Guidance for Industry and FDA

Guidance for Neurological Embolization Devices

Document issued on: November 1, 2000

This document supersedes documents "Guidance Document for Neurological Embolization Devices" dated 8/13/99.

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

Plastic and Reconstructive Surgery Devices Branch
Division of General, Restorative, and Neurological Devices
Office of Device Evaluation

Preface

Public Comment:

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. 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.

For questions regarding the use or interpretation of this guidance contact, contact Keith E. Foy, M.S., at 301-594-3090 or by electronic mail at kxf@cdrh.fda.gov.

Additional Copies:

Additional copies are available from the World Wide Web/CDRH home page at http://www.fda.gov/cdrh/ode/guidance/1151.pdf or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system and enter the document number 1151 followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

Guidance for Neurological Embolization Devices

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create nor confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

I. INTRODUCTION

This guidance document replaces "Guidance Document for Neurological Embolization Devices" dated August 13, 1999. The original guidance was presented to the Neurological Devices Panel on September 17, 1999. This revised guidance reflects Panel and industry input.

The purpose of this document is to provide guidance to sponsors of neurological embolization devices intended for neurovascular use. This guidance contains information specific to neurological embolization devices submitted for premarket notification (510(k)), investigational device exemption (IDE) and premarket approval (PMA) submissions. As science changes and scientific techniques are improved, CDRH will periodically revise the document. Additional guidance regarding 510(k), IDE, and/or PMA submissions may be obtained from the FDA website at www.fda.gov/cdrh.

This guidance is intended to address issues for both preamendments class II products such as polyvinyl alcohol (PVA) particles, detachable balloons and embolization coils and post amendment and/or transitional class III products such, as cyanoacrylates. This guidance document includes special controls for class II neurological artificial embolization devices. Cyanoacrylates and other liquid polymeric embolic devices for neurological use are class III devices that require PMA approval prior to marketing.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be approved/cleared for marketing. 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 comply with 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 information is being requested that is not relevant to the regulatory decision for your pending application or 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 webpage at: http://www.fda.gov/cdrh/modact/leastburdensome.html

II. REGULATORY HISTORY

The following Federal Registry (FR) notices and Neurological Device Panel meetings are presented to provide a brief history regarding embolization devices for neurological use.

- Classification Proposed Rule: Vol. 43, No. 229, FR, page 55730 - November 28, 1978.
  The Panel recommended that the artificial embolization device(s) be classified into class III (premarket approval).

- Classification Final Rule: Vol. 44, No. 172, FR, page 51777 - September 4, 1979.
  FDA classified the neurological, artificial embolization device(s) into class III (premarket approval).

- Neurological Devices Panel meeting held on September 15, 1995.
  The Panel discussed trial design, study population, risk-benefit ratio, emergency use, and labeling for the neuro-interventional devices under consideration (platinum coils, detachable balloons, and N-butyl cyanoacrylate).

- Neurological Devices Panel meeting held on June 12, 1998.
  The Panel considered the information in three 515(i) submissions of safety and effectiveness information on three types of neurological, artificial embolization devices (PVA particles, detachable balloons, and coils) and recommended that these devices be reclassified to class II for the following indications: to permanently obstruct blood flow to an aneurysm or other vascular malformation, not excluding hypervascular tumors.

III. REGULATORY CLASSIFICATION

§ 882.5950 – Artificial embolization device (neurological), Class II

An artificial embolization device is an object that is placed in a blood vessel to permanently obstruct blood flow to an aneurysm or other vascular malformation.

Procode: **HCG** – Device, Neurological Embolization (Class II)
This device category includes PVA particles and embolization coils of various shapes and sizes.

MZQ – Balloon, Detachable, for Neurovascular Occlusion (Class II)

Note: Class II devices that use a novel detachment system or a new process of embolization may need clinical data to assess their equivalence to predicate devices.

MFE – Agent, Injectable, Embolic (Class III)
Devices which solidify/polymerize *in-situ* are contained within this category. This includes cyanoacrylates for neurological use.

IV. INTENDED USES / INDICATIONS

The intended use(s) and/or indication(s) for use of the device should be explicitly stated in the submission and in the labeling of the device. The intended use describes the objective intent of the persons legally responsible for the labeling of devices, while the indication describes a general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

The examples provided below are not intended to limit a device indication or imply that other indications have not been cleared by the agency. They are provided simply to give guidance.

Two examples of intended use statements for the PVA particles, embolization coils or detachable balloons are to embolize blood vessels and/or hypervascular lesions and to decrease blood flow to hypervascular lesions; and/or to reduce or block the rate of blood flow in vessels.

Examples of indications for use statements for these devices are:

PVA particles

- for vascular occlusion of blood vessels within the neurovascular systems. They are intended for use in the endovascular management of arteriovenous malformations (AVMs) and neoplastic lesions when presurgical devascularization is desirable.

Detachable balloons

- for artificial embolization of symptomatic carotid cavernous fistulae (CCF) in patients for whom, in the judgement of the neurosurgical management team, other medical or neurosurgical means would not be indicated.

Embolization coils

- for selective vessel supply to AVMs and other vascular lesions of the brain, spinal cord and spine when surgical resection is anticipated or desired.
- for the interventional radiologic management of AVMs, arteriovenous fistulas (AVFs) and other vascular lesions of the brain, spinal cord and spine.

V. DEVICE DESCRIPTION

The premarket submission should provide information on the device assembly, materials (both raw and finished materials, including compositions), material chemistry, range of device sizes/shapes/designs, and any accessory devices and/or materials that are used in conjunction with the proposed occlusive device. A complete device description should contain the following items:

- an identification of the raw materials used in the construction of the device and any voluntary material conformity standards;

- a written description of the components of the device and its assembly;
- the dimensions and/or range of dimensions, shapes, and device designs, including the same information for any accessory devices or materials used;
- engineering drawings of the occlusion device;
- a description of how the device is provided (sterile, assembled, single use, etc.);
- a description of the principle of operation (method of deployment and embolization), and
- any special storage or handling conditions.

VI. PRECLINICAL TESTING

Specific preclinical test methods are not described below. Rather, information that has been historically requested for clearance is provided separated by the device type.

Mechanical/Chemical Testing

When conducting testing, it is important to note that testing should be performed on an appropriate number of finished, sterilized devices or samples formed from finished, sterile devices. When multiple sizes, shapes or designs are proposed, the agency may accept testing conducted on the smallest and largest device sizes and/or on the singular worst case device type as representative of the range of proposed device sizes and designs when this information is accompanied by a scientifically valid justification for each such assumption.
Each material and/or component of the respective occlusive device should be identified and characterized. An explanation of the assembly, method of delivery and component interactions should be provided along with supporting *in vitro* and/or *in vivo* testing. Any testing provided should include the specific purpose of the test, a description of the test setup, the methodology, the results, and a comparison to the predicate device. For test standards that have been recognized by the agency, a statement/declaration of conformity to the standard and the results should be provided.

Testing should be representative of and compared to the final release criteria specifications of the device, i.e., chemistry, dimensions, strength, etc. For 510(k) submissions, this information should be compared to the proposed predicate device(s).

A. For PVA particles, the following information should be provided:

1. the chemical analysis of the final sterilized device, including explanation for the presence of processing additives, contaminants, etc.;
2. the manufacturing and test method(s) used to validate the particle sizes;
3. the explanation of how formaldehyde and/or other processing materials are removed from the particles and validation of the method used, if any; and
4. the testing to demonstrate particle size compatibility with the recommended delivery catheter(s), when mixed with the recommended contrast agent(s) or other interactive material(s), and delivered in accordance with the labeling.

B. For detachable balloons, the following information should be provided:

1. the inflation/deflation rates for each balloon size;
2. the pressure(s) required to rupture the balloon(s);

3. the volume to inflation pressure ratio; and
4. the method and force needed to detach the balloon.

C. For coils, the following information should be provided:

1. the coil strength, e.g., the force required to deform the coil shape;
2. the ease of delivery, as measured by friction when advancing and/or retracting the coil through a recommended catheter positioned in a simulated tortuosity;
3. the fiber pull-out force (for coils with fibers); and
4. the detachment time. (Changes to the detachment method of the coil device may warrant explanation of the release mechanism and final positioning (migration) of the coil.)

D. For liquid polymeric embolic agent(s), e.g., cyanoacrylate, the following information should be provided:

1. a chemical analysis and description of the final activated/polymerized material, i.e., volume displacement per quantity of material, percent material composition(s) including additives, the beginning and final hardness and/or the material viscosity;
2. a description and risk assessment of the material solidification and/or activation/polymerization process and degradation byproducts, which may include: the heat of reaction, reaction byproducts, tissue interactions during this process, material migration, material activation/polymerization time in blood, material penetration into the tissues, etc; and
3. testing which addresses the embolic agent interaction with the delivery catheter.

In addition to information requested above, also include the following preclinical information:

E. Interaction with other components

Embolization devices are routinely delivered to the operative site via various types of delivery catheters. Furthermore, the assembly of the embolization device may include the addition of a contrast additive(s) and/or flushing agent(s). Since an adverse interaction between any component of the embolization device and these procedural components might pose a safety concern, the compatibility between the embolization device and any of its system components, e.g., the delivery catheter, contrast agent(s), etc, should be assessed and included in the embolization device submission. For liquid embolic agents, testing should address the potential of one component to degrade, deteriorate, and/or dissolve other system components, i.e., dissolve and transport a catheter coating to the embolization site.

F. Shelf life

If a shelf life is proposed for a device, the testing protocol should include parameters that represent expected shipping and storage conditions. Accelerated aging test protocols should be supported/validated with confirmatory real-time, shelf life testing.

The preclinical issues listed above represent a guide to some of the testing that should be provided to adequately characterize an embolization device for the purpose of supporting a regulatory decision. However, additional testing and/or explanation(s) may be needed in some cases.

Biocompatibility Testing

A standard battery of toxicological tests is recommended in the ISO-10993 "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing." This guidance suggests short-term and long-term biological tests that might be applied to evaluate the safety of implanted medical devices.

Standard protocols such as those identified by the United States Pharmacopeia (USP) or American Society for Testing and Materials (ASTM) may be used in conducting the biocompatibility testing. Such tests should be performed on finished, sterile devices, or samples formed from finished sterile devices. These tests include the following:

- cytotoxicity (Agar gel and MEM test);
- sensitization assay;
- irritation or intracutaneous reactivity;
- acute systemic toxicity (mouse);
- mutagenicity or genotoxicity;
- hemolysis; and
- implantation.

For those products that remain in the body for longer than 30 days, the following additional test results should also be provided:

- subchronic toxicity - 90 days (with histology of the surrounding tissue);
- chronic toxicity - 180 days (with histology of the surrounding tissue); and
- long-term carcinogenicity testing should be performed for any device in which a positive genotoxicity test result was obtained.

The sponsor may also refer to the guidance, "Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices - 5/1/95 - (G95-1)" which can be obtained at http://www.fda.gov/cdrh/g951.html. This guidance provides an overview of the general types of toxicity testing that should be considered for a medical device.

Animal Testing

In the absence of appropriate *in-vitro* models and appropriate bench testing, animal testing may be needed to adequately support the safety, effectiveness and/or principle of operation of the device and any accessory components. Along with a description of the study design, test apparatus, and data, an explanation of how the animal model relates to the human condition should be provided. This explanation should include literature references and/or supporting test data. The animal study may evaluate issues such as:

- ease of delivery (friction and tortuosity);
- rupture and/or puncture of the blood vessels;
- recanalization of the vessels;
- local and systemic foreign body reactions; and
- device migration.

VII. CLINICAL DATA

The following guidance regarding clinical data is applicable to both 510(k) and PMA submissions. 21 CFR 812 describes the general information to be provided to the agency for an Investigational Device Exemptions (IDE) submission. Some additional information specific to neurological embolization clinical trials is provided below. If a sponsor has questions about protocol design not addressed in this guidance, the sponsor is encouraged to contact FDA.

A. The protocol should define the primary and secondary endpoints and include success/failure criteria for each and define device/procedural complications. These definitions should be consistent with the intended use of the device. Examples of effectiveness endpoints are the reduction in size of the vascular lesion, percentage occlusion of an aneurysm, or the occlusion of a parent vessel as measured by angiography. Other endpoint considerations might include the recanalization rate of the embolized vascular lesion, and/or the determination of the benefit of the presurgical embolization procedure, i.e., reduction in surgical time and blood loss. Safety endpoints include the incidence of new neurological deficits (transient and permanent), the rate of pre-embolization deficits (improving, staying the same, or worsening), and/or the rate of non-neurological complications.

B. The measurement tools used to assess patient neurological endpoints should be identified. While a measure like the NIH Stroke Scale may be appropriate with patients with neurological deficits, it is not particularly appropriate for patients who are normal or minimally impaired. All patients, at a minimum, should be evaluated pre-embolization and at post-embolization timepoints using a standard neurological examination that tests cranial nerves, sensory function, motor function, reflexes, gait and coordination, and mentation. A copy of the neurological examination should be provided as a case report form on which the clinician will record results. Other means of measuring endpoints may include functional outcome scales, patient self-report, and clinician or surgeon self-report (World Federation of Neurosurgeons grade (WFNS), Glasgow Outcome Scale (GOS), Glasgow Coma Scale (GCS), NIH Stroke Scale, and/or Barthel Index). As much as is possible, the evaluation of endpoints should be independent and masked. For any scale used, the directions for determining values in the test need to be part of the CRF and the scale range should be indicated on the CRF where the score will be entered. When appropriate, neuropsychological testing, e.g., personality, associations and/or IQ, should be considered.

C. 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. The methods used to measure the lesion, e.g., angiography, MRI, MRA and/or CT, as well as the follow-up intervals should be completely described. Because the vascular disorder and device use may determine

which imaging tools are used and the length and interval of follow-up, the rationale for these protocol designs should be provided along with any supporting literature/studies, e.g., liquid/polymeric embolization agents may require follow-up MRIs to verify the lack of a histotoxic effect.

In addition to providing technically detailed information on how and when the measurements of the lesion/embolized lesion are obtained, it is important to consider internal and intra reader variability so that reader bias can be diminished or eliminated. A single reader may address reader bias.

D. Follow-up evaluation intervals should be specified. However, patients with lesions that aren't surgically removed should be followed to at least one year.

E. A full description of the embolization procedure should be provided, including:

1. device/component assembly and preparation;
2. monitoring of neurological function during the procedure, in patients under local anesthesia;
3. use of anticoagulation medication, i.e., drug, dose, etc.;
4. use of antibiotics;
5. circumstances under which adjunctive embolization devices may be used during the procedure;
6. whether there is a plan for staged embolization and the features of that plan;
7. the therapy available in the event of stroke or other complication during the embolization procedure; and
8. the time interval between embolization and definitive resection when embolization is a pre-surgical procedure.

VIII. LABELING

Copies of all proposed labeling for the device, including any information, literature, or advertising that constitutes labeling under Section 201(m) of the Act, should be submitted. General labeling requirements for medical devices are contained in 21 CFR Part 801. These regulations specify the labeling requirements for all devices. Additional guidance regarding device labeling can be obtained from FDA's publication "Labeling: Regulatory Requirements for Medical Devices," and from the Office of Device Evaluation's "Device Labeling Guidance". Both documents are available upon request from the Division of Small Manufacturers Assistance (HFZ-220), Center for Devices and Radiological Health, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 or through the internet at http://www.fda.gov/cdrh/dsma/dsmamain.html.

The intended use statement should include the specific indications for use and identification of the target populations. Specific indications, target populations, expiration dating, and/or storage conditions should be supported by the data provided.

Labeling includes the following:

- device outer labels;
- packaging labels;
- package insert; and
- instructions for use, including appropriate wording, limitations, precautions, and/or warnings.