

# Guidance for Industry and FDA Staff

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## Coronary and Carotid Embolic Protection Devices - Premarket Notification [510(k)] Submissions

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Food and Drug Administration  
Center for Devices and Radiological Health**

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Division of Cardiovascular Devices  
Office of Device Evaluation**

# Preface

## Public Comments

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to <http://www.regulations.gov>. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

## Additional Copies

Additional copies are available from the Internet at: <http://www.fda.gov/cdrh/ode/guidance/1658.html>. You may also send an e-mail request to [dsmica@fda.hhs.gov](mailto:dsmica@fda.hhs.gov) to receive an electronic copy of the guidance or send a fax request to 240-276-3151 to receive a hard copy. Please use the document number (**1658**) to identify the guidance you are requesting.

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# Guidance for Industry and FDA Staff

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## Coronary and Carotid Embolic Protection Devices - Premarket Notification [510(k)] Submissions

*This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.*

### 1. Introduction

FDA has developed this guidance document to assist industry in preparing premarket notification submissions for Coronary and Carotid Embolic Protection Devices. These devices are designed to capture and remove embolic material that may be dislodged during the interventional treatment of carotid arteries or saphenous vein bypass grafts with the intention of reducing the incidence of adverse cardiac or cerebrovascular events. We recommend that members of industry and FDA staff who perform or review clinical and non-clinical evaluations and prepare labeling of coronary and carotid embolic protection devices should use this guidance.<sup>1</sup>

We recommend that you use this guidance to develop and apply clinical and non-clinical evaluation protocols, methods, and reports that support the safety and effectiveness of coronary and carotid embolic protection devices. You should also use this guidance to develop labeling for these devices. We intend to use this guidance to review clinical and non-clinical evaluation protocols, methods, data, and reports provided in 510(k) submissions to demonstrate the substantial equivalence of coronary and carotid embolic protection devices.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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<sup>1</sup> The terms “you” and “your” in this document refer to members of industry, also known as sponsors or applicants. The terms “we,” “us,” and “our” refer to FDA.

## **The Least Burdensome Approach**

The issues identified in this guidance document represent those that we believe should be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the “A Suggested Approach to Resolving Least Burdensome Issues” document. It is available on our Center web page at: <http://www.fda.gov/cdrh/modact/leastburdensome.html>.

## **2. Background**

A manufacturer who intends to market a device of this generic type should conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the Act), including the premarket notification requirements described in [21 CFR 807](#) Subpart E, and obtain a substantial equivalence determination from FDA prior to marketing the device. (See also [21 CFR 807.81](#) and [807.87](#).)

This guidance document identifies the classification regulation and product codes for coronary and carotid embolic protection devices (refer to **Section 4: Scope**). In addition, other sections of this guidance document provide additional information to manufacturers on addressing risks related to these devices in premarket notification submissions (510(k)s).

This document supplements other FDA documents regarding the specific content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87 and "**How to Prepare a 510(k) Submission**" on FDA Device Advice at <http://www.fda.gov/cdrh/devadvice/314.html>.

Under “**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**,” <http://www.fda.gov/cdrh/ode/parad510.html>, a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA has issued a guidance document addressing that device. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

## **3. The Content and Format of an Abbreviated 510(k) Submission**

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should

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describe how you may have used this guidance document during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of section 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

### **Coversheet**

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this guidance document.

### **Proposed Labeling**

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. Please refer to **Section 11: Labeling** for specific information that should be included in the labeling for coronary and carotid embolic protection devices covered by this guidance document.

### **Summary Report**

We recommend that the summary report contain the following:

#### **Description of the device and its intended use**

We recommend that you describe the performance specifications and, when appropriate, include detailed, labeled drawings of the device. Please refer to **Section 5: Device Description** for specific information that we recommend you include in the device description for coronary and carotid embolic protection devices of the types covered by this guidance document. You should also submit an “indications for use” enclosure.<sup>2</sup>

#### **Description of device design**

We recommend that you include a brief description of the device design requirements.

#### **Identification of the risk analysis method**

We recommend that you identify the risk analysis method(s) you used to assess the risk profile, in general, as well as the specific device’s design and the results of this analysis. Please refer to **Section 6: Risks to Health and Mitigation Measures** for the risks to health generally associated with the use of coronary and carotid embolic protection devices that FDA has identified.

#### **Discussion of the device characteristics**

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<sup>2</sup> Refer to <http://www.fda.gov/cdrh/ode/indicate.html> for the recommended format.

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We recommend that you discuss the device characteristics that address the risks identified in this guidance document, as well as any additional risks identified in your risk analysis.

### **Description of the performance aspects**

We recommend that you include a brief description of the test method(s) you have used or intend to use to address each performance aspect identified in **Sections 7- 10** of this guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.<sup>3</sup> (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

### **Reliance on standards**

If you choose to rely on a recognized standard for any part of the device design or testing, you may include either of the following:

- a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed; or
- a declaration of conformity to the standard.<sup>4</sup>

Because a declaration of conformity is based on results from testing, we believe you cannot properly submit a declaration of conformity until you have completed the testing the standard describes. For more information, please refer to section 514(c)(1)(B) of the Act and the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA.**<http://www.fda.gov/cdrh/ode/guidance/1131.html>.

If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(1), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

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<sup>3</sup> If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

<sup>4</sup> See **Required Elements for a Declaration of Conformity to a Recognized Standard** (Screening Checklist for All Premarket Notification [510(k)] Submissions), <http://www.fda.gov/cdrh/ode/reqrecstand.html>.

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As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

The following is a specific discussion of how you should apply this guidance document to 510(k)s for coronary and carotid embolic protection devices.

### **4. Scope**

This guidance document addresses coronary and carotid embolic protection devices. Typically, the embolic protection device is deployed proximal or distal to a lesion (narrowed portion of the vessel) prior to other intervention taking place, such as balloon angioplasty or stenting. The embolic protection device is intended to prevent debris generated by the intervention from traveling downstream in the coronary or carotid circulation where it could impede flow partially or fully in smaller vessels, leading to damage to the myocardium or to neurological impairment. These devices are classified as percutaneous catheters (21 CFR 870.1250).

The scope of this guidance includes embolic protection devices used along with other interventional devices (e.g., stents or angioplasty balloons) for the treatment of:

- diseased saphenous vein grafts (SVGs) in patients with stable ischemic coronary artery disease; and
- diseased carotid arteries that could potentially contribute to strokes or other neurological adverse events.

The scope of this document is limited to the devices shown in **Table 1** below.

**Table 1: Classification and Product Codes of Coronary and Carotid Embolic Protection Devices Addressed in this Guidance**

Classification Regulation (21 CFR)	Class	Product Code	Description
870.1250	II	NFA, device, coronary saphenous vein bypass graft, temporary, for embolization protection	Temporary device intended for placement in a coronary saphenous bypass graft for the purpose of providing embolization protection.
870.1250	II	NTE, catheter, carotid, temporary, for embolization	Temporary device intended for placement in a native carotid artery for the purpose of

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		capture	providing embolization protection.
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This guidance also cites a number of voluntary standards, many of which are recognized by FDA. You may access a list of the FDA-recognized standards from the CDRH web site, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>. See also the guidance, **Recognition and Use of Consensus Standards**, <http://www.fda.gov/cdrh/ost/guidance/321.html>.

This document does not address thrombectomy devices or embolic protection devices used for peripheral indications other than in the carotid vasculature. You should contact the Peripheral Vascular Devices Branch in the Division of Cardiovascular Devices for information about embolic protection devices used in peripheral indications outside the carotid arteries.

## 5. Device Description

We recommend that you identify your device by the regulation and product code described in **Section 4. Scope**, that you describe the device characteristics and performance specifications, and that you include detailed, labeled drawings of the device. We recommend that you describe the method of operation for the device. You should also provide a comparison between your device and the predicate device(s) to which you claim substantial equivalence that covers the relevant device attributes such as device design, size, materials, indications for use, and principle of operation.

## 6. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the coronary and carotid embolic protection devices addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. We recommend that you also conduct a risk analysis, before submitting your 510(k), to identify any other risks specific to your device and include the results of this analysis. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, then you should provide sufficient detail to support the approach you have used to address that risk.

FDA encourages manufacturers of embolic protection devices to work with FDA early in your product development, especially if your device incorporates novel technology or you plan to conduct a non-traditional clinical study. The Interventional Cardiology Devices Branch and Peripheral Vascular Devices Branch are available to discuss non-clinical test protocols and clinical trial designs for embolic protection devices through the Pre-IDE process.<sup>5</sup>

**Table 2: Risks to Health for Coronary and Carotid Embolic Protection Devices**

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<sup>5</sup> For additional information regarding the Pre-IDE process, please refer CDRH Device Advice, [http://www.fda.gov/cdrh/devadvice/ide/approval.shtml#pre\\_ide](http://www.fda.gov/cdrh/devadvice/ide/approval.shtml#pre_ide) and ODE Blue Book Memorandum D99-1, <http://www.fda.gov/cdrh/ode/d99-1.pdf>.

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<b>Identified Risk</b>	<b>Recommended Mitigation Measures</b>
<b>Tissue and Blood Damage</b>	Section 7. Biocompatibility
<b>Device Failure</b>	Section 8. Bench Testing
<b>Embolization</b>	Section 9. Animal Assessment Section 10. Clinical Information
<b>Vessel Damage</b>	Section 9. Animal Assessment Section 10. Clinical Information
<b>Infection</b>	Section 11. Sterilization and Shelf-Life

## 7. Biocompatibility

FDA recommends that you conduct biocompatibility testing as described in the FDA-modified **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing** (<http://www.fda.gov/cdrh/g951.html>) for external devices in contact with the circulating blood for a limited duration (less than 24 hours). We recommend that you select biocompatibility tests appropriate for the duration and level of contact with your device. If identical materials and identical material processing are used in a predicate device with the same type and duration of patient contact, you may identify the predicate device in lieu of providing biocompatibility testing.

For biocompatibility testing conducted using extraction samples, we recommend that you:

- determine the appropriate amount of test material as outlined in **ISO 10993-12 (Biological Evaluation of Medical Devices: Sample Preparation and Reference Materials)** or an equivalent method, using surface area to extractant volume ratios (mass to extractant volume ratios should only be used if surface area cannot be calculated);
- use both polar and nonpolar extractants;
- describe the condition of the extraction vehicle (e.g., color, presence of any particles);
- explain any changes in the post-extraction vehicle (compared to pre-extraction); and
- describe the details of storage conditions, if applicable.

If extraction samples are not used immediately, we recommend that you follow the storage conditions described in **ISO 10993-12** or an equivalent method. We also recommend that you explain how storage does not affect your test results.

FDA recommends that your biocompatibility test regimen incorporate the elements discussed below.

### **Cytotoxicity**

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We recommend that vehicles include both mammalian cell culture media (MEM) and 5% serum, as these materials will allow for extraction of both polar and nonpolar constituents from the test sample.

### **Sensitization (Guinea Pig Maximization Method)**

We recommend either that you run concurrent controls, or that the test laboratory run controls within 3 months of the test samples. We also recommend you provide protocols and results from positive control testing to confirm that you used the same methods for both the positive control testing and the test samples and to demonstrate that the methods continue to be capable of detecting a positive sensitization response.

You can conduct local lymph node assay (LLNA) testing as an alternative to guinea pig maximization testing to assess sensitization.

### **Hemocompatibility**

For blood-contacting devices (regardless of contact duration), we recommend that you consider hemolysis, immunology (complement activation), and *in vivo* thromboresistance.

Immunology testing should appropriately address the various complement activation pathways. We recommend that you assess *in vitro* C3a and SC5b-9 fragment activation using standard testing methods, such as those outlined in **ASTM F2065-00e1 (Standard Practice for Testing for Alternative Pathway Complement Activation in Serum by Solid Materials)** and **ASTM F1984-99 (2003; Standard Practice for Testing for Whole Complement Activation in Serum by Solid Materials)**, or an equivalent method. Alternatively, you may provide a rationale for omitting this testing, if all the materials used in the formulation and processing of the device have a history of previous use in blood-contacting devices with similar contact duration.

In addition, you may assess *in vivo* thrombogenicity during preclinical animal testing in lieu of a separate canine *in vivo* thrombogenicity test.

### **Material-mediated Pyrogenicity**

We recommend that you assess pyrogenic responses to chemical leachants over the duration of device contact with the patient using a standard method, such as those described in **USP 30 <151> Rabbit Pyrogen Test**. We also recommend that you assess material-mediated pyrogenicity using traditional biocompatibility extraction methods, such as 50°C for 72 hours, 70°C for 24 hours, or 120°C for 2 hours).

### **Endotoxin-Mediated Pyrogenicity**

We recommend that you consider pyrogenic responses to gram-negative bacterial endotoxin using a standard method, such as those outlined in the **USP 30 <85> Bacterial Endotoxin Limulus Amoebocyte Lysate (LAL) Test**, or an equivalent method. We recommend that your specifications include the test procedure and acceptance criteria for endotoxins. All blood-contacting cardiovascular devices and combination products should be pyrogen-free.

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Pyrogenicity testing is used to help define limits to protect patients from the risk of febrile reaction.

## **8. Performance Characteristics/Bench Testing**

We recommend that bench testing demonstrate device durability and adequate performance/handling characteristics based on the device description and the indications for use as described in the instructions for use. We recommend that you provide complete test reports that include presentation of the test results, the test methods, predetermined acceptance criteria, study analysis, and a discussion of the results and conclusions drawn from the studies. You should describe the clinical relevance of the acceptance criteria for each bench test and explain why the test results demonstrate acceptable clinical performance of your device. Test conditions should simulate the worst-case conditions that your device is likely to encounter during clinical use.

We recognize that there is variation in the design of embolic protection systems. In designing a bench testing plan for an embolic protection system, you should address the specific risks and performance characteristics for your device. We recommend that you evaluate the device attributes/performance characteristics described below in your bench testing regimen. If you believe that a recommended test is not necessary for your device, you should provide a scientific rationale for each recommended test that you do not conduct. You should also conduct any additional testing that your risk analysis identifies as necessary to fully mitigate the device-related risks, even if this document does not identify these tests. If you modify the design of your device, we recommend that you conduct a new risk analysis based on the modified device design.

### **1. Embolic Capture Efficiency and Retrieval Ability**

#### Significance

The amount of embolic debris captured and the efficiency of debris removal from the patient determines how much embolic material migrates downstream to the end organ.

#### Recommendation

We recommend that you quantitatively assess the ability of your device to contain embolic debris during simulated clinical use. Your assessment should compare the amount of debris captured by your device to the amount of debris available for capture (typically the total amount of embolic material introduced into your test system). You should specify the composition and size distribution of the simulated embolic material and explain its clinical relevance. If your simulated embolic material includes particles of different sizes, you should stratify your capture efficiency results according to particle sizes or size ranges.

We also recommend that you quantify how much of the captured embolic debris is liberated during retrieval and withdrawal of the filter element. To simulate worst-case clinical conditions, the filter element should be completely full of embolic material when conducting this assessment.

### **2. Stent Compatibility**

#### Significance

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If the target lesion is stented, the embolic protection device should be able to be tracked proximally through the stented region and retrieved successfully without entanglement with or damage to the deployed stent.

### Recommendation

For embolic protection devices designed for deployment distal to the target lesion, we recommend that you demonstrate that the embolic protection device can be tracked proximally through a deployed stent or series of stents and retrieved without entanglement or other complication. Overlapping stents should be used if you expect your device to be used in this configuration, based on your risk analysis. If your device is filter-based, you should conduct this test using a full filter element to simulate worst-case clinical conditions. You should examine the embolic protection device as well as the stent(s) after testing for any evidence of damage, such as coating delamination and strut fractures.

If your device is indicated for use during intervention in previously stented vessels, you should also demonstrate that your device can be tracked distally through a previously deployed stent or series of stents without complication. You should use drug-eluting stents in this assessment if your embolic protection device is indicated for use during saphenous vein graft intervention.

### **3. Simulated use**

#### Significance

The operator should be able to prepare and use the embolic protection device without difficulty. A benchtop model for simulated use assessment allows for data reproducibility and comparability of results obtained using different devices.

#### Recommendations

FDA recommends that you evaluate the ability to prepare, deliver, and withdraw the embolic protection device under conditions that simulate as closely as possible the clinical setting without difficulty or damage to the device. Your evaluation should include performance assessment of key attributes that represent the ease or difficulty involved in using your embolic protection device. Examples of key attributes include the following:

- ease of preparing the embolic protection device for use;
- compatibility of the embolic protection device with appropriate accessory devices, such as guidewires, stent delivery systems, and balloon catheters;
- ability to advance/retract the embolic protection device;
- ability to deploy and collapse any protective elements, such as filters or balloons;
- ability to completely withdraw the embolic protection device after the procedure; and
- ability to visualize the embolic protection device under fluoroscopy.

Evaluation of these key attributes should include a scoring system or another quantitative method, and should involve multiple users. Any test fixture that you use should mimic the target anatomy. You should provide a schematic of the test fixture(s) and explain how the fixture(s) simulate worst-case patient anatomy.

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If you identify the need for any special steps involving device preparation or usage as a result of simulated use testing, you should incorporate these steps in the device labeling or training program (if any).

### **4. Deployment/retrieval forces**

#### Significance

The operator typically applies force to the catheter in order to deploy or retrieve the embolic protection device. Excessive deployment or retrieval forces may make the device difficult to operate and can lead to vascular adverse events.

#### Recommendation

We recommend that you quantify the maximum force required to completely deploy or retrieve your embolic protection device during simulated clinical use. Any test fixture that you use should mimic the target anatomy. You should provide a schematic of the test fixture(s) and explain how the fixture(s) simulate worst-case patient anatomy.

### **5. Filter capacity**

#### Significance

The amount of embolic debris that a filter-based embolic protection system can capture is limited by the size of the filter element. A full filter basket can no longer capture embolic debris and may prevent anterograde blood flow within the vessel, potentially leading to ischemia of downstream organs or less efficient embolic capture.

#### Recommendation

We recommend that you quantify the maximum amount of embolic material that your device is expected to capture. We also recommend you measure this parameter experimentally using bench testing data.

### **6. Resistance to filter rupture during removal of a fully loaded filter**

#### Significance

Retrieval of a filter-based embolic protection device has a risk of filter rupture and subsequent release of captured embolic material. Embolic protection systems should be able to be retrieved without damage to the filter element and excessive release of embolic debris.

#### Recommendation

We recommend that you demonstrate that a completely full filter basket can be retrieved under simulated clinical conditions without filter rupture, catheter damage, or other adverse device effect. This assessment may be combined with the assessment described in **2. Stent Compatibility** above.

### **7. Flow characteristics**

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### Significance

A deployed embolic protection device may have an adverse effect on blood flow. For filter-based devices, blood flow perturbation as a result of filter placement could adversely affect embolic capture or damage the surrounding endothelium. For balloon-based devices intended to occlude the treatment vessel, lack of complete vessel occlusion can result in incomplete embolic capture.

### Recommendation

We recommend that you characterize fluid flow in a simulated vessel after activation/deployment of your embolic protection system. You should explain why the observed flow characteristics are clinically acceptable. If you expect flow characteristics to vary depending on vessel geometry, such as in a straight versus a curved vessel segment, you should conduct additional assessments that span the range of anticipated vessel geometries.

## **8. Radial outward force**

### Significance

It is important to characterize the radial outward force of self-expanding embolic protection devices. Excessive radial force could injure the surrounding tissue, while a radial force that is too low can result in incomplete apposition of the device to the vessel wall.

### Recommendation

We recommend that you measure the radial force exerted by the embolic protection device against the vessel wall as a result of device expansion. If a particular device size or model is indicated for use in a range of vessel sizes, your assessment should cover the range of possible vessel sizes, or should include a rationale for not assessing the entire indicated size range.

## **9. Tip flexibility**

### Significance

The distal tip of catheter-based devices can cause vessel dissection or perforation if the tip does not buckle sufficiently when force is applied.

### Recommendation

We recommend that you quantify the minimum amount of force needed to deflect the tip of your embolic protection device as well as any bundled accessory devices (such as guidewires) that may be traumatic to the vasculature. You should provide a rationale for the critical test parameters you select, such as the location(s) at which the force is applied and the extent to which the tip is deflected at the time of force measurement. We recommend that the device configuration used for this assessment incorporate any accessory devices that may affect the tip stiffness.

## **10. Tensile Strength**

### Significance

Embolic protection devices should be able to be manipulated axially without failure of any joints or bonds, which could lead to device failure and device embolization.

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### Recommendation

We recommend that you assess the tensile strength of all key bonds and joints in your embolic protection device. Each bond and joint should be tested individually, unless you provide a scientific rationale for why multiple bonds or joints can be tested without affecting the validity of the results.

## **11. Torque Strength**

### Significance

Embolic protection devices should be able to be manipulated circumferentially without failure of catheter shaft integrity or any bonds, which could lead to device failure and device embolization.

### Recommendation

We recommend that you assess the torque strength of the catheter shaft and all key bonds in your embolic protection device. The catheter shaft and all bonds should be tested individually, unless you provide a scientific rationale for why multiple device elements can be tested without affecting the validity of the results.

## **12. Torque Response**

### Significance

Application of torque to the proximal end of a catheter-based device can potentially result in uneven or incomplete force transmission to the distal end. Potential adverse effects of inadequate torque response include lack of torque transmission to the distal end of the device, or severe “whipping” or abrupt and uncontrolled distal rotation due to the buildup of torque that can potentially result in vascular trauma.

### Recommendation

We recommend that you demonstrate that application of proximal torque results in adequate torque transmission to the distal end of your device. Your results should demonstrate that the distal end of the device experiences a satisfactory torque response after application of torque to the proximal end, and that guidewire and/or catheter whip will not be clinically significant.

## **13. Kink resistance**

### Significance

Tracking the embolic protection device through tortuous vascular anatomy can result in permanent deformations within the device. These deformations may result in device failure or other adverse clinical effects.

### Recommendation

We recommend that you demonstrate that your embolic protection device and any bundled accessory devices (such as guidewires) can be tracked to the target location under simulated clinical conditions without undergoing permanent deformation. Your test apparatus should mimic the size and tortuosity of the vasculature through which the device will be tracked

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clinically. Alternatively, you may conduct this assessment by subjecting your device to bending deformations using cylindrical mandrels that simulate the most extreme radius of curvature that you expect your device will encounter clinically without permanent deformation.

### **14. Occlusion balloon characteristics**

#### Significance

Balloon failure can result in unintended balloon deflation or injury to the treated vessel or downstream organ, therefore, the performance of the occlusion balloon components of embolic protection devices should be sufficiently characterized.

#### Recommendation

We recommend that you characterize the performance of any balloon components of your embolic protection device. You should characterize the following performance attributes:

- balloon compliance (balloon diameter vs. inflation pressure),
- balloon burst pressure,
- inflation/deflation time, and
- balloon fatigue.

See also **Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems**<sup>6</sup> for additional guidance on evaluation of the performance of catheter-based balloons.

### **15. Dimensional verification**

#### Significance

The size of embolic protection devices affects the size and location of the vessels in which they can effectively be used, therefore, it is important that all dimensions are accurately characterized.

#### Recommendation

We recommend that you measure and report all clinically relevant dimensions for your device to verify that these dimensions conform to your design specifications.

### **16. Catheter coating integrity**

#### Significance

Embolic protection devices incorporating surface coatings, such as those intended to increase lubricity or decrease thrombogenicity, are at risk for loss of coating integrity due to frictional forces generated by blood flow and device manipulation. Coating delamination can lead to loss of coating functionality and embolization of coating particulates.

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<sup>6</sup> <http://www.fda.gov/cdrh/ode/guidance/1545.pdf>

## *Contains Nonbinding Recommendations*

### Recommendation

We recommend that you characterize the resistance of your device coating to delamination. As part of this characterization, you should measure the number and size distribution of particulate matter generated during simulated clinical use. You should provide a scientific rationale for the test setup and the acceptance criteria for this test. You should also inspect the embolic protection device after testing for signs of focal areas of delamination. Additionally, you should characterize the performance or activity of the coating before and after particulate generation testing to ensure that coating functionality is not lost during simulated clinical use.

## **17. Electromagnetic compatibility**

### Significance

Electrically powered devices may interfere with other powered devices when active, therefore, it is important to characterize the electromagnetic compatibility of any electrically powered devices.

### Recommendation

If your device is electrically powered, we recommend that you demonstrate that your device can be operated without any interference to or from other powered devices. We recommend that you conduct this assessment as described in **EN 60601-1 (General Requirements for Safety)**, **EN 60601-1-1 (Safety Requirements for Medical Electrical Systems)**, **EN 60601-1-2 (Electromagnetic Compatibility – Requirements and Tests)**, or equivalent methods.

## **18. Software Validation**

### Significance

Devices that rely on software for operation may not function properly if the software has not been appropriately designed and tested.

### Recommendation

If your device incorporates any software, you should demonstrate that the software component has been appropriately validated. We recommend that you conduct this assessment following the recommendations in FDA's **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices**.<sup>7</sup>

## **9. Animal Assessment**

We recommend you conduct testing in animals to demonstrate preliminary device safety prior to initiating clinical studies in humans. We recommend that you evaluate coronary and carotid embolic protection devices in an animal model with acute and chronic observation timepoints, and that you provide this information in the 510(k) submission. We recommend that you consider the following points when conducting non-clinical animal testing of coronary and carotid embolic protection devices.

### **1. Animal Model**

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<sup>7</sup> <http://www.fda.gov/cdrh/ode/guidance/337.pdf>

## *Contains Nonbinding Recommendations*

The animal model for your study should mimic as closely as possible the anatomy in which your embolic protection device will be used clinically.

### For embolic protection devices indicated for use in saphenous vein grafts

We recommend that your animal studies use challenging arterial vessels that reasonably simulate the size and shape of saphenous vein grafts, such as swine carotid arteries and larger coronary arteries.

### For embolic protection devices indicated for use in carotid arteries

FDA does not consider the porcine carotid anatomy to be as tortuous as human carotid artery anatomy. Therefore, we recommend that you use another, more tortuous segment of the porcine anatomy for evaluation of device handling characteristics and vascular trauma, such as the subclavian vasculature. It may be appropriate, however, to evaluate other characteristics of your device, such as placement accuracy, in the porcine carotid anatomy.

## **2. Study Protocol**

We recommend that your animal studies follow Good Laboratory Practices (GLP) or are GLP-like in quality. You should refer to 21 CFR Parts 58 and 812 for additional information on reporting requirements for animal studies.

Your study protocol should mimic, as closely as possible, a coronary or carotid interventional procedure in a human, including introduction, deployment, and retrieval of the embolic protection device, as well as the use of a stent system or balloon catheter if you expect that these devices will also be used. All study variables, including selection of device models, and implantation location, should represent worst-case clinical conditions, and you should support your selections with an appropriate rationale. In addition, you should provide a rationale for the number of animals and devices used in the study.

Your protocol should specify whether the animal will be placed on a mechanical ventilator or allowed to breathe spontaneously. FDA recommends that you allow the animals to breathe spontaneously because mechanical ventilation may limit the operator's ability to ascertain neurological dysfunction during the procedure.

The studies should use the actual device models proposed for use in the clinical setting, including any delivery and retrieval catheters. The studies should include a reasonable representation of all device sizes, and the device-to-artery size ratios should span the range proposed for clinical use.

We recommend that you evaluate the use of your device when overlapping stents are implanted, if your device is indicated for use in this situation.

We recommend that you simulate embolic debris using a thrombosis model rather than using resin or other solid material. Solid particles, such as polyvinyl alcohol, may not be an appropriate model for thrombus because thrombus is more friable and more likely to release when the device is collapsed for retraction. We recommend you address whether the embolic material model used reflects device performance in the clinical setting by providing a scientific rationale for the number, size distribution, and composition of the particles chosen.

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Because procedure time can affect patient outcomes, we recommend that the minimum device deployment time used in your animal study reflects the worst-case device deployment time expected in actual clinical use.

You should explain the method by which you determine whether the embolic protection device was deployed at the intended vascular location.

### **3. Study Endpoints**

You should assess the potential for your device to provoke an inflammatory response or injure the surrounding vasculature, and ensure that downstream organs are not adversely affected by the use of your device. To this end, pathology evaluations performed on necropsied animals should include a gross pathological assessment of the relevant end organ (heart or brain) and a careful histological examination of the segment where the embolic protection device was deployed. Your assessment should include evaluation of vessel injury and inflammation in the animals followed for both acute and long term assessments (described below). You should also evaluate the neointimal response in animals evaluated for chronic performance. The descriptive pathology of the vascular inflammation and injury should incorporate the use of a validated grading scale, and you should explain the criteria for each grade. The study report should include the full pathology report, providing line listings and clear copies of photographs and photomicrographs.

We recommend that the pathology studies include observations from 2 interventions in each of 4 - 6 animals at 24 to 72 hours post-treatment for acute assessments and at 1 month post-treatment for longer-term assessments. If healing is not complete at 1 month post-treatment or if your device design differs significantly from legally marketed device designs, FDA may recommend you collect 6 months animal data to demonstrate that the use of the device does not cause any long term effects.

Your studies should include assessments of the potential to cause hemolysis over the course of the procedure. Examples of appropriate endpoints for this assessment include changes in red blood cell count, plasma-free hemoglobin, and/or haptoglobin levels.

Your study should demonstrate that a device containing embolic material can be removed without damage to the device, vessel, and/or a series of stents consistent with its intended use as described in the labeling. This assessment should be conducted using a full filter basket to mimic worst-case clinical conditions. You should observe the position of the implanted stent(s) following deployment of the embolic protection device. In addition, you should assess damage to both the implanted stent and the embolic protection device. FDA recommends the use of radiological methods to assess damage to the implanted stent because this method will still allow a histological analysis at the same site.

Some filter-based devices may be designed to be only partially retracted into a sheath after deployment and embolic capture and prior to removal. We recommend that your submission indicate the extent of retraction of the device necessary for removal. If the device's instructions for use specify that the device should be fully retracted before removal, we recommend you conduct this assessment using both partially and fully retracted filters to simulate worst-case clinical conditions in which the filter cannot be fully retracted due to filter overload.

Angiographic assessment during procedures should include evaluation of blood flow rate, thrombus formation, and vessel injury.

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During the procedure, you should assess the handling characteristics and visibility of the embolic protection device in as quantitative a manner as possible. You may wish to compare these device characteristics to those of a legally marketed predicate device. For carotid embolic protection devices, you should record any behavioral changes or other neurological abnormalities observed in the treated animals.

Your studies should include targeted observation of potential damage to the embolic protection device and deployed stent(s), including high-quality gross images of these devices. You should also assess the extent of thrombus formation on the embolic protection device after use. In addition, you should identify any locations that appear to be damaged or thrombogenic, and provide magnified images of these regions.

### **4. Data Presentation**

To facilitate FDA review of your animal studies, we recommend a tabular format that provides an overview of all the studies you conducted and a separate table for each study that summarizes the study objectives, methods, and results. We recommend that you include high-quality photographs of the images used for your analyses and high-resolution electronic copies of these images. In addition, you should include electronic files that contain the line listing (individual) data used for your analyses.

You should provide the full animal study report as well as signed copies of any pathology reports from your studies. In addition, you should account for all animals proposed for use in the study, including those that died prior to the study procedure.

## **10. Clinical Information**

In accordance with the Act, the agency will rely upon well-designed bench and/or animal testing rather than requiring clinical studies for new devices unless there is a specific justification for asking for clinical information to support a determination of substantial equivalence. However, FDA has found that animal and bench testing of embolic protection devices is generally not adequate to demonstrate the substantial equivalence of these devices due to a number of factors. First, *in vitro* model flow characteristics may not provide an adequate representation of *in vivo* conditions. Second, ideal animal models do not exist for diseased SVGs and carotid arteries. Third, there is no proven model for generating embolic material for use in bench and animal testing. Finally, animal and bench testing may not fully characterize embolic protection devices that differ in their fundamental technology from predicate devices. These differences may have unpredictable effects on procedural success and complication rates. Thus, while satisfactory animal and bench testing results are needed to establish preliminary safety before initiating clinical trials, data from appropriately designed clinical trials are generally necessary to establish substantial equivalence to a legally marketed device.

Clinical data may not be necessary to support minor changes to the device, such as design changes to the EPD catheter shaft proximal to the distal tip. In such cases, bench and/or animal data may be sufficient to demonstrate substantial equivalence. If you believe that clinical data are not needed to demonstrate substantial equivalence for your device, you should provide a scientifically based rationale for why clinical data are not necessary in your 510(k) submission.

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We recommend that you contact either the Interventional Cardiology Devices Branch or the Peripheral Vascular Devices Branch to discuss your proposed testing plan for coronary and carotid embolic protection devices, respectively.

For both coronary and carotid indications, the target patient population may be heterogeneous and difficult to characterize using a standard set of measurable risk factors. Variability in procedure-related and adverse event outcome rates has been reported in the literature<sup>8</sup> across a range of embolic protection devices, including devices studied using similar patient populations. Some risk factors for adverse events have been characterized, such as SVG age, carotid artery tortuosity, and lesion length, but the association between many other variables and clinical outcomes is less well understood. Because it may be difficult to predict the risk of complications for a particular patient population or lesion subset, the baseline clinical and lesion characteristics become important considerations and underscore the importance of selecting an appropriate control group or performance goal.

There are several approaches to designing a clinical investigation for a new coronary SVG embolic protection system. One approach is a single-arm study using historical controls. This approach may be ideal for a first-generation device trial when there is an appropriate historical control group available for comparison and the IDE sponsor has full access to patient-level data for the control group. With access to such a comparative data set, you should employ appropriate clinical and statistical methodologies in order to minimize in any comparison the effects of possible confounding or bias.

When designing a clinical investigation for a coronary embolic protection device, you should consider the need to identify which patients benefit most from embolic protection, particularly given potential interactions between a newly developed embolic protection device and baseline disease and/or lesion characteristics. If you cannot identify an appropriate control group with access to patient-level data (as may be the case if you are seeking a new indication), FDA recommends the use of randomized, controlled trials in order to be able to clearly compare treatment and control group results.

Single-arm studies employing historical controls may be appropriate for assessing clinical performance of a second-generation coronary embolic protection device and/or modifications to a currently marketed device, provided the modified device is sufficiently similar to the first-generation device. Examples of minor design changes for which a single-arm study may be appropriate are modifications to the distal end of a device, or introduction of smaller/larger sizes of the same device design.

Carotid embolic protection devices are frequently studied clinically in conjunction with carotid stent systems that are also investigational.<sup>9</sup> Single-arm studies involving comparisons to either a retrospective control group or a performance goal derived from previously reported clinical data are able to generate sufficient safety and effectiveness data to support certain carotid stenting indications, and it may be impractical to include an active control for the embolic protection device alone in these studies. However, clinical data from a randomized, controlled trial may be

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<sup>8</sup> Mauri et al., *Circulation* 113:2651 – 2656 (2006)

<sup>9</sup> Carotid stents are Class III devices, requiring Premarket Approval.

## *Contains Nonbinding Recommendations*

appropriate if your device incorporates indications, technology, or a design that differs significantly from those of currently marketed devices.

### **Clinical Protocol Recommendations for All Indications**

Clinical studies conducted in the United States in support of 510(k) clearance must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. FDA believes that coronary and carotid embolic protection devices addressed by this guidance document are significant risk devices as defined in 21 CFR 812.3(m). Such studies require an FDA-approved IDE (21 CFR Part 812) and sponsors must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

You should conduct your study using a number of patients that provides sufficient statistical power for the primary study endpoint. FDA recommends that your patient population be larger than the minimum statistically based sample size to account for patients that withdraw from the study or are lost to follow-up over time. FDA recommends that all follow-up visits consist of office visits. Telephone follow-up may not allow you to fully assess the incidence of all primary and secondary endpoint events.

You should capture all adverse events and provide a narrative history for each patient in which a major adverse event occurs. You should capture all instances of device failure, including malfunctions and inaccurate device placement.

Because a high number of protocol deviations can significantly affect the validity of the clinical study data, you should capture all protocol deviations that occur during the study. In addition, your 510(k) should include a discussion of the impact of the protocol deviations on the validity of the clinical study results.

We recommend that you employ a core laboratory to minimize the introduction of bias or subjectivity into the data analysis process. We recommend that you incorporate a sensitivity analysis into your statistical plan to quantitatively assess the impact of any missing clinical data on the statistical analysis.

FDA recommends that your study employ a Clinical Events Committee (CEC) to provide independent adjudication of clinical events. Similarly, we recommend that you use an independent Data Monitoring Committee (DMC) to provide ongoing assessment of safety during the course of the clinical trial.

FDA encourages the use of flexible or adaptive study designs to assess the safety and performance of embolic protection devices. We recommend that you contact the Interventional Cardiology Devices Branch (for coronary embolic protection devices) or the Peripheral Vascular Devices Branch (for carotid embolic protection devices) to discuss the design of such a study prior to submission of your IDE.

### **Saphenous Vein Coronary Artery Bypass Graft Indications**

#### Study Endpoints

## *Contains Nonbinding Recommendations*

FDA recommends a primary endpoint of the combined rate of major adverse cardiac events (MACE) at 30 days post-procedure, including all cardiac deaths, all myocardial infarctions (Q wave and non-Q-wave), target vessel revascularization, and emergency coronary artery bypass grafting.

Recommended secondary endpoints include the following:

- component endpoints of MACE
- device success (delivery, deployment, and retrieval of the device per protocol without complication)
- angiographic endpoints
- freedom from procedure-related serious adverse events (i.e., clinical success)
- access site complications
- post-procedure levels of creatine kinase (CK) or its isoenzyme, CK-MB
- MACE during the hospital stay for the index procedure
- post-procedure Thrombolysis In Myocardial Infarction (TIMI) flow.

Because of the causal relationship in SVGs between distal embolization of debris and non-Q wave myocardial infarction, adequate collection of post-procedure CK or CK-MB is essential to rule out these events. Given that non-Q-wave myocardial infarctions are a component of the composite endpoint of MACE, missing enzyme data can confound interpretation of the trial results. FDA recommends that you assess the impact of missing cardiac enzyme data on the trial results using sensitivity analysis, or an equivalent method.

We recommend that you evaluate the impact of any unbalanced (random or systematic) baseline variables with respect to treatment assignment using a propensity score analysis or an equivalent method. A propensity score analysis should include hypothesis testing using propensity-adjusted outcomes.

### **Carotid Indications**

#### Study Considerations

You should provide a clinically and statistically based rationale for the control group or performance goal you select for your study. Your rationale should include a discussion of the comparability of the clinical data from which you derived the performance goal and the clinical data that you expect your study to generate. For example, you should compare the patient populations, study endpoints, treatment type, and other factors that may affect the study results. This rationale affects the acceptability of the proposed performance goal for your study.

FDA recommends that the statistical hypothesis for any comparison of single-arm study results to a performance goal derived from previously reported clinical data incorporate comparisons of the study results to the performance goal itself without any claims of non-inferiority or superiority. Hypotheses and claims involving non-inferiority or superiority of your device to the performance

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goal or to any device for which clinical data were used to derive the performance goal may not be appropriate statistically.

You may evaluate the performance of your embolic protection device in a study that includes either an approved carotid stent system or in a clinical study that is designed to also investigate the safety and effectiveness of a carotid stent system. In the second instance, FDA's assessment of the carotid embolic protection device would be linked to our assessment of the investigational carotid stent. Accordingly, FDA could not complete the review of the embolic protection device labeling until approval of the stent PMA. Therefore, if you choose to pursue the latter option above, FDA recommends that you submit the 510(k) for your carotid embolic protection device either with the PMA for your carotid stent or after the PMA is approved.

### Study Endpoints

FDA recommends a primary endpoint of the combined rate of major adverse cardiac and cerebrovascular events at 30 days post-procedure, including all deaths, strokes, and myocardial infarctions.

Recommended secondary endpoints include:

- device success (delivery, deployment, and retrieval of the device per protocol without complication),
- freedom from procedure-related serious adverse events (clinical success),
- access site complications,
- neurological events at 30 days post-procedure, including strokes and transient ischemic attacks, and
- neurological intolerance to vessel occlusion (for devices designed to occlude the target vessel).

## **11. Sterilization and Shelf Life**

FDA recommends that you provide sterilization information in accordance with the **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**, <http://www.fda.gov/cdrh/ode/guidance/361.html>. You should sterilize the device to a sterility assurance level (SAL) of  $1 \times 10^{-6}$  using a sterilization cycle that has been validated in accordance with the Quality System Regulation (21 CFR Part 820).

Because embolic protection devices are in direct contact with circulating blood, we recommend you test the devices for pyrogenicity. We also recommend you provide the following:

- description of the method used to make the determination, such as the limulus amoebocyte lysate (LAL) method;
- identification of the testing endpoint reached and rationale for selecting that endpoint;
- description of the extraction technique used to obtain the test fluid from the test device, showing that all clinically relevant contact surface of the test device were assessed; and

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- identification of any reference method used, such as **AAMI ST72 (Bacterial Endotoxins - Test Methodologies, Routine Monitoring, and Alternatives to Batch testing)**, an FDA guidance document, or an equivalent method.

FDA recommends that shelf life testing address package integrity to ensure sterility and stable device functionality over the labeled shelf life. To evaluate device functionality, we recommend that you identify the device performance characteristics that may be affected by aging and repeat the bench tests that evaluate those characteristics using aged samples. For example, aging can affect the performance of most polymer materials used for embolic protection device catheters; therefore, tests that evaluate the integrity and performance of the catheter should be repeated after aging. For those bench tests that you do not repeat, you should provide a rationale explaining why the performance characteristics assessed by the tests are not expected to be affected by aging. We also recommend that you provide the protocol used for your shelf life testing, the results of the testing, and the conclusions drawn from your results.

## **12. Labeling**

The premarket notification must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR Part 801.<sup>10</sup>

### **Directions for use**

As a prescription device, the device is exempt from having adequate directions for lay use when the conditions identified in 21 CFR 801.109 are met. You must provide information for use by health care practitioners in the device labeling (21 CFR 801.109(c), (d)). We recommend submitting clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients. We recommend the directions for use include a comprehensive summary of the results from any clinical study, including any applicable warnings or precautions based on those study findings. In addition, we recommend the instructions encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

As part of your 510(k) submission, we recommend that you provide a description of the device failure modes and malfunctions observed during non-clinical and clinical evaluation, as well as any steps that users should take to minimize the incidence of these events. You should also explain how you will communicate these failure modes and mitigation steps to device users, for example, as part of the device training program.

### **Contraindications**

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<sup>10</sup> Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR Part 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of Part 801.

## *Contains Nonbinding Recommendations*

The information for use by health care practitioners that you provide in the labeling must address contraindications, where the risk of harm from use in a patient population or situation clearly outweighs any possible benefit. The contraindications for an embolic protection device should generally include the following:

- patients for whom anti-coagulant or anti-platelet therapy is contraindicated,
- patients with uncorrected bleeding disorders,
- patients with vascular anatomy tortuous enough to prevent safe introduction and passage of interventional devices, and
- patients with a known or suspected allergy to a primary material of construction for the embolic protection device that will be in prolonged contact with the vasculature.

You should add contraindications if clinical or non-clinical data suggest they might be appropriate.

### **Warnings**

FDA recommends that you add device warnings for any situation for which there is reasonable evidence of a serious hazard with the use of the device, or to identify situations in which embolic protection devices are commonly used but for which there is a lack of scientific evidence supporting such use. FDA recommends that you include warnings to address the following:

- patient sub-populations with specific anatomic features, co-morbid conditions, or other characteristics who you suspect would suffer unreasonable risk of harm as a result of treatment with your device; and
- clinically important patient sub-populations for whom safety and effectiveness data are not available (For SVG indications, if you do not have clinical data regarding the use of your device in patients that have been treated with drug-eluting stents in the target vessel, FDA recommends that you add a warning that the safety and effectiveness of your device has not been established in these patients.).

For carotid embolic protection devices, labeling should identify the specific stent-embolic protection device combinations for which clinical safety and effectiveness data are available and state that the safety and effectiveness of the use of other such combinations has not been determined. Labeling should also identify the specific stent-embolic protection device combinations for which bench or animal data are available that show device compatibility and state that the compatibility of other such combinations has not been determined.

You should add warnings if clinical or non-clinical data suggest they might be appropriate.

### **Precautions**

You should include as precautions any special measures, such as handling methods, that the operator should take during device preparation and use.

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## Appendix A: Referenced Standards

The following tables include all standards referenced in this document.

<u><b>AAMI Standards</b></u>
ST72 Bacterial Endotoxins - Test Methodologies, Routine Monitoring, and Alternatives to Batch Testing

<u><b>ASTM Standards</b></u>
F1984 Standard Practice for Testing for Whole Complement Activation in Serum by Solid Materials
F2065 Standard Practice for Testing for Alternative Pathway Complement Activation in Serum by Solid Materials

<u><b>IEC/EN Standards</b></u>
60601-1 General Requirements for Safety
60601-1-1 Safety Requirements for Medical Electrical Systems
60601-1-2 Electromagnetic Compatibility – Requirements and Tests

<u><b>ISO Standards</b></u>
10993-1 Biological Evaluation of Medical Devices: Evaluation and Testing
10993-12 Biological Evaluation of Medical Devices: Sample Preparation and Reference Materials

<u><b>USP Standards</b></u>
USP 30 <85> Biological Tests and Assays, Bacterial Endotoxin Test (LAL)
USP 30 <151> Pyrogen Test (USP Rabbit Test)

A list of FDA-recognized standards is available at:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>