This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer 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. This guidance will be updated in the next revision to include the standard elements of GGP's.

Carotid Stent - Suggestions for Content of Submissions to the Food and Drug Administration in Support of Investigational Device Exemption (IDE) Applications

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Division of Cardiovascular, Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

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

Draft Suggestions for Carotid Stent IDE Applications

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Introduction

The purpose of this guidance is to describe the format and content of an investigational device exemption (IDE) application for carotid stenting. The guidance is **tailored towards sponsor/investigator IDEs.** If you have a well designed study and your protocol has been reviewed by an institutional review board (IRB), you may have already met many of the IDE requirements.

The Food and Drug Administration (FDA) considers a stent in the carotid artery a significant risk device. Legal and ethical considerations require that such studies involving US patients be carried out under an IDE.

The *Suggested IDE Content* section of this document is developed from the check-list used by ODE staff in reviewing IDEs. While the order is not critical, the inclusion of these items is important. Presenting the information in this order will facilitate review. The *Informed Consent* section of this document is also developed from the reviewer check-list and, while not a complete guidance, includes some items commonly found lacking in submissions to the agency.

If you can readily provide the information outlined below, you may submit an IDE directly. However, if you are uncertain about the adequacy of your data and/or protocol, you may submit a pre-IDE. A pre-IDE is the mechanism whereby FDA can provide informal feedback regarding specific aspects of your application and serves to initiate discussions between a submittor and the review division.

Additional general information regarding investigational device exemption (IDE) applications may be obtained from CDRH's **Division of Small Manufacturer's Assistance** by calling (800) 638-2041 or (301) 443-6597. If you have questions regarding this Guidance, please call one of the contacts listed below at (301) 443-8320 or e-mail at BDZ@FDADR.CDRH.FDA.GOV

DCRND Contacts

Name	E-mail	Voice phone	fax
Bram Zuckerman	{BDZ}	301-443-8243	301-480-4204
Dan Spyker	{DXS}	301-443-8320	301-594-3076
Judy Danielson	{JJD}	301-443-8243	301-480-4204
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Tara Ryan	{TXR}	301-443-8243	301-480-4204
Wolf Sapirstein	{WYS}	301-443-8320	301-594-3076

Suggested IDE Content

1. **Report of Prior Investigations**
   a. Describe your prior clinical (including adverse events), animal, and bench testing relating to this study.
   b. Provide a bibliography of relevant publications. Include copies of any important articles(not listed in Attachment A.
   c. Describe any other important unpublished information (or state there is none).
   d. State whether the animal or bench testing was done in compliance with good laboratory practices (GLP) or state that this question "does not apply".

2. **Overall Clinical Plan (all studies planned)**

   A Clinical Plan (about one page) should be included in the initial submission and updated as necessary. The Clinical Plan should include a brief description (not a complete protocol) of each of the clinical studies planned (pilot, feasibility, market entry, or other).

   The Clinical Plan should include for each study:
   - descriptive title
   - study design including whether concurrent or non-current controls will be used
   - sample size
   - primary outcome measures
   - principal results (achieved or expected)

   Taken together, these studies must provide sufficient valid scientific evidence of safety and effectiveness and form the basis for the labeling of the device (see *Attachment C. Methodology Suggestions*).

   While an initial feasibility study without concurrent controls may be appropriate, a randomized clinical trial against carotid endarterectomy will be necessary to determine the importance of carotid stenting in patients with carotid disease.

3. **Investigational Plan (this study)**
   a. **Purpose** should clearly define:
      - Name and intended use of the device
      - Objectives of this investigation
      - Duration of the investigation
      - The number of patients to be involved
   b. **Protocol and Case Report Forms** (CRF) -- Protocol must provide an adequate description of the methodology involved. If the treatment is randomized, describe any differences in follow-up between groups or state that the follow-up will be the same for both groups. Include a blank copy of the CRF.
   c. **Risk analysis** should support the finding of an adequate benefit to risk ratio
      - Describe and analyze the patient risks, especially problems encountered in your own or other reported studies
      - Describe how the risks will be minimized and justify those which remain
      - Describe the patient population (age, sex, medical condition)
   d. **Description of the Device**
      - List each component of the stent system and provide current labeling

- State the principle of operation
- Describe any changes to the procedure or modifications to the device system

e. **Monitoring Procedures.** If this is a multi-center study, then provide:
- Description of the monitoring procedure
- Name and address of the study monitor
- The manufacturer's tracking of these devices should be adequately described

4. **Manufacturing Information** -- The IDE application should include information on the device manufacturing, materials, processing, packaging, storage, and installation information. This is usually accomplished by including a letter from the manufacturer granting the agency access to this information.

5. **Investigator Information**
   a. Provide a sample of sponsor's investigator agreement
   b. If there will be multiple investigators, certify that all investigators will sign the investigator agreement
   c. Name, address and *curriculum vitae* of each principal investigator

6. **Institutional Review Board (IRB) Information and Informed Consent Form**
   a. Provide the name & address of the IRB chairperson
   b. Include a copy of the informed consent form (see *Informed Consent -- Required Elements*)
   c. Describe the action taken by the IRB, i.e., study approval
   d. If this is a multicenter study, how many IRBs have approved and how many are currently reviewing the study protocol and informed consent

7. **Sales Information**
   a. Is the stent to be sold? (yes or no)
   b. If yes, how much will be charged?
   c. Explain why sale does not amount to commercialization.

8. **Other Information**
   a. Labeling -- if appropriate state "This is a currently marketed device for ... ". If not, the device should be labeled: "CAUTION -- For Investigational Use Only".
   b. Environmental Impact Statement -- state "I claim categorical exclusion from the requirement for environmental impact assessment since devices shipped under Investigational Device Exemption are intended to be used for clinical studies in which waste will be controlled or the amount of waste expected to enter the environment may reasonably be expected to be nontoxic"
   c. Verify your understanding of the need for reporting of unanticipated adverse events, progress reports, and a final report with Significant Risk Device studies per 21 CFR 812.40 (a copy of *Sponsor Responsibilities for a Significant Risk Device Investigation* will be included with your approval letter)

Informed Consent -- Required Elements

Elements expected in the informed consent include:

1.__ a statement that the study involves research

2.__ an explanation of the purposes of the research

3.__ the expected duration of the subject's participation

4.__ a description of the procedures to be followed

5.__ identification of any procedures which are experimental

6.__ a description of any reasonably foreseeable risks or discomforts to the subject including the risk of stent crush and a description of steps which the patient can take to avoid stent crush

7.__ a description of any benefits to the subject or others

8.__ a disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject

9.__ a statement describing the extent to which confidentiality of the subject's records will be maintained and that notes that FDA may inspect the records

10.__ an explanation as to whether any compensation and/or medical treatments are available if injury occurs and, if so, what they consist of or sources of further information

11.__an explanation of whom to contact for answers to questions about the study and the subject's rights and whom to contact in the event of a research-related injury

12.__ a statement that participation is voluntary and that subjects may refuse to participate or discontinue participation at any time without penalty or loss of benefits

When appropriate:

13.__ a statement that the procedure or treatment may involve unforeseeable risks to subject, or to the embryo or fetus should the subject become pregnant

14.__ anticipated circumstances under which the investigator may terminate the subject's participation without regard to the subject's consent

15.__ any additional costs to subject as a result of participation

16.__ consequences of a subject's decision to withdraw and procedures for withdrawal

17.__ a statement that significant new findings which may relate to the subject's willingness to participate will be provided to the subjects

18.__ the approximate number of subjects involved in the study

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Attachment A. Carotid Stent Bibliography

Center for Devices and Radiological Health

This document collects books, citations to the primary literature, and other published and unpublished documents relevant to intravascular stenting, particularly of the carotid artery collected by the CDRH Division of Cardiovascular, Respiratory and Neurological Devices (DCRND). Any citation marked with a *, is on file in the DCRND (HFZ-450) offices, 130L, 9200 Corporate Boulevard, Rockville, MD 20850. Questions -- call Dan Spyker 301-443-8320, fax 301-594-3076, InterNet: dxs@fdadr.cdrh.fda.gov.

1. US DHHS, National Center for Health Statistics. Advance report of final mortality statistics, 1986. Monthly vital Statistics Report, vol. 37, no. 6. Hyattsville, Md.: Public Health Service, 1988. (Publication no. DHHS (PHS) 88-1120)

2. Becker GJ. Should metallic vascular stents be used to treat cerebrovascular occlusive disease. Radiology 1994:191:309-312

3. Heyman A, Wilkinson WE, Heyden S, et al. risk of stroke in asymptomatic persons with cervical arterial bruits: a population study in Evans County, Georgia. N Engl J Med 1980; 302:838-41

4. Wolf PA, Kannel WB, Sorlie P, et al. Asymptomatic carotid bruit and risk of stroke: the Framingham study. JAMA 1981; 245:1442-5.

5. North American symptomatic Carotid Endarterectomy Trial collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325:445-453.

6. European Carotid Surgery Trialists; Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or mild (0-29%) carotid stenosis. Lancet 1991;337:1235-1243.

7. US VA, Veterans Affairs Cooperative Studies Program 309 Trialist Group. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. JAMA 1991;266:3289-3294.

8. Bergeon P, Rudondy P, Benichou H, et al. Transluminal angioplasty for recurrent stenosis after carotid endarterectomy. Prognostic factors and indications. Int Angiol 1993;12:256-9

9. Yellayi SS, Schatz RA. Indications and use of the Palmaz-Schatz coronary stent. Cardiol Clin. 1944;12:651-63.

10. Fry ET, Hermiller JB, Peters TF, et al. Indications for and applications of the Gianturco-Roubin coronary stent. Cardiol Clin. 1994;12:631-49.

11. Saltiel FS; Grant G; Dake MD; Fischell TA: Comparative effectiveness of intravascular stents in resisting arterial vasoconstriction: evaluation with use of intact elastic (rabbit aorta) and muscular (dog carotid) arteries in an ex vivo model. J Vasc Interv Radiol 1995 May-Jun;6(3):379-85.

Abs: PURPOSE: The ability of three different intravascular stents (Gianturco-Roubin, Palmaz-Schatz, and CV Rad), and two different metals (stainless steel and tantalum) to resist vasoconstriction was evaluated in an intact artery *ex vivo* model. MATERIALS AND METHODS: Stents were deployed in 21 rabbit thoracic aortae and five dog carotid arteries, which were constricted with phenylephrine and serotonin, respectively. Vasoconstriction was measured with the use of high-frequency ultrasonic imaging. RESULTS: The maximal vasoconstriction of the control segment was 37.7% +/- with rabbit aortae and 36.3% +/- 4.1 with dog carotid arteries, while the average maximal constriction for all segments in which stents were placed was 5.7% +/- 1.1 ($P < .01$). The maximal constriction of the Gianturco-Roubin stainless steel stent was 9.4% +/- 2.7

versus 7.9% +/- 1.6 with the tantalum version (P = .65). Both designs showed somewhat greater constriction compared with either the Palmaz-Schatz (3.3% +/- 0.9) or the CV Rad (1.4% +/- 1.1) stents. CONCLUSIONS: Although all of the stents tested substantially resist arterial vasoconstrictive forces, the Palmaz-Schatz and CV Rad stents resist vasoconstriction to a greater degree than the Gianturco-Roubin stents. Tantalum and stainless steel stents of the same design (Gianturco-Roubin) appear similar in their ability to resist vasoconstrictive forces. CENTER: Division of Cardiovascular Medicine, Stanford University School of Medicine.

12. Dietrich EB, Rodreguez-Lopez J, Lopez-Galarza L: Stents for vascular reconstruction in the carotid arteries (abstract). Circulation 1995; 92(8): I-383.

13. Iyer SS, Yadav S, Vitek J, *et al:* : Technical approaches to angiographic stenting of the extra-cranial carotid arteries (abstract). Circulation 1995; 92: I-383.

14.* Satler LF, Hoffman R, Lansky A, et al: Carotid stent-assisted angioplasty: preliminary technique, angiography, and intravascular ultrasound observations. J Invas Cardiol 1996; 8: 23-30

15.* Beebe HG, Archie JP, Baker WH, et al: Concern about safety of carotid angioplasty. Stroke 1996; 27(2): 197-8.

16.* Moore WS, Barnett HJM, Beebe HG, Bernstein EF, et al: Guidelines for carotid endarterectomy -- a multidisciplinary consensus statement from the ad hoc committee, Americah Heart Association. Stroke 1995; 26: 188-201.

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2. Becker GJ. Should metallic vascular stents ..treat cerebrovascular occlusive disease. Radiology 1994
15. Beebe HG, Archie JP, Baker WH, et al: Concern about safety of carotid angioplasty. Stroke 1996; 27(2)
8. Bergeon P..Transluminal angioplasty for recurrent stenosis.. carotid endarterectomy.. Int Angiol 1993
12. Dietrich EB, Rodreguez-Lopez J,*et al:* :Stents for vascular reconstruction in the carotid arteries Circulation 1995
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3. Heyman A, Wilkinson.. Risk of stroke in asymptomatic .. cervical arterial bruits:.. N Engl J Med 1980
13. Iyer SS, Yadav S*et al:* : Technical approaches to angiographic stenting .. carotid arteries Circulation 1995
16. Moore WS, Barnett HJM.. Guidelines for carotid endarterectomy - AHA. Stroke 1995; 26: 188-201.
5. North American symptomatic..Beneficial effect of carotid endarterectomy carotid stenosis. N Engl J Med 1991
11. Saltiel FS; Grant G.. Comparative effectiveness of intravascular stents .. J Vasc Interv Radiol 1995
14. Satler LF, Hoffman R, Lansky A, et al: Carotid stent-assisted angioplasty: J Invas Cardiol 1996
1. US DHHS NCHS. Advance report of final mortality statistics, 1986 USPHS, 1988. (Pub no. 88-1120)
7. US VA ..Cooperative Studies Program... Carotid endarterectomy..symptomatic carotid stenosis. JAMA 1991
4. Wolf PA, Kannel WB, Sorlie P, et al. Asymptomatic carotid bruit and risk of stroke: JAMA 1981; 245:1442-5.
9. Yellayi SS, Schatz RA. Indications and use of the Palmaz-Schatz coronary stent. Cardiol Clin. 1944;12:651-63.

Attachment B. Recommended Stent and Delivery System Testing

STENT TESTING

The description of the methods and results of three types of testing is recommended prior to the start of a carotid stent IDE, including feasibility/pilot studies:

1. Crush Test should include:
   a) Testing on the smallest and largest diameter stents of each separate design proposed in the study.
   b) Estimated external forces applied over an adequate length of the stent (~10-15 mm).
   c) A justification of all estimated forces and a detailed description of how they were calculated should be included with the results.

2. Stress Analysis should include:
   a) A finite element analysis (FEA) on a sample of each different stent design.
   b) Loading conditions should include, at a minimum, bending and internal pressure.
   c) Fatigue testing to a 10 year equivalent. This testing can be carried out concurrently with clinical studies.

3. Kinking Test should include:
   a) An assessment of the potential for kinking of each stent design
   b) Special assessment of long stents (longer than 15 mm).

DELIVERY SYSTEM TESTING

The testing recommended for the balloon depends on the balloon type (high pressure or not) and approval status (cleared for marketing or not).

	Currently marketed balloon	Balloon NOT currently marketed
High Pressure Balloon	• Balloon burst within the stent • Repeat inflation within the stent	• ICDG Guidance Document* tests • Balloon burst within the stent • Repeat inflation within the stent
NOT high pressure balloon	*and protocol calls for post-deployment stent expansion with a different balloon* • Balloon burst within the stent	• ICD Guidance Document *tests • Balloon burst within the stent

If applicable, describe the crimping technique that will be used and conduct the tests using the crimped devices.

**See Interventional Cardiovascular Devices Group (ICDG) Guidance Document, May 1994. Questions regarding these tests should be directed to Lynette Gabriel or Tara Ryan, 301-443-8243.*

Attachment C. Methodology Suggestions

Although there are no methodological requirements, the unique nature of carotid disease and the established safety and effectiveness of carotid endarterectomy suggest the following:

1. Outcome Measures & Methodology

Important outcome measures should include:

- perioperative morbidity;
- ipsilateral stroke (major and minor) with actuarial (survival or life table) reporting;
- symptom resolution (if applicable).

Include an independent, qualified neurological assessment before and after the procedure and appropriate neurological monitoring of the patient during the hospital course and at specified follow-up intervals. All endpoints, especially stroke (major and minor), must be precisely and prospectively defined.

Other measurements which have been recommended include:

- carotid duplex imaging before and after the procedure including plaque characterization;
- brain imaging (MRI, CT, etc.) before and after the procedure for evidence of embolism.
- assessment of patency (carotid angiography, etc.).

2. Interdisciplinary Investigator Team

Develop a multidisciplinary team including a physician skilled in neurology, a physician skilled in interventional neuroradiology, and a surgeon skilled in performing carotid endarterectomy.

3. Study Design

A long-term, randomized concurrent-control trial (RCT) *versus* carotid endarterectomy will likely be necessary to demonstrate the safety and effectiveness of carotid stenting due to the low rate of stroke in patients after carotid endarterectomy. The design of an equivalency (similarity) trail must include the specification of the confidence interval which defines a successful outcome of the trial. This could be specified in as an absolute difference or as a proportion of the control success rate. Several professional organizations are working with NIH to design and carry out such a trial.

Feasibility (pilot) studies will probably be needed prior to the randomized control trial in order to:

- qualify the device (stent and delivery system);
- develop more objective and refined primary outcome measures;
- optimize the procedure (device/lesion, concurrent use of antiplatelet agents & other medications);
- qualify the interventional team (learning curve).

4. Events Committees

Study methodology should include the development of a Data Safety and Monitoring Committee (DSMC) for the evaluation of overall study outcome. DSMC members should include an interventionalist, neurologist, vascular surgeon and a statistician. All members should be independent of the sponsor and the investigator. Stopping rules for adverse outcome should be specified by the DSMC before the study begins.

All major study adverse events should be audited and reviewed by an independent Critical Events Committee (CEC). Events reviewd by the CEC should always be blinded to the treatment received by the patient and as many other demographic details as possible.

5. **Qualification of the Device**

Assess deliverability and develop the best match of device and delivery system to patient and lesion.

6. **Qualification of the Interventional Team**

Develop a rational approach to training, monitoring and acceptance of each member of the multidisciplinary team.

Attachment D. Sample IDE Cover Letter

October 26, 1996

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health, FDA
9200 Corporate Boulevard
Rockville, MD 20850

Re: Investigator IDE {or pre-IDE} for Carotid Stent Study

Dear Dr. Callahan:

I understand that the FDA considers a stent in the carotid artery a significant risk device which requires an investigational device exemption (IDE). I am requesting your consideration of a IDE {or pre-IDE} submission for a study involving carotid stents. A protocol has already been approved by my institutional review board (IRB).

Applicant: Daniel Roberts, MD
Professor of Interventional Cardiology
Southwest University Health Sciences Center
Tucson, Arizona 85710
phone 520-977-0000, fax 520-977-0001, Email: robertsd@uahc2.edu

Device: Stent: Volar-Cuttler, models 35.08, 35.10, 35.12
Intended Use: carotid artery stent

Manufacturer: Mueller Research, Inc
4600 Corporate Boulevard
Rockville, MD 20850
contact: Eric Hastings
phone 301-666-7000, fax 01-666-7001, Email: Eric@MRI.com

Document ref: IDE G990033, PMA P990021 Volar-Cuttler Stent Delivery System

Thank you for your consideration.

Sincerely,

Daniel Roberts, MD
Professor of Cardiology

Enclosures:
1. Report of Prior Investigations
2. Overall Clinical Plan
3. Investigational Plan (this study)
4. Manufacturing Information
5. Investigator Information
6. Institutional Review Board (IRB) Information and Informed Consent Form
7. Sales Information
8. Other Information