Guidance Document for Dura Substitute Devices; Guidance for Industry

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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

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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 Peter L. Hudson, Ph.D. at 240-276-3600 or by electronic mail at peter.hudson@fda.hhs.gov.

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Guidance Document for Dura Substitute 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.

This guidance replaces "Guidance Document for Dura Substitute 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 guidance is to provide a summary of the information to include in a premarket notification (510(k)) submission for a dura substitute, including devices prepared from both synthetic and natural materials. Dura substitutes are class II devices (Panel 84, Procode GXQ) which are described in 21 CFR 882.5910 as "a sheet or material that is used to repair the dura mater (the membrane surrounding the brain.)" Such devices should not be confused with Lyophilized Human Dura Mater (Panel 84, Procode LEM) which are also currently regulated as medical devices.

Manufacturers who intend to market a dura substitute must demonstrate the substantial equivalence of their product to a device that is legally marketed in the United States. To obtain marketing clearance for a dura substitute, a manufacturer should supply the following information:

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.

I. INTRODUCTION

A. The trade or proprietary name of the device.

B. The common or usual name or classification name of the device. The classification name is dura substitute.

C. The establishment registration number of the owner or operator submitting the premarket notification submission.

D. The class in which the device has been placed under section 513 of the Act and the panel. Currently, these products are class II.

E. The name, address, and telephone number of the contact person responsible for the submission.

II. TABLE OF CONTENTS

III. SUMMARY OF INFORMATION REGARDING SAFETY AND EFFECTIVENESS upon which an equivalence determination can be made, or a statement that such information will be made available to interested persons upon request.

IV. STATEMENT OF INTENDED USE FOR THE DEVICE. The indications for use for the device should comply with the labeling information in Section XII of this document.

V. TRUTHFUL AND ACCURATE STATEMENT

VI. DESCRIPTION OF THE DEVICE

Provide a complete description of the device, including the physical dimensions, materials, and physical properties of the device. A table comparing the similarities and differences in these parameters between the device and predicate devices of this type should also be presented.

VII. SPECIFICATION OF ALL MATERIAL COMPONENTS OF THE DEVICE

Alternatives to human dura include bovine pericardium, silicone, synthetic bioabsorbable polymer sheets, and synthetic cellulose. All material components of the device should be identified, including the base material of which the device is composed, all preservatives and crosslinking reagents. Such information should identify the source and purity of each component. If this information is referenced in a Master File, the appropriate letter of cross reference should be included. Submission of a Certificate(s) of Analysis (CoA) and/or a Materials Safety Data Sheet(s) (MSDS) is also useful for the evaluation of components not in common use.

For recommendations regarding information to be included in submissions for medical devices which either contain or are exposed to animal-derived materials during manufacture, manufacturers should obtain the guidance document, *Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices)*, issued by the CDRH BSE Working Group on November 6, 1998. In addition to the recommendations in the guidance document, if the dura substitute contains material derived from animals, please provide the following information:

A. The species and tissue from which the animal material was derived.

B. How the health of the herd is maintained and monitored, e.g.,
   1. Is the herd closed?
   2. What vaccinations are standard for the herd?
   3. Are veterinarian inspections performed and if so, how frequently?
   4. What is the composition of the animal feed?
   5. Is the slaughterhouse USDA approved (or inspected)?

6. Is there certification that the herd is from a country free of BSE if the animal material is of bovine origin?
7. What is the age of the animal at sacrifice?
8. Are pre- and/or post-mortem inspections performed?

VIII. DEVICE MANUFACTURE

The application should contain information about all reagents and processing steps used in device manufacture. Information similar to that discussed above for device components (i.e., reagent source, purity, CoA and/or MSDS) can be very helpful in evaluating the substantial equivalence of the proposed and legally marketed devices. The application should also identify the concentration in the final device of any manufacturing reagent (e.g., organic solvents, heavy metals, cross-linking reagents) that is potentially toxic.

A. Sterilization

With regard to device sterilization the application should state:

1. The method of sterilization;
2. The validation method for the sterilization cycle;
3. The sterility assurance level (SAL) to be achieved;
4. The method for monitoring the sterility of each production lot; and
5. A description of the packaging to be used to maintain device sterility.

If radiation sterilization is used, the dose should be specified. If the method of sterilization is ethylene oxide (EtO), the maximum levels of ethylene oxide, ethylene chlorohydrin, and ethylene glycol residues which remain on the device should be identified. Residual levels of ethylene oxide, ethylene chlorohydrin, and ethylene glycol which remain on the device following EtO sterilization should comply with the maximum limits proposed in:

- the FEDERAL REGISTER of June 23, 1978 (43 FR 27474-27483) or
- the ANSI/AAMI/ISO guidance 10993-7:1995, *Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals* and in AAMI TIR-19.

Since ethylene oxide is neurotoxic, in addition to measuring the EtO residue levels, additional testing should be performed on the finished EtO sterilized device using intracranial implantation to assess irritation. Evidence should be provided demonstrating that the level of sterilant residues remaining in the device do not raise concerns over the safe use of the product.

In general, a SAL of 10^{-6} is important for dura substitutes, unless there is scientific justification for not being able to achieve this level and that it does not create a safety concern. The processing methods and sterilization techniques should be demonstrated to be sufficient to reduce the amount of virus in the final product by at least 10^{6} fold. Such data can be obtained by determining the viral inactivation properties of scaled down versions of specific production techniques and sterilization methods using appropriate model viruses.

Review of the International Conference on Harmonisation's "Q5A Viral Safety Evaluation of Biotechnology Products from Cell Lines of Human or Animal Origin" is recommended with regard to the design of such studies and the selection of model viruses. The final results of these studies should demonstrate that the sum of the log clearance of virus from the selected process steps and sterilization processes are at least six logs greater than the concentration of virus anticipated in the unprocessed source material.

B. **Pyrogenicity testing**

The pyrogen level of the final sterilized device should be less than 0.06 EU/ml, unless there is adequate justification for not being able to achieve this level and that it does present a safety concern.

C. **Product expiration dating**

Data supporting the expiration date for a product should be submitted. Such data should be collected from at least three product lots. Stability studies should monitor the critical parameters of a device that are required to ensure it will perform safely and effectively during its entire shelf-life.

The appropriateness of accelerated stability data is determined by device composition. The value of accelerated stability test data relies on equivalent decomposition pathways at both the standard and elevated temperatures. Therefore, in situations where device failure occurs by different mechanisms at the standard and elevated temperatures of accelerated stability testing, (e.g., loss of sterility at 25°C and protein denaturation at 50°C), accelerated stability test data could not be used to support claims for product stability. In addition, accelerated stability test data may only be used to extend product expiration dating for six months beyond the date demonstrated by real time stability testing. For example, if accelerated stability testing indicates that the product should be functional for 3 years and only 12 months of real time test data have been collected, then an expiration date of 18 months is appropriate.

IX. PRODUCT CHARACTERIZATION

Information about the product structure is critical in determining the equivalence of proposed and legally marketed devices. For dura substitutes, such data could include:

- photographs;
- engineering diagrams; and
- product overview.

Testing of the physical and mechanical properties of the device should be performed on the final sterilized product. Types of testing could include:

- device thickness;
- tensile strength;
- suture retention strength;
- burst strength;
- shrink temperature range; and
- surface structure (e.g., scanning electron microscopy).

It is important to provide a biocompatibility profile for the device. In accordance with the FDA Guidance, G95-1: Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing", results should be supplied for the biological tests listed below. Standard protocols such as those identified by the USP or ASTM should be used in conducting the biocompatibility testing. Such tests should be performed on devices ready for surgical use (i.e., after manufacture, sterilization and packaging for commercial distribution).

- cytotoxicity;
- sensitization assay;
- irritation or intracutaneous reactivity;
- acute systemic toxicity;
- mutagenicity or genotoxicity; and
- hemolysis.

For products that remain in the body for greater than 30 days, the following additional tests are recommended:

- subchronic toxicity - 90 days (with histology of the surrounding tissue); and
- chronic toxicity - 180 days (with histology of the surrounding tissue).

Long-term carcinogenicity studies should be performed with any device in which a positive genotoxicity test result was obtained.

X. FINAL PRODUCT SPECIFICATIONS

The sponsor should provide information about all in-process and final product tests. Such data should identify the test method and time of testing during manufacture. Examples of final product release specifications may include:

- device thickness;
- pore size;
- burst strength;
- residual levels of manufacturing reagents (leachables);
- residual levels of heavy metals;

- pyrogen levels; and
- sterility.

XI. ANIMAL STUDIES

The device should be evaluated by conducting implantation studies at the intended anatomic site. Complete laboratory reports of the studies conducted should include a histologic assessment of the tissue immediately surrounding the device. In addition, such studies should evaluate the following:

a. cerebral spinal fluid leakage;
b. adhesion formation;
c. implant anchorage;
d. device resorption and replacement by host tissue;
e. device vascularization;
f. incidence of infection;
g. incidence of hydrocephalus;
h. hemorrhage;
i. foreign body reactions; and
j. other tissue reactions.

XII. CLINICAL EXPERIENCE

The application should provide a summary of any clinical experience obtained with the device. The sponsor needs to demonstrate that the substitute material will perform as safely and effectively as another legally marketed dura substitute device. To this end, clinical data for dura substitutes composed of material which has not been previously used in neurological applications should be provided from a multicenter clinical trial. This clinical data should demonstrate that the product performs similarly when compared to another legally marketed product. In general, the number of patients should be determined based on the expected incidence of adverse events.

A. **Study Design**

Randomized, concurrently controlled, multicenter studies provide many advantages over other types of study designs for comparing results to a predicate device. Alternative study designs which include assessments for bias in the interpretation of results and biases in study participant enrollments may be proposed. If the study involves literature controls, the sponsor should provide adequate information including: (1) copies of the articles (the methods employed for identifying this body of literature should be clearly stated); (2) a table that includes the device used, inclusion/exclusion criteria for the population implanted, length of follow-up, number of patients at each follow-up, outcome measures, adverse events, and reoperations, including the reason for subsequent surgical intervention and deaths.

The study should be designed and conducted in a manner such that it provides data that will constitute valid scientific evidence within the meaning of 21 CFR 860.7. The directions for use should contain comprehensive instructions regarding the preoperative, perioperative and postoperative procedures to be followed. This information includes but is not necessarily limited to (1) a description of any pre-implant training necessary for the surgical team; (2) a description of how to prepare the patient (e.g., prophylactic antibiotics); (3) instructions for implantation, including sizing, device handling, and intraoperative test procedures to ensure implant integrity; and (4) instructions for follow-up, including whether patient antibiotic prophylaxis is recommended during the post-implant period.

The investigational plan should include both implant and explant case report forms to allow the sponsor to adequately monitor device experience. The explant case report form should allow collection of all relevant data, including the reason for the explant, any complications experienced and their resolution, and any action planned (e.g., replacement with another implant).

B. Target Population

The inclusion/exclusion criteria used to identify the patient population should be clearly defined. Patients who have undergone prior neurosurgery should be analyzed as "Revision" patients. It is recognized that patients who have had previous neurosurgical procedures may have a greater likelihood of adverse events than patients without any previous neurosurgery. Therefore, the sponsor is encouraged to collect information regarding the number of prior surgeries and type of prior surgeries to allow for a determination of whether previous surgeries have an effect on outcome.

Other populations, such as infants with meningomyeloceles or patients who have had trauma or have tumors of the CNS may be included in the clinical study. In general the locations, e.g., skull-based tumors, and etiology of the defects are important factors when comparing study cohorts. In all cohorts studied (control and treated), information related to the size of the defect, whether the patient is immunosuppressed, whether the site is infected, if the patient has hydrocephalus or seizure activity, or if the patient has adhesions in the surgical site should be provided.

Exclusion criteria to be considered include: a systemic infection or infection at the site of surgery, an allergy to any component of the investigational device, pregnancy or interest in becoming pregnant during the duration of the study (the duration of the study is defined as the period of time that the patients will be followed for clinical evaluation), prior neurosurgery, radiation or chemo-therapy, current involvement in a study of another investigational product for similar purpose, a known malignancy, a concurrent disease process that would place the patient in excessive risk to surgery, and implanted metallic devices which may preclude the use of MRIs.

The sample size should be based on the expected incidence of complications with the device as compared to the control device, in order to compare the product to a legally marketed predicate device. Statistical justifications for pooling across several variables such as etiology, patient age, device usage (initial implant versus revision), type and size of device, and implantation site (brain versus spinal cord) should be provided. The data collected and reported should include all possible relevant variables in order to permit stratification and analysis of the study data.

C. **Clinical Evaluation of Device Performance**

Patients implanted with most dura substitutes should be followed for one year. However, a sponsor may be able to justify a shorter follow-up depending on the similarities and differences to predicate dura substitutes.

To evaluate the risks to the patient from the dura substitute, a time course distribution of all complications should be presented. The adverse events should be separated into intraoperative and postoperative complications, including, but not limited to hypertension, seizures, neurological changes in sensory, motor, and reflex activity, increased intracranial pressure, infection, hydrocephalus, toxicity, evidence of disease transmission, CSF leakage, and hemorrhage. If the site is reoperated, data should be collected on the vascularity of the tissue and the presence of adhesions; in addition a biopsy should be performed for histological analysis to determine inflammation as well as whether the material has resorbed and been replaced with the patient's own dura. The patients should be followed for one year. Provisions for conducting MRI scans should be described in the protocol. Clinical manifestations of possible device failure should guide the clinician's decision for performing an MRI. Examples of clinical manifestations that might suggest the need for an MRI are postural headaches, dizziness, CSF leakage, the onset of seizures and fever.

D. **Effectiveness Evaluation**

The product should be shown to be as effective as a legally marketed product. The effectiveness of the dura substitute should be compared to a predicate device in regards to CSF leakage. The sponsor should clearly state and justify the pre-specified allowable difference (delta) used to define "no worse than". A questionnaire for investigators to fill out immediately post-implantation regarding ease of handling and device conformability is recommended as another means of assessing device efficacy. Answers to the questions posed could be rated on a 0-10 scale.

XIII. 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 provided. General labeling requirements for medical devices are contained in 21 CFR Part 801. These regulations specify the minimum 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.

The intended use statement should include the specific indications for use and identification of the target populations.