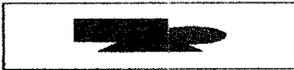


Draft Guidance for Industry and FDA Staff

Class II Special Controls Guidance

Document: Vascular and Neurovascular Embolization Devices



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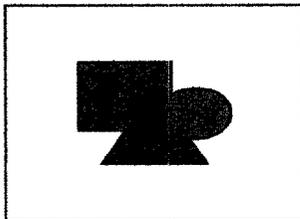
Draft Guidance

**This guidance document is being distributed for comment purposes only.
Document issued on: February 25, 2004**

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance document. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document, contact Peter L. Hudson, Ph.D., Plastic and Reconstructive Surgery Branch, 301-594-3090, ext. 194 or plh@cdrh.fda.gov, Elisa D. Harvey, D.V.M., Ph.D., Peripheral Vascular Devices Branch, 301-443-8262, ext. 167 or edh@cdrh.fda.gov, or Colin M. Pollard, Obstetrics and Gynecology Devices Branch, (301) 594-1180 or CMP@cdrh.fda.gov.

When final, this document will supersede “Guidance for Neurological Embolization Devices” dated November 1, 2000.



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U.S. Department of Health and Human Service:
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation

Peripheral Vascular Devices Branch, Division of Cardiovascular Device:
Plastic and Reconstructive Surgery Devices Branch, Division of General, Restorative, and Neurological Device:
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Preface

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Draft Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Vascular Embolization Devices and Neurovascular Embolization Devices

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

This draft guidance document was developed as a special controls guidance document to support the reclassification of the vascular embolization device and the neurovascular embolization device into class II.

The vascular embolization device, as proposed, is intended to control hemorrhaging due to aneurysms, certain types of tumors (e.g., nephroma, hepatoma, and fibroids), and arteriovenous malformations. The neurovascular embolization device, as proposed, is intended to permanently occlude blood flow to cerebral aneurysms and cerebral arteriovenous malformations.

FDA believes that the risks to health associated with the intended uses of the vascular embolization and the neurovascular embolization devices are the same, therefore, FDA believes that a single guidance document can serve as the special control for both device types.

This draft guidance document will be issued in conjunction with a Federal Register notice announcing the proposal to reclassify these device types. This guidance document is issued for comment purposes only. If a final rule to reclassify these device types is not issued, this guidance document will not be issued as a special control.

Following the effective date of a final rule reclassifying these devices, any firm submitting a premarket notification (510(k)) for a vascular embolization device or a neurovascular embolization device will need to address the risks identified in the special control guidance document. However, the firm need only show that its device meets the recommendations of the guidance document or in some other way provides equivalent assurances of safety and effectiveness.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents 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 guidance documents means that something is suggested or recommended, but not required.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of the vascular embolization device and the neurovascular embolization device. Thus, a manufacturer who intends to market a device of one of these generic types should (1) conform to the general controls of the Federal Food, Drug, & Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with these devices identified in this guidance document, and (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This special control guidance document identifies the classification regulations and product codes for these devices (Refer to Section 4 – Scope). In addition, other sections of this special control guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these devices and lead to a timely 510(k) review and clearance. This document supplements other FDA documents regarding the specific content requirements of a 510(k) submission. You should also refer to CDRH's Device Advice <http://www.fda.gov/cdrh/devadvice/> and 21 CFR § 807.87.

As described in the guidance document entitled, **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 a class II special controls guidance document has been issued. 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 describe how this special control guidance document was used 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 21 CFR § 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 special controls guidance document.

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 11 for specific information that should be included in the labeling for devices of the types covered by this guidance document.)

Summary report

We recommend that the summary report contain:

- A description of the device and its intended use. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. (Refer to Section 5 for specific information that we recommend you include in the device description for devices of the types covered by this guidance document.) You should also submit an "indications for use" enclosure.¹
- A description of device design requirements.
- Identification of the Risk Analysis method(s) used to assess the risk profile in general as well as the specific device's design and the results of this analysis. (Refer to Section 6 for the risks to health generally associated with the use of this device that FDA has identified.)
- A discussion of the device characteristics that address the risks identified in this class II special controls guidance document, as well as any additional risks identified in your risk analysis.
- A brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Sections 7-11 of this class II special controls 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.² (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)
- If any part of the device design or testing relies on a recognized standard, (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed, or (2) a declaration of conformity to the standard.³ Please note that testing must be completed before submitting a declaration of conformity to a recognized standard. (Section 514(c)(1)(B) of the Act). For more information, refer to the FDA guidance document, **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(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

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 document. 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 general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a 510(k) submission for a vascular embolization device or a neurovascular embolization device. The recommendations made in this guidance document apply to both, unless vascular or neurovascular is specified.

4. Scope

The scope of this document is limited to the following two device types:

Device Type	Classification on Regulation (21 CFR)	Product Code	Examples
Vascular embolization device	§ 870.3300	KRD device, embolization, arterial	<ul style="list-style-type: none"> embolization coils detachable balloons polyvinyl alcohol particles nonresorbable particles
		NAJ agents, embolic, for treatment of uterine fibroids	<ul style="list-style-type: none"> nonresorbable particles
Neurovascular embolization device	§ 882.5950	HCG device, artificial embolization	<ul style="list-style-type: none"> embolization coils polyvinyl alcohol particles nonresorbable particles
		MZQ balloon, detachable, for neurovascular occlusion	<ul style="list-style-type: none"> detachable balloons

In the companion proposed rule, FDA is proposing the revisions below to the names and identifications of these embolization device types, §§ 870.3300 and 882.5950:

§ 870.3300 – Vascular embolization device.

(*Identification.* A vascular embolization device is an intravascular implant intended to control hemorrhaging a due to aneurysms, certain types of tumors (e.g., nephroma, hepatoma, uterine fibroids), and arteriovenous) malformations. This does not include cyanoacrylates and other embolic agents, which act by polymerization or precipitation. Embolization devices used in neurovascular applications are also not included in this classification, see 21 CFR 882.5950.

(*Classification.* Class II (special controls). The special control for the device is FDA’s “Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices.”)

§ 882.5950 – Neurovascular embolization device.

(*Identification.* A neurovascular embolization device is an intravascular implant intended to permanently

- a occlude blood flow to cerebral aneurysms and cerebral arteriovenous malformations. This does not include
) cyanoacrylates and other embolic agents, which act by polymerization or precipitation. Embolization devices used in other vascular applications are also not included in this classification, see 21 CFR 870.3300.

(
 b *Classification.* Class II (special controls). The special control for the device is FDA's "Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices."
)

Cyanoacrylates and other embolic devices (product code NPE), which act by polymerization or precipitation, continue to be regulated as postamendments class III devices and require premarket approval (PMA) applications.

5. Device Description

We recommend that you identify your device by regulation number and product code and include the following information:

- identity of the reagents and raw materials (i.e., reagent source, purity, Certificates of Analyses (CoA), or Material Safety Data Sheets, (MSDS)) used in the construction of the device and any voluntary material conformity standards

COMMENT: the presence of any residuals which remain on the device (such as reagents) is already assessed through biosafety/biocompatibility testing; therefore, there is no need to provide this additional information to ensure safety. If the Agency has particular concerns about specific raw materials, and associated processing, this could be addressed on a case by case basis with the manufacturer.

- identity and quantity of any manufacturing reagent (e.g., organic solvents, heavy metals, cross-linking reagents remaining in the device) that is potentially toxic

COMMENT: same comment as above

- a description of the components of the device and its assembly
- a description of any accessories and ancillary devices used with the device, e.g., delivery catheters

COMMENT: added "ancillary devices" to provide clarity for harmonization with European Medical Device Directive terminology. Accessories are not devices in their own right, but are intended specifically to be used together with a device to enable the device to be used in accordance with its intended use; accessories are typically supplied with the device. Ancillary devices are devices in their own right, and are intended to be used together with a device to enable the device to be used in accordance with its intended use; ancillary devices are not typically supplied with the device, but are specifically recommended in the Directions for Use.

- the range of dimensions, shapes, and device designs
- engineering drawings
- a description of the principle of operation (i.e., method of deployment and embolization)
- a description of how the device is provided (e.g., sterile, assembled, single use).

6. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the 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, prior to submitting your 510(k), to identify any other risks specific to your device. For example, a device with gynecological indications may present additional risks, such as damage to the uterine wall, diffuse uterine necrosis, primary ovarian failure, reproductive toxicity, or carcinogenicity, as well as other risks related to the chemistry, toxicology, and healing response in the uterine environment. The 510(k) should describe the risk analysis method. 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.

Identified risk	Recommended mitigation measures
Blood vessel perforation or rupture	Sections:

	7. Preclinical Testing 9. Animal Testing 10. Clinical Testing 11. Labeling
Unintended thrombosis	Sections: 7. Preclinical Testing 9. Animal Testing 10. Clinical Testing 11. Labeling
Adverse tissue reaction	Sections: 7. Preclinical Testing 9. Animal Testing 10. Clinical Testing
Infection	Section 8. Sterility
Hematoma formation	Sections: 7. Preclinical Testing 9. Animal Testing 10. Clinical Testing 11. Labeling

7. Preclinical Testing

We recommend that you conduct the preclinical testing below to establish the performance characteristics of the device.

Polyvinyl Alcohol (PVA) Particle Testing

We recommend that you provide the following for PVA particles:

- chemical analysis of the final sterilized device, including identification and quantification of any processing additives, contaminants, etc.
- if applicable, an explanation of how formaldehyde and/or other processing materials are removed from the particles and data evaluating the removal process
- particle size ranges
- assessment of particle size compatibility with the recommended delivery catheter(s)
- evaluation of the uniform dispersion and suspension of particles within the catheter when mixed with the recommended contrast agent(s) or other interactive material(s) according to the labeled instructions.

Detachable Balloon Testing

We recommend that you provide the following for detachable balloons:

- the inflation/deflation rates for each balloon size
- the pressure(s)/volume(s) required to rupture the balloon(s) and the specification for the maximum inflation pressure/volume
- a plot of volume versus inflation pressure/volume

COMMENT: some balloons are inflated by volume and not pressure.

- the force needed to detach the balloon
- the balloon permeability with recommended contrast

COMMENT: permeability should be assessed specifically with the contrast that is recommended in the Directions for Use.

- the reliability of the detachment mechanism.

Embolization Coil Testing

We recommend that you provide the following for embolization coils:

- the coil strength (i.e., the force required to deform the coil shape)

COMMENT: Does this refer to loss of secondary diameter or coil unraveling (i.e. primary diameter), or both?

- the ease of delivery, as measured by friction when advancing and/or retracting the coil through a recommended catheter positioned in a simulated tortuosity
- for coils with fibers, a description of the fiber attachment mechanism and pull-out force
- a description of the detachment mechanism and data on the detachment time
- the reliability of the detachment mechanism.
- strength (e.g. tensile, torsional, fatigue – as applicable) of critical design elements of the final, finished device.

COMMENT: critical design elements should be assessed.

Delivery Catheter Testing

COMMENT: the Agency may wish to consider adopting the EN/ISO 10555 series for this aspect, because manufacturers are likely already doing this testing to achieve CE-mark.

If your 510(k) includes a new delivery catheter, we recommend that you provide the following information for that catheter:

- tensile strength
- catheter burst pressure
- flexibility
- a plot comparing the flow rate of fluid through the catheter versus the applied internal pressure
- hub attachment strength
- kink resistance
- radiopacity
- coefficient of friction of the external surface of the catheter.

Shelf Life

We recommend that you conduct both preclinical and packaging testing to establish the shelf life (i.e., expiration date) of the device as a part of the validation activities required by the Quality Systems Requirements (21 CFR Part 820). Accelerated test results should be supported by validated test information, and, depending on the device component, should also be supported by real time test data. For mechanical testing, you should conduct both preclinical and packaging testing on representative aged samples. For packaging testing, we recommend that you conduct testing on the final finished package measuring initial integrity and the maintenance of integrity. We recommend that you use test methods that are either validated or standardized. The documentation from these validation activities must be maintained in the Design History File for the device (21 CFR § 820.30).

Biocompatibility

FDA recommends that you select tests appropriate for implant devices with tissue/bone and blood contact 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>.

We recommend that you perform carcinogenicity studies with devices in which a positive genotoxicity test result was obtained. We recommend that you take into consideration identities of the chemical components and available information regarding their toxicity in your evaluations of potential carcinogenicity.

For neurovascular embolization devices, because ethylene oxide (EO) may cause neurotoxicity, in addition to measuring the EO residue levels, we recommend that you perform biocompatibility testing on the finished EO-sterilized device using intracranial

implantation to assess any adverse tissue response. You should demonstrate that the level of sterilant residues remaining in the device do not raise concerns over the safe use of the product.

COMMENT: intracranial implant testing is not necessary if the device has less/equal residual EO and ECH than a device which has been on the market with a clinical history of safe use and with zero reports of neurotoxicity. In the Introduction section of this document, the Agency states, "Following the effective date of a final rule reclassifying these devices, any firm submitting a premarket notification (510(k)) for a vascular embolization device or a neurovascular embolization device will need to address the risks identified in the special control guidance document. However, the firm need only show that its device meets the recommendations of the guidance document or in some other way provides equivalent assurances of safety and effectiveness." Establishing substantial equivalence with regard to EO and ECH levels does provide equivalent assurances of safety and effectiveness.

Pyrogenicity

Because of the potential for contact with the intrathecal space, the amount of endotoxin in the final, sterilized, neurovascular embolization device should be less than 0.06 Endotoxin Unit (EU)/mL and in the vascular embolization devices, less than 0.5 EU. These recommendations are described in the "Guideline on validation of the Limulus Amebocyte Lysate test as an end-product endotoxin test for human and animal parenteral drugs, biological products, and medical devices," December 1987, <http://www.fda.gov/cder/guidance/old005fn.pdf>.

8. Sterility

FDA recommends that you provide sterilization information described in the **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**, <http://www.fda.gov/cdrh/ode/guidance/361.html>. The device should be sterile with a sterility assurance level (SAL) of 1×10^{-6} . Refer to the Biocompatibility section above for testing related to EO-sterilized devices.

9. Animal Testing

We generally recommend that you conduct a pre-clinical animal model evaluation to evaluate these devices to show that you have adequately addressed the risks identified in this guidance document if there is no appropriate bench model for the attribute to be assessed. For new device design features affecting the embolic agent itself (e.g., coatings to coils, coil structural design, coil materials, particle materials, particle shape, sizes), the mechanism of detachment, or the catheter itself, we recommend that the animal study evaluate, if appropriate based on the risk analysis:

- case of delivery (friction and tortuosity)
- ~~rupture or puncture of the blood vessels~~ acute complications

COMMENT: Animal testing should be considered in the absence of an appropriate bench model. Rupture or puncture of blood vessels would be reported in the context of acute complications. Rupture or puncture can be caused by other procedure-related factors (e.g. device sizing and microcatheter manipulation) and are addressed in the manufacturer's Risk Management system.

- recanalization of the vessels/~~durability of occlusion~~

COMMENT: durability of occlusion cannot be demonstrated in animals in simulated aneurysms (e.g. venous pouch or rabbit elastase models). There are no clinically relevant animal models which are representative of diseased human vessels to assess durability of occlusion.

- local ~~and systemic~~ foreign body reactions

COMMENT: assessment of systemic foreign body reaction is not needed for devices that do not have a drug component

- device migration
- embolization effectiveness.

Because changes in embolization agent design and materials of construction may influence the healing process of the embolization site, we recommend that you perform follow-up evaluations with appropriate frequency ~~and after sufficient time has passed to evaluate acute as well as chronic toxicity.~~ We also recommend that you provide an explanation of how the animal model relates to the human condition through any pertinent literature references and/or supporting testing.

COMMENT: acute and chronic toxicity are already addressed in biocompatibility testing. What additional animal assessment is necessary and why? What study design does the Agency anticipate would satisfy this?

10. Clinical Testing

In accordance with the least burdensome provisions of the FDA Modernization Act of 1997, FDA 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. While, in general, clinical studies will not be needed for most vascular or neurovascular embolization devices, FDA may recommend that you collect clinical data for a vascular or neurovascular embolization device with:

- designs or material formulations (e.g., coatings to coils, coil structural design, coil materials, particle materials, particle shape, sizes, mechanism of detachment, novel catheter design) dissimilar from designs or material formulations used in legally marketed devices of the same type
- new technology, i.e., technology different from that used in legally marketed devices of the same type
- indications for use dissimilar from devices of the same type.

Vascular and neurovascular embolization devices are classified as different generic types of devices, thus FDA does not consider them to be "of the same type" in the criteria described above.

FDA will always consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale. The review branches identified on the cover of this guidance document are available to discuss any clinical testing with you before you initiate your studies.

If a clinical study is needed to demonstrate substantial equivalence (i.e., conducted prior to obtaining 510(k) clearance of the device), the study must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. FDA believes that the vascular and neurovascular embolization devices addressed by this guidance document are significant risk devices as defined in 21 CFR § 812.3(m).⁴ In addition to the requirement of having an FDA-approved IDE, sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

After FDA determines that the device is substantially equivalent, clinical studies conducted in accordance with the cleared indications, including clinical design validation studies conducted in accordance with the quality systems regulation, are exempt from the investigational device exemptions (IDE) requirements. However, such studies must be performed in conformance with 21 CFR Part 56 and 21 CFR Part 50.

We recommend that you consider the following information specific to embolization clinical studies.

Endpoints

We recommend that the study protocol include clearly defined primary and secondary endpoints and specific success/fail criteria for the study. We recommend that you define and report all serious adverse events, device-related adverse events, and procedure-related adverse events.

COMMENTS: "all" adverse events is too broad and would capture irrelevant information. We propose that the following adverse events are relevant in assessing safety and effectiveness of the device: serious, device-related, and procedure-related.

We recommend that effectiveness endpoints include ~~the reduction in size of the vascular lesion, percentage occlusion of an aneurysm, or the occlusion of a parent vessel~~ as measured by angiography. We also recommend that you consider other endpoints, such as the recanalization rate of the embolized vascular lesion and/or the determination of the clinical benefit. For example, for devices used for presurgical embolization, a reduction in surgical time and blood loss may be appropriate endpoints.

COMMENT: There is no standard methodology for how to measure reduction in size and percentage occlusion. It is very subjective and inherently problematic to quantify.

For neurovascular embolization devices, we recommend that the safety evaluation include:

- the incidence of new neurological deficits (transient and permanent)
- ~~grading of neurological deficit status (i.e., did the deficit lessen, stay the same, or deteriorate)~~ neurological outcome assessment

COMMENT: grading of neurological deficit status is rarely seen in the literature and would involve every cranial nerve, which is overly burdensome and not relevant to assessing safety and effectiveness of the device.

- the rate of serious neurological complications, and device-related non-neurological complications, and procedure-related neurological complications

COMMENTS: "all" complications is too broad and would capture irrelevant information. We propose that the following complications are relevant in assessing safety and effectiveness of the device: serious neurological, device-related non-neurological, and procedure-related neurological.

- distal migration of particular material.

We recommend that you identify the measurement tools used to assess patient neurological endpoints. We recommend that you evaluate all patients, at a minimum, pre-embolization, immediate post-embolization, and at a follow-up examination using a standard neurological examination that tests:

- cranial nerves
- sensory function
- motor function and reflexes
- gait and coordination

- mentation.

We recommend that you provide a copy of the neurological examination as a case report form on which the clinician will record results. Other means of measuring endpoints may include:

- functional outcome scales
- patient self-reports
- clinician or surgeon self-reports (~~World Federation of Neurosurgeons grade (WFNS)~~, Glasgow Outcome Scale (GOS), Glasgow Coma Scale (GCS), NIH Stroke Scale, Modified Rankin Scale, and/or Barthel Index).

COMMENT: WFNS is not used in the U.S., Barthel is rarely used. Modified Rankin is most commonly used.

We recommend that, when possible, the evaluation of endpoints be independent and masked. For any scale used, we recommend that the directions for determining values in the test be part of the case report form and that the scale range be indicated on the case report form where the score will be entered. ~~When appropriate, we recommend that you consider neuropsychological testing (e.g., personality, associations, IQ).~~

COMMENT: neuropsychological testing is not standard of care.

Description of Embolization Procedure

We recommend that you provide a full description of the embolization procedure in the protocol, including:

- device/component assembly and preparation
- use of anticoagulation medication (e.g., drug, dose)
- ~~use of antibiotics~~

COMMENTS: what does the Agency believe to be the relevance to safety and effectiveness of capturing antibiotic information?

- circumstances under which adjunctive embolization devices may be used during the procedure
- whether there is a plan for staged embolization and the features of that plan
- the therapy available in the event of stroke or other complication during the embolization procedure
- the time interval between embolization and definitive resection if embolization is a pre-surgical procedure.

In addition, we recommend that you monitor the neurological function during implantation of neurovascular embolization devices in patients under local anesthesia.

Imaging

Pre-operative imaging procedures are standard of care for patients requiring embolization. In addition to pre-operative evaluation, post-embolization angiography and short-term and long-term follow-up imaging scans may be appropriate when evaluating embolization agents with novel design features. We recommend that you describe the methods used to measure the lesion (e.g., angiography, MRI, MRA, CT), as well as the follow-up intervals. Because the vascular disorder and device use may determine which imaging tools are used and the length and interval of follow-up, we recommend that you provide the rationale for these ~~protocol designs~~ along with any supporting literature/studies.

COMMENTS: "imaging tools" and "follow-up" are not "protocol designs".

Patient Follow-up

We recommend that you specify how often patients should be evaluated during follow-up.

11. Labeling

The 510(k) should 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 § 807.87(e).⁵

Prescription Use

As a prescription device, under 21 CFR § 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, under 21 CFR § 807.87(e), we expect to see clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients. Instructions should encourage appropriate 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.

COMMENTS: training programs which take place locally at the institution may not necessarily be the best method for training. For example, training off-site, at a different institution, or in a specialized training facility may be more appropriate.

Instructions for Use

We recommend that the instructions for use include:

- the minimum and maximum internal diameter of the embolization delivery catheter
- information on any contrast media and flushing agent used with your device

- for a detachable balloon, the pressure required to rupture the balloon and the specification for the maximum inflation pressure/volume

COMMENT: some balloons are inflated by volume and not pressure.

¹Refer to <http://www.fda.gov/cdrh/ode/indicate.html> for the recommended format.

²If 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).

³See 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>.

⁴Refer to Blue Book Memorandum entitled "SIGNIFICANT RISK AND NONSIGNIFICANT RISK MEDICAL DEVICE STUDIES" at <http://www.fda.gov/cdrh/d861.html>.

⁵Although 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.

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