Guidance for Industry and FDA Staff: Guidance for Cardiovascular Intravascular Filter 510(k) Submissions

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U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Interventional Cardiology Devices Branch
Division of Cardiovascular and Respiratory Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to, Nicole Ibrahim, Center for Devices and Radiological Health. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Nicole Ibrahim at 301-796-5570 or by e-mail at **nicole.ibrahim@fda.hhs.gov (mailto:nicole.ibrahim@fda.hhs.gov)**.

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Guidance for Cardiovascular Intravascular Filter 510(k) Submissions

This guidance document describes a means by which cardiovascular intravascular filter devices may comply with the requirement of special controls for class II devices. Designation of this guidance document as a special control means that manufacturers attempting to establish that their device is substantially equivalent to a predicate cardiovascular intravascular filter device should demonstrate that the proposed device complies with either the specific recommendations of this guidance or some alternate control that provides equivalent assurances of safety and effectiveness.

I. Scope:

This draft guidance has been developed in an attempt to identify important preclinical tests and clinical design considerations for cardiovascular intravascular filters (filters). This guidance addresses filters that are permanently implanted in the inferior vena cava for the purpose of preventing thromboemboli generated in the lower limbs from flowing into the right side of the heart and the pulmonary circulation. It is limited in scope to those filters that are designed in such a way as to be seated within the vena cava via a series of hooks which are at the end of several legs or struts which converge at an apex. Filters that have a design that is significantly differs from this may require premarket approval and submission of a premarket approval application (PMA) or a completed product development protocol (PDP). This guidance is further limited to filters indicated for use for the prevention of recurrent pulmonary embolism via placement in the vena cava in the following situations:

- Pulmonary thromboembolism when anticoagulants are contraindicated
- Failure of anticoagulant therapy in thromboembolic diseases
- Emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced
- Chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated

Manufacturers who wish to pursue other indications should contact FDA to determine the data necessary to support a new indication and the appropriate regulatory pathway.

The firm must show that its device addresses the issues of safety and effectiveness identified in this guidance, either by meeting the recommendations of this guidance or by some other means that provides equivalent assurances of safety and effectiveness.

II. Introduction

Pulmonary embolism (PE) is a serious clinical issue causing significant morbidity and mortality. It has been estimated that more than 600,000 cases of clinically significant PE occur and result in approximately 200,000 deaths annually in the United States[2,3,4] . The patient often survives the first embolism but is at high risk that a second fatal PE will occur. PE recurs in approximately 6% to 25% of treated patients[2]. Additionally, the incidence of PE in patients with deep venous thrombosis (DVT) is 19% to 28%[5]. Treatment of PE has been shown to be effective in reducing the mortality from 30% to 8%1. Normally, patients with DVT and, or PE are treated with anticoagulation therapy. However, in some patients anticoagulation is ineffective, contraindicated or results in complications which require that it be discontinued. For these patients, vena caval interruption with a filter is recommended. The goal of filter placement is to try to obtain high filtering efficiency (large and small emboli) without impedance of blood flow and with reduced device related thrombosis while minimizing migration and without penetration of the vessel wall.

The following are the criteria for an ideal filter:

- Nonthrombogenic
- High filter efficiency without impedance of blood flow
- Secure fixation within the vena cava
- Rapid and safe percutaneous insertion
- Low rate of associated morbidity
- Magnetic resonance imaging (MRI) compatibility

The necessary array of tests for a particular filter will depend, in part, on the specific design. Therefore, this document may not reflect the complete battery of pre-clinical testing necessary to qualify all filters/designs. However, there are certain aspects of filter design that are general in nature and should be assessed. The degree to which a proposed device is similar to a currently marketed filter will indicate the level of testing necessary, i.e., whether the design characteristics can be assessed via *in vitro* bench testing, *in vivo* animal testing, clinical testing or some combination of all three.

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[2]Dalen, J.E. and J.S. Albert, "Natural history of pulmonary embolism," *Progressive Cardiovascular Diseases*, 17:259-270,1975.

[3]Smith B.A., "Vena Caval Filters," *Emergency Medicine Clinics of North America*, Vol. 13, No.3:645-654,1994.

[4]Nunnelee, J.D., and A. Kurgan,"Interruption of the inferior vena cava for venous thromboembolic disease," *Journal of Vascular Nursing*, 11:80-2,1993.

[5]Mohan, C.R., J.J. Hoballah, W.J. Sharp, T.F. Kresowik, C.T. Lu and J.D. Corson, "Comparative efficacy and complications of vena caval filters," *Journal of Vascular Surgery*, Vol.21 No. 2:235-246,1995.

III. Pre-Clinical Testing

A. Biocompatibility

Biocompatibility testing should be conducted in accordance with FDA guidance document "**Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing (ssLINK/ucm080735.htm)**", which includes an FDA matrix that designates the type of testing needed for various medical devices. Cardiovascular intravascular filters are defined as permanent implant, blood-contacting devices.

B. Filter Performance

Below is an outline of the general issues that need to be addressed when seeking premarket clearance for a filter. It is the submitter's responsibility to conduct testing which adequately addresses the concerns outlined below as well as any others which may arise due to the unique design of the given device. The goal of this outline is to identify the objective(s) of the pre-clinical test. Test protocols and acceptance criteria for these tests are the responsibility of the submitter. FDA recognizes that there are many different testing methods that may be used to satisfy the objective(s). Where appropriate, some of these tests may be combined. These tests may best be carried out in bench top models or in animal models or in a combination of both. FDA advises that prior to the initiation of animal studies, the submitter should contact FDA and discuss the proposed animal study to ensure general agreement on the adequacy of the animal study protocol.

All tests should be performed on filters fabricated by representative manufacturing processes. An adequate number of samples should be tested. The objectives, test methodologies, results, and conclusions should be clearly defined for each test performed. The performance specifications, test conditions and acceptance criteria for all tests should be completely explained and justified by comparison to expected clinical conditions. Where appropriate, testing should be conducted in an environment simulating clinical conditions. The results of all tests should be reported in a statistically meaningful format, i.e., specification of the number of samples, range of values, mean, standard deviation, and a 95 percent confidence interval where appropriate. A probability measure that is indicative of the statistical significance of any comparisons made should be provided.

1. **Simulated deployment**

An assessment of the ability to completely deploy the filter reliably in the chosen location under simulated clinical conditions should be made. This test should take into consideration the various routes by which the filter can be introduced into the patient, e.g., femoral, jugular, etc. Although it is recognized that the left femoral route is the most tortuous, all labeled routes should be examined.

2. **Introducer/sheath suitability**

The objective(s) of this test should be to demonstrate that the sheath will adequately resist kinking when used in the most tortuous pathway. In addition, all bonds of the introducer/sheath should be assessed for their pull strength.

3. **Clot trapping ability**

This test should demonstrate that the device can capture clinically significant emboli yet still permit sufficient blood flow around trapped emboli without caval occlusion. It should also examine whether the filter achieves this efficiency immediately post-deployment. If it does not, the time period necessary to achieve full filtering efficiency should be characterized.

4. **Filter fracture**

The filter's response to worst-case respiratory and diaphragmatic movements in the vena cava under simulated respiratory cycles should demonstrate sufficient fatigue resistance of the filter design. In addition, there should be an examination of corrosion resistance and weld strength following cycling.

5. **Caval perforation/filter migration**

This test should demonstrate that the filter fixes itself within the vena cava at the deployment site and undergoes sufficient endothelialization. The force necessary for device fixation should be characterized over the range of labeled inferior vena cava (IVC) diameters. In addition, this force should not suggest a tendency to perforate the caval wall.

6. **Thrombogenicity**

The thrombogenic potential of the filter should be examined. This test should demonstrate that the effect of the device on the blood flow would not be sufficient to cause stasis, which could lead to thrombus formation in and around the device.

7. **MRI compatibility**

The extent to which the filter is compatible with MR imaging should be assessed (see the **Attachment**).

IV. Clinical Investigations

It is anticipated that human clinical investigations could be necessary in the development of a "new" vena cava filter to establish its equivalency to currently marketed filters. Such a study may also be necessary for a modified filter design. The need for such a study should be discussed with FDA

prior to submission of an investigational device exemption (IDE) application. In those cases in which a study is deemed necessary, the sponsor should carefully consider the following items:

- the appropriate study design
- the study hypothesis
- appropriate sample size
- definitions of success and failure
- the clinically relevant endpoints necessary for the demonstration of substantial equivalence

For the indications outlined previously, the risks and benefits to the patients are well documented. The intent of the clinical study should be to demonstrate that the rates of complications for the investigational filter are comparable to other marketed vena cava filters. Although the risks themselves are well described in the literature, the definitions and methods used to determine the rates are inconsistent and highly variable. Therefore, it is critical to prospectively define and identify the methods of analysis for each potential complication. The complications identified and analyzed during the course of the clinical investigation should include the following:

1. **Complications during filter insertion**

In the course of trying to place the filter in the vena cava the following complications have been noted[6,7]:

- Sheath perforation
- Introducer tip detachment
- Guidewire kinking
- Sheath kinking

These complications can result in[8]:

- Filter deformation
- Fracture
- Premature release or insufficient opening
- Improper placement
- Thrombus formation which may result in insufficient opening

There have also been reports of problems with[9]:

- Filter sticking to and/or getting caught in the introducer while the device is being deployed
- Practitioner difficulty with inserting and/or retrieving failed insertions of the device

- Filter legs breaking during insertion
- Deployment within the introducer
- Breakage of the filter /filter legs upon placement of the device in the patient

The protocol should identify these potential complications and ensure that they will be captured by the investigator on the appropriate data collection forms.

2. **Recurrent pulmonary embolism**

Patients who present with symptoms suggestive of recurrent PE should undergo a lung scan and/or an arteriogram. If recurrent PE is confirmed, a contrast vena cavogram should be performed to check for any clot within the filter. Some of the mechanisms, which may be responsible for PE after filter insertion, are the following[8]:

- Ineffective filtration
- Continuous growth of trapped thrombi through the filter
- Development of thrombosis on the proximal end of the filter
- Filter migration to a position where it does not function optimally
- Filter retraction from the caval wall at thrombus retention (occurring if some of the hooks have grasped the thrombus, which creates a channel between the filter and the caval wall)
- Embolization through collaterals that may be lumbar
- Embolization that may occur via the ovarian/spermatic veins
- Embolization from thrombi proximal to the filter (arm veins, renal or hepatic veins, the right heart)
- Incorrect position of the filter

For those patients who experience a recurrent PE, every attempt should be made to determine the probable mechanism.

3. **Death**

Deaths attributable to filter complications have been reported to result from:

- cardiac arrest immediately following filter placement
- misplacement of the filter during insertion
- cephalic migration of a filter to the heart after placement.

All patients with suspected filter complications who died during the clinical investigation should undergo an autopsy. A complete report of the findings should be provided for review.

4. **Filter migration**

Minor filter migration in the caudal or cephalic direction is commonly reported and does not appear to be associated with clinically significant events. The walls of the vena cava are known to move with respiration and changes in intra abdominal pressure induce flexion on the limbs of the filter. The filter may appear to have migrated due to x-ray equipment variation, patient position, measurement error, and respiration. Much of the reported filter movement may actually be due to measurement error resulting from differences in patient positioning, breathing, and parallax. True migration may be caused by an excessively large vena cava, inadequate positioning and massive embolization into the filter with caval dilatation[8]. It is recommended that any movement of the filter with relation to the spine that is 5 mm or greater be recorded as filter migration. Assessment of distal migration should be determined from post implant and follow-up anterior-posterior and lateral films after correction for magnification. When follow-up images are obtained, efforts should be made to closely reproduce patient positioning and patient respiration to reduce errors in the interpretation of filter migration.

5. **Caval penetration**

Determination of caval penetration is complicated. Examination via cavography may show filter hooks or legs outside the flow of contrast. This is not necessarily due to penetration. It may be due to endothelialization or tenting of the vena cava or locations in tributary veins. Computed tomography (CT) scans can be used to help rule out some false positives. After correction for magnification, filter base diameter from hook to hook should be recorded from both the implant and follow-up plain films. If an increase in filter base diameter of 5 mm is recorded, a CT scan should be performed to confirm or exclude the position of filter legs outside of the inferior vena cava. Any other changes, which may be suggestive of possible filter leg penetration of the vena cava, should trigger a CT scan, regardless of increase in the filter base diameter.

6. **Filter tilting and angulation**

The significance of tilting and angulation of caval filter after placement is controversial. There is a theoretical loss of filtering efficacy of any filter when tilted or angulated significantly; however there is no good clinical data to support a definite increased incidence in PE or failure to trap thrombi. All instances of tilting or angulation should be noted as well as any associated clinical sequelae.

7. **Caval occlusion**

Caval occlusion is related to filter thrombogenicity, design and flow patterns[8]. Small or moderate sized emboli trapped in a filter are usually asymptomatic since the residual patency of the vena cava and the normal paravertebral collateral veins permit adequate venous return. A large trapped embolus or a cluster of small emboli may occlude a filter completely and thus block the vena cava. After a period of days or weeks, the occlusion occurs and causes a sudden swelling of both lower limbs. In almost all cases the symptoms of IVC occlusion are transient and resolve almost

completely within a few weeks or a few months since the thrombi undergo spontaneous lysis. Since it is often clinically difficult or impossible to distinguish IVC filter occlusion from extension of the preexisting DVT because the symptoms may be similar, all instances should be recorded as occlusion unless the extension of DVT can be ruled out.

8. **Filter embolization**

The risk of filter embolization is primarily limited to the first two weeks after implantation. Embolization of the filter is a serious complication with variable clinical consequences, comparable to pulmonary thromboembolism. These range from being totally asymptomatic to sudden death. Therapy also ranges from no therapy to open chest surgery and removal of the device. All cases of filter embolization should be recorded and the reasons for occurrence immediately assessed. The subsequent treatment should also be described in detail.

9. **Other risks**

Complications that occur at the puncture site such as: hematoma formation and A-V fistula, DVT at the puncture site, pneumothorax and air embolism after jugular insertion, should all be recorded on data collection forms and analyzed.

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[6]Becker, D.M. et al., "Inferior Vena Cava Filters Indications, Safety, Effectiveness," *Archives of Internal Medicine*, 152:1985-1994,1992.

[7]Greenfield, L.J., et. al., "Extended evaluation of the titanium Greenfield vena caval filter," *Journal of Vascular Surgery*, September 1994:458-465.

[8]Bergqvist,D.,"The Role of Vena Caval Interruption in Patients with Venous Thromboembolism," *Progress in Cardiovascular Diseases*, 37(1):25-37,1994.

[9]FDA MDR database

V. Labeling

The Division of Cardiovascular, Respiratory and Neurological Devices (DCRND) of the Office of Device Evaluation (ODE) conducted a review of the labeling for marketed cardiovascular intravascular filters (vena cava filters). Based on that review, the Food and Drug Administration (FDA) believed that several changes should be made to existing labels to ensure consistency among device manufacturers and to facilitate appropriate use of the devices clinically.

The following sections of the labeling were affected:

- Indications for use
- Contraindications

- Warnings

The Attachment contains a copy of the labeling format developed for this device.

ATTACHMENT

INDICATIONS FOR USE

The labeling should include the following text:

The [NAME OF DEVICE] is indicated for the prevention of recurrent pulmonary embolism via placement in the vena cava in the following situations:

- **pulmonary thromboembolism when anticoagulants are contraindicated;**
- **failure of anticoagulant therapy in thromboembolic diseases;**
- **emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced; and**
- **chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated**.

CONTRAINDICATIONS

The labeling should include the following contraindication:

Vena Cava filters should not be implanted in patients with risk of septic embolism.

Your labeling may include other contraindications which are specific to your particular device design.

WARNINGS

The labeling should include information regarding the use of the device in patients undergoing magnetic resonance imaging (MRI). The following terminology should be used:

MRI-Safe:	**No additional risk to the patients, but may affect the quality of the diagnostic information.**
MRI-Compatible:	**MRI-Safe and neither interferes with nor is affected by the operations of a MRI device.**
Non-Compatible:	**Neither MRI-Safe nor MRI-Compatible and should not be used in conjunction with MRI systems.**

Data to support the chosen warning should be included in your 510(k) notification.

More in Guidance Documents (Medical Devices and Radiation-Emitting Products) (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm)

Cross-Center Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081752.htm)

Office of Compliance Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070269.htm)

Office of the Center Director Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110228.htm)

Office of Communication and Education Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070271.htm)

Office of Device Evaluation Final Guidance 2010 - 2016 (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm198577.htm)

Office of Device Evaluation Final Guidance 1998 - 2009 (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070272.htm)

Office of Device Evaluation Final Guidance 1976 - 1997 (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080283.htm)

Office of In Vitro Diagnostics and Radiological Health Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070274.htm)

Office of Surveillance and Biometrics Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070275.htm)

Office of Science and Engineering Laboratories Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070277.htm)

Draft Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm407274.htm)

Radiation-Emitting Products Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm283507.htm)

Withdrawn Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm425025.htm)