Guidance for Industry and FDA Staff

Pre-Clinical and Clinical Studies for Neurothrombectomy Devices

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For questions regarding this document contact Carlos Peña, Ph.D., M.S., at (301) 827-3340 or carlos.pena@cdrh.fda.gov or Neil Ogden at (240) 276-3600 or neil.ogden@cdrh.fda.gov.

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

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

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Preface

Public Comments

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Guidance for Industry and FDA Staff

Pre-Clinical and Clinical Studies for Neurothrombectomy 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 guidance document describes FDA's recommendations for pre-clinical and clinical studies that involve neurothrombectomy devices conducted to support premarket submissions for neurothrombectomy devices indicated for ischemic stroke. A neurothrombectomy device is intended to retrieve or destroy blood clots in the cerebral neurovasculature by mechanical (i.e., snare or suction), laser, ultrasound technologies, or combination of technologies.

This guidance document does not describe all elements required for premarket notification (510(k)) submissions, investigational device exemption (IDE), or premarket approval (PMA) applications. This guidance document supplements other FDA publications on 510(k) submissions, IDE, and PMA applications and is not a replacement for these documents.

Premarket Notification -510(k) Information

For general information on 510(k), refer to 21 CFR 807.87, the guidance entitled **Format for Traditional and Abbreviated 510(k)s**[1] and "**Premarket Notification 510(k)**" in the (Center for Devices and Radiological Health) **CDRH Device Advice** at http://www.fda.gov/cdrh/devadvice/314.html.

Investigational Device Exemption Information

For general IDE information, refer to 21 CFR Part 812 or to the "**Introduction IDE Overview**," at http://www.fda.gov/cdrh/devadvice/ide/index.shtml.

Premarket Approval Application (PMA) Information

For general information about PMA applications, refer to 21 CFR 814 or "**Application Methods**," at http://www.fda.gov/cdrh/devadvice/pma/app_methods.html.

[1] http://www.fda.gov/cdrh/ode/guidance/1567.html

FDA's guidance documents, including this guidance document, 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.

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 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. Regulatory Pathway

The regulatory pathway, i.e., premarket notification submission (510(k)), *de novo* classification, or premarket approval application (PMA), for a neurothrombectomy device depends on the identification of an appropriate predicate device, the technology of the device, and its indications for use. Mechanical neurothrombectomy devices indicated for retrieval of clots in patients with ischemic stroke are regulated as class II devices, product code NRY, requiring 510(k), 21 CFR 870.1250.

In general, FDA will attempt to review neurothrombectomy devices that are based on methods or technologies, other than mechanical, as class II devices. If we are unable to make a substantial equivalence determination from the descriptive characteristics and performance data you submit, we will first consider whether *de novo* classification can provide the proper degree of regulatory control. If so, we will communicate this to you in a not substantially equivalent letter, which begins the *de novo* process.[2]

Whether *de novo* classification is appropriate depends, in part, on the risk profile of your device. If we are unable to find a device substantially equivalent to a legally marketed predicate device, and *de novo* classification is not appropriate, a premarket approval application may be required.[3] Regardless of the regulatory pathway, you should conduct a thorough evaluation of device safety and effectiveness. The remainder of this document describes the preclinical and clinical studies

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[2] For information about the *de novo* classification process, please see "**New Section 513(f)(2) - Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff**" at http://www.fda.gov/cdrh/modact/classiii.html.

[3] See section 513(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360c(a)). See also the discussion of PMA applications at http://www.fda.gov/cdrh/devadvice/pma/ and **"Quality System Information for Certain Premarket Application Reviews, Guidance for Industry and FDA Staff**" at http://www.fda.gov/cdrh/comp/guidance/1140.pdf.

we generally recommend to ensure a thorough evaluation for all neurothrombectomy devices indicated for ischemic stroke.

3. Biocompatibility

We recommend you provide biocompatibility testing of the device materials, as described in the guidance entitled **Use of International Standard Organization (ISO) standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.**"[4] We recommend you select tests appropriate for the duration and level of contact with your device. For a 510(k) submission, if identical materials, with identical material processing, are used in a predicate device with the same type and duration of subject contact, you may identify the predicate device in lieu of providing biocompatibility testing.

4. Pre-clinical Evaluation

Pre-clinical evaluation through bench and animal testing helps assess the usability, safety, and effectiveness of neurothrombectomy devices indicated for ischemic stroke. Our recommendations for bench and animal testing are described below. However, depending on the design, technology, and performance of your device, we may recommend additional pre-clinical evaluation.

A. Test Protocols

We recommend the test protocol describe clearly defined test objectives and a rationale in support of your belief that the endpoints and pass/fail criteria are meaningful and clinically relevant.

B. Test Methods and Conditions

We recommend you provide a clear description of the test methodology and actual test conditions. We recommend you conduct pre-clinical testing, where appropriate and feasible, in an environment that simulates actual clinical conditions.

C. Actual Device Evaluated

We recommend you indicate whether you used a neurothrombectomy device fabricated by representative manufacturing process. Otherwise, we recommend you submit a rationale explaining your belief that the device you used in testing will provide a sufficient assessment of the final finished device.

D. Statistical Analysis

We recommend you provide your sample size justification. We recommend the results you report include, where appropriate:

- number of samples
- range of values
- mean

[4] http://www.fda.gov/cdrh/g951.html

- standard deviation
- 95% confidence interval.

We also recommend you provide a probability measure that is indicative of the statistical significance of any comparisons you make to other devices or control groups.

5. Bench Testing

We recommend you conduct bench testing to evaluate your device's:

- maneuverability
- flexibility
- durability
- torque strength.

We recommend you establish device failure endpoints for each of these characteristics so that appropriate information can be conveyed in the instructions for use.

6. Animal Testing

If you conduct any animal testing, we recommend the testing address usability, (i.e., maneuverability and flexibility), safety, and effectiveness, as described below. The General Surgery Devices Branch is available to answer your questions about animal testing.

A. Usability

We recommend you evaluate the maneuverability and flexibility of the neurothrombectomy device in an animal model. We recommend you evaluate the users' ability to reliably deploy and use the neurothrombectomy device under clinical conditions in a location in the animal (i.e., cerebral neurovasculature) that reflects the indications for use of the device. We also recommend that you use animal testing to evaluate the maximum number of attempts that the user can safely retrieve or destroy blood clots.

B. Safety

Cerebrovascular vessels lack support from adjacent tissues and may pose additional, increased safety concerns compared to the peripheral vasculature. If the device will contact or interact with the vessel wall (e.g., laser or suction devices), we recommend you evaluate the extent of potential tissue damage the device may cause, preferably in a vessel of comparable size in an animal model.

We also recommend you evaluate the vessel wall integrity and monitor blood vessels proximal, adjacent, and distal to the clot site during device deployment, clot retrieval or clot destruction. For devices that emit energy, we recommend you monitor any temperature changes in the vessel wall and adjacent tissue during use of your device.

We recommend you evaluate the hemorrhagic and thrombogenic potential of the neurothrombectomy device.

To evaluate the hemorrhagic potential of the device, we recommend you perform histological evaluation of the vessels and tissues at the site of the clot following use of the device.

To evaluate the thrombogenic potential of the device, we recommend you quantify thrombus, including number, size, and location proximal, adjacent, or distal to the clot site in a vessel of comparable size in an animal model.

C. Effectiveness

We recommend you demonstrate that the device captures or destroys thrombi of variable size, coagulation, and composition (e.g., fibrin, plasminogen, platelet composition). We also recommend you characterize whether your device causes the formation of smaller blood clots, either during or after its use.

We recommend you characterize revascularization success by using injected clots in an animal model with a comparison control group.

7. Clinical Studies

FDA believes that neurothrombectomy devices addressed by this guidance document are significant risk devices as defined in 21 CFR 812.3(m)(4).[5] Therefore, clinical studies of neurothrombectomy devices must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. In addition to the requirement for 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). The General Surgery Devices Branch is available to discuss any questions you have about the development of an IDE protocol or to discuss clinical data collected outside the United States.

Your clinical study should address the recommendations below:

A. Subject Selection

Inclusion Criteria

We recommend your clinical study enroll patients with evidence of a treatable occlusion, such as angiographic evidence of occlusion (Thrombolysis in Myocardial Infarction [TIMI] grade 0 flow) or contrast penetration with minimal perfusion (TIMI grade I flow) in a vascular distribution consistent with the subject's neurologic findings. We recommend you assess the degree of occlusion with cerebral angiography. If you plan to use a different method, you should contact the General Surgery Devices Branch.

Your inclusion criteria should also specify subjects who present with a National Institutes of Health Stroke Scale (NIHSS) ≥4. We recommend you employ a randomization scheme that will stratify sufficient numbers of subjects by NIHSS score to ensure a similar distribution of scores between treatment and control arms. We believe this randomization scheme improves outcome comparisons.

[5] See http://www.fda.gov/oc/ohrt/irbs/devices.html#risk.

Your protocol should specify whether you intend to enroll patients who will be receiving approved drug therapy for ischemic stroke, who have failed approved drug therapy for ischemic stroke or who are not eligible for approved drug therapy for ischemic stroke. If you intend to study your device in combination with drug therapy that has not been approved for this indication for use or route of administration, we recommend that you contact the FDA Office of Combination Products to determine jurisdiction. Further information is available at the Office of Combination Products website, available at http://www.fda.gov/oc/combination.

Exclusion Criteria

We recommend you exclude subjects with:

- neurologic signs that are rapidly improving at the time of randomization or treatment
- NIHSS >30 or coma because subjects in poor neurologic condition have a very high mortality and are unlikely to benefit from revascularization and the risk of hemorrhage in this population is exceedingly high
- pregnancy
- known serious sensitivity to radiographic contrast agents
- current participation in another investigational drug or device study
- CT or Magnetic Resonance Imaging (MRI) evidence of hemorrhage on presentation
- CT scan showing hypodensity involving greater than 1/3 of the middle cerebral artery (MCA) territory (or suspected stroke region) on presentation
- CT or MRI evidence of mass effect or intracranial tumor (except small meningioma)
- angiographic evidence of carotid dissection, high grade stenosis that will prevent access to the clot, or vasculitis
- uncontrolled hypertension defined as systolic blood pressure >185 or diastolic blood pressure >110 that cannot be controlled except with continuous parenteral antihypertensive administration.
- use of IV heparin in the past 48 hours with PTT > 2.0
- use of warfarin anticoagulation with INR > 3.0
- platelet count < 30,000.

Onset to Treatment with Neurothrombectomy Devices

We recommend initiating treatment using the neurothrombectomy device within 8 hours of symptom onset. If you plan to initiate treatment in subjects more than 8 hours after symptom onset, we recommend you explain the delay. We recommend you record the time of symptom onset.

The initiation and completion of treatment with the neurothrombectomy device relative to the onset of symptoms should fall within the time window defined by the study protocol. (Therefore, we recommend you exclude subjects who awaken from sleep with symptoms.) We recommend you record the time from symptom onset to initiation and to completion of treatment with the neurothrombectomy device and that you exclude subjects treated outside the time window designated by your protocol. If your trial is designed to initiate treatment in subjects more than 8 hours after symptom onset, we recommend you discuss your trial design with the General Surgery Devices Branch before you submit your IDE.[6]

Magnitude of the Clot Load: Location, Size, and Etiology

To obtain meaningful comparisons of the treated and control population, we recommend that you include only subjects with stroke in either the anterior or posterior circulation. We are aware of the difficulty in enrolling subjects for either the anterior or posterior circulation and will, therefore, consider studies including both types. If you include both types, we recommend that you provide a subset analysis of each type.

We recommend you assess the source, size, and density of the subject's clot. These assessments can include CT-Angiograms or other techniques to assess clot properties.

Subject variables that impact the likelihood of an embolic source versus an atheromatous or stenotic occlusion are important to document to identify subjects for future study. Therefore, we recommend you document the following subject variables:

- presence of atrial fibrillation or other arrhythmias that predispose to embolic strokes
- results of cardiac echocardiograms
- the presence and degree of carotid stenosis
- history of other atheromatous (cardiac) disease.

Control Groups

We are aware of the difficulty in recruiting subjects for stroke treatment studies, and the need to provide control subjects with the current standard of care for ischemic stroke. Due to these challenges, we will consider various study designs if they are scientifically sound and addresses the relevant safety and effectiveness questions including randomized comparison to other legally marketed devices or therapies, or concurrent controls comparing treatment arm to standard of care. We recommend you discuss your study design and any statistical issues with the General Surgery Devices Branch before you submit your IDE.

B. Initial Assessments

Initial assessments should include the following measurements.

Angiography

[6] Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke 2005;36(7):1432-8.

We recommend you use an angiographic grading scheme. Stroke studies published to date have used the TIMI grading scale of flow.[7,8,9] The TIMI scale has grades 0-3, with 0 being complete occlusion, and 3 normal flow. We recommend you include a grading of the collateral flow.[10] For further discussion on revascularization, refer to Section 12. Endpoints.

Imaging Assessments

We recommend the initial evaluation include CT scans to rule out intracranial hemorrhage or other excluded pathology. The CT scans should also be used to assess the volume of hypodensity. In centers where MRI scans of subjects with acute stroke are used instead of CT scans, MRI scans may be used to demonstrate lack of hemorrhage.

We also recommend you assess subjects with 3 or 4-vessel cerebral angiography. We recommend you document the location of clot and flow (TIMI scale). We also recommend you document the presence or lack of collaterals because this can be an important predictor of clinical outcome.[11]

We recognize that the use of diffusion and perfusion mismatch on MRI imaging, or evidence of ischemic penumbra on CT perfusion scans may be useful for selecting subjects who are more likely to benefit from revascularization. If your study is designed to evaluate effusion and diffusion mismatch, we recommend that you discuss this with the General Surgery Devices Branch before you submit your IDE.

Neurologic Evaluation

We recommend you evaluate subjects using the NIHSS score before enrollment and before treatment begins. We also recommend you obtain the subject's historical Barthel Index and modified Rankin scale (mRS) scores from the subject or caregiver to determine pre-event status.

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[7] G J del Zoppo, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M; the PROACT Investigators. PROACT: A Phase II Randomized Trial of Recombinant Pro-Urokinase by Direct Arterial Delivery in Acute Middle Cerebral Artery Stroke. Stroke 1998; 29:4-11.

[8] Intra-arterial Prourokinase for Ischemic stroke. The PROACT II Study: A Randomized Controlled Study. JAMA 1999;282(21):2003-2011.

[9] Gobin YP, Starkman S, Duckwiler GR, Grobelny T, Kidwell CS, Jahan R, Pile-Spellman J, Segal A, Vinuela F, Saver JL. MERCI 1: a phase 1 study of Mechanical Embolus Removal in Cerebral Ischemia. Stroke 2004;35(12):2848-54.

[10] Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, Dillon W, Warach S, Broderick J, Tilley B, Sacks D; Technology Assessment Committee of the American Society of Interventional and Therapeutic Neuroradiology; Technology Assessment Committee of the Society of Interventional Radiology. Trial design and reporting standards for intra-arterial cerebral thrombolysis for ischemic stroke. Stroke. 2003 Aug;34(8):e109-37.

[11] Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, Dillon W, Warach S, Broderick J, Tilley B, Sacks D; Technology Assessment Committee of the American Society of Interventional and Therapeutic Neuroradiology; Technology Assessment Committee of the Society of Interventional Radiology. Trial design and reporting standards for intra-arterial cerebral thrombolysis for ischemic stroke. Stroke. 2003 Aug;34(8):e109-37.

C. Follow-Up Assessments

Follow-up assessments should include the following measurements.

Angiography

We recommend all subjects have angiography to assess the extent of restoration of flow immediately following the procedure. We recommend an independent radiologist review all angiograms and any other imaging used to evaluate restoration of flow. Independent scoring of the TIMI grade is important when follow-up angiography is used in efficacy analyses.

Imaging Assessments

We recommend you obtain CT scans within 24 hours after neuro-thrombectomy, and at discharge to assess for hemorrhage or other events. We also recommend you obtain follow up MRI scans, CT scans, or other imaging assessments at 30 and 90-day follow-up time points. We recommend you document the occurrence and rate of all asymptomatic and symptomatic hemorrhages. We also recommend you obtain CT scans immediately after any neurologic decline that occurs within the 90-day follow period.

Neurologic Evaluation

We recommend you obtain the NIHSS and mRS immediately following the procedure, as well as at 24 hours, 7-10 days (or at discharge from hospital), 30 days, and 90 days following the procedure. We recommend a certified examiner or neurologist who is masked to the treatment group perform assessments. We also recommend you obtain the NIHSS score, mRS, Barthel Index and Glasgow Outcome Scale scores, or any other scores used in the primary outcome measure at 30 and 90-days following the procedure. During the study, we recommend you document the severity of any subject experiencing a neurologic deterioration with the NIHSS.

D. Outcome Measures

Outcome measures should include the following measurements.

Safety Endpoints

We recommend you record and report all adverse events, regardless of whether you believe they are device-related, for all subjects, including those excluded based on angiographic findings for adverse events for 24 hours, or until alternative stroke treatment is initiated, whichever comes first.

The adverse events recorded should include:

- failure to deploy the device or remove the clot
- perforation, dissection or other damage to the vessel wall
- vessel rupture
- hemorrhage, including subarachnoid hemorrhage from vessel injury

- hemorrhagic transformation of the treated stroke
- thrombus formation proximal, adjacent, or distal to the clot site
- death from any cause
- re-occlusion or stroke in other territories previously not involved
- partial restoration[12]
- distal thrombus formation
- neurologic deterioration.

We also recommend that you categorize the severity of adverse events. Serious adverse events (which preclude treatment success in a subject) should include symptomatic intracerebral hemorrhage, arterial dissection, myocardial infarction, and death. We recommend you report asymptomatic hemorrhage rates and new strokes in a previously uninvolved anterior or posterior circulation.

We recommend you document separately adverse events related to neurological worsening, and we believe that a change in the NIHSS of ≥4 points should be recorded as neurologic deterioration and an adverse event.

We also recommend you document adverse events that occurred during deployment of the device and include that information when you identify these events.

Effectiveness Endpoints

Determination of the primary efficacy endpoint for your device will depend upon its design, technology, and indications for use. Endpoints should address the following measurements.

Clinical Endpoints

Your clinical effectiveness endpoint should be outcome assessments at 30 days and 90 days by any appropriate, validated neurologic impairment scale, disability measure, or handicap scale. Examples of appropriate measures include the mRS, NIHSS score, Barthel Index, and Glasgow Outcome Scale. The selection of appropriate clinical endpoints and statistical approaches depends on the device and study design.

Imaging Endpoints

We recommend you record revascularization success using TIMI grading of flow before and after treatment with your device. Revascularization success should be defined as establishment of TIMI grade II or III flow in all vessels on angiography following the procedure. We also recommend you assess the reproducibility of any technique in your study to assess infarct volume and include an appropriate control group to validate this surrogate endpoint. We believe size of infarct on CT as a

[12] Treatment of Basilar Artery Embolism with a Mechanical Extraction Device. Stroke 2002;33:2232-2235.

surrogate endpoint has not been validated, however, it may be appropriate as a secondary surrogate endpoint.

8. Measures of Success

Definition of study success depends on the primary efficacy measures you select. For studies using clinical outcomes using mRS, we recommend you define success as a significantly increased number of subjects having a good (score of 0-2) outcome compared to untreated controls, or equivalent outcome compared to treatment with other efficacious devices or therapies. We recommend you measure safety success in comparison to the control (equivalence or superiority). The primary safety and efficacy endpoints should include an analysis of intent-to-treat subjects, treated subjects, and observed subjects.

9. Alternative Sources of Clinical Information

If you believe published reports may be adequate to support safety and effectiveness of your device, you may submit them for our review.[13]

[13] See the guidance, **The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry** at http://www.fda.gov/cdrh/ode/guidance/1332.html.