachment without fluoroscopic guidance involves the risk of aneurysm or vessel rupture.
6. If at any time during the procedure resistance is encountered, discontinue any further advancement until the cause of the resistance can be determined to minimize risk of aneurysm or vessel rupture.
7. Use caution during adjunctive device usage, as excessive manipulation should cause aneurysm or vessel rupture.
8. At no time should the cPAX and/or D3 be torqued.
9. When using the cPAX System in conjunction with any adjunctive devices, follow all operative and post-operative medication recommendations (e.g. anti-platelet therapy) as stated in the device labeling or as prescribed by the physician.
10. Do not use Power Sources other than the cPAX Power Supply specially built for the cPAX System.
11. Ensure the availability of any necessary equipment needed for concomitant treatment methods.

Precautions:

1. Exercise care in handling of the cPAX, D3 (delivery/detacher device) during the procedure to reduce the possibility of accidental breakage, bending, or kinking.
2. Excessive tightening of the hemostasis valve on the microcatheter to the cPAX may cause the shaft to collapse. This will results in the inability to flush the

cPAX or advance or retract the D3. Ensure that only enough tightening torque is used to prevent fluid from leaking between the microcatheter and the cPAX.

3. If resistance is encountered in withdrawing the cPAX which is at an acute angle relative to the microcatheter distal tip, it is possible to avoid cPAX damage by carefully repositioning the distal tip of the microcatheter at the ostium of the aneurysm, or, just slightly inside the parent artery. By doing so the aneurysm and artery act to "funnel" the cPAX back into the microcatheter.
4. Never perform a cPAX detachment outside the tip of the microcatheter.
5. Ensure that the electrical connectors on the D3 and the Jumper Cable are kept dry.
6. Remove the batteries from the Power Supply when not in use. Insert new AA batteries into the Power Supply at the beginning of each procedure.
7. Read and follow the IFU of all agents or contrast media used with the microcatheter or other accessories.
8. High quality, digital subtraction fluoroscopic road mapping is mandatory to achieve safe catheterization of the aneurysm or vessel and correct placement of the cPAX.
9. Do not sterilize the Power Supply.
10. Angiographic controls should be performed during the implant procedure and prior to detachment to ensure that the cPAX is not protruding into the parent vessel.
11. If at any time during the procedure the "Low Battery" light illuminates on the Power supply, switch to back-up Power Supply or install fresh batteries.
12. To maintain stability, the maximum mounting height of the Power supply should be 6 feet on a standard 27 inch wheel base IV pole.
13. The Power supply is not suitable for use in the presence of flammable anesthetics.
14. Medical electrical equipment needs special precautions regarding electromagnetic compatibility (EMC) and needs to be installed and put into service according to the EMC.
15. Portable and mobile radio frequency (RF) communications equipment can affect medical electrical equipment. This product is intended for use in the electromagnetic environments. The end user of this product should assure it is used in such an environment. Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.

V. Device Description

The NeuroVasx cerebral aneurysm treatment device is comprised of the polymeric aneurysm filling material (cPAX) and the means to percutaneously deliver the filler material into the aneurysm.

The complete cPAX System components include the polymeric filling implant material (cPAX), the D3 (delivery and detachment device), the cPAX Jumper Cable (connection between the detacher device and the power supply) and the cPAX Power Supply (supplies energy to the detacher device to assist in the detachment process). Figure 1. cPAX Aneurysm Treatment System below shows a picture of the cPAX Aneurysm Treatment System.

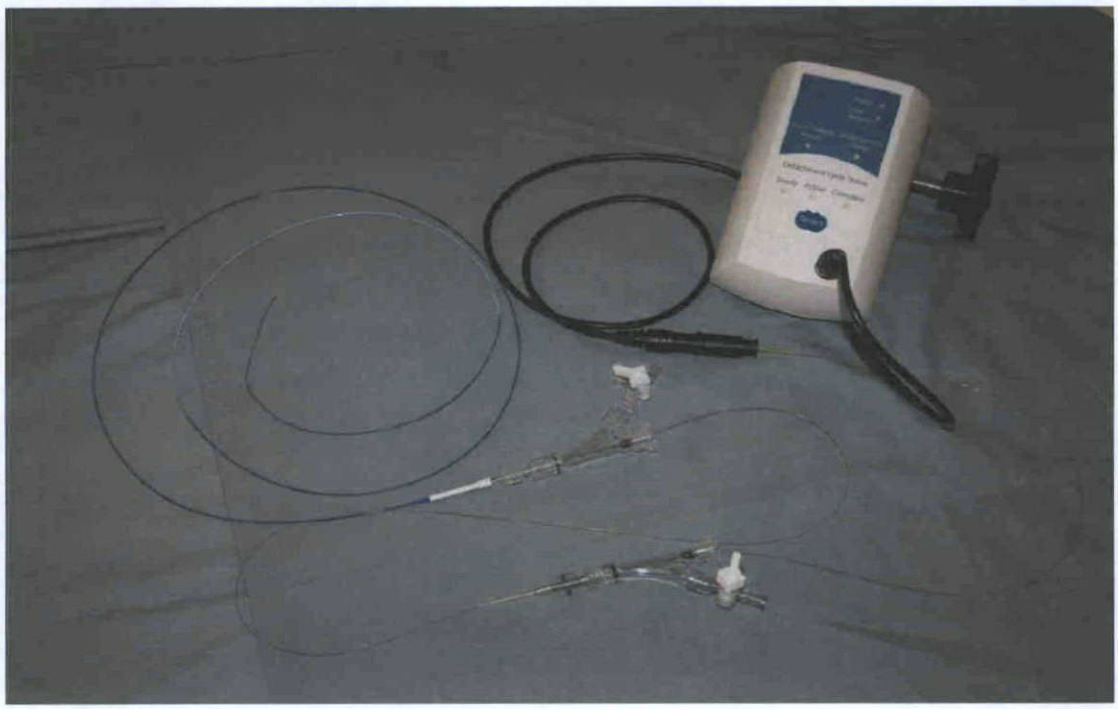

Figure 1. cPAX Aneurysm Treatment System

The implant material is delivered over the D3 device through a standard microcatheter. cPAX is deployed into the aneurysm over the D3 device, using the D3 device as a 'rail' system. The D3 device has a heater coil in the distal end that is used to thermally detach the cPAX material when the physician determines that adequate aneurysm filling is achieved, or when the entire cPAX implant portion has been deployed into the aneurysm. The Jumper Cable is used to connect the D3 device to the power supply, which supplies energy to the D3 to assist in the thermal detachment process. Following detachment the remaining cPAX, along with the D3 wire, is withdrawn through the microcatheter.

Components and Materials

cPAX

cPAX (see Figure 2. Illustration of cPAX (Implant Material) and Pusher) is a 1.4 Fr sterile device that is designed to fit within a standard 3Fr microcatheter. cPAX is provided straight and consists of the cPAX (Implant Material, with the bumper tip) and

the Proximal Pusher Shaft. The overall length of the cPAX is 247 cm; the working length is 160 cm and the implant length of the cPAX is 80 cm.

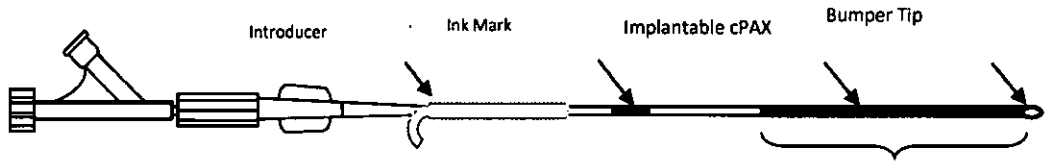

Figure 2. Illustration of cPAX (Implant Material) and Pusher

cPAX is a hydrophilic coated, polyethylene compounded with Tungsten (to provide radiopacity).

The Pusher is the proximal section of the cPAX. The Pusher is a hydrophilic coated polyethylene shaft with a polyurethane strain relief and polycarbonate hub at the proximal end. The polyethylene shaft has a short, more flexible polyethylene bridge at the distal end to facilitate the thermal bonding of cPAX to the Pusher. A hemostasis valve is provided at the proximal end for flushing cPAX prior to use.

Prior to the packaging of cPAX, the cPAX D3 is inserted into the cPAX lumen. The cPAX is contained in a protective plastic hoop. The hoop is placed onto a plastic packaging card. The hoop and a hemostasis valve are sealed in a conventional Tyvek/polyester pouch and placed in a paperboard carton. The cPAX D3 System is provided sterile and is intended for single use only.

cPAX D3

The cPAX Delivery Detacher Device (D3) is an 0.011" diameter device used to facilitate the delivery of cPAX through the cerebral vasculature towards and into the aneurysm. The D3 is also used for detachment of the cPAX. The D3 consists of a core wire with an electric lead wire attached to a heater coil at the distal end. The heater coil is welded to the core wire at the distal tip and soldered to the copper lead wire. A gold marker-band, platinum/tungsten marker coil, and stainless steel proximal coil are located proximal to the heater coil. The marker coil and proximal coil are coated with polyimide. The coils and markerband are adhesively adhered to the core wire. The heater coil, marker-band and marker coil create a radiopaque section of the wire that assists in the fluoroscopic navigation and placement the cPAX and alignment of the D3 within the cPAX for detachment. The copper lead is bound to the core wire over the entire length. The core wire and copper lead are soldered and crimped to the electrical connector at the proximal end. The core wire is constructed from Super Elastic Nitinol. It has an ink mark located 150 cm from the distal end to assist in positioning the heater coil prior to detachment. The Detacher Device is coated with a hydrophilic coating and the useable length is ~265 cm.

The cPAX D3 is activated for detachment by connecting it to the reusable battery operated cPAX Power Supply using the cPAX Jumper Cable.

Prior to packaging, the D3 is inserted into the cPAX lumen. cPAX, with the D3, is contained in a protective plastic hoop, sealed in a conventional Tyvek/polyester pouch and packaged in a paperboard carton. The cPAX with D3 is provided sterile and is intended for single use only.

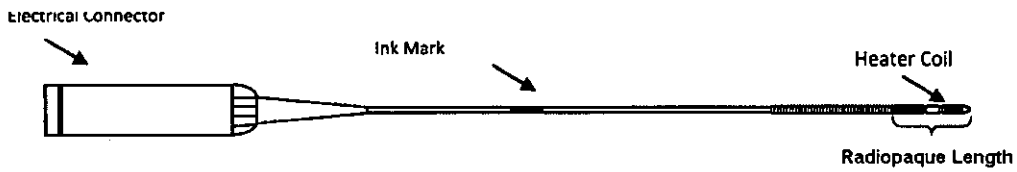

Figure 3. Illustration of cPAX D3

cPAX Jumper Cable

The cPAX Jumper Cable (see Figure 4. Illustration of cPAX Jumper cable) is a sterile, non-patient contacting component that connects the Detacher Device to the Power Supply. The cable is 120 cm in length and provides a continuous electrical connection between the Power Supply and Detacher Device. The cPAX Jumper Cable is a 4-lead coated PVC cable designed with a proprietary 4-pin male connector at each end designed to mate with the female connectors on the Detacher Device and the Power Supply.

The cPAX Jumper Cable is looped in a circular fashion, sealed in a conventional Tyvek/polyester pouch and packaged in a paperboard carton. The cPAX Jumper Cable is provided sterile and is intended for single use only.

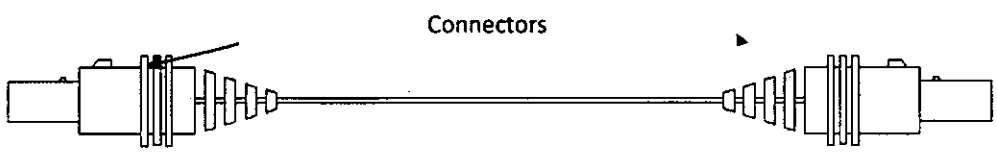

Figure 4. Illustration of cPAX Jumper cable

cPAX Power Supply

The cPAX Power Supply (see Figure 5. Photo of cPAX Power Supply) is a non-sterile, non-patient contacting, battery-operated, pole-mounted device. Using two AA batteries, the cPAX Power Supply provides sufficient, controlled energy to conduct the detachment process and subsequently run alarms. The cPAX Power Supply has pre-set levels for

output current, output voltage, and detachment cycle time. The cPAX Power Supply has several display lights that are visible on the front face of the power supply: power, low battery, power supply status, detacher status, ready, active and complete. When the clinician presses the "Detach" button, the cPAX Power Supply outputs a constant current of 170-180mA for a fixed cycle time of 4 seconds. When the cPAX Power Supply, the cPAX Detacher Device and the cPAX Jumper Cable are connected for activation they form a closed loop circuit for energy delivery. Electrical energy is delivered through this circuit to activate the heating coil at the distal tip of the cPAX Detacher Device, thereby melting and detaching cPAX.

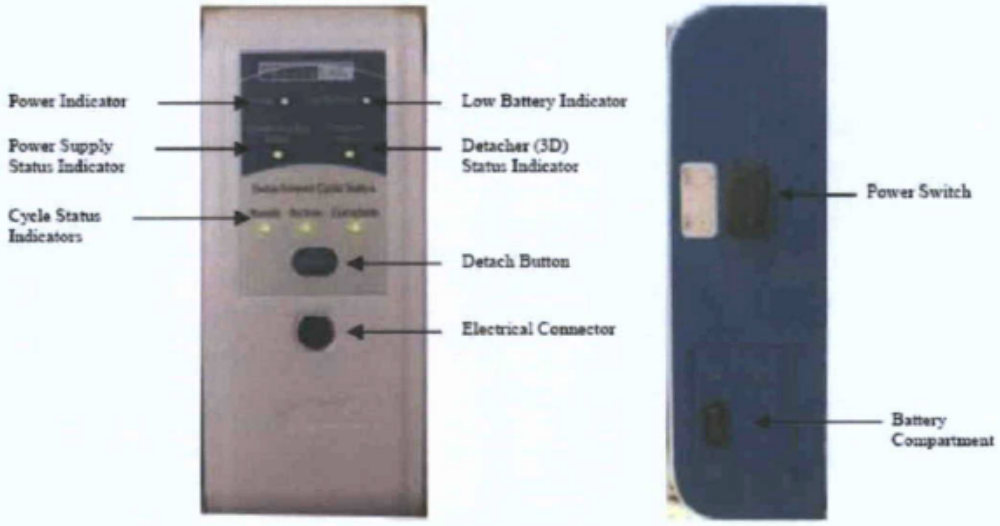

Figure 5. Photo of cPAX Power Supply

The cPAX Power Supply is placed in a poly bag and packaged in a corrugated carton. The Power Supply is provided non-sterile and is intended to be a reusable device.

Principles of Operation

The cPAX System is intended to be used for the embolization of intracranial aneurysms > 10 mm in size. This approved HDE indication for use is for use in the adult population (22 years of age and older) for the treatment of wide-necked large and giant cerebral aneurysms (> 10 mm), which require use of adjunctive assist-devices such as stents or balloons.

The overall concept is similar in usage to that of metallic coils; material is introduced into the aneurysm to fill the void space and reduce the risk of aneurysm rupture. The cPAX utilizes a soft polymer base material rather than metallic coils. In both the cPAX and metallic coils, the embolization material is pushed through a microcatheter into an aneurysm and then detached in order to occlude the aneurysm by reducing blood flow

into the aneurysm. The cPAX is placed into an aneurysm in a continuous fashion until angiographic filling is achieved. The cPAX is then detached via an internal wire with a heating tip system. The cPAX remains a permanent implant within the aneurysm. A detailed description of each step is provided below:

Access: The cPAX material is introduced into the aneurysm through a microcatheter placed within the neck of the aneurysm to fill the void space and prevent aneurysm rupture.

Preparation: With the cPAX System, a standard microcatheter, such as a Cordis Prowler Plus, is inserted into the neurovasculature and navigated into the aneurysm. A hemostasis valve is attached and cPAX (with D3 inserted, as packaged) is flushed with saline.

Delivery: The cPAX is then inserted into the microcatheter. With the aid of fluoroscopy, cPAX, with the D3 inserted, is navigated to the distal tip of the microcatheter.

Deployment: The D3 is then withdrawn (about 3 cm) within the cPAX. The cPAX and the D3 are then advanced together until the tip of the D3 is seen fluoroscopically at the distal end of the microcatheter; thereby deploying the first 3 cm of cPAX alone into the aneurysm. Again, the D3 is withdrawn (about 3 cm) into the cPAX and both are advanced together until the tip of the D3 is seen at the distal end of the microcatheter; thereby deploying another 3 cm of cPAX into the aneurysm. This stepwise progression delivers the implant material into the aneurysm, resulting in the cPAX conforming to and filling the void space. The delivery of cPAX continues until the physician determines that the procedure is complete as viewed fluoroscopically. More than one cPAX may be delivered during the procedure. Once each strand of cPAX is delivered, the next step of the procedure is the detachment process.

Detachment: The process of detachment requires melt separation of cPAX. The cPAX D3 contains a heater coil at the distal end and radiopaque markers to assist with guidance and navigation towards the aneurysm site. Once the proximal cPAX D3 marker is aligned with the proximal marker of the microcatheter the Jumper Cable is connected, bridging a connection between the D3 and the battery-powered cPAX Power Supply.

To detach the delivered cPAX, the physician verifies that the cPAX Power Supply 'ready' light is illuminated and then presses the 'detach' button. During the heating cycle, an audible tone and the illumination of the 'active' display light indicate that power is being supplied to the heater coil. A change in tone will then indicate when the physician is to gently pull on the cPAX to detach the cPAX Implant Material within the aneurysm. The 'complete' display light is illuminated when the active current cycle is complete. An additional detachment session may be initiated if fluoroscopy indicates that the initial detachment was unsuccessful.

Confirmation: Once detachment is confirmed by fluoroscopy, the D3 and remaining cPAX section are removed from the patient simultaneously.

VI. Alternative Practices and Procedures

Wide-neck, large and giant (> 10 mm in size) aneurysms are difficult to treat both surgically and endovascularly. Current treatments of these aneurysms include surgical clipping, or endovascular embolization with metallic coils.

In the procedure for surgical clipping, a tiny clip is placed across the neck of the aneurysm to stop or prevent an aneurysm from bleeding. The goal of surgical clipping is to isolate an aneurysm from the normal circulation without blocking off any small perforating arteries nearby. Under general anesthesia, a craniotomy is performed. The brain is retracted to locate the aneurysm. The clip is placed across the neck of the aneurysm. Failures of the procedure include: the clip slipping down and off the neck of the aneurysm, inadvertent occlusion of the parent artery, or no discernable neck evident at parent artery junction. It is not uncommon to employ multiple surgical strategies to effectively clip giant aneurysms, i.e.; thrombus evacuation of the aneurysm, wrapping of the outside of the aneurysm, or surgical bypass.

The second treatment option includes the use of metallic coils. One type of metallic coil are platinum coils, which are made from wound Platinum / Tungsten alloy wire and are formed into predetermined shapes and sizes. The coils range in sizes from 2 mm to 24 mm in diameter and are manufactured in a variety of shapes and flexibilities in an effort to accommodate the treatment of different sizes of aneurysms encountered. The coils are deployed into the aneurysm through a microcatheter. Prior to deployment, the physician must measure the aneurysm to determine the appropriate size coil to implant. This can be complicated due to the irregular shape of aneurysms encountered and the inexact sizing capabilities of imaging equipment used in the procedure. Failure to accurately size the aneurysm can result in the wrong size coil being delivered. This in turn may lead to the coil potentially falling out of the aneurysm if too small; protrusion out of the aneurysm neck if the coil is too large, or possibly, it could rupture the aneurysm. In many instances, a procedure with platinum coils may require a progression of three different types of coils to complete the procedure. First, a framing coil is deployed to create a basket inside the aneurysm. This basket is then filled with "filling" coils to try and pack the aneurysm. Finally, a finishing coil may be used to complete the procedure. This progression may take multiple coils in numerous shapes and sizes to treat the aneurysm.

VII. Marketing History

The cPAX Aneurysm Treatment System was approved for CE Mark in March of 2009. The cPAX Aneurysm Treatment System was approved for a device license in Canada in August of 2009. There have been no withdrawals of the cPAX Aneurysm Treatment System from marketing in any country for any reason related to the safety and effectiveness of the device.

VIII. Potential Adverse Effects of the Device on Health

Potential complications include, but are not limited to:

Hematoma at the site of entry
Vessel perforation, aneurysm rupture
Parent artery occlusion
Incomplete aneurysm filling
Hemorrhage including intracerebral, retroperitoneal or in other locations.
Embolism of air, blood clots, cholesterol fragments
Ischemia
Vasospasm
Implant material migration or misplacement
Premature or difficult implant material detachment
Clot formation
Revascularization of the aneurysm
Neurological deficits including stroke
Chemical or aseptic meningitis* (see note below)
Hydrocephalus* (see note below)
Headaches
Infection
Cranial neuropathy
Hair loss
Reactions due to radiation exposure
Reactions to anesthesia and related procedures
Reactions to antiplatelet/anticoagulant agents
Reactions to contrast agents including allergic reactions and renal failure
Death

*The safety concerns for polymer containing neurovascular embolization devices like cPAX System Aneurysm Treatment System include hydrocephalus and aseptic meningitis that has been observed at a rate as high as 5% or greater with a time course of months to years post-implant. However, no conclusion can be made regarding the risk of hydrocephalus/aseptic meningitis following treatment with cPAX Aneurysm System due to the limited number of the subjects included in the clinical study.

IX. Summary of Preclinical Studies

a. Performance Evaluation

NeuroVasx has completed performance evaluations (Bench Testing) consistent with the recommended testing in FDA Guidance Document "Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices". The FDA guidance document is written for embolization coils and certain adjustments were made in the recommended testing to account for the differences between the cPAX and the platinum coils. The tests results as described in Table 1 demonstrate that the cPAX system components meet the product specification requirements and confirm the performance of the system. As the cPAX system is a multi-component system, mechanical performance testing occurred at the system level to evaluate overall performance and to demonstrate component compatibility. The Bench testing was completed on the final device design.

Table 1. Bench Testing on cPAX Aneurysm Treatment System

Test	Purpose	Number of samples tested	Acceptance Criteria	Results and Conclusions
System Compatibility / Track Test	The objective of the test was to measure the force required to retract and advance the cPAX, with the delivery/detacher device inside, through a microcatheter in a simulated glass model of cerebral arteries. Specific locations within the cerebral vascular mode are selected to represent typically treated aneurysm configurations.	28	**Advancement:** (a) Advancement force of the cPAX not to exceed 50 grams when tested in a simulated anatomical location at 37°C through a standard Microcatheter and a hemostatis valve seal. (b) Advancement force of the D3 in cPAX not to exceed 100 grams when tested in a simulated anatomical location at 37°C. **Retraction** (a) Retraction of cPAX	All devices were shown to be compatible and all specifications were met.

Test	Purpose	Number of samples tested	Acceptance Criteria	Results and Conclusions
			(b) Retraction force of D3 in cPAX not to exceed 100 grams when tested in a simulated anatomical location at 37°C through a standard Microcatheter and a hemostatis valve seal.	
Tensile strengths of the cPAX material and bonds (joints)	The objective of these tests was to ensure that the tensile strength of the main body of the cPAX (extruded material), joints and bonds, and the junction between the hub/strain relief of the cPAX did not separate below the specification requirements.	28	The tensile strengths of the device must be greater than the advancement/retraction forces that will be experienced by the device.	All specification requirements were met.
Tip deflection Force	The objective of this test was to measure the force required to deflect the distal leading edge of the cPAX with the delivery/detacher device within the cPAX lumen, when deployed into a simulated aneurysm.	28	7 gram max	The specification requirement was met
cPAX D3 Device - Joint Integrity / Detachment Test	The objective of the test was to evaluate the detachment of the cPAX implant material and the integrity of the D3 Device coil bonds through simulated detachment of the cPAX with the thermal detachment system.	29	D3 coils must be visually intact following simulated use. D3 distal tip weld and coils joints are to withstand one advancement, two detachment cycles, and retraction through the cPAX polymer with no visual separation from the core wire	The test requirements were met.

Test	Purpose	Number of samples tested	Acceptance Criteria	Results and Conclusions
		29	D3 must have a heating element located at the distal tip that must visually melt and/or detach the cPAX implant material within 2 detachment cycles when a current of 170 – 180 mA is applied for 4 seconds	The test requirements were met.
		29	The resistance of the D3 must be 181.5 – 230 Ω.	The test requirements were met.
		26	D3 must detach cPAX implant material within 2 detachment cycles following simulated use.	The test requirements were met.
Coating Integrity	The cPAX, as well as the delivery/detacher device, are coated with a hydrophilic coating that is applied to enhance the device lubricity. The coating integrity testing evaluated the coating consistency.	29	Catheter coating must be present after advancement and retraction cycle testing	There was no visible delamination, flaking, or erosion of the cPAX's hydrophilic coating after simulated advancement and retraction.
cPAX Jumper Cable – Continuous Connection Test	The objective of the test was to evaluate the ability of the cPAX Jumper Cable to provide continuous electrical connection from the cPAX Power Supply to the Delivery/Detacher Device.	30	The Jumper Cable shall provide continuous electrical connection after 5 detachment cycles.	The test requirements were met.

The cPAX Power Supply has been validated. The functionality of the Power Supply has been confirmed through the use of the Power Supply for the cPAX Jumper Cable Continuous Connection Test and the D3 detachment testing shown above. The Power Supply has been shown to meet the specification requirements.

b. Biocompatibility

Biocompatibility testing was performed on all patient contacting materials per ISO 10993-1 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process. cPAX consists of the cPAX Implant Material and the Pusher. The cPAX Implant material is intended for permanent implantation into the arterial vascular system and is categorized per ISO 10993-1 as a permanent implant device in contact with blood. The Pusher catheter is a limited patient contact device intended for assisting the delivery of the implant polymer. The Pusher is categorized per ISO 10993-1 as an external communicating device in contact with circulating blood with limited exposure time. The cPAX Delivery/Detacher Device (D3) is a limited patient contact device and intended for assisting the delivery and final detachment and implantation of the implant material. The D3 is categorized per ISO 10993-1 as an externally communicating device in contact with circulating blood with limited exposure time.

The biocompatibility test data on the cPAX implant material are presented in Table 2 below.

Table 2. Biocompatibility data on cPAX Implant Material

Test	Description	Results
Cytotoxicity	MEM Elution Test (ISO 10993-5)	No evidence of cytotoxicity
Sensitization	Guinea pig maximization sensitization test (ISO 10993-10) with device extracts (saline and cottonseed oil extracts)	No evidence of sensitization
Intracutaneous Reactivity	Intracutaneous reactivity test (ISO 10993-10) with device extracts (saline and cottonseed oil extracts)	No evidence of irritation
Acute Systemic Toxicity	Acute systemic toxicity test (ISO 10993-11) with device extracts (saline and cottonseed oil extracts)	No evidence of systemic toxicity
Material-mediated pyrogenicity	Rabbit pyrogen test (ISO 10993-11) with saline extract of the device	No pyrogenic response
Hemocompatibility	In vitro hemocompatibility test (ISO 10993-4) with human blood and with saline extract of the device	No adverse effects on any of the hematological parameters tested (complete blood count, hematocrit, erythrocyte indices, and platelet count)
	Direct contact hemolysis test (ISO 10993-4) using rabbit blood	No hemolytic response
	Indirect contact (extract) hemolysis test (ISO 10993-4) with saline extract of the device and rabbit blood	No hemolytic response

Test	Description	Results
Genotoxicity	Bacterial Reverse Mutation Assay (ISO 10993-3) conducted with Device Extracts (Saline and PEG extracts)	No evidence of mutagenicity
	In Vitro Chromosomal Aberration Assay (ISO 10993-3) conducted with Device Extract (cell culture medium extract)	No evidence of clastogenicity
	Mouse Bone Marrow Micronucleus Assay (ISO 10993-3) conducted with saline extract of the device	No evidence of clastogenicity
Implantation/Subchronic and Chronic Toxicity	Evaluated in a canine bifurcate aneurysm model at 14 and 90 days)	No treatment related adverse effects were noted. No lesions indicative of systemic toxicity or emboli were noted in the tissues. There were no adverse tissue reactions due to implant material.

In addition to biocompatibility testing on the cPAX implant material, chemical characterization study was conducted on the implant extracts prepared by the exhaustive extraction method in polar and non-polar solvents and the risks associated with the leachable/extractable compounds were assessed using a toxicological risk assessment approach. No significant risks of toxicity were identified by the toxicological risk assessment of leachables/extractables.

Biocompatibility test data on Pusher are presented below in Table 3.

Table 3. Biocompatibility data on Pusher

Test	Description	Results
Cytotoxicity	MEM Elution Test (ISO 10993-5)	No evidence of cytotoxicity
Sensitization	Guinea pig maximization sensitization test (ISO 10993-10) with device extracts (saline and cottonseed oil extracts)	No evidence of sensitization
Intracutaneous Reactivity	Intracutaneous reactivity test (ISO 10993-10) with device extracts (saline and cottonseed oil extracts)	No evidence of irritation

Test	Description	Results
Acute Systemic Toxicity	Acute systemic toxicity test (ISO 10993-11) with device extracts (saline and cottonseed oil extracts)	No evidence of systemic toxicity
Hemolysis	Indirect contact (extract) hemolysis test (ISO 10993-4) with saline extract of the device and rabbit blood	No hemolytic response

Biocompatibility data on D3 Delivery/Detacher device are presented below in Table 4.

Table 4. Biocompatibility data on D3 Delivery/Detacher Device

Test	Description	Results
Cytotoxicity	MEM Elution Test (ISO 10993-5)	No evidence of cytotoxicity
Sensitization	Guinea pig maximization sensitization test (ISO 10993-10) with device extracts (saline and cottonseed oil extracts)	No evidence of sensitization
Intracutaneous Reactivity	Intracutaneous reactivity test (ISO 10993-10) with device extracts (saline and cottonseed oil extracts)	No evidence of irritation
Acute Systemic Toxicity	Acute systemic toxicity test (ISO 10993-11) with device extracts (saline and cottonseed oil extracts)	No evidence of systemic toxicity
Hemolysis	Indirect contact (extract) hemolysis test (ISO 10993-4) with saline extract of the device and rabbit blood	No hemolytic response
Unactivated Partial Thromboplastin time (UPTT)	UPTT test (ISO 10993-4) using human plasma and saline extract of the device	The UPTT of the plasma exposed to the test article extract was not significantly decreased as compared to the untreated plasma and the plasma exposed to the negative control article.

c. Pre-Clinical Animal Studies

A GLP study in a canine bifurcate aneurysm model was completed to confirm the results of the bench testing. The objective of the study was to assess the safety and performance characteristics of the cPAX System. The canine bifurcate aneurysm study was performed with a previous design of the cPAX Aneurysm Treatment System. The primary difference between the previous and the final device design is that the previous design had two wires. One wire (delivery wire) was designed for delivering the cPAX to the aneurysm location, and this wire acted as a rail over which the cPAX was pushed into the aneurysm sac. When angiographic occlusion had been achieved, or the complete strand of cPAX had been implanted into the aneurysm, the delivery wire was removed from the lumen of the cPAX and a detacher device was inserted. The detacher device contained a heater coil that was used to thermally detach the cPAX implant material. In the device design under this HDE, the delivery wire and the detacher device have been combined into one device. This device is referred to as the delivery/detacher device, or the D3. The cPAX implant material, mechanism of delivering the cPAX to the aneurysms, as well as the technology used to thermally detach the cPAX implant material, are the same as in the devices used in the canine bifurcate aneurysm study. A second difference between the devices used in the canine bifurcate aneurysm study and the final device design is the addition of a loop (referred to as the bumper tip) on the distal end of the cPAX implant catheter and an addition of an introducer to assist in introducing the cPAX with the bumper tip into the microcatheter. The bumper tip allows for an atraumatic leading edge into the aneurysm. The bumper tip is manufactured from the exact material as the implant catheter except the hydrophilic coating. The introducer is non-patient contacting. The design changes described above are not significant with respect to the evaluation of the implant material for safety and effectiveness in the canine bifurcate aneurysm model. Additional animal studies were conducted in porcine model to assess the device changes.

(i) Assessment of safety and performance characteristics of cPAX in a chronic canine bifurcate aneurysm model (GLP study)

The study objectives in the Canine Bifurcate Aneurysm Study were developed to be consistent with the FDA Guidance document "Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices". Per the protocol, a bifurcation and aneurysm was created in each right carotid artery of 22 canines. The aneurysms were allowed to heal for two-weeks prior to treatment. The animals were then randomized into two treatment groups: 14 day follow-up (11 animals), 90 day follow-up (11 animals). In each treatment group one aneurysm was left untreated as a negative control. Angiograms were performed on each aneurysm created and their dimensions recorded for the purpose of calculating their internal volume, neck size, and assessing their patency. Treatment with cPAX system was then performed either as a standalone treatment or in conjunction with platinum "framing Coils" and/or balloon assist procedure. Repeat angiograms were performed at the pre-determined follow-up

time points to assess the status of the aneurysms and determine the stability of the implanted material within each treated aneurysm. Analysis was performed on the explanted aneurysms to determine the tissue response immediately in contact with the implant material. All histopathological analysis was performed on aneurysms that had at least two or more detachments performed within each aneurysm. Histopathological evaluation was conducted lung, mediastinal lymph node, hear, cervical lymph node, liver, spleen, adrenals, kidney, and brain to assess overall systemic toxicity of the implantation of the cPAX material. Also, the tungsten level in blood was analyzed by inductively coupled plasma – mass spectrometry (ICP-MS) prior to and after implantation of the cPAX material at two weeks and 90 days. Table 5 below documents the results from the canine bifurcate aneurysm study.

Table 5. Results from canine bifurcate aneurysm model

FDA Guidance Document recommendation	**Chronic canine bifurcate aneurysm study objective**	**Chronic canine bifurcate aneurysm study results**
Ease of delivery (friction and tortuosity)	To demonstrate that the delivery and trackability of the AF material are acceptable based upon subjective, principal investigator assessment.	The study objective was met. All parameters (fluoroscopic visualization, trackability, ease of feeding over the delivery wire, ease of aneurysm filling, ease of retrievability) were evaluated as 100% acceptable.
Acute complications (e.g. rupture or puncture of the blood vessels)	To demonstrate that the acute (local and systemic) effects of cPAX deployment are acceptable with regard to vessel perforation, life threatening alterations in vital signs, and any other notable effects.	The study objective was met. There was a 0% incidence rate of acute complications.
Recanalization of the vessels/durability of occlusion	To demonstrate that cPAX material can achieve aneurysm filling and occlusion results statistically comparable to literature reviewed results of Guglielmi detachable Coils (GDCs) using a similar model. The occlusion results would be measured by: • Volumetric filling of ≥ 30% for each treated aneurysm based on angiographic calculation of aneurysm volume and calculation of cPAX material volume based on length used • Occlusion of 100% in ≥ 30% of treated aneurysms on treatment day and on sacrifice (follow-up) day	Volumetric Filling: The study objective was met. The amount of filling exceeded the results for platinum coils as reported in bifurcate aneurysm animal studies or human use side-wall studies. Occlusion Rate: The study objective at treatment and follow-up was not met. However, cPAX results are similar to the results achieved with the use of a platinum coil device in the same animal model. See effectiveness results below.

Local and systemic foreign body reactions	To determine whether the acute (local and systemic) effects of the cPAX are acceptable via assessment based on angiographic evaluation for vessel perforation, life threatening alterations in vital signs and any other notable effect(s). Determine the carotid tissue's response to treatment with cPAX based on the evaluation of histopathology by the Study Pathologist. Determine organ response to the cPAX treatment based on the evaluation of histopathology by the Study Pathologist.	Local and systemic foreign body reactions were evaluated. There were no noted local or systemic reactions identified in the animal study.
Device migration	The evaluation of device migration was not a specific study objective. However, migration has been evaluated under the following study objective: To demonstrate that incidence of cPAX material compaction is statistically comparable to literature reviewed results of platinum coils using a similar model.	cPAX results are similar to platinum coil animal study results. There was a 5% rate of migration in the cPAX study.
Effectiveness	Effectiveness was evaluated as % occlusion at follow-up.	cPAX results are similar to the similar platinum coil animal study results. All aneurysms treated were wide-necked aneurysms. The mean packing density was 53.01%, and was ≥ 30% for each aneurysm treated. Fifteen percent of the aneurysms were 100% occluded at follow up. The occlusion rate was nearly identical to that of platinum coils in the same wide-necked aneurysms (16%). In 100% of the aneurysms, embolization was stable or improved at follow up versus treatment. There was a 0% rate of compaction.

Follow up to evaluate acute as well as chronic toxicity	1. To determine the carotid tissue's response to cPAX treatment by histopathological evaluation 2. To determine organ response to cPAX treatment by histopathological evaluation 3. To determine tungsten levels in the blood prior to and after implantation of the cPAX material at two-weeks and 90-days.	There were no adverse tissue reactions noted due to the cPAX material or the detachment process. There were no indications of systemic toxicity or emboli noted in the tissue samples. There was no difference between the cellularity of the tissue associated with the cPAX and that associated with the platinum coils. The cPAX material generated similar tissue response as that of platinum coils. There were no detectable changes in levels of tungsten in the blood post-implantation of the cPAX material.
Explanation of how the animal model relates to the human condition through any pertinent literature references and/or support testing	To provide a discussion on the canine bifurcate aneurysm model	A discussion of the canine bifurcate aneurysm model was provided. All study results have been compared to human literature where applicable.

FDA identifies specific risks associated with embolization devices within the guidance document as well. The risks and the evaluation of the risks in the canine bifurcate aneurysm model are described below:

- *Blood vessel perforation or rupture*: This risk was evaluated in a study objective. There were no vessel perforations or ruptures in the animal study.
- *Unintended thrombosis*: This risk was evaluated in several study objectives. There was one case where the parent artery was partially occluded by the cPAX. The artery remained patent and there was no adverse reaction. There was no thrombosis or clotting noted at the tip of the cPAX during material implantation or detachment.
- *Adverse tissue reaction:* This risk was evaluated in multiple study objectives. There were no cases of adverse tissue reaction in the animal study.
- *Infection*: This risk is evaluated in the four study objectives. There were no incidents of infection in the animal study.
- *Hematoma* formation: There was no hematoma formation.

(ii) D3 Performance Evaluation in Animal Study

A feasibility animal study in swine model was conducted to access the detachment performance of the D3 device. Two aneurysms were created in one animal. One was created in the carotid artery and one was created in the superior mesenteric artery. Both aneurysms were created in such a manner that the aneurysms could be opened and closed to remove materials between treatments. The cPAX filler material was placed in the aneurysms either by detaching a defined amount or by putting as much material that would fit into the aneurysm, i.e., when resistance was felt. The operators performing the detachment process were varied. Twenty D3/cPAX devices were subjected to filling/detachment. Two devices used the variable current power supply (10 second "Frankie", 175-176 mA); the remaining 18 devices used the D3 Power Supply with a current setting at 175.6 mA. Data was taken to evaluate the detachment success and the condition of the melted region of the implant material (if detached, both ends were evaluated). The implanted section of the cPAX material was removed after treatment in preparation for the next detachment.

Four devices were implanted and detached in the aneurysm created in the mesenteric artery. Sixteen devices were implanted and detached in the aneurysm created in the carotid artery. Four different operators were used to perform detachment. Twenty out of 20 devices detached within 2 detachment attempts. Eighteen out of 20 devices detached within 1 detachment attempt. This study met the engineering requirement that D3 must deliver and visually melt and/or separate the cPAX implant material within 2 detachment cycles when a current of 170 – 180 mA is applied for 4 seconds when tested in vivo (animal).

(iii) Bumper Tip Animal Study

An animal study was conducted in a swine model to assess the system performance of D3/bumper tip cPAX device. Three animals were used in the study. All animals and aneurysms were prepared per protocol. Thirty four out of 34 devices were delivered into the aneurysms successfully. Of the 34 attempts of detachment in the study, there were 31 successful detachments. Two attempts were excused due to a power supply failure; 1 attempt was determined a failure after 3 detachment attempts.

d. Packaging and Sterilization

The sterile components of the cPAX System are the cPAX, D3 (Delivery/Detacher device) and the cPAX Jumper Cable. cPAX is packaged as one component with the D3 inserted into the lumen of the cPAX. Each component is sealed individually into a Tyvek/polyester pouch and packaged in a paperboard carton. The product is sterilized via 25 kGy dose gamma radiation method and labeled as a sterile (single use only) device.

The sterilization cycle for the cPAX System sterile components has been validated to achieve an SAL of 10^{-6}. The validation was performed in compliance with ISO 11137-1: Sterilization of Health Products – Radiation – Part 1: Requirements for development. Validation and routine control of a sterilization process for medical devices.

Periodic endotoxin evaluation will be performed which will be validated per ANSI/AAMI ST22:202 "Bacterial endotoxin – test methodologies, routine monitoring and alternatives to batch testing." Testing will be completed on a minimum number of consecutive manufacturing lots. The endotoxin levels will be maintained at < 0.06 EU/ml.

e. Shelf Life:

The sterile cPAX with D3 packaged inside will be labeled with an expiration data of 6 months from the date of sterilization. The cPAX Jumper Cable will be labeled with an expiration date of 2 years from the date of sterilization. The following tests were performed to establish the shelf life of the product:

- ASTM F88 Standard Test Method for Seal Strength of Flexible Barrier Materials
- ASTM F1929-98: Standard Test Method for detecting seal leaks in porous medical packaging by dye penetration
- ASTM F1980Standard Guide for Accelerated Aging of Sterile Medical Device Packages
- ASTM 2096 Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test)
- ASTM D4169 Performance Testing of Shipping Containers and Systems
- ISO 11607 Packaging for terminally sterilized medical devices ISTA-2A Partial Simulation Performance Tests
- ISTA-2A Partial Simulation Performance Tests

X. Summary of Clinical Information

Two separate prospective, single-center, open-label, single arm studies (Protocol 70083 and 70118) were conducted in Brazil to evaluate this device for aneurysm embolization and to assess its safety and performance. Data from these two studies were pooled in support of the safety and probable benefit for the cPAX Aneurysm Treatment System for this HDE. These data included aneurysms that fall outside of the indications for use approved in the HDE (i.e., wide-necked large and giant-sized cerebral aneurysms (> 10) mm that require use of adjunctive assist-devices such as stents or balloons). Specifically, the clinical study inclusion criteria allowed enrollment of subjects with aneurysms < 10 mm, irrespective of neck size and the use of adjunct devices. Overall, 43 subjects with 44 aneurysms were enrolled, treatment was attempted on 39 aneurysms in 38 subjects, and 36 subjects with 37 aneurysms were treated. Of the 32 subjects available for 90-day

follow-up, all were angiographically assessed at 90 days. Out of 36 treated subjects, 15 aneurysms in 14 subjects treated meet the intended use criteria for treatment under this HDE.

Of note, these clinical data were obtained utilizing a previous design of the cPAX Aneurysm Treatment System. The cPAX implant material in this previous design is the exact same material as that in the current HDE design. The primary difference between the previous and current systems is that the previous design had two components, one for the delivery of the cPAX (delivery wire) and one for the detachment of the cPAX (detacher wire); whereas the current design has one component for the delivery and detachment (referred to as the D3). A second difference between the device design studied in the clinical study and the current design is the addition of a loop (referred to as the bumper tip) of implant material at the distal end of the implant catheter. The bumper tip allows for an atraumatic leading edge into the aneurysm during implant of the cPAX. The technology of delivery and detachment in the new system in comparison to the old are identical. There are no new clinical risks associated with the current device design in comparison to the design studied in the clinical trial. Therefore, the clinical data obtained is relevant for this application.

Demographics

Of the 38 subjects enrolled, 31(81.6%) were female, and 7(18.4%) were male. The subjects ranged in age from 32 to 75 years with an average age of 53.6 years. Table 6 below summarizes the characteristics of the aneurysms treated in the two studies.

Table 6. Aneurysm Characteristics

Variable	Protocol 70083	Protocol 70118	Total
	n (% of 23)	n (% of 14)	n (% of 37)
Aneurysm Size (mm)			
7-10 mm	8 (34.8%)	2 (14.3%)	10 (27.0%)
> 10 mm	15 (65.2%)	12 (85.7%)	27 (73.0%)
Neck Type			
Normal	4 (17.4%)	3 (21.4%)	7 (18.9%)
Wide	16 (69.6%)	8 (57.1%)	24 (64.9%)
Unable to determine	3 (13.0%)	3 (21.4%)	6 (16.2%)

	Protocol 70083	Protocol 70118	Total
Aneurysm Location			
Left	9 (39.1%)	7 (50.0%)	16 (43.2%)
Right	3 (13.0%)	0 (0.0%)	3 (8.1%)
Midline	11 (47.8%)	7 (50.0%)	18 (48.7%)

Safety

A summary of all adverse events that occurred within the HDE cohort is summarized in Table 7 below. A total of 8 serious adverse events occurred in 5 subjects; 35.7% of subjects in this cohort experienced at least one adverse event. Five (5) non-serious adverse events occurred in 5 subjects.

Table 7. All Adverse Events in HDE population w/identification of adjunctive device used

ADVERSE EVENT	Subject ID	Subjects with event	Rate of 14 subjects	Type of Assist Device Used
SERIOUS AE		5	35.7%	
Ischemic Stroke	02-18			Stent & Balloon
	02-21	2	14.3%	Stent & Balloon
Monoparesis	02-30	1	7.1%	Balloon
Death	02-12	1	7.1%	
Hemorrhage	02-12	1	7.1%	Stent
Parent Artery Occlusion	02-22	1	7.1%	Stent
Hemiparesis or Hemiparesis/Aphasia	02-22	1	7.1%	Stent

ADVERSE EVENT	Subject ID	Subjects with event	Rate of 14 subjects	Type of Assist Device Used
Somnolence	02-30	1	7.1%	Balloon
NON-SERIOUS AE		5	35.7%	
Parent artery occlusion	02-27	1	7.1%	Stent
Mild headache	04-02	1	7.1%	Stent & Balloon
Confusion, no aggressiveness	04-06	1	7.1%	Balloon
Paretic	04-11	1	7.1%	Stent
Vasospasm	04-11	1	7.1%	Stent
Chemical meningitis	04-02	1	7.1%	Stent & Balloon
ANY AE		**9**	**64.3%**	

In the overall study cohort of 38 subjects, 23 serious adverse events were observed in 13 subjects; 34.5% of subjects experienced at least one serious adverse event. Ten non-serious adverse events were observed in 7 subjects as noted below in Table 8.

Table 8. All adverse events in Overall Study Cohort

ADVERSE EVENT	Subject ID	Subjects with event	Rate of 38 subjects	Assist Device Used
SERIOUS AE		13	34.2%	
Parent Artery Occlusion	02-14 02-22 02-29	3	7.9%	Stent Stent Balloon
Ischemic Stroke	02-14 02-18 02-21 02-29	4	10.5%	Stent Stent & Balloon Stent & Balloon Balloon
Hemorrhage	02-29 04-10 02-12 04-13	4	10.5%	Balloon n/a Stent Stent

ADVERSE EVENT	Subject ID	Subjects with event	Rate of 38 subjects	Assist Device Used
Monoparesis	02-30 04-07 04-08	3	7.9%	Balloon Balloon n/a
Vessel rupture	04-13	1	2.6%	Stent
Hemiparesis or Hemiparesis/Aphasia	02-22 04-08	2	5.3%	Stent n/a
Death	02-12 02-25 04-09 04-13	3	7.9%	Stent n/a Balloon Stent
Basal ganglia and mesial temporal hematoma	04-07	1	2.6%	Balloon
Somnolence	02-30	1	2.6%	Balloon
Other Access site bleed GI bleed Cardiac Arrest	04-09 04-09 04-09	1	2.6%	Balloon
NON-SERIOUS AE		7	18.4%	
Access site vascular complication	02-17	1	2.6%	Stent
Parent artery occlusion	02-27	1	2.6%	Stent
Mild headache	04-02	3	7.9%	Stent & Balloon
Confusion, no aggressiveness	04-06			Balloon
Paretic	02-04 04-11	2	5.3%	Stent Stent
Vasospasm	04-11	1	2.6%	Stent
Chemical Meningitis	04-02	1	2.6%	Stent & Balloon
Hemiparesis and hemidysesthesia	04-04	1	2.6%	Balloon
ANY AE		**20**	**52.6%**	

In conclusion, the observed incidence of adverse events in the limited cPAX HDE cohort is consistent with that observed with other HDE-approved stent-assisted coiling devices in this large and giant wide-necked aneursym patient population and supports a reasonable assurance of safety for the cPAX Aneurysm Treatment System.

Probable Benefit

Although demonstration of effectiveness is not required for approval of an HDE, the sponsor provided assessment of two performance endpoints pooled data from the two clinical studies in support of probable benefit of the cPAX Aneurysm Treatment System:

Primary Performance Endpoint: Percent of aneurysms ≥ 90% occluded at 90-day follow-up. Success criteria: 60% of subjects with ≥ 90% occlusion at 90-day follow up.
Overall Population : 60.7% [CI40.6% - 78.5%]
HDE Population : 66.7% [CI 34.9% – 90.1%]1

In the HDE cohort of 15 aneurysms, there were three aneurysms which were unable to be assessed for the primary performance endpoint at 90 days: two subjects who underwent an angiogram but had parent artery occlusion such that an assessment of aneurysm occlusion was not feasible, and one subject who died prior to the 90 day visit. Therefore, the endpoint was summarized on 12 aneurysms. Eight out of 12 aneurysms (66.7%) assessed for occlusion met the primary performance endpoint of complete or near complete occlusion.

Secondary Performance Endpoint: Rate of Aneurysms requiring retreatment at 90 days post-treatment
Overall : 39.4% [CI 22.9% - 57.9%]
HDE Population : 42.9% [CI 17.7% - 71.1%]

In the analysis of all aneurysms treated in the cPAX clinical study, 60.6% (20 of 33) of subjects did not require retreatment within 90 days post-treatment and 39.4% (13 of 33) "required retreatment." In the HDE cohort, 6/14 aneurysms were retreated at 90 days post-treatment for a retreatment rate of 42.9%, with a CI of 17.7% - 71.1.0%. This analysis excludes the two PAO's and the one subject who died from a rupture of an untreated aneurysm (per the independent, expert adjudicator).

XI. Risk/Probable Benefit Analysis

The cPAX treatment system's implantable material is a shapeless hollow strand that randomly fills the cavity of an aneurysm. Platinum coils come in pre-determined two or three dimensional shapes which do not always conform to large or giant aneurysms. In the case of large (>10mm) and giant (>25mm) aneurysms there is not a coil that is of a size to effectively treat large and giant aneurysms. Hence, the smaller two or three dimensional coils can migrate or float within the large and giant aneurismal sac, preventing acceptable filling and embolization of the aneurysm.

The cPAX's implant material also is larger in cross-sectional diameter so an equal length of cPAX increases the filling volume (packing density) within the aneurysm sac.

It has been shown through *in-vitro* bench testing, *in-vivo* animal testing, and human clinical testing that the cPAX system can densely pack large and giant aneurysms. This is relevant because the main reason for platinum coils failing to effectively treat large and giant aneurysms is because of the instability of the implanted mass of coils within the aneurysm. Because of their lower packing density there is room to move within the aneurysm sac and, over time, they can compact within the aneurysm mass often requiring re-treatment, or they can migrate out of the aneurysm into the parent artery. The cPAX animal and clinical studies have shown minimal evidence of compaction or migration with the cPAX.

Overall, in the HUD population, 66.7% of the aneurysms treated with cPAX were $\geq$ 90% occluded. In the HUD population, the retreatment rate was 33%, lower than that which occurs in aneurysms treated with the currently available devices in this population.

The cPAX human clinical testing shows that there were no new types of adverse events that occurred in the use of cPAX in comparison to other embolization devices currently marketed through a 510(k) or an HDE in the large and giant wide-necked aneurysm patient population.

Based upon these results, it is reasonable to conclude that the features the cPAX system will benefit the patient with more effective and complete initial treatment of their large or giant aneurysm when used in conjunction with assist-devices, reducing or obviating the need for re-treatment.

XII. Panel Recommendation

This HDE was not taken to a meeting of the Neurological Devices Advisory Panel because it was determined that the preclinical and clinical issues raised by the HDE did not require panel review for the proposed indication.

XIII. CDRH Recommendation/Decision

CDRH has determined that , based on the data submitted in the HDE, that the cPAX Aneurysm Treatment System will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issed an approval order on April 1, 2011.

XIV. Approval Specifications

Directions for use: See Physician's Labeling.