Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance

Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh

Document issued on: March 2, 1999

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 and Restorative 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 Plastic and Reconstructive Surgery Branch, HFZ-410, 9200 Corporate Boulevard, Rockville, MD 20850. 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 Charles N. Durfor, Ph.D. at (301) 594-3090, ext.134 or by electronic mail at cmd@cdrh.fda.gov.

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Guidance[1] for the Preparation of a Premarket Notification Application for a Surgical Mesh

This guidance document serves as a supplement to "Premarket Notification 510(K): Regulatory Requirements For Medical Devices," (HHS Publication FDA 95-4158)" and provides specific guidance regarding the information to be contained in a premarket notification submission for general surgical meshes described in 21 CFR 878.3300. This guidance is not intended to address meshes for orthopedic or dental uses. Specifically, this guidance covers Surgical Mesh (79 FTM) and Polymeric Surgical Mesh (79 FTL) for general surgical uses such as implantation to reinforce soft tissue where weakness exists (e.g., hernia repair, suture line/staple line reinforcement, muscle flap reinforcement, gastric banding, etc.).

Manufacturers who seek permission to market these devices must demonstrate substantial equivalence of their product to a device that is legally marketed in the United States. To obtain marketing clearance for a surgical mesh, manufacturers should supply the following information:

I. Introductory information

   A. The trade or proprietary name of the device.

   B. The common or usual name or classification name of the device.

   C. The establishment registration number, if applicable, 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.

   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.

[1]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.

IV. Statement of intended use for the device (see Attachment #1). The indications for use for the device should comply with the labeling recommendations in Section XI of this document.

V. A Truthful and Accuracy Statement (see Attachment #2).

VI. Description of the device.

Provide a complete description of the mesh, including the physical dimensions, materials, and physical properties of the device. A table comparing the similarities and differences in these parameters between the proposed product and a legally marketed device should also be presented.

VII. Specification of all material components of the device.

All material components of the device should be described. Such information should identify the source and purity of each component. Such information may also be supplied by reference to a Master File(s), (if the appropriate letter of cross reference is included). Submission of a Certificate(s) of Analysis (CoA) and/or a Materials Safety Data Sheet(s) (MSDS) can also greatly simplify review of components.

If collagen or other animal-derived material is a device component, the application should also identify:

1. The species and tissue from which the animal material was derived (including the specific type of collagen or other material used).

2. How the health of herd is maintained and monitored, e.g.,
   a. Is the herd closed?
   b. What vaccinations are standard for the herd (e.g., focus on live modified viruses)?
   c. Are veterinarian inspections performed and if so how frequently?
   d. What is the composition of the animal feed?
   e. Is the abattoir USDA approved (or inspected)?
   f. If the animal material is of bovine origin, certification that the herd is from a Bovine Spongiform Encephalopathy-free country.

3. How the health of each animal is maintained and monitored, e.g.,
   a. What is the age of the animal at sacrifice?
   b. Are pre and/or post morteum inspections performed?
   c. What tests are performed to determine that the material is accessible for further processing or pooled with material from other animals?

If the product contains synthetic (e.g., polymeric or metallic) components, the application should identify the concentration in the final device of any component (e.g., organic solvents, heavy metals, cross-linking reagents) that is potentially toxic, carcinogenic or immunogenic.

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 comments (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.

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; and
4. The method for monitoring the sterility of each production lot.

If radiation sterilization is performed, the dose should be specified. If the method of sterilization is ethylene oxide (EtO) exposure, 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 chlorhydrin, 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 for small (<10 grams), medium (10-100 grams) or large (>100 grams) implantable medical devices (see below).

[Parts per million]

Implant Size	Ethylene Oxide	Ethylene Chlorohydrin	Ethylene Glycol
Small	250	250	5,000
Medium	100	100	2,000
Large	25	25	500

In general, a SAL of 10^{-6} is necessary for all devices unless there is substantial justification why this level cannot be achieved. The sterility assurance level should be determined by an appropriate and recognized Standard or a complete description of the validation process should be provided.

In addition to demonstrating the ability of sterilization methods to inactivate bacteria, yeast and fungi, the processing methods and sterilization techniques for devices derived from animal material should be validated with regard to the inactivation and removal of viruses. In specific, sterilization methods should reduce the amount of virus in the final product below 1 infectious particle per 10^6 devices. Such data can be obtained by determining the amount of virus in the unprocessed source material and the viral inactivation properties of scaled down versions of specific production and sterilization methods (e.g., acid extraction of collagen or dry heat sterilization) using appropriate model viruses. Review of "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin", (ICH Harmonized Tripartite Draft Guideline) 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 processing steps and sterilization processes are at least six logs greater than the concentration of virus anticipated in the unprocessed source material.

IX. A description of the packaging to be used to maintain the sterility of the device.

X. Product Characterization

1. Biocompatibility - In accordance with the Blue Book Guidance G95-1, ("Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing"), acceptable test 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, if possible. Such tests should be performed on devices ready for surgical use (i.e., after manufacture, sterilization and packaging for commercial distribution).

    Cytotoxicity
    Sensitization
    Irritation or Intracutaneous reactivity
    Systemic toxicity (acute)
    Genotoxicity
    Implantation (with histology of the surrounding tissue)
    Hemolysis
    Pyrogenicity

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

    Subchronic toxicity
    Chronic toxicity

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

    The above tests may not be relevant or necessary in all cases, such as when a manufacturer submits a marketing application for a device which has the exact same material specifications as a previously marketed product, and/or for which the tradename and device claims are the only changes being made.

2. Product Characterization - Information about the product structure is critical in determining the equivalence of a proposed device. For a surgical mesh, such data would include information about:

    Mesh thickness
    Mesh weave characteristics
    Pore size
    Mesh density
    Tensile strength
    Device stiffness
    Suture pullout strength
    Burst strength
    Tear resistance

3. Final Product Specification - The sponsor should provide information about the relevant 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 can include:

   Device Thickness
   Pore Size
   Bursting Strength
   Residual levels of manufacturing reagents
   Residual levels of heavy metals
   Pyrogen levels
   Sterility

   For biodegradable devices information should be provided that documents the rate of product resorption and how specific device properties (e.g., suture pullout strength, burst strength and/or tear resistance) change as a function of time. Such studies should be performed *in vivo* or in a manner expected to accurately predict product decomposition (e.g., in comparable cellular and proteolytic environments at 37°C).

4. Product Expiration Dating - Data supporting the expiration date for a product should be submitted. Such data should be collected from at least three production lots. Stability studies should monitor the critical parameters of a device that are required to insure it will perform consistently 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 identical decomposition mechanisms at both standard and elevated temperatures. When device failure/decomposition occurs by different mechanisms at the standard and elevated temperatures of accelerated stability testing, (e.g., loss of sterility at 25°C versus protein denaturation at 50°C), accelerated stability test data should not be used to support claims for product stability.

   Finally, changes in device expiration date do not require a new 510(k) (see "Deciding When to Submit a 510(k) for a Change to an Existing Device"). Such changes are properly within the scope of GMPs. However, where methods or protocols, not described in the original 510(k), are used to support new package integrity or shelf-life claims, a new 510(k) may be necessary.

XI. Labeling.

All labeling information for the surgical mesh should be supplied, including individual package labeling, package inserts, and available promotional literature. The labeling should specify the intended use of the device, contraindications, warnings, precautions, directions for use if applicable, and product claims. The following issues should be considered for product labeling:

1. If the mesh is to be labeled "pyrogen free" or "nonpyrogenic," satisfactory results from the USP Pyrogen Test (Rabbit) or an equivalent test, performed on the final end product, should be provided and lot release criterion for pyrogenicity need to be identified (see section X.3.) above.

2. The device may not be labeled as a treatment for reducing the incidence and/or the severity of post-surgical adhesions. A PMA application is required for this intended use.

XII. Final consideration.

Recent technological advances have resulted in surgical mesh and film devices that involve device formation, assembly or polymerization after introduction into the patient. Review of such products may require additional information than that described in this Guidance document, because the products can raise new types of questions about device safety and effectiveness, e.g.,

1. Will the device assemble in a safe and effective manner?

2. Will excess, unreacted material migrate to new locations in the body and form unwanted polymer at new anatomic sites?

3. Will chemical reactions with adjacent human tissues occur?

Attachment #1

Indications for Use Form

Page___of

510(k) Number (if known):_____

Device Name:

Indications For Use:

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

_____ _____ _____ _____ _____ _____

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use___ OR Over-The-Counter Use
(Per 21 CFR 801.109) (Optional Format 1-2-96)

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Attachment #2

PREMARKET NOTIFICATION

TRUTHFUL AND ACCURATE STATEMENT*
(As Required By 21 CFR 807.87(j))

I certify that, in my capacity as [*The Position Held In Company*] of [*Company Name*], I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.

[*Signature*]

_____

[Typed Name and Title]

_____

[Company] [Date]

_____

[*Premarket Notification (510(k)) Number*]

* Must be signed by a responsible person of the firm required to submit the premarket notification (e.g., not a consultant for the 510(k) submitter.)