HPA INC
HEALTH POLICY ASSOCIATES INC

HPA INC. REGULATORY OPINION

TO:	ENDOSHUNT INC.
FROM:	VIN BUCCI, SAM HENNESSEY, ANNIE KIM
SUBJECT:	REGULATORY OPINION OF ENDOSHUNT
DATE:	FEBRUARY 22, 2023
CC:	HPA REGULATORY FILE

BACKGROUND:

Endoshunt Medical, Inc. (hereinafter, "Endoshunt Inc.") has requested that Health Policy Associates Inc. located in Westwood, Mass. (hereinafter, "HPA Inc.") provide an opinion relating to the regulatory needs of a medical device known as Endoshunt. Endoshunt is a single use sterile endovascular shunt designed to temporarily staunch blood flow out of the inferior vena cava (IVC) or aorta through lacerations to the blood vessel, peripheral vessels, or solid organs, while continuing perfusion to the rest of the body. Indications for use include the emergency control of hemorrhage in patients whose blood pressure is difficult to compensate for with transfusions alone (but whose vitals are not at a point requiring immediate resuscitation) and whose nature of injury is known (either through imaging, surgical visualization, or a well-known injury pattern). The Endoshunt device allows trauma surgeons to shunt blood past hemorrhaging vessels endovascularly, allowing time for definitive repair with continued blood flow. The device features two self-expandable nitinol frames that allow the shunt to be deployed and retracted, each time expanding to its desired shape to push an ePTFE lining against the vessel walls, while also retracting into a P-Bax catheter. The resulting structure resembles an aortic stent graft. The overall shunt diameter is 2.5 cm upon full deployment, and the length of the shunt can be adjusted from 5 cm to 20 cm using a relative motion of the two frames. The device is inserted non-operatively through percutaneous femoral access and is deployed and retracted without a guidewire, allowing for deployment in under 30 seconds, following access. The endovascular shunt's temporary nature enables this rapid deployment, reducing the need for the surgeon to ensure precise placement in emergency situations.

Historically, hemorrhage control through intravascular occlusion as an early intervention to exsanguination has been largely beneficial and lifesaving. On a regulatory standpoint, a significant inflection point in 2016 (following FDA clearance of the ER-REBOA™ by Prytime Medical Inc., Boerne, TX) instituted a wider implementation of and clearance by FDA of devices in utilization of resuscitative endovascular balloon occlusion of the aorta

(REBOA)[1]. Following 2016, FDA became very familiar with the technology of REBOA devices through numerous 510(k) clearances. REBOA devices, however, presented complications of ischemia-reperfusion (IR) injury (exacerbation of cellular dysfunction and death following restored blood flow to previously blood-restricted tissue) to distal organs, and cerebral edema (swelling of brain from supra-physiologic blood pressure), both as result of full vascular occlusion[2]. Hence, application of REBOA has been discretionally modified by surgeons to perform "partial" or "intermittent" REBOA (cycling inflation-deflation to buy time and avoid prolonged ischemia) in lieu of full occlusion. Currently there is one medical device (pREBOA-PRO™ by Prytime Medical Inc., Boerne, TX) that is FDA-cleared for the performance of a partial-REBOA, through its intended design. The device achieves partial occlusion, reducing risk of IR injury; however, it does not fully control the hemorrhage.

The Endoshunt device is a succeeding approach to endovascular hemorrhage control which addresses the aforementioned limitations of both REBOA devices (IR injury and edema) and partial REBOA devices (no full occlusion of hemorrhage). The Endoshunt device allows both perfusion of the blood and full occlusion at the point of vascular laceration. Specifically, the device implements a targeted partial occlusion at the hemorrhaging vessel, where it is fully occluded at the vascular wall while also open for perfusion through an open lumen, mitigating risk of IR injury and cerebral edema. The Endoshunt device, like the pREBOA-PRO™ device, achieves a "partial intravascular occlusion" by description, however through different technological characteristics. The pREBOA-PRO™ device uses a bilobed balloon to achieve partial aortic occlusion which allows an off-load of proximal pressure by permitting low-volume distal blood perfusion around a secondary spinal lobe. In contrast, the Endoshunt device is unilobed and achieves partial occlusion by an open lumen for perfusion while fully occluding the hemorrhaging vascular wall.

REGULATORY OPINION:

FDA classifies medical devices into three regulatory classes (Class I, Class II, and Class III) based on the level of safety and effectiveness of the device. It is the opinion of HPA Inc. that Endoshunt will be categorized as a moderate risk, Class II device, according to FDA regulations that govern other endovascular aortic occlusion catheters (vascular clamp/percutaneous catheter for regulatory purposes).

FDA has for several years formally codified the regulation of all vascular clamps and percutaneous catheters in both regulation and internal policy. Vascular clamps and

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[1] Thrailkill, M.A., Gladin, K.H., Thorpe, C.R., Roberts, T.R., Choi, J.H., Chung, K.K., Necsoiu, C.N., Rasmussen, T.E., Cancio, L.C. and Batchinsky, A.I. (2021). Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA): update and insights into current practices and future directions for research and implementation. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, 29(1). doi:10.1186/s13049-020-00807-9.

[2] Necsoiu, C., Jordan, B.S., Choi, J.H., Moon, J.J., Espinoza, M.D., Gremmer, B.J., Batchinsky, A.I. and Cancio, L.C. (2021). Mitigating Ischemia-Reperfusion Injury Using a Bilobed Partial REBOA Catheter: Controlled Lower-Body Hypotension. *Shock*, [online] 55(3), p.396. doi:10.1097/SHK.0000000000001640.

percutaneous catheters are governed by FDA regulation 21 CFR Sec. 870.4450 and 21 CFR Sec. 870.1250, accordingly, which states,

Sec. 870.4450 Vascular clamp.

(a) Identification. A vascular clamp is a surgical instrument used to occlude a blood vessel temporarily.

(b) Classification. Class II (performance standards).

Sec. 870.1250 Percutaneous catheter.

(a) Identification. A percutaneous catheter is a device that is introduced into a vein or artery through the skin using a dilator and a sheath (introducer) or guide wire.

(b) Classification. Class II (performance standards).

FDA further defines these products under a specific "product code" system developed for all medical devices, which in the case of vascular clamps and percutaneous catheters, have been defined with the three (2) product code of "MJN" and "DQY".

The "MJN" product code is defined by FDA as:

(a) Device: Catheter, Intravascular Occluding, Temporary
(b) Class II

The "DQY" product code is defined by FDA as:

(a) Device: Catheter, Percutaneous
(b) Class II

These regulations and product codes, if confirmed applicable to Endoshunt by FDA, categorize the Endoshunt device as a Class II medical device per FDA regulation.

HPA is also aware FDA may classify the Endoshunt device as a vascular graft under 21 21 CFR Sec. 870.3450. Due to the technological difference between products classified under the product code MJN. However, regardless of the three letter code classification, the preclinical testing will likely be the same.

The "DSY" product code is defined by FDA as:

(a) Identification. A vascular graft prosthesis is an implanted device intended to repair, replace, or bypass sections of native or artificial

vessels, excluding coronary or cerebral vasculature, and to provide vascular accessClass II

(b) Classification. Class II (special controls).

Class II devices, most commonly, seek approval with FDA through a 510(k) submission by proving substantial equivalence (SE) to a predicate device that is currently on the market and approved by FDA. However, if there is no valid predicate device, novel devices with moderate risk by which general and special controls provide reasonable assurance of safety and effectiveness for the intended use, may seek approval through the De Novo pathway. The 510(k) review standard is comparative, whereas the De Novo review standards rely on an independent demonstration of safety and effectiveness.

In the case of Endoshunt, it is the opinion of HPA Inc. that an initial Pre-Submission (Pre-Sub) be the first step in the regulatory pathway. It is also the recommendation of FDA to consider submitting a Pre-Sub to obtain feedback from the appropriate premarket division, upon determination that there is no legally marketed device upon which to base a determination of substantial equivalence.

Pre-Submissions are made to FDA to request feedback prior to an intended submission. Pre-subs may prove to be highly valuable and strategic, if done properly, as they may provide clarification to questions, insight into potential hurdles for approval or clearance, and initiate early interaction with FDA about the product, which altogether contribute to a more transparent review process. Well-constructed Pre-Subs also improve the quality of subsequent submissions and have the potential to shorten total review times. Pre-Subs are submitted in the form of a formal written application whereby a meeting may also be requested. Feedback from FDA is provided in the form of a written response within 70 days from receipt of submission or 5 days prior to the scheduled meeting, whichever is sooner.

HPA believes the pREBOA-PRO™ device (K200459) is an appropriate predicate based on the FDA guidance document “Evaluating Substantial Equivalence in Premarket Notifications [510(k)]”. In order to find an appropriate predicate, the intended use of the product must be the same. Both the Endoshunt device and the pREBOA-PRO™ are intended to stop emergency hemorrhaging in vessels in order to allow repair of the vessel. Even though there are technological differences between the two products, bench testing allows Endoshunt to show there are no new questions of safety or effectiveness in this device. Please see the excerpt from the 510(k) guidance below.

(ii)(I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by the Secretary or a person accredited under section 523, that demonstrates that the

device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety and effectiveness than the predicate device.

The Pre-Sub will determine whether the pREBOA-PRO™ device (K200459) by Prytime Medical Inc. will suffice as an acceptable predicate device for 510(k) pathway or if FDA views this device as a vascular graft. It should also provide guidance on specific preclinical and clinical testing required to support pre-market clearance or approval application.

If FDA feedback from the Pre-Sub states validity of the pREBOA-PRO™ device (K200459) as a predicate device for 510(k) pathway, FDA will have 90 days to review and response with their decision, following submission. The 510(k) pathway will be the least burdensome pathway to market approval.

Alternatively, if FDA feedback from the Pre-Sub indicates a pathway via De Novo submission, FDA will have 150 days to review and response with their decision, following submission. It should be noted that the timeline for a De Novo clearance is often extended due to additional data or clarification requested by FDA. However, despite the prolonged timeline, working with FDA to determine the special controls and regulatory requirements for a new device category may be an advantageous opportunity for Endoshunt Inc. to set in place a competitive standard for subsequent market entry. Following a De Novo clearance, follow-on competitors would use your device as a predicate for future clearances. However, it is HPA's view that this device is not a De Novo device.

Basic Data Requirements

If FDA determines a De Novo submission is the appropriate regulatory pathway for Endoshunt (which we think unlikely), the data requirements will depend upon FDA feedback. On the other hand, if FDA determines a 510(k) is the appropriate pathway for Endoshunt which we think most likely, the basic data requirements will be quite clear. Endoshunt Inc. will be required to show that its medical device is "substantially equivalent" to the predicate device. The process by which a company determines the specific testing that is required is by referring to FDA's prior approval of the predicate device. These approvals are documented in the approval order which FDA issues for every 510(k) known as 510(k) "summaries".

In reviewing the "summary" for the pREBOA-PRO™ device (K200459), one can know with great certainty the precise data requirements for obtaining FDA approval for such a device.

Non-Clinical Testing - Performance (Bench) and Comparative Testing

The following performance *in vitro* bench testing are tests typical for a vascular product of this type and these tests would ensure that the Endoshunt device meets the applicable design and performance requirements throughout its shelf life, verifies conformity to applicable standards, and demonstrates substantial equivalence to the predicate system. While some of these tests will need to be slightly modified depending on final design of the product, the following list would likely reflect the bench testing FDA would expect to see for the Endoshunt product:

- Lumen Break Testing
- Lumen Expansion/Retraction Testing
- Simulated Use Testing in accordance with ISO 14971:2019.
- Torque Testing
- Kink Diameter Testing
- Fatigue Testing
- Freedom From Leakage Testing
- Tensile Strength Testing
- Dimensional Testing
- Shelf-Life Validation
- Human Factors/Usability Testing
- Sterilization Validation: In accordance with ISO 11135:2014 - Sterilization of health-care products- Ethylene oxide- Requirements for the development, validation, and routing control of a sterilization process for medical devices.
- EO/ ECH residuals evaluation in accordance with ISO10993-7:2008 – Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals
- Stability Testing (accelerated aging followed by seal integrity and seal strength testing)
- Packaging Testing (sealing process): Demonstrate that the proposed terminally sterilized packaging system allows sterilization, provides physical protection,

maintains sterility up to the point of use and allows aseptic presentation. In accordance with ISO 11607-1 – Packaging for Terminally Sterilized Medical Devices.

- Biocompatibility Testing: The patient-contacting (direct/indirect fluid path) components of the Endoshunt device should fulfill the requirements as set forth in ISO 10993: Biological evaluation of medical devices – Part 1: Guidance on selection of tests for and External Communicating Device, Circulating Blood, A-Limited (<24 hr) duration.
    - Cytotoxicity, Sensitization, Irritation/Intracutaneous Reactivity, Acute Systemic Toxicity, Hemocompatibility, and Material-Mediated Pyrogenicity.

Clinical Testing

The *in vivo* test below would be performed to demonstrate that the Endoshunt device meets applicable design and performance requirements and is therefore substantially equivalent to the predicate device:

- Performance evaluation of the Endoshunt device in the aorta of an acute Porcine model.

Regulatory Pathway and Timelines:

It is the opinion of HPA Inc. that the first step in regulatory pathway for Endoshunt Inc. be an initial Pre-Submission to FDA. The Pre-Sub will determine the subsequent regulatory pathway and timeline for the Endoshunt device. FDA feedback from the Pre-Sub is provided 70 days within receipt of submission or 5 days prior to the scheduled meeting, whichever is sooner.

Following the Pre-Sub, if FDA deems a 510(k) submission the appropriate regulatory pathway forward, FDA will have 90 days to review and response with their decision, following submission. Alternatively, if FDA deems a De Novo submission the appropriate regulatory pathway forward, FDA will have 150 days to review and response with their decision, following submission.

It should be noted, FDA can "stop" the 90-day or 150-day clock once the Agency issues an initial response to the company. In other words, FDA can ask for additional data or clarification of existing data while suspending the ongoing 90-day clock review period.

Summary

In closing, it is HPA Inc.'s assessment that Endoshunt Inc.'s Endoshunt device will be categorized as a moderate risk, Class II medical device. Per review of all previously FDA-cleared endovascular aortic occlusion catheters in the FDA database, the pREBOA-PRO™ (K200459) device by Prytime Medical Inc. has been identified as the most approximate device to the Endoshunt device, in its intended use. An initial Pre-Submission to FDA should be the first course of action, to determine the appropriate regulatory pathway forward: 510(k) pathway or De Novo pathway. If FDA approves the pREBOA-PRO™ (K200459) as a valid predicate device, Endoshunt will be permitted the 510(k) pathway and be subject to governance by FDA regulations 21 CFR Sec. 870.4450 Vascular Clamp and 21 CFR Sec. 870.1250 Percutaneous Catheter and product codes MJN (Catheter, Intravascular Occluding, Temporary) and DQY (Catheter, Percutaneous). In a 510(k) submission, the basic data requirements for clearance will be quite clear, as they are outlined in the 510(k) summary of the predicate device. FDA may also identify this under product code DSY (vascular graft), this would require a different predicate, however, would not change the bench testing requirements or change the timeline of the 510(k) submission. Alternatively, in the unlikely event FDA determines there is currently no valid predicate device for the Endoshunt device, market clearance will be sought through a De Novo submission, in which the special controls and regulatory requirements will be set forth by FDA in collaboration with Endoshunt Inc. The 510(k) pathway may be less burdensome (~90 days) with clear basic data requirements, but the De Novo pathway, though lengthier (~150 days), may provide a unique opportunity to set special controls with FDA for the device category and consequentially set a competitive standard in place for future competitors.