Quintessential Capital Management
Penumbra Jet7 Flex Assessment

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Background:

Interventional Cardiologist University of Maryland 2003-2005, Private Practice 2005-2007

FDA Medical Officer, Office of Device Evaluation (ODE), Division of Cardiovascular Devices (DCD), Peripheral Interventional Devices Branch (PIDB) 2007-2014

VP Regulatory Affairs & Health Economics Ablative Solutions 2015-2017

Expert Consultant **NDA Partners** 2016-Present

Bio:

Dr. Brooks is a multi-faceted health care consultant, publisher, and clinical trialist. Interests include regulatory strategy, scientific and medical due diligence, and medical technology commercialization. An Interventional Cardiologist who performed peripheral vascular intervention, Steve worked six years as a Medical Officer for the FDA in the Office of Device Evaluation (ODE). While there he worked on the full product life cycle, including premarket, clinical study design and monitoring, as well as post-market compliance. He is currently an Expert Consultant with NDA Partners. In this role Steve is active in developing thought leadership, content, and consultation on multiple interconnected strategic areas of medical technology commercialization. His primary focus is regulatory strategy and clinical evidence development, with a concentration in cardiovascular technology. Steve holds industry and board positions with medical technology companies and continues to teach and mentor at Johns Hopkins University.

Background:

Penumbra's Jet7 Flex has experienced malfunctions in the US and internationally that have raised the concern of inherent product risk, and a significant risk to patient safety. Quintessential Capital Management wishes to understand the nature of these malfunctions and the regulatory implications.

Regulatory History:

The Jet7 Catheter was first cleared via 510(k) K173761 on August 17, 2018. The catheter was declared substantially equivalent (SE) to Penumbra's ACE68 catheter. Testing was done that was typical for any extruded catheter – biocompatibility and bench testing. The following bench tests were reported in the 510(k) summary:

Attribute	Specification	Results
Dimensional / Visual Inspection	These evaluations confirm that the units used in this Design Verification testing meet all product specifications.	Pass
Simulated Use [Intracranial Access, Vessel Access Entry Performance, Delivery/Retrieval Forces & Clot Removal]	Simulated use testing of the Penumbra System Reperfusion Catheter JET 7 was performed with accessory devices in an anatomical model which simulated the tortuosity of the neurovasculature. Devices were delivered through the tortuous anatomical model to evaluate the effectiveness of the devices to remove clots and that the Reperfusion Catheter does not collapse under vacuum.	Pass
Physician Evaluation [Deliverability & Clot Removal]	Multiple Physician performance evaluation of the Penumbra System Reperfusion Catheter JET 7 in a simulated neurovascular tortuosity model with the predicate Penumbra System Reperfusion Catheter ACE 68 used as a baseline.	Pass
Kink Resistance (Distal, Midshaft, Proximal)	No kinking when formed in a 2.5 mm, 10 mm, and 25 mm radius	Pass

Attribute	Specification	Results
Particulate testing	≥ 10 µm will be ≤ 6000 particles	Pass
	≥ 25 µm will be ≤ 600 particles	Pass
	≥ 75 µm will be measured for informational purposes only (FIPO)	FIPO
	≥ 125 µm will be measured for informational purposes only (FIPO)	FIPO
Coating Integrity	Coating has not delaminated, peeled, or flaked prior to or after simulated use particulate testing	Pass
Markerband Visibility	The markerband is fluoroscopically visible	Pass
Hub Air Aspiration	No leaks detected when vacuum is pulled on the injection lumen	Pass
Pressure Test	45 psi for 30 sec minimum	Pass
JET 7 / Sheath or 8F Guide Catheter Friction Force	Maximum value per specification	Pass
JET 7 / 0.014 in. Guidewire Friction Force	Maximum value per specification	Pass
Joint sections bond strength	Minimum value per specification	Pass
Markerband Section Bond Strength	Minimum value per specification	Pass
Hub to Shaft Bond Strength	Minimum value per specification	Pass
Hub to Hypotube Bond Strength	Minimum value per specification	Pass
Elongation to failure	Elongation ≥ 5%	Pass
Torsion	Number of turns will be recorded for informational purposes only.	FIPO
Corrosion	No visible corrosion on Reperfusion Catheter immediately after corrosion testing procedure	Pass

Of note, the product did undergo pressure testing to 45 psi for 30 seconds, which it passed. All manner of pull tests and sectional integrity was tested. The final testing was a design validation in animals to demonstrate safe simulated use. For perspective on the issue of catheter dilation and burst and the testing done to ensure safety, a 10ml syringe, which would be commonly used in the interventional lab to inject through a syringe, generates a mean of 53 ± 29 psi[1]. A max of 72 psi (actual pressure could be greater with a more vigorous hand-injection force), exceeds the tested pressure for the success criterion for the Pressure testing, which was 45 psi. The pressure testing done by Penumbra was reviewed by FDA and the standards, set by international bodies and supported by FDA, were exceeded. Typically, catheters have higher reserve or will test to burst just to know the rated burst pressure. This information would be contained in the 510(k) submission but is not routinely made public. It can be requested via a FOIA request. That said, the catheter exceeded recognized testing limits and this

[1] WAP Hayward, LJ Haseler, LG Kettwich, AA Michael, WL Sibbitt Jr & AD Bankhurst (2011) Pressure generated by syringes: implications for hydrodissection and injection of dense connective tissue lesions, Scandinavian Journal of Rheumatology, 40:5, 379-382, DOI: 10.3109/03009742.2011.560892

information along with the other testing led FDA to conclude that the Jet7 Flex was substantially equivalent to the predicate catheters.

Comparing this testing to two competing catheters is interesting. The Medtronic React 68 and React 71 catheters provide a table of testing, but do not provide success criteria. The two state:

- The React™ 68 Catheter was evaluated per ISO 10555-1. Annex C. The React™ 68 Catheter met the acceptance criteria for liquid leak.
- The React™ 71 Catheter was able to withstand pressures that are typical of clinical use."

This likely indicates the same standard of ISO 10555-1, and a threshold of 45 PSI. The Microvention Sofia catheter was tested to ISO 10555-1 to 46 psi, but also did dynamic burst testing to a threshold of 300 psi. This represents testing to a level far higher than routine clinical use. The clearance standards likely do not require burst testing or testing beyond the threshold of 45 psi.

Two more iterations of the Jet7 were cleared under K190010 on 6-16-2019 and K191946, the Jet7 Max, on 2-27-2020. All of these iterations were declared substantially equivalent to the predicate devices, the earlier Jet7 catheters, via comparative bench and biocompatibility testing. As the design and materials were demonstrated to have not changed significantly and justifications for this assumptions were agreed upon by FDA, no further animal testing of the new iterations was required for subsequent clearances.

The Jet7 Flex was cleared in the US via K191946 on 8-31-2020 after being demonstrated SE to K191946. From the summary:

> *Comparison of Technological Characteristics with the Predicate Device: There are no differences in the technological characteristics between the subject device and predicate device. The changes made to the subject device are solely labeling changes for more clarity to include additional warnings, precautions, and instructions to enhance the safety of device use.*
> *Performance Data: There are no differences in technological characteristics between the subject and predicate devices and therefore no verification and validation studies were required.*

Bench testing and biocompatibility were performed to demonstrate SE to the predicate device. No additional animal studies were conducted.

FDA MAUDE Database Search

A search of the FDA MAUDE database beginning on June 17, 2019, the day after of the Jet7 clearance for the Brand name Jet7 and the event type Death revealed 12 reports, the first on 10-3-2019, the most recently reported 9-30-2020.

13 records meeting your search criteria returned- **Brand Name:** *jet7* **Event Type:** *Death* **Report Date From:** *06/17/2019* **Report Date To:** *10/31/2020*

New Search | Export to Excel | Help

Manufacturer	Brand Name	Date Report Received
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	09/30/2020
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	08/21/2020
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	07/03/2020
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	06/11/2020
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	06/05/2020
PENUMBRA, INC.	PENUMBRA JET7 KIT	05/28/2020
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	05/22/2020
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	05/15/2020
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	02/28/2020
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	02/14/2020
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	01/30/2020
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	01/30/2020
PENUMBRA, INC.	PENUMBRA SYSTEM JET7 REPERFUSION CATHETE	10/03/2019

Further searches for the same date period from the Jet7 yielded 35 reports for injuries, and 182 malfunctions.

Review of the individual reports reveals common circumstances of use, mechanism of malfunction and patient injury. In nearly all instances that resulted in death, the distal catheter expanded/dilated and/or ruptured with injection of contrast/saline mix through the catheter, or the distal tip separated and embolized. Reports showed use of adjunctive interventional equipment manufactured by Penumbra as well as other manufactures during the procedures in question.

In several of the MAUDE reports, Penumbra had addended onto the MAUDE reports an accompanying Manufacturers Narrative which referred to the clinical findings which “ARE NOT LIMITED TO, ARTERIOVENOUS FISTULA, VESSEL SPASMS, THROMBOSIS, DISSECTION, OR PERFORATION, HEMATOMA OR HEMORRHAGE AT THE SITE, INABILITY TO COMPLETELY REMOVE THROMBUS, INTRACRANIAL HEMORRHAGE, ISCHEMIA, INCLUDING DEATH. THEREFORE, IT WAS DETERMINED THAT THE REPORTED ADVERSE EVENTS WERE ANTICIPATED COMPLICATIONS.” The company absolved themselves of blame because the complications are seen in this type of neuroradiologic complication and have been previously noted and listed in product labelling as known device related complications. In addendums where the catheters were received by Penumbra and analyzed, they attributed operator error and not innate product issues as the cause of the adverse events.

A second mechanism of malfunction observed has been the catheter tips stretching to a breaking point, fraying and rupturing. Fragments have embolized, causing damage, as well as frayed catheters causing friction and possibly intravascular damage upon pullback.
These complications were noted in the US and OUS. In Japan in June of 2020 the Japanese PMDA published a warning letter to physicians, and the product was removed from the Japanese market.

Clinical Practice:

In the treatment of acute stroke, reaching the target lesion in the neurovasculature for intervention or aspiration of thrombus can be challenging. An array of wires, microcatheters and aspiration catheters are used to evacuate thrombus. Techniques that involve multiple wire or catheter exchanges risk intravascular damage and so exchanges are minimized as much as possible. A frequently employed technique is to inject contrast directly through any hollow-bore catheter that can both reach the desired vasculature to visualize the anatomy and pathology and will allow minimization of the amount of contrast used. Injecting contrast from the guide catheter uses larger amounts of contrast dye, a nephrotoxin, and may also sub-optimally illuminate distal vasculature and allow visualization through thrombus. It is therefore common to inject small amounts of contrast by hand at low pressures through an interventional catheter such as the Jet7, and it would be expected that this could also be done through the Jet7 Flex catheters.

Furthermore, it is common in clinical practice to use different manufactures equipment that is compatible based on catheter sizing. Hospital purchasing may be a mosaic of equipment based on a multitude of factors. While there may be a full line of Penumbra neuro-interventional equipment, operator preference may lead individual physicians to use different equipment together.

As a result, operators in the MAUDE reports appeared to be practicing medicine that is standard of care, and not outside what would be considered usual practice or usual technique for neuro-intervention.

Company Response:

In the original catheter IFUs, there was a labelled warning against the use of automated high-pressure contrast injection equipment, as it may damage the device. This would be an unusual practice in the neuro-vasculature and implies that a lower pressure hand injection would be suitable. In bench testing for 510(k) clearance, the catheters were pressure tested to 45 PSI.

In response to reports of catheter malfunction, Penumbra published a Notification to Healthcare Providers on July 27, 2020. In it they acknowledged reports of the Penumbra JET 7 Reperfusion Catheter with Xtra Flex technology (JET 7 Xtra Flex) distal tip expansion or rupture when used during injection of contrast media. They stated that contrast injections through the catheter is not consistent with the intended use of the catheters, or the instructions for use. As a result, they updated their labelling to include the following:

> **Warning: Do not inject contrast media through the Penumbra JET 7 Reperfusion Catheter with Xtra Flex technology using a syringe or automated high-pressure contrast injection equipment. Injecting contrast media through the Penumbra JET 7 Reperfusion Catheter with Xtra Flex technology may cause the distal tip of the catheter to expand or rupture, resulting in potential vessel damage and subsequent patient injury or death. When injecting contrast media for angiography, always inject through the guide catheter.**
>
> **Precaution: The Penumbra JET 7 Reperfusion Catheter with Xtra Flex technology has not been tested for compatibility with other manufacturers' revascularization devices. The safety and effectiveness of combined use is unknown and could result in damage to the Penumbra JET 7 Reperfusion Catheter with Xtra Flex technology.**

Precaution: Use caution and slowly flush heparinized saline. If you see expansion of the Penumbra JET 7 Reperfusion Catheter with Xtra Flex technology, immediately discontinue use of the catheter.

Revision: Obtain a post-treatment angiogram by injecting contrast media through the guide catheter. Remove the Reperfusion Catheter from the guide catheter if necessary for adequate visualization.

They further state that the company had not received any reports of malfunction resulting in patient injury or death for the Penumbra JET 7 Reperfusion Catheter (without the Xtra Flex technology) or the ACE 68 Re perfusion Catheter in 2019 or 2020.

Assessment:

The malfunction seen with the Jet7 Flex catheters carries a very high risk of patient injury and death, and the mechanism of malfunction is poorly mitigated by labeling modifications. The catheters are utilized in very small diameter intracranial vessels with extremely tortuous anatomy, and with a risk of disruption which if it occurs causes catastrophic injury. The risk of dilatation of the Penumbra catheters is dissection, perforation, stroke and intracranial hemorrhage, any one of which could lead to death. Additionally, if the malfunctioning catheters dilate and are unable to be deflated, pullback to remove the catheters may do further damage along the path of the catheter as they are withdrawn to the sheath and out of the patient. Catheter rupture causes a very high pressure burst of saline ± contrast to be ejected from the catheter into the vessels. Again, dissection and perforation are possible, leading to occlusion or intracranial hemorrhage. These events are associated with stroke and loss of function, as well as death. Embolization of particulates and catheter materials may similarly cause mechanical trauma as well as vascular occlusion and stroke. All of these events are extremely difficult to remedy and all are possible sources of great morbidity and mortality.

Given the risk, and the common and standard practice of contrast injection through microcatheters, as well as saline injection alone through these catheters, it is unreasonable to believe that a labeling warning or contraindication will be enough to protect lives. For starters, the messages do not reach all intended users. Also, some of bench testing performed by physicians in videos provided by Quintessential Capital Management show the malfunction can occur with saline injection alone, not only with the more viscous saline/contrast mix. The risk of even one operator utilizing this method and having a malfunction with this mechanism of action is too great, because of the risk involved to patients.

Given the risk and severity of the events, it is highly likely that FDA will investigate for a possible recall.

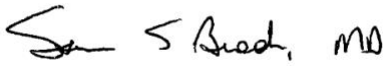
It is possible that one is underway now, but it would be confidential. It is also conceivable that FDA compliance activities are extremely delayed by the COVID pandemic, both in terms of the challenge to carry them out, but also because of the urgent public health threat that the FDA compliance department is currently investigating regarding COVID testing and adjunctive medical devices. If FDA were to undertake an investigation of Penumbra, which is likely given the high profile attention this problem is garnering, as well as the severely high risk due to the malfunctions themselves, it is very likely that a Class 1 recall will result. Penumbra will have performed a CAPA investigation, and to date has only

publicly suggested labeling mitigation. For the reasons stated above, a labeling mitigation is not adequate.

I am not a lawyer and would not be able to opine on the legality and liability of the company. However, given the publicly available data on the device malfunctions in the MAUDE database, the timing of deaths, the timing in relation to Penumbra's public letter, it is conceivable that they have placed themselves at considerable risk for liability for legal action.

Given the risk of complications which appear to be of much greater frequency with the Jet7 Flex catheter and the availability of competing technology, physicians are likely to change their adoption practices. Penumbra is at risk for a significant drop in sales of this catheter and possibly the entire line of catheters. Penumbra has also pointed to use of other manufactures equipment concurrently with the Jet7 Flex as a possible cause of complications, and therefore to use the catheter only with other Penumbra equipment. Due to the complexities of hospital purchasing and contracting, individual labs may not have access to the full Penumbra lineup, even if operators wanted to use the Jet7 Flex. This reality could further limit sales.

In conclusion, the Jet7 Flex catheter appears to have an important design flaw. While it passed premarket testing to achieve 510(k) clearance, the boundary conditions and test criteria did not reflect real world use, or the device was not developed to high enough tolerances for real world use. Regardless, the product has an extremely high safety risk that can result in stroke or death. Nothing short of not using the devices will fully protect patients for this risk. Pre-procedural inspection and in-factory visual inspection of the catheters are clearly not curtailing this risk. Labeling mitigations will not adequately penetrate to all operators and may be inadequate anyway. It seems highly likely that FDA will investigate this product, and if/when they do, it is likely that they will mandate a Class 1 recall. Penumbra's revenues are likely to be damaged by decreased sales and the possibility of legal action for their denials and misleading characterizations of the injuries and their inadequate responses in the face of the malfunctions.



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