Appendix 5 – COCOA 2010 Annual Report

COCOA is an ongoing IDE study of coils vs. PED for the treatment of small, saccular intracranial aneurysms of the internal carotid artery.

Chestnut Medical

IDE Annual Report

Chestnut Medical Technologies, Inc.
173 Jefferson Drive
Menlo Park
California 94025-1114

main: 650 566.0057
fax: 650 566.0072

May 21, 2010

Joe Hutter, PhD
IDE Document Mail Center (HFZ-401)
Center for Devices and Radiologic Health
Food and Drug Administration
IDE Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: [redacted]Pipeline™ Embolization Device (PED)
COCOA Study (3 copies) IDE Annual Report

Dear Joe,

Attached is an **IDE Annual Report** for the above-referenced IDE. As we have discussed previously, we are also reporting compassionate use and emergency use cases in this IDE study.

We consider the contents of this submission to be confidential commercial information and request that it be treated as such by FDA. We understand that the submission to the government of false information is prohibited by 18 USC 1001 and 21 USC 331(q).

Please contact me if you have any questions.

Sincerely,

Daniel Cher

Daniel Cher, MD
Vice President of Clinical and Regulatory Affairs
dcher@chestnutmedical.com
[redacted]

Confidential

IDE Annual Report
Complete Occlusion of Coilable Aneurysms (COCOA) Study

Chestnut Medical Technologies
173 Jefferson Drive

Table of Contents

1 IDE Number

[redacted]

2 Device Name

Pipeline Embolization Device (PED) and Marksman™ Catheter

3 Indications for Use

PED is intended for the embolization of intracranial aneurysms.

4 Sponsor Name/Address

Chestnut Medical Technologies
173 Jefferson Drive
Menlo Park, CA 94025
[redacted]

5 Contact Person

[redacted]

6 Study Progress

6.1 Executive Summary

Enrollment in COCOA began in October 2008. To date, 16 patients have been enrolled. Three patients spontaneously withdrew prior to the index procedure. Two patients voluntarily withdrew prior to the procedure and one patient was found not to meet eligibility criteria and was therefore withdrawn from the study. 13 patients were treated, 8 with PED and 5 with coils. One coil-treated patient crossed over (per protocol) to PED.

All patients treated with PED who have had 180-day follow-up have shown complete occlusion of the target IA. One patient treated with PED died 3 days after discharge. The circumstances of his death are described below. Other adverse events were mild-to-moderate and were typically procedure-related.

Study follow-up has been excellent. All patients treated with PED who have had 180-day follow-up have shown complete occlusion of the target IA. Data collection and

monitoring is in progress and is going well. The number of protocol deviations is low and they do not affect the scientific validity of the study.

6.2 Data Extract Date

Data were exported from the EDC system on [redacted]

6.3 Investigator List

To date, 4 sites are enrolling. The site/principal investigator list is shown in **Table 1**. One site previously reported to be close to study initiation is no longer participating.

Table 1. Principal investigator at each participating site.

Site #	Name/Address	N Enrolled
[redacted]	[redacted]	6
		3
		4
		3
		16

6.4 Subjects

To date, 16 patients have been enrolled in COCOA (**Table 1**). 3 patients withdrew prior to treatment (**Table 2**). Baseline characteristics of the 13 treated patients are shown in **Table 3**.

Table 2. Reason for study withdrawal.

Patient	Reason for Withdrawal
[redacted]	History of illicit drug use but was thought to be "clean" at time of enrollment. Prior to treatment he failed a drug screening test and was withdrawn due to ineligibility (exclusion criterion "s").
[redacted]	Voluntarily withdrew after randomization
[redacted]	Voluntarily withdrew after randomization

Table 3. Baseline characteristics of treated patients.

	PED (n=8)*	Coils (n=5)
Age, mean (SD, range)	58 (13.8, 31.8-75.8)	46 (12.3, 34.3-69.0)
Female, n (%)	7 (87.5%)	5 (100%)
Aneurysm Maximum fundus diameter, mean (SD, range) Neck, mean (SD, range)	 7.2 (3.9, 2.2-13.0) 3.5 (1.4, 1.8-6.0)	 6.6 (2.7, 4.5-10.6) 3.7 (1.0, 2.8-5.2)

*The number of PED patients is larger than coil patients because randomization favors PED by a 2:1 ratio.

6.5 Summary of Results

6.5.1 Patient Flow

Figure 1 shows a summary of patient flow. 13 patients underwent the assigned treatment. In one patient, coils could not be placed. The patient crossed over per protocol and was treated with PED. All available patients have either had 180-day follow-up or have 180-day follow-up visits scheduled.

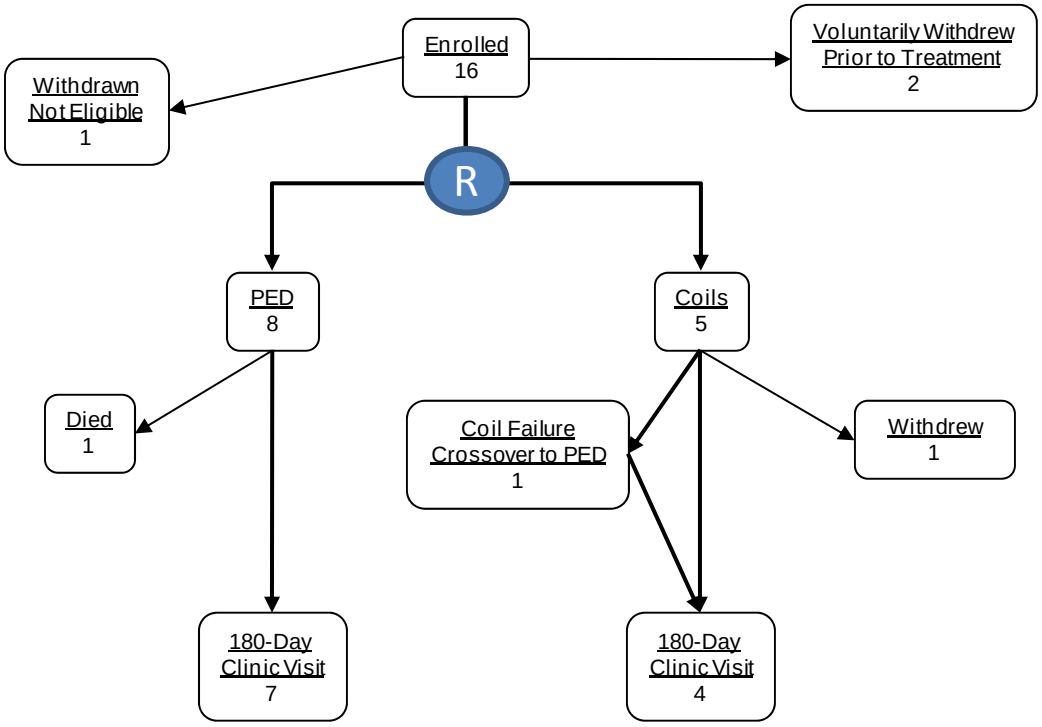


Figure 1. Patient flow. "R" indicates "randomize."

6.5.2 Procedure Information

All patients underwent the study procedure under general anesthesia. Procedure and fluoroscopy times were lower in the PED group (statistical significance was not tested). In the PED group, PEDs of various sizes were used. On average, 2 PEDs were used per patients.

Table 4. Procedure characteristics.

Characteristic	PED (n=8)*	Coils (n=5)
Procedure time, mean (SD, min-max)	93.1 (36.3, 48-157)	126.8 (13.6, 111-140)
Fluoroscopy time, mean (SD, min-max)	36.0 (15.1, 16-55)	65.3 (20.0, 45-85)
PED diameter, mm		
3.5	2	N/A
3.75	7	
4.0	4	
4.25	1	
4.5	1	
5.0	1	
PED length, mm		
10	5	N/A
12	3	
14	2	
16	1	
18	3	
20	2	
Num PEDs used		
1	3	N/A
2	2	
3	3	

6.5.3 Device Failures

No device failures occurred. A single device was introduced into the delivery microcatheter but not deployed (**Table 5**).

Table 5. PEDs placed into body and then removed.

Patient	Description
[redacted]	The physician pulled on the PED wire after inserting PED into the rotating hemostatic valve (attached to the microcatheter). The proctor noted that this maneuver is not recommended in the IFU and tends to push the PED further into the capture coil, making release more difficult. Therefore, PED was removed and another PED opened and successfully placed.

6.5.4 Device Accountability

Sites have carefully tracked devices sent to them. All devices have been accounted for.

6.5.5 Clinical Follow-Up

180-day follow-up. As noted above, 9 patients have had 180-day follow-up. Of the 6 patients assigned to PED who have 180-day follow-up, all target aneurysms but one appeared to be

completely occluded (official core lab interpretation is pending) with patent parent arteries and no major stenosis (one aneurysm showed minor residual). One patient who crossed over from coils to PED also had complete occlusion on 180-day angiogram. One patient assigned to coils broke her hip following PED placement (unrelated to the placement procedure), requiring surgery and repeat surgery for wound non-healing. She withdrew because trial participation was a medical hardship. Of the remaining 3 patients treated with coils, 1 crossed over (described above) and 2 had complete aneurysm occlusion on 180-day angiogram. **Figure 2** shows an example of complete occlusion of a small target aneurysm after PED.

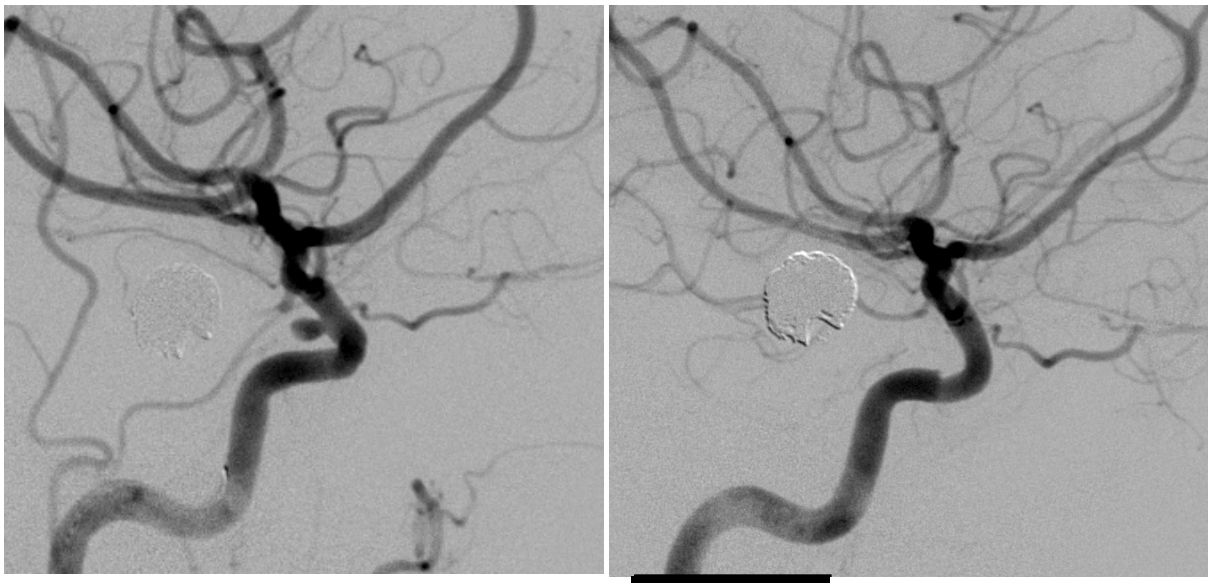


Figure 2. Baseline and 180-day angiograms from patient [redacted], showing complete occlusion of the target aneurysm. Lateral view is shown. Note that patient previously had prior coiling of a contralateral aneurysm.

6.6 Anticipated and Unanticipated Adverse Events

6.6.1 Primary Safety Endpoint

One PED patient ([redacted]) had a fatal stroke 3 days after discharge (see **Table 6** for description and **Appendix 1** for autopsy report). This event was judged by the clinical events committee to have met the primary safety endpoint (major ipsilateral stroke or neurologic death). Although there was no product complaint, a device investigation was performed (**Appendix 2**). An interim statistical analysis performed after the above-described event indicated that clinical study still has a high likelihood of success from the safety perspective and that the benefits were likely to outweigh the risks.

Table 6. Patient who met primary safety endpoint.

[redacted] was a 75-year-old man with an 8 mm ophthalmic segment IA. He had a history of chronic lymphocytic leukemia in remission, L4/5 fusion with residual back pain, benign prostatic hyperplasia. Medications include Lipitor (atorvastatin calcium), Flomax (tamsulosin), Singulair (montelukast), oxycodone, multivitamin, and occasional Ambien (zolpidem). The preoperative complete blood count was normal. The patient underwent placement of a single PED on October 1, 2009. He was discharged from the hospital the next

day. On postoperative day 4, he was found in his backyard unresponsive. CT scan at a local hospital showed ipsilateral brain hemorrhage. Autopsy showed intraparenchymal hemorrhage in the ipsilateral frontal lobe. There was no subarachnoid blood, the aneurysm was intact, and ICA did not show any unexpected findings. There were no other gross pathologic findings. Histopathology confirmed that the aneurysm had not ruptured. There was evidence of a small amount of basophilic foreign body material in the distal brain arterioles (see Autopsy Report, **Appendix 1**).

In retrospect, the investigator noted that the case itself was smooth. No exchange wire was used. However, the patient did not take the pre-procedural antiplatelet medications as mandated by the study protocol. In addition, he received a bolus of Reopro (abciximab, a potent platelet inhibitor) at the end of the placement procedure because he had not taken the protocol-mandated antiplatelet medication Whether these medications were related to or caused his postoperative intracranial hemorrhage is not known.

6.6.2 Serious Adverse Events

The ISO14155 definition for serious adverse event[1] was used, which includes hospitalization for any reason or prolongation of hospitalization for any reason. Eight serious adverse events have been reported to date (**Table 7**). All events but 1 (reported recently) were evaluated by the clinical events committee (CEC). There were no unanticipated adverse device events. The rate of serious adverse events was not unexpected.

Table 7. Serious adverse events to date in COCOA.

Patient ID	Treatment	Description
[redacted]	PED	Hospitalization for toe cellulitis vs. gout on postoperative day 212. Patient treated with medications and discharged to home 2 days later.
	PED	Retroperitoneal hematoma developed immediately after PED placement. No specific therapy was provided but her hospitalization was prolonged.
	PED	Same patient as above. One day after discharge, she presented to the local ER with increasing groin pain, increased hematoma and urinary urgency. A CTA of the abdomen showed a new pseudoaneurysm 2.4 x 2.1 cm in diameter. She was admitted to the hospital and underwent a local thrombin injection on July 19, 2009. Arterial duplex ultrasound 24 hours later showed no evidence of pseudoaneurysm.
	PED	Experienced groin discomfort after PED procedure. CT of abdomen confirmed retroperitoneal hematoma. Patient required blood transfusion. Hospitalization was prolonged.
	Coils	Experienced a GI bleed on POD 91, requiring brief hospitalization at an outside hospital and transfusion. Diagnosed with upper GI ulcer.
	PED	Postoperative stroke, described above
	Coils	Hip fracture with hip surgery x 2; patient eventually withdrew from study

[1] SAE defined per ISO14155:2003 (section 3.19) as any adverse event that:

1. Led to a death
2. Led to a serious deterioration in the health of the subject that
    a. resulted in a life-threatening illness or injury
    b. resulted in a permanent impairment of a body structure or a body function
    c. required in-patient hospitalization or prolongation of existing hospitalization
    d. resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Patient ID	Treatment	Description
[redacted]	Coils	The FemStop Femoral Compression Device was placed after PED procedure and was inadvertently left on all night. The patient had leg weakness in the morning but pulses were preserved. Doppler ultrasound showed preserved arterial and venous flow. Leg weakness resolved and the patient was discharged. The patient continues to have leg pain.

*Event reported very recently, not yet evaluated by CEC

6.6.3 Other Adverse Events

Other, non-serious adverse events have occurred at a low rate and were primarily related to the angiographic procedure and not PED itself. **Table 8** lists non-serious adverse events reported to date. Note that data collection is ongoing so the list is not necessarily complete.

Table 8. Summary of non-serious adverse events.

Patient ID	Description
[redacted]	Occasional blurry vision
	Hypotension related to retroperitoneal hematoma
	Nausea related to retroperitoneal hematoma
	Intermittent fever related to retroperitoneal hematoma
	Heavy menses
	Headache
	Headache
	Headache
	Nausea related to contrast sensitivity
	Headache

6.7 Deviations

To date, 10 minor protocol deviations have occurred (**Table 9**). Deviations did not affect patient safety. Whether clopidogrel dosing inconsistent with the protocol was related to the postoperative stroke in patient [redacted] is not known. Overall, deviations did not affect the scientific validity of the study.

Table 9. Protocol deviations to date.

Deviation Type	Patient ID	Comment
Test not done	[redacted]	Gait not assessed due to bedrest
		Reflexes not assessed
		Baseline visual field examination could not be done since patient could not tolerate sitting upright
		Baseline ACT not done in procedure
Medication at different dose		Aspirin loaded the morning of the procedure
		Patient decided to take 3 tablets of 81 mg aspirin (243 mg) instead of 1 tab 325 mg
		Patient decided to take 81 mg aspirin instead of 325 mg
Test/procedure/visit outside window		Screening angiogram for eligibility more than one month prior to procedure
Other		Baseline imaging measurements of ICA aneurysm from MRA measured less than 4 mm neck. Patient random
		Loading dose of clopidogrel given within 24 hours before procedure instead of day before procedure.

7 Other Clinical Information – Compassionate and Emergency Use Cases

Several patients have been treated with PED under compassionate use or as emergency use cases. After discussion with FDA in [redacted] it was decided to report compassionate use/emergency cases under the COCOA study IDE. FDA is referred to Section 12.7 of the PED PMA [redacted], in which compassionate use and emergency cases in the US are described in detail. An electronic copy of this section is included as **Appendix 3**.

8 Risk Analysis

8.1 New Adverse Information

One patient in the PED arm of COCOA died on postoperative day 4. See **Appendix 2** for a detailed analysis.

8.2 Reprints

Study data from COCOA have not yet been published.

8.3 Risk Analysis Update

No update to the risk analysis has been performed as a result of patients treated with PED in COCOA.

9 Other Changes

9.1 Manufacturing and Quality Control Changes

The reader is referred to **Section 7** of the recently submitted PED PMA (May 12, 2010), which is included as **Appendix 4**. In summary there were no changes to design and minor changes to PED manufacturing.

9.2 Investigational Plan Changes

COCOA was initiated under Revision C [redacted]) of the clinical protocol. In [redacted] FDA approved Revision D, in which the preoperative and 180 day postoperative ophthalmology examination was limited to those patients with signs/symptom potentially related to the target aneurysm.

10 Future Plans

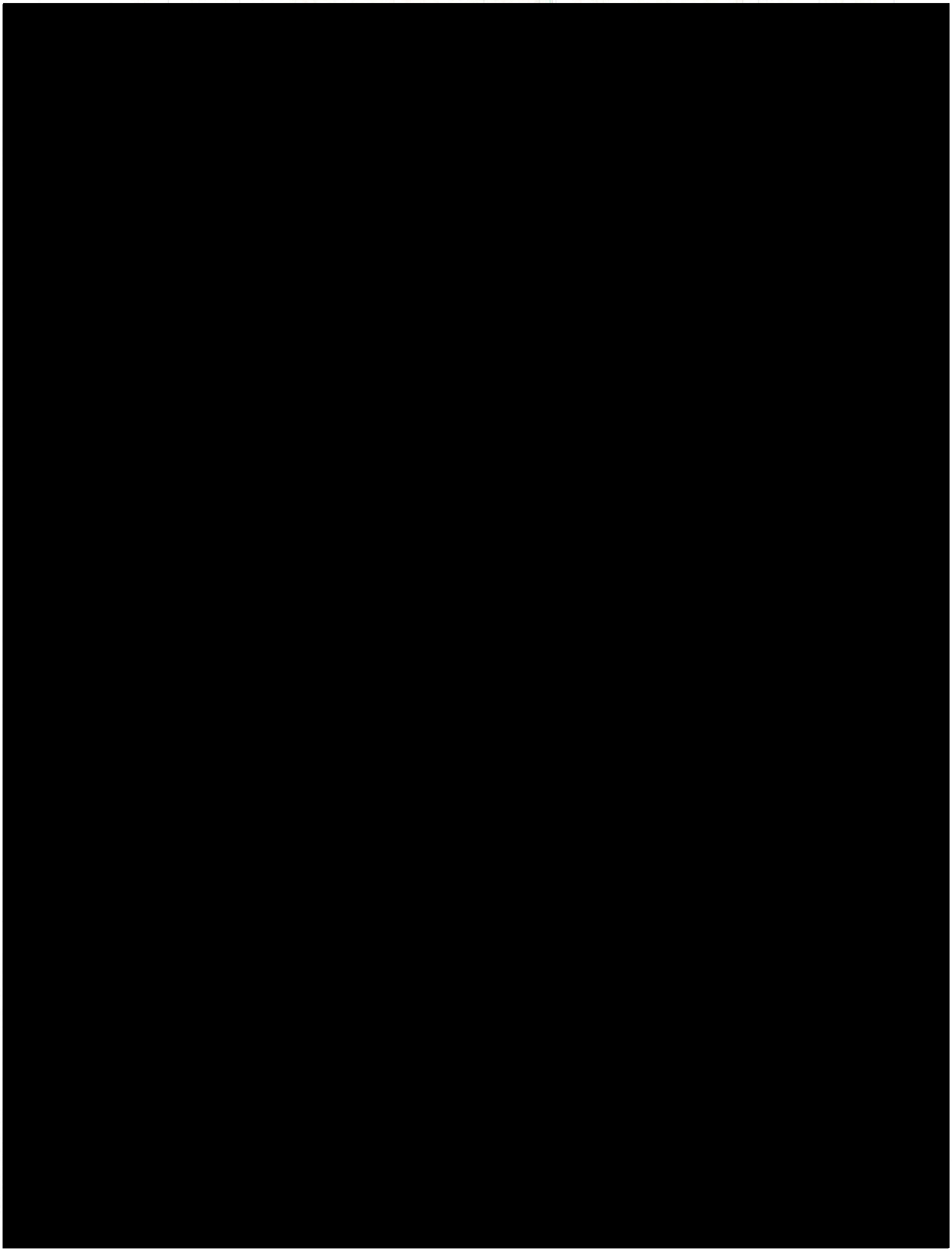
10.1 Product Approval

COCOA will continue to enroll patients, with the goal of obtaining a dataset sufficient to meet study goals and support product approval/labeling. The timing of complete enrollment is not known.

10.2 Planned Investigational Protocol Changes

No plans are currently in place to change the investigational protocol.

Appendix 1. Autopsy Report – [redacted]



Appendix 2. Device Investigation

The death of patient [redacted] 3 days after discharge is described in **Table 6**. A single PED was placed and the physician reported no device malfunction. Although the physician has not made a product complaint, a device investigation was performed. Since the case was a technical success, no accessory devices (wires, catheters, etc.) are available for analysis at this time.

Autopsy performed at St. Joseph's Hospital (Phoenix, AZ) showed intraparenchymal hemorrhage. In addition, basophilic material was seen in a small number of arterioles. The portion of the skull base with PED in the ICA was sent to CV Path, a cardiovascular pathology laboratory specializing in cardiovascular pathology. The CV Path report is found in **Appendix 1**. Small fibers of basophilic non-human material were found on the inner surface of the ICA adherent to PED. The material was termed "hydrogel" in the CV Path report. The aneurysm itself was intact.

The patient had several risk factors for hemorrhage, including 1) recent neurovascular procedure, 2) new use of antiplatelet agents (aspirin and clopidogrel), 3) dosing of clopidogrel in a manner not consistent with the study protocol, 4) history of chronic lymphocytic leukemia, and 5) use of a potent antiplatelet agent (Reopro) at the end of the procedure. The presence of basophilic material in arterioles and on PED raises the possibility that embolization of hydrophilic coating may have played a role in this patient's death. **Table 10** lists endovascular devices used during the procedure; at least 5 of these devices, including Chestnut's Marksman catheter, are hydrophilic coated. An investigation of Marksman catheter was undertaken.

Table 10. Devices* used during [redacted] I procedure.

Device (Manufacturer)	Hydrophilic Coating
[redacted]	

[2] http://www.arrowintl.com/products/boms/CL07665.asp?cat=14&item=CL-07665&xsec=
[3] http://www.terumois.com/administration/pdfs/collateral%20library/Glidewire%20Advantage%20Sell%20Sheet.pdf
[4] http://www.cookmedical.com/di/content/mmedia/PI-BM-KCF-EN-200801.pdf
[5] http://www.penumbrainc.com/products/neuron-system/
[6] http://www.cookmedical.com/di/dataSheet.do?id=4423

Chestnut engineers tested Marksman catheters, including a catheter from the same lot that was used in the clinical case. Catheters were tested in a benchtop model designed to mimic the use of Marksman catheter during deployment of the PED in tortuous human intracranial anatomy. The collected particulate samples were shipped to Nelson Laboratories for particulate count. Particulate counts met the USP<788> standard, which allows for <600 particulates of ≥25µ and <6000 particulates of ≥10µ. The results obtained were low: mean=19 particulates ≥25µ and mean=346 particulates ≥10µ.

Appendix 3. Compassionate Use Case Experience

Chestnut Medical recently submitted Module 3 of its Modular PMA application for PED. Compassionate use of PED was described in Section 12.7 of the Modular PMA. This section is reproduced on the following pages.

Excerpt from Module 3 of PED PMA, submitted to FDA on May 12, 2010

12.6.4 Additional Endpoints Discussion

PUFS pre-specified several additional endpoints (**Table 12-44**). Each endpoint was intended to be supportive of the primary and secondary endpoints of the study. In each case, positive outcomes were observed that supported the study's main goals.

Table 12-44. List of additional endpoints in PUFS.

- Technical success
- IA occlusion ranking
- Complete occlusion rate including salvage treatment
- Incidence of neurologic death by 180 days
- Change in visual field examination at 180 days
- Frequency of worsened eye alignment by clinical examination by the ophthalmologist
- Frequency of > 2 lines lost in visual acuity by Snellen chart
- Frequency of > 2 lines gained in visual acuity by Snellen chart
- Incidence of secondary treatments for the target IA
- Distal PED migration
- Stenosis in PED

12.6.5 Discussion of Other Aspects of Study

Several other aspects of PUFS merit comment. Patient follow-up in PUFS was excellent and much better than most published studies. Only 3 of 107 (2.8%) treated patients either withdrew or were lost to follow-up. 99 of 100 patients still participating in the study at 180 days underwent study-related angiograms. It should be noted that many patients were referred by their neurosurgeons to participating study centers in distant locations, requiring substantial patient travel for follow-up visits. Major protocol deviations were few in number and did not affect the scientific validity of the study.

12.7 Compassionate and Emergency Use Cases

Compassionate, emergency and other clinical use of PED for IAs is discussed here prior to drawing conclusions regarding PED.

12.7.1 US Compassionate/Emergency Use Cases

PED has been used in 28 compassionate use cases in the US (**Table 12-45**) as of [redacted] These cases were characterized by complex lesions or emergency uses of PED for iatrogenic aneurysms. Patients typically did not meet criteria for any open clinical trials.

12.7.1.1 Compassionate Use Cases in the ICA

PED was used in the ICA in 12 lesions in the ICA that were qualitatively similar to those enrolled in PUFS. In all cases in which PED was placed in the ICA and follow-up is available, the target IAs were completely occluded at follow-up. Patient symptoms (when present) improved, in some cases remarkably. 1 patient had severe postoperative headaches that resolved with oral steroids. 1 patient

had esophageal injury related to an anesthesia complication. The overall experience of patients with IAs of the ICA treated under compassionate use approval was similar to that of PUFS, with a very high effectiveness success rate and a low rate of complications.

12.7.1.2 Compassionate Use Cases in the Posterior Circulation

PED was used in 15 cases in the posterior circulation (vertebral or basilar arteries) in which conventional endovascular or neurosurgical treatment was not possible. In several cases, the patient had been referred to centers using PED by neurosurgeons who had nothing to offer the patient. Several posterior circulation cases were very complex and some patients had marked symptoms related to brain stem compression. Most patients did very well, with resolution of symptoms and complete occlusion of the target IA. Several cases were published in the medical literature as case reports or have been accepted for publication.[40-43]

Additional information regarding compassionate use cases in the US is provided in **Appendix 21**.

Table 12-45. Compassionate use cases in the US. Shaded rows indicate aneurysms in the ICA that were qualitatively similar to those in PUFS.

#	Initials/ Name Code	Age	Proc date	Location Physician	Aneurysm location	Neck size, mm	Maximum fundus diameter, mm	Symptoms	Adverse event	Device malfunction?	Follow-Up
1	[redacted]	50	1/11/2007	[redacted]	Vertebral V4	Fusiform	12	Headache, neck pain	None	No	Complete occlusion @1 yr, no symptoms. Continued asymptomatic at 1.5 years.
2		57	2/5/2007		Vertebral V4	Fusiform	14	Stroke, recurrent paresthesias	None	No	Complete occlusion @1yr, death from medication error and progressive disease @2 yrs
3		13	4/11/2008		Basilar trunk	Fusiform	28.9	Headache, nystagmus	None	No	Complete occlusion @7 mo, reduced aneurysm size, all symptoms resolved
4		51	6/26/2008		ICA cavernous	Fusiform	20	Ptosis, diplopia	Headache	No	Complete occlusion @7 mo, reduced headaches, ophthalmoplegia resolved
5		87	11/18/2008		ICA paraophthalmic	15	36	Intractable retroorbital pain	No	No	Could not complete case as could not catheterize parent vessel
6		36	12/9/2008		ICA paraophthalmic and fusiform distal ICA	SHA area was fusiform. Paraophthalmic aneurysm neck was 13 mm	25	Headache, vision loss due to optic nerve compression	None	No	Complete occlusion @4 mo. Headaches resolved, blurry vision much improved
7		56	1/9/2009		Basilar artery	Dolichoectatic	20 x 33 x 24	Headache, vertigo, disequilibrium	None	No	Near complete occlusion @1mo. However, progressive aneurysm symptoms occurred, patient eventually died of stroke
8		55	2/2/2009		Basilar artery into SCA	Dolichoectatic	>30mm	Headache, weakness	Stroke	No	Progressive occlusion of aneurysm, slow recovery from stroke. Died of multiorgan failure about 6 mo after PED treatment
9		42	2/19/2009		Basilar trunk	10-15 mm	~20mm	Dizziness, perioral numbness, difficulty swallowing	Artery (not aneurysm) rupture	No	Patient died during catheterization. No Chestnut products used
10		54	1/25/2009		ICA paraophthalmic	~4 mm	~8 mm	Unknown	None	No	Angiogram @5 months showed complete occlusion
11		65	5/11/09		ICA, iatrogenic pseudoaneurysm	~1.5 mm	~2.5 mm	None	None	No	Angiogram @6 months showed complete occlusion. Patient doing well clinically
12		61	6/22/2009		ICA, iatrogenic pseudoaneurysm after brain tumor surgery	<4	7	None	Seizure @7 mo due to residual tumor	No	Angiogram @7 mo showed complete occlusion.
13		52	8/25/2009		Supraclinoid ICA	Fusiform/multilobulated	12	Incidental	None	No	Angiogram @4.6 mo showed complete occlusion
14		24	8/25/2009		Basilar trunk	Fusiform	20	Headache	None	No	Headache resolved @30 d. Angiogram @3 mo showed tiny residual, but otherwise perfect reconstruction
15		34	8/25/2009		Basilar	Fusiform	NS		Retroperitoneal hematoma & medial medullary infarct with pain syndrome	No	Improving symptoms related to medullary infarct. Angiogram @6 months showed complete occlusion.
16		57	8/20/2009		Supraclinoid ICA	Fusiform	20	Headache, crescendo symptoms suggesting impending rupture	None	No	Headaches resolved, angiogram @day 6 showed near-complete occlusion
17		26	8/21/2009		Vertebral artery	Fusiform	15	Headache	Headache/n/v 1mo after procedure, resolved	No	Angiogram @6 mo showed complete occlusion. Marked reduction in headaches.

#	Initials/ Name Code	Age	Proc date	Location Physician	Aneurysm location	Neck size, mm	Maximum fundus diameter, mm	Symptoms	Adverse event	Device malfunction?	Follow-Up
18	[redacted]	63	9/1/2009	[redacted]	Basilar trunk	NR	35	Sudden deterioration, mental status changes	None	No	Post op course complicated by hydrocephalus and sepsis. Expired @3 months from hemorrhagic transformation of infarct
19		61	9/29/2009		Basilar	~10 mm	25	Headache, neck pain, dizziness, gait instability	None	No	Angiogram @3 mo showed complete occlusion
20		66	11/19/09		Vertebrobasilar	Fusiform	38	Gait instability, slurred speech, aspiration, behavioral/cognitive changes	Hydrocephalus requiring placement of a VP shunt	No	Stabilization of neurologic status. Angiogram @4 mo showed complete occlusion
21		63	11/24/09		Paraophthalmic	N/A	~30	Progressive visual loss	None	No	Near complete occlusion at 4 mo by angiogram. Vision stable.
22		61	12/2/09		Cavernous carotid	Fusiform	14 mm	Diplopia and abducens palsy	None	No	Clinically improving, angiogram pending
23		86	11/6/09		Paraophthalmic	N/A	~20 mm	Aneurysm recurrence with progressive contralateral blindness due to aneurysm despite two prior coiling procedures	Esophageal injury due to orogastric tube placed as part of anesthesia	No	Angiogram @3 mo showed complete occlusion. Clinically improved, but formal visual field testing pending
24		56	11/19/09		Supraclinoid carotid	>10 mm	20 mm	Headache and visual loss	None	No	Transient worsening of symptoms, now back to baseline. CTA showed complete occlusion, catheter angiogram pending
25		61	11/23/09		Basilar	Fusiform	~40 mm	Headache	Post-operative aneurysmal hemorrhage	No	Fatal SAH 3 days after PED placement
26		48	12/28/09		Cavernous carotid	Fusiform	16 mm	Headache	No	No	Pending
27		18	1/5/10		Cavernous carotid	N/A	N/A	Headaches, diplopia with abducens palsy	Epistaxis on POD#3, easily controlled. Patient has history of nosebleeds.	No	At hospital discharge, decreased diplopia. Patient is back in school full time, headaches and nosebleeds have resolved. Angiographic follow-up pending
28		45	1/14/10		Cavernous carotid	N/A	29.3	Nausea, retro-orbital pain, abducens palsy	Readmitted on POD3 for nausea and ptosis	No	Pending

* “ icates emergency u

12.7.1.3 Summary of Compassionate Use Cases in US

Use of PED in these patients clearly met the definition for compassionate use. Most cases were referred to physicians by neurosurgeons and interventional neuroradiologists who had nothing else to offer the patient. The majority of cases had excellent outcomes, often with marked improvement in symptoms related to the target IA. The cases with poor outcomes were those with the worst underlying disease. In several cases, adverse events were related to the procedure, not to PED. In summary, compassionate use cases in the ICA were highly supportive of results in PUFS, and PED shows excellent promise for use in the posterior circulation.

12.7.2 Canada Special Access Cases

As of [redacted], 55 special access PED cases were performed in Canada from early 2008 until [redacted] Cases were performed by Dr. Alain Weill (Centre Hospitalier Université de Montréal, 7 cases), Michael Kelly (University of Saskatoon, 9 cases), Tom Marotta (St. Michael's Hospital) and Robert Willinsky (Toronto Western Hospital) in Toronto (39 cases total). All cases were performed under the Special Access provision of Canadian medical device law.

Appendix 22 provides a detailed description of the experience at the two Toronto hospitals. **Table 12-46** summarizes cases performed by Drs. Weill and Kelly. The overall experience in Canada was similar to that in PUFS: the rate of angiographic occlusion in complex, uncoilable IAs was high and the rate of stroke and other serious adverse events was low. The Canadian experience is highly supportive of the PUFS experience.

Appendix 4. Design and Manufacturing Changes

Chestnut Medical submitted Module 3 of its Modular PMA application for PED on [redacted] 2010. Changes in the design and manufacturing of PED were described in Sections 7 and 8 of the Modular PMA. These sections are reproduced on the following pages. In summary, there were no design changes to PED and minor changes to manufacturing processes.

Excerpt from Module 3 of PED PMA, submitted to FDA on May 12, 2010

The tip is designed to be soft and flexible, to allow placement into distal neurovasculature with minimal trauma to vessels. The protective coil is designed to hold PED in the collapsed state until the operator deploys PED. Rotating the proximal delivery wire "unscrews" the coil from the distal tip of PED, allowing it to spontaneously expand into the parent artery. Other than being held in place by the protective coil, PED is not physically attached to the guidewire. A proximal marker is soldered to the core wire; the function of the proximal pusher is to push PED out of the microcatheter when the wire is advanced.

The PED delivery system is manufactured by soldering the components into place with the proximal marker position varying based upon PED implant length.

5 Device Materials

Table 5-1 shows PED materials and their relative degree of contact with the patient.

Table 5-1 PED Materials Table w/ Patient Contact

Component	Material
IMPLANT	**Blood Path Contact**
[redacted]	

6 Marketing History

PED is currently CE marked and available for sale in Europe. PED use in Europe was formally launched in September 2009. PED is also commercially available in Australia, Hong Kong, Singapore, and Turkey. Over 1,000 patients have been treated worldwide to date. Experience with PED outside of the US has been similar to that in the US (described below).

7 Design Changes

This document describes results from the PUFS study, conducted under [redacted]. There have been no design changes to PED since the IDE approval for clinical use.

8 Manufacturing Changes

Some manufacturing processes have been revised to improve consistency (**Table 8-1**). These changes do not impact safety and effectiveness of the device have been reported in the IDE. Tests have validated that these changes improve the manufacturability of the device while meeting the same product specifications. All other documentation changes that do not affect the product design, performance or validated processes are documented in our internal Document Change Order (DCO) system.

Table 8-1. Changes to PED during clinical study

Component	Change	Reason for Change	Reported
Distal tip solder joints of delivery system	Surfaces of components are electro-plated rather than manually sanded. Electroplating introduces no new materials or chemicals.	Improve consistency of soldering	IDE Supplement [redacted]
Marker band solder joint of delivery system	The in-process tolerance of the internal diameter (ID) of the marker band was tightened (within the original ID range) and customized for the various sizes of delivery system.	Improve soldering of marker band to wire. Originally the tolerance of the ID was uniform for all sizes, which resulted in variation of the soldering gap. The change results in a more optimal soldering gap and concentric alignment of the parts appropriate for each of the various sizes of delivery system.	IDE Supplement [redacted]
Inspection procedures	Inspection sampling was increased to include statistically valid sampling plan and acceptance quality levels.	Improve sampling procedures	IDE Supplement [redacted]
Sterilization procedures	A second-source sterilizer has been qualified for future use.	Second sterilizer has higher capacity	IDE Supplement [redacted]
Cleaning procedures	Set limit to number of devices to be cleaned in each test tube of solution.	Improve procedure	Will be reported in upcoming annual reports