Draft Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Absorbable Hemostatic Device

DRAFT GUIDANCE

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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

Preface

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This draft guidance document, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 document. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance document.

1. Introduction

This draft guidance document was developed as a special control guidance to support the reclassification of the absorbable hemostatic device into class II (special controls). The device, as proposed, is intended to be implanted during surgical procedures to produce hemostasis by accelerating the clotting process of blood. This draft guidance document does not apply to devices intended to control bleeding at femoral artery puncture sites or for blood vessel anastomosis sites. The device may include a licensed thrombin.[1]

This draft guidance document will be issued in conjunction with a **Federal Register** notice announcing the proposal to reclassify this device type. This guidance document is issued for comment purposes only. If a final rule to reclassify this device type is not issued, this guidance document will not be issued as a special control.

Following the effective date of a final rule reclassifying the device, any firm submitting a 510(k) for an absorbable hemostatic device will need to address the issues covered in the special control guidance document. However, the firm need only show that its device meets the recommendations of the guidance document or in some other way provides equivalent assurances of safety and effectiveness.

[1] Thrombin is a biologic, which may be licensed through application to the Center for Biologics Evaluation and Research (CBER), see http://www.fda.gov/cber/gdlns/fibrinocc.pdf or call the CBER Office of Communication, Training, and Manufacturers Assistance at (301) 827-1800 or 1-800-835-4709.

Absorbable hemostatic products that include biological or drug components are considered by the agency to be combination products. Although FDA jurisdiction over combination products is determined by the product's primary mode of action, to date, for combinations of licensed thrombin and an absorbable hemostatic device, the device component has been deemed responsible for the product's primary mode of action with CDRH being assigned the lead for premarket review and regulation. Thus, combinations of licensed thrombin and an absorbable hemostatic device would be reviewed under 510(k) under the proposed rule while other combinations of a biologic or drug component with an absorbable hemostatic device that are assigned to CDRH may require a PMA. Additionally, any of these combination products that contain an unlicensed biological product or an unapproved drug may be subject to additional regulatory controls applicable to the biological or drug component. In accordance with the least burdensome provision of the Act, FDA will consider the least burdensome means of demonstrating substantial equivalence for these products and will request information accordingly.

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

This draft guidance document reflects our careful review of what we believe are the relevant issues related to the absorbable hemostatic devices and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether there is a less burdensome approach, however, please submit your comments as indicated on the cover of this document.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of the absorbable hemostatic device. Thus, a manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the act), including the 510(k) requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with the absorbable hemostatic device identified in this guidance document, and (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This draft special control guidance document identifies the classification regulation and product code for the absorbable hemostatic device (Please refer to **Section 4. Scope)**. In addition, other

sections of this special control guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with the absorbable hemostatic device and lead to a timely premarket notification [510(k)] review. This document supplements other FDA documents regarding the content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87, the guidance, **Format for Traditional and Abbreviated 510(k)s**,[2] and "**How to Prepare a 510(k) Submission"** on FDA Device Advice at http://www.fda.gov/cdrh/devadvice/314.html.

As described in the guidance document entitled, **The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**, http://www.fda.gov/cdrh/ode/parad510.html, a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA issues a class II special controls guidance document. Manufacturers considering certain modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this special control guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied to address the risks identified in this guidance document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of section 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this special controls guidance document.

Proposed labeling

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

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Please refer to **Section 11. Labeling** for specific information that should be included in the labeling for devices of the types covered by this guidance document.)

Summary report

We recommend that the summary report contain:

Description of the device and its intended use

We recommend that you describe the performance specifications and, when appropriate, include detailed, labeled drawings of the device. You should also submit an "indications for use" enclosure.[3]

Description of device design requirements

We recommend that you include a brief description of the device design requirements.

Identification of the risk analysis method

We recommend that you identify the risk analysis method(s) you used to assess the risk profile, in general, as well as the specific device's design and the results of this analysis. (Please refer to **Section 5. Risks to Health** for the risks to health generally associated with the use of this device that FDA has identified.)

Discussion of the device characteristics

We recommend that you discuss the device characteristics that address the risks identified in this class II special controls guidance document, as well as any additional risks identified in your risk analysis.

Description of the performance aspects

We recommend that you include a brief description of the test method(s) you have used or intend to use to address each performance aspect identified in **Sections 6-10** of this class II special controls guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.[4] (See also 21 CFR 820.30,

[3] Refer to http://www.fda.gov/cdrh/ode/indicate.html for the recommended format.

[4] If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into

Subpart C - Design Controls for the Quality System Regulation.)

Reliance on standards

If any part of the device design or testing relies on a recognized standard, we recommend that you include either:

- a statement that testing will be conducted and meet specified acceptance criteria before the device is marketed
- a declaration of conformity to the standard.[5]

Because a declaration of conformity is based on results from testing, we believe you cannot properly submit a declaration of conformity until you have completed the testing the standard describes. For more information, please refer to section 514(c)(1)(B) of the act and the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/1131.html.

If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance document. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering certain modifications to their own cleared devices should consider submitting Special 510(k)s.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a 510(k) submission for an absorbable hemostatic device.

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interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

[5] See Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist for All Premarket Notification [510(K)] Submissions), http://www.fda.gov/cdrh/ode/reqrecstand.html.

4. Scope

The scope of this guidance document is limited to the following device as described in 21 CFR 878.4490. The product codes associated with these devices are LMF (absorbable hemostatic agent, collagen based) and LMG (absorbable hemostatic agent, not collagen based).

In addition to reclassification into class II (special controls), FDA is proposing the revised name and identification below for the device for clarity.

> **§ 878.4490 – Absorbable hemostatic device.**
>
> *Identification.* An absorbable hemostatic device is an absorbable device that is placed in the body during surgery to produce hemostasis by accelerating the clotting process of blood.

This device type does not include devices intended to control bleeding at femoral artery puncture sites (vascular hemostasis device, product code MGB) or for blood vessel anastomosis sites (polymerizing sealant, product code NBE). These devices are class III and require premarket approval applications before marketing, Section 513(a)(1)(C) of the act.[6] This device type also does not include devices for temporary occlusion of blood vessels (vascular clamp, product code DXC). This device is class II and requires 510(k), 21 CFR 870.4450. For information about this device, contact the Division of Cardiovascular Devices, Circulatory Support and Prosthetics Branch.

5. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the absorbable hemostatic devices addressed in this guidance document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. We recommend that you conduct a risk analysis to identify any other risks specific to your device and include the results of this analysis. The 510(k) should also describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this guidance document, or have identified risks additional to those in this guidance document, you should provide sufficient detail to support the approach you have used to address that risk.

[6] Devices intended as lung sealants and dura sealants are also class III, requiring premarket approval before application. The Plastics and Reconstructive Surgery Branch is available to answer your questions about these devices.

Identified Risk	Recommended Mitigation Measures
Uncontrolled bleeding	Section 6. Material and Performance Characteristics Section 7. Animal Testing Section 8. Clinical Studies Section 11. Labeling
Hematoma	Section 7. Animal Testing Section 8. Clinical Studies Section 11. Labeling
Infection	Section 7. Animal Testing Section 9. Sterility Section 11. Labeling
Wound dehiscence	Section 11. Labeling
Foreign body reactions	Section 7. Animal Testing Section 10. Biocompatibility Section 11. Labeling
Immunological reactions	Section 7. Animal Testing Section 10. Biocompatibility Section 11. Labeling
Adhesion formation	Section 7. Animal Testing Section 8. Clinical Studies
Failure to be absorbed	Section 6. Material and Performance Characteristics Section 7. Animal Testing Section 10. Biocompatibility
Interference with methylmethacrylate adhesives	Section 7. Animal Testing Section 11. Labeling
Aspiration into blood transfusion filters	Section 11. Labeling
Embolization	Section 11. Labeling
Paralysis/nerve damage/tissue necrosis	Section 11. Labeling

6. Material and Performance Characteristics

We recommend that you provide the information below to establish the material and performance characteristics of the device.

A. Material Specification

We recommend that you identify the material components of your device, including the source and purity of each component. This information may also be supplied by reference to a Master Access 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 FDA's review of material components.

Collagen or Animal-Derived Material

If collagen or other animal-derived material is a device component, we recommend that you describe the species and tissue from which the animal material was derived, including the specific type of collagen or other material used.

If the animal material is of bovine origin,[7] we recommend that you include:

- description of how the individual animal's (or when appropriate, the herd's) health was maintained and monitored (e.g., whether or not the herd was closed, composition of food)
- certification that the animal is from a country free of bovine spongiform encephalopathy
- standard vaccinations given to the animal (herd) (we recommend focusing on live modified viruses)
- type and frequency of veterinarian inspections performed
- age of the animal at sacrifice
- confirmation that the abattoir (slaughterhouse) is USDA-approved or USDA-inspected
- any pre-mortem or post-mortem inspections performed
- tests performed to determine that material is acceptable for further processing or pooling with material from other animals.

We also recommend that you provide the rate of product absorption, according to studies

[7] See also List of USDA-Recognized Animal Health Status of Countries/Areas Regarding Specific Livestock or Poultry Diseases, http://www.aphis.usda.gov/vs/ncie/country.html.

performed *in vivo* or in a manner expected to accurately predict product decomposition (e.g., in comparable cellular and proteolytic environments at 37°C). Please see **Section 7. Animal Testing**.

B. Product Characterization

For product characterization information, we recommend that you provide:

- the time to complete device resorption determined in animal studies
- cross-linking reagent identity and known toxicity characteristics
- initial cross-linking reagent concentration and any residual concentration.

C. Final Product Specification

We recommend that you provide information about and the final product release specifications, including:

- specific amino acid content
- residual levels of manufacturing reagents
- residual levels of heavy metals
- pyrogen levels
- sterility.

D. Shelf Life

If you propose a shelf life for your device, we recommend that you provide:

- stability testing of the device
- packaging testing to establish the shelf life (i.e., labeled expiration date).

Accelerated testing should be supported or validated by real-time shelf life testing. We recommend that you provide the results from the applicable test(s) described in **Section C. Final Product Specification** on representative aged samples. For packaging testing, we recommend that you provide results for the final finished package for initial integrity and maintenance of integrity after selecting the appropriate materials and qualifying the package configuration. We also recommend that you use test methods that are either validated or standardized.

7. Animal Testing

FDA recommends that you conduct animal testing that models each surgical application your device is indicated for. For example, for general surgical use, we recommend that the animal testing include arteriolar, venous, and capillary bleeding from various tissues and organs. If you

intend to include a specific arterial bleeding indication as part of a general surgical indication, you should design your studies to support this specific indication.

FDA recommends that your animal study evaluate:

- the time to reach hemostasis
- the time for resorption of the hemostatic device
- complications related to resorption.

We also recommend that you monitor complications, such as:

- infection
- hematoma
- coagulopathies
- increased wound healing time.

Your animal study should include a comparison with a legally marketed predicate device of similar components and manufacture.

8. Clinical Studies

In accordance with the Least Burdensome provisions of the act, FDA will rely upon well-designed bench testing (i.e., material and performance characteristics) and/or animal testing rather than requiring clinical studies for new devices unless there is a specific justification for asking for clinical information to support a determination of substantial equivalence. While, in general, clinical studies may not be needed for most absorbable hemostatic devices, FDA may recommend that you collect clinical data for an absorbable hemostatic device with:

- indications for use dissimilar from legally marketed absorbable hemostatic device of the same type
- designs dissimilar from designs previously cleared under a premarket notification
- new technology, i.e., technology different from that used in legally marketed predicates.

FDA will always consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale. The Plastic and Reconstructive Surgery Devices Branch is available to discuss any questions you may have about clinical testing before you initiate your studies.

If a clinical study is needed to demonstrate substantial equivalence, i.e., conducted prior to obtaining 510(k) clearance of the device, the study must be conducted under the Investigational

Device Exemptions (IDE) regulation, 21 CFR Part 812. FDA generally believes that the absorbable hemostatic device addressed by this guidance document is a significant risk device as defined in 21 CFR 812.3(m).[8] In addition to the requirement of having a 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).

Recommendations about clinical studies of absorbable hemostatic device are outlined below. The Plastic and Reconstructive Surgery Devices Branch is available to answer questions you may have about protocol design not addressed in this guidance document.

Absorbable hemostatic devices are primarily applied during surgical procedures in order to control bleeding that is not readily controlled via conventional means, such as cautery or ligation. At other times, an absorbable hemostatic device may be applied due to the inaccessibility of a site to conventional hemostatic methods. We recommend that your clinical studies reflect the intended use of your device.

We recommend that you design your study as described below.

A. Study Design

We recommend that you compare your device to a legally marketed predicate device in a controlled, prospective, randomized study. The predicate should be manufactured from similar materials and have similar indications for use as your device.

B. Number of Institutions

The number of institutions should be sufficient to ensure your device will perform adequately under use conditions where technical and procedural differences are likely to occur.

C. Patient Follow-Up

We recommend that you follow patients for the time required for complete absorption of your device or for 1 month, whichever is longer. We also recommend that relevant blood work be performed before and after application of the device. For example, if your device uses a combination of hemostatic products (e.g., collagen and thrombin), we believe it is appropriate to assess antibody formation at the time antibody production is expected reach its maximum level (approximately 4 to 6 weeks after exposure).

D. General Surgery Indication

If your device is labeled for a general surgery indication, we recommend you assess the use

[8] See Significant Risk and Nonsignificant Risk Medical Device Studies, http://www.fda.gov/oc/ohrt/irbs/devices.html#risk.

of your device in three or four different surgical procedures.

If your device is labeled for any indications in surgical specialties, i.e., beyond general surgery, we may recommend that you conduct additional studies to assess the performance of your device when used as indicated unless you provide a sound scientific rationale explaining why additional studies are not relevant.

E. Study Endpoints

The effectiveness endpoint in your clinical study should be either the amount of time to achieve hemostasis or an observation of whether hemostasis occurred within 5 minutes (as a pass/fail, i.e., yes/no response).

To assess safety, we recommend that you submit a full evaluation of all adverse events observed during the administration of the device and recovery period from surgery until the patient exits the study.

9. Sterility

FDA recommends that you provide sterilization information in accordance with the **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/361.html. You should sterilize the device to a sterility assurance level (SAL) of 1×10^{-6} using a sterilization cycle that has been validated in accordance with the QSR.

Absorbable hemostatic agents are implanted devices, therefore we recommend you test the devices for pyrogenicity. We also recommend you provide a:

- description of the method used to make the determination, e.g., limulus amebocyte lysate (LAL);
- identification of the testing endpoint reached and rationale for selecting that endpoint;
- description of the extraction technique used to obtain the test fluid from the test device, showing that all clinically relevant contact surfaces of the test device were assessed and;
- identification of the reference method used, e.g., USP, ANSI/AAMI ST 72, or FDA guidance.

10. Biocompatibility

FDA recommends that you conduct biocompatibility testing as described in the FDA-modified **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1:**

Evaluation and Testing, http://www.fda.gov/cdrh/g951.html for blood-contacting, long-term implanted devices. We recommend that you select biocompatibility tests (Parts 5 and 10 of ISO-10993) appropriate for the duration and level of contact with your device. If identical materials and identical material processing are used in a predicate device with the same type and duration of patient contact, you may identify the predicate device in lieu of providing biocompatibility testing.

11. Labeling

The 510(k) must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR 801.[9]

A. Instructions for Use

We recommend that you include the following in your instructions for use that clearly explain the device's technological features and instructions for its use on patients.

B. Warnings

Blood Salvage Systems

Fragments of an absorbable hemostatic device may pass through filters of blood salvage systems and occlude the systems or the patient's vasculature. Labeling should warn against the use of absorbable hemostatic devices in conjunction with blood salvage systems.

Methylmethacrylate Adhesives

Some types of absorbable hemostatic devices have been reported to reduce the strength of methylmethacrylate adhesives used to fixate orthopedic prosthetic devices to bone. Therefore, we recommend that labeling warn against the use of absorbable hemostatic devices in conjunction with these products.

C. Precautions

Embolization

[9] Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR Part 801 before a medical device is introduced into interstate commerce. In addition, we recommend that final labeling for prescription medical devices comply with 21 CFR Part 801.109. Labeling recommendations in this guidance document are consistent with the requirements of Part 801.

Absorbable hemostatic devices used near moderate to large blood vessels may result in embolization of the blood vessel. Such embolization has been associated with severe adverse effects, including fever, duodenal and pancreatic infarct, embolization of lower extremity vessels, pulmonary embolization, splenic abscess, necrosis, asterixis, and death. Therefore, we recommend that labeling caution physicians to exercise care in assuring that particles from the absorbable hemostatic device do not enter the vasculature.

Swelling of the Device

Absorbable hemostatic devices absorb liquid and swell to varying degrees, up to 35 to 40 times their weight in liquid. This absorption of liquid is accompanied by a concomitant swelling of the device. Therefore, we recommend that labeling caution physicians to use only the minimum amount of the device necessary to achieve hemostasis and to carefully remove all excess device material once hemostasis is attained.

The use of an absorbable hemostatic device in small body cavities is sometimes necessary. Therefore, we recommend that labeling caution physicians to allow room for any swelling expected with use of the device. We also recommend providing directions to remove the device after use in procedures involving the spinal cord and foramina in bone once hemostasis is achieved. This may help to avoid paralysis, pain, nerve damage, constriction of adjacent blood vessels, and tissue necrosis.

Allergic Response

Patients allergic to bovine thrombin containing hemostatic devices may form antibodies to bovine Factor V_a that may cross react with human Factor V_a resulting in a potentially fatal coagulopathy. The potential for an allergic response exists for any animal or plant component present, therefore, we recommend that labeling advise physicians to screen patients for allergies to any animal or plant components present in your device.