DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL - 2 2003

Dear Panel Member,

Thank you for agreeing to attend the July 24 meeting of the General and Plastic Surgery Devices Advisory Committee (Panel) and taking part in a vote to either recommend or not recommend reclassification of the absorbable hemostatic agent and dressing products that do not contain bovine thrombin from regulatory Class III to Class II.

The agency's rationale for recommending that this device be down classified are summarized as follows:

- We have years of experience regulating this device category
- We understand the device specifications and performance characteristics (bench testing, animal testing and clinical data) needed to evaluate and control their safe and effective use.
- We have successfully down classified a number of similar device categories, and provide a suture guidance special control as a specific example.
- Down classification meets the FDA mandate to apply the "least burdensome" approach to regulating medical devices
- At a Panel meeting last year on this topic, the Panel indicated they would like to review the content of the draft special control for absorbable hemostatic agents, and this information is provided now for your review in this memo.

The absorbable hemostatic agent and dressing products were regulated as drugs from the time the first ones, Gelfoam and Oxycel, were introduced into the market place in the early 1940s. A number of products, including the absorbable hemostatic agent and dressing products, were transferred to device regulations shortly after President Ford signed the Medical Device Amendments to the Food, Drug and Cosmetic Act in 1976. All of these "transitional" devices were regulated as Class III medical devices. Some of these products, e.g., sutures, were reclassified to Class II when enough safety and effectiveness information was obtained in order to support such a change in class.

The Agency's rationale for recommending this change in regulatory class is based on the long history of safe and effective use of these products over the past 60 years and the scarcity of adverse event reports in the medical literature and the FDA's Medical Device Reporting System. The Agency proposes that all of the potential risks to health can be ameliorated via a special controls guidance document that includes recommendations and advice on device materials, product performance, animal testing, clinical testing, product sterilization, biocompatibility and product labeling.

A search of the small number of adverse event reports in the medical literature and in the FDA's Medical Device Reporting System has identified the most common adverse reactions to the

absorbable hemostatic agent and dressing products. These are discussed below as well as the recommended method of amelioration.

The most recent amendment to the FD&C Act, the Medical Device User Fee Modernization Act (MDUFMA), passed in 2002, directed the Agency to regulate medical devices in the "least burdensome" manor possible based on the available safety and effectiveness information. It is with this in mind that we are requesting that you vote to reclassify the absorbable hemostatic agent and dressing products into regulatory Class II.

Introduction to Regulatory History of Absorbable Hemostatic Agents and Dressings:

Absorbable hemostatic agent and dressing products were regulated as drugs and required a New Drug Application (NDA) for marketing approval up until 1976. At that time these transitional devices were transferred to device regulations in the Center for Devices and Radiological Health. All transitional products were automatically classified as Class III medical devices. The 1976 Device Amendments as amended by the Safe Medical Device Act (SMDA) of 1990, the FDA Modernization Act (FDAMA) of 1997, and MDUFMA provide regulations for the reclassification and regulation of medical devices intended for human use. FDA may elect to reclassify a medical device, including the Class III medical devices into a lower regulatory class that can reasonably assure their safety and effectiveness for their intended use.

The Act established three categories (classes) of medical devices depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three classes are Class I (general controls), Class II (special controls), and Class III (pre-market approval). General controls are sufficient to provide reasonable assurance of the safety and effectiveness of Class I devices. General controls include the following: prohibition against adulterated or misbranded devices, premarket notification (510(k)), banned devices, the quality system regulation that includes design controls and good manufacturing processes (GMPs), registration of manufacturing facilities, listing of device types, record keeping, etc.

Class II devices are those that cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of such devices. These devices are regulated using special controls and general controls. Special controls include guidelines (guidance documents), performance standards, postmarket surveillance, clinical data, labeling, tracking requirements, and other appropriate actions the Secretary of the Department of Health and Human Services deems necessary to provide such assurance.

Class III devices are those for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness. These devices are life sustaining, life supporting, or substantially important in preventing impairment of human health, or they present unreasonable risk of illness or injury. Class III devices are regulated by using "valid scientific evidence" to establish the safety and effectiveness of the device. Valid scientific evidence includes well-controlled investigations, partially-controlled studies, uncontrolled studies, well-documented case histories, and reports of significant human experience.

When most devices were classified in the late 1970s and early 1980s, most Class I and Class II devices were cleared for marketing via the 510(k) process. Some Class I devices were also exempted from 510(k) clearance. Now many Class I devices and a few Class II devices are exempt from 510(k) clearance because their safety and effectiveness can be reasonably assured by other general controls, particularly by the quality system regulation general control.
The absorbable hemostatic agents and dressings approved via the PMA or NDA regulatory process to date contain porcine or bovine gelatin, bovine collagen, or regenerated oxidized cellulose. The two most recently approved absorbable hemostatic agents and dressings, FloSeal and CoStasis, additionally contain bovine thrombin and therefore are combination products, i.e., products containing both a device and biological component.

FDA has regulated absorbable hemostatic agents under regulation number 21 CFR §878.4490, "Absorbable hemostatic agent and dressing". These products are defined as "a device intended to produce hemostasis by accelerating the clotting process of blood. It is absorbable. As of May 28, 1976, it has required an approval under section 515 of the act to allow commercial distribution of an absorbable hemostatic agent." Note: while the name of the device classification includes "Dressing," we have interpreted this absorbable device to be surgical hemostatic agents. Wound dressings are topical and some contain an indication for hemostasis and have been regulated as 510(k)s for many years. Consequently, we are proposing to modify the name of hemostatic agents to clarify that topical dressings are not included in the device classification of an absorbable hemostatic agent...

Since 1976, CDRH has approved ten absorbable hemostatic agents. A number of hemostatic agents were approved through the new drug process and then transferred to CDRH for regulation after 1976. Most of these products should be familiar to you. Table 1 identifies products included in the absorbable hemostatic agent device group.

The proposal for reclassification of the absorbable hemostatic agent was presented to the General and Plastic Surgery Devices Panel on July 8, 2002. During that meeting the panel voted to table any recommendation on the reclassification of these products until the panel had the opportunity to review the proposed special controls guidance document. At this meeting, the Agency plans to present to the panel the information that will be included in such a special controls guidance document for the absorbable hemostatic agent and dressing products.

Table 1

Absorbable Hemostatic Agents Approved Through PMA or NDA

Product	Present Application Holder	Application Number**	Characteristics	Approval Date
Gelfoam	Pharmacia and Upjohn	N18286	Porcine Gelatin molded into a sponge	Available 1945 July 8, 1983
Oxycel*	Becton Dickinson	N5798	Sponge made of Oxidized Cellulose	September 12, 1945
Surgicel	Ethicon	N12159	Sponge made of Regenerated Oxidized Cellulose	October 14, 1960
Avitene	Davol	N17600 and P800002	Bovine Collagen	August 26, 1976 October 24, 1980
Collastat	Integra LifeSciences	P810006	Bovine Collagen	December 10, 1981
Superstat*	Superstat	P810040	Bovine Collagen	January 29, 1982
Instat	Ethicon	P830079	Bovine Collagen	October 10, 1985
Helistat Helitene	Integra LifeSciences	P850010	Bovine Collagen	November 8, 1985
Hemopad Novacol	Datascope	P850023	Bovine Collagen	May 27, 1986
Actifoam*	Coletica	P930030	Bovine Collagen	August 15, 1995
Surgifoam Spongistan	Ethicon	P990004	Porcine Gelatin sponge	September 30, 1999
FloSeal Hemostat	Baxter Healthcare	P990009	Flowable Bovine Gelatin Matrix and Licensed Bovine Thrombin	December 8, 1999
CoStasis	Cohesion Technologies	P990030	Flowable Bovine Collagen and Licensed Bovine Thrombin combined with Autologous Platelets	June 13, 2000

* Not sold in the US at this time.
** Application Numbers starting with "N" indicate products submitted to the Center for Drugs (CDER) and Numbers starting with "P" are products submitted to the Center for Devices (CDRH). Some of the applications with numbers starting with N were approved in CDRH even though they were submitted to CDER.

Risks to Health

FDA regulates many other medical devices manufactured from similar animal source materials as Class III, Class II, and unclassified devices. For example, the femoral artery sealing device,

which may have a porcine or bovine collagen or gelatin component, is regulated as a Class III medical device. Collagen surgical mesh, gelatin coated surgical mesh, collagen suture, collagen dura replacement, and other collagen/gelatin-containing implants are regulated as Class II medical devices. Other collagen/gelatin-containing medical devices, such as the collagen-based wound dressings, are currently regulated as unclassified medical devices.

In order to summarize the potential risks associated with the use of the absorbable hemostatic agents, we reviewed the adverse event reports submitted to the agency via the Medical Device Reporting (MDR) System which was voluntary from 1992 until 1996 when it became mandatory for manufacturers to report any device failures they were aware of. The MDRs (up until June 13, 2003) for the absorbable hemostatic agents received by the Agency are summarized in Table 2.

Table 2: Adverse Events Reported

Adverse Event	Absorbable Hemostatic Agents without Thrombin	Absorbable Hemostatic Agents with Thrombin	Total Events
Product failure (continued bleeding observed)	1	8	9
Product deployment failure	0	7	7
Abdominal Infection	2	4	6
Sinus Infection	1	5	6
Paralysis following off-label placement in vertebral column	5	0	5
Infection following tooth extraction	5	0	5
Granuloma	2	0	2
Abscess	2	0	2
Foreign Body Reaction	1	1	2
Allergic Reaction	0	2	2
Interference with wound healing	0	2	2
Respiratory Difficulty	0	2	2
Bowel Obstruction	1	0	1
Hematoma	1	0	1
Intermittent ischemia	0	1	1
Stroke	0	1	1
Seroma	0	1	1
Tissue Necrosis	1	0	1
Couldn't figure out how to store	1	0	1
Erythema	0	1	1
Edema	0	1	1
Total	23	36	59

The following literature articles are indicative of the published literature on absorbable hemostatic agents. These articles discuss absorbable hemostatic agents and also describe some potential risks of using these devices. Copies of these articles are provided in Tab 4.

1. Arand AG and Sawaya R. Intraoperative chemical hemostasis in neurosurgery. Neurosurgery 18(2): 223-33 (1986).

2. Bloom AL and Thomas DP. Eds. "*Haemostasis and Thrombosis*" Churchill Livingstone (London, England, 1987) pp. 614-5.

3. Browder IW and Litwin MS. Use of absorbable collagen for hemostasis in general surgical patients. Am. Surg. 52(9): 492-4 (1986).

4. DeLustro F, Dasch J, Keefe J and Ellingsworth L. Immune responses to allogeneic and xenogeneic implants of collagen and collagen derivatives. Clin. Orthop. 260: 263-79 (1990).

5. Evans BE. Local hemostatic agents. NY State Dent. J. 47(4): 109-14 (1977).

6. Light RE. Hemostasis in Neurosurgery. J. Neurosurgery 2(5): 414-34 (1945).

7. Light RE and Prentice HZ. Surgical investigation of a new absorbable sponge derived from gelatin for use in hemostasis. J. Neurosurgery 2(5): 435-55 (1945).

8. Lindstrom PA. Complications from the use of absorbable hemostatic sponges. AMA Arch. Surg. 73: 133-41 (1956).

9. Schwartz SI. Ed. "*Principles of Surgery, 7th Edition*" McGraw-Hill (New York, 1999) pp. 92-93.

These articles, as well as others, and absorbable hemostatic agent labels were reviewed in order to compile the risks identified in Table 3. Tables 3 also identifies the methods that will be proposed to ameliorate these risks.

Table 3: Table of Potential Risks and Controls

Potential Risk	Control
Uncontrolled bleeding due to device failure	Animal Studies and/or Clinical Data
Hematoma as a result of continued bleeding following device application	Animal Studies and Product Labeling
Potentiation of bacterial growth leading to increased infections and Fever	Animal Studies and Product Labeling
Wound dehiscence due to device interposition at the wound edge	Product Labeling
Inflammation and/or edema due to foreign body reaction	Product Labeling and biocompatibility
Adhesion formation	Animal Studies
Failure to be absorbed	Bench Testing and Animal Studies
Reduced strength of methylmethacrylate adhesion when used to attach prosthetic devices to bone surfaces	Product Labeling
Aspiration into transfusion filters may activate coagulation *in vitro*	Product Labeling
Use of antiplatelet drug therapy, systemic heparinization and cardiopulmonary bypass may increase risk for hemostatic agent failure	Product Labeling
Use of the hemostatic agent in closed spaces may result in pressure causing nerve damage or tissue necrosis	Product Labeling
Accidental injection into the intravascular space may result in embolization	Product Labeling
Paralysis due to swelling of the product and exertion of pressure onto nerves	Product Labeling
Infection due to improper sterilization	Bench Testing and QSR

Table 4 lists the additional risks for absorbable hemostatic agents that contain bovine thrombin.

Table 4: Table of Additional Potential Risks for Products with Thrombin

Potential Risk
Allergic reaction (antibodies to collagen, gelatin, thrombin) and potential antibody cross reaction (bovine Factor Va antibodies may cross react with human Factor Va resulting in coagulopathy
Inability to assemble or deploy the device, mechanical failure of the device and device malfunction such as clogging

Proposed Reclassification:

The Agency is proposing that the absorbable hemostatic agents that do not contain bovine thrombin may be reclassified to a lower classification (Class II, special controls). These devices have been regulated by CDRH since 1976, and previous to that were regulated as drugs since the 1940s when both Gelfoam and Oxycel were introduced into the marketplace. During this time a great deal of clinical and preclinical data has been collected that indicate that these devices are safe and effective in controlling bleeding when used in accordance with their approved labeling. The data reported in the literature and medical device reporting have identified the greatest potential risks to the patients. These are identified in Table 2. The Agency feels that all of these potential risks can be addressed via special controls in the form of a guidance document. The applications affected by this reclassification would include all of those listed in Table 1 except those that contain bovine thrombin. The products within this category are currently manufactured from the following materials:

Absorbable Gelatin Sponge: The gelatin sponge is an absorbable material created from porcine gelatin through which nitrogen has been bubbled in order to produce a porous product. This method was first introduced by Correll and Wise in 1945. The sponge has no intrinsic hemostatic action but induces hemostasis through its intensely porous structure, which enables it to absorb 45 times its weight in blood. As it fills with blood the platelets come into close contact and begin to collide initiating the clotting cascade.

Oxidized Cellulose: Oxidized cellulose is a fabric material that is obtained by the oxidation of cotton, gauze, or other cellulose fabric using nitrous oxide to achieve oxidation. The process was first described by Yackel and Kenyon of Eastman Kodak Laboratories in 1942. This reaction converts certain of the hydroxyl radicals to carboxyl groups and makes the material soluble at physiological conditions. The low pH of the cellulosic acid within the product has caustic properties that lead to hemostasis via the initial denaturation of blood proteins.

Regenerated Oxidized Cellulose: Similar to oxidized cellulose, but cellulose is first dissolved and then extruded as a continuous fiber. The fabric made from the fiber is very uniform in chemical composition and its oxidation is more closely regulated. This uniform oxidation results in less variation in absorbability of the material. The regenerated oxidized cellulose induces hemostasis in a manner identical to oxidized cellulose.

Microfibrillar Collagen: Microfibrillar collagen is a water-insoluble, partial hydrochloric acid amino salt of natural collagen in the form of fibers containing microcrystals prepared from purified bovine dermal collagen. Microfibrillar collagen acts primarily by reaction with platelets. Platelets attach to specific sites on collagen and degranulate initiating the hemostatic cascade leading to a fibrin clot.

Continued Class III Status for Absorbable Hemostatic Agents containing Bovine Thrombin:

While the Agency feels that the absorbable hemostatic agents and the associated risks are well understood for those that do not include bovine thrombin the same cannot be said for absorbable

hemostatic agents that do contain thrombin. A number of recent publications have drawn attention to safety concerns for bovine thrombin, in particular antigenic reactivity in humans. These concerns may not be adequately addressed by special controls and therefore, the FDA believes that those hemostatic agents, which include bovine thrombin, should remain Class III and continue to require a PMA for marketing.

Proposed Identification for Absorbable Hemostatic Agents for the Code of Federal Regulations:

PRESENT CFR LISTING for ABSORBABLE HEMOSTATIC AGENT and DRESSING

(a) *Identification.* An absorbable hemostatic agent is a device intended to produce hemostasis by accelerating the clotting process of blood. It is absorbable
(b) *Classification.* Class III.
(c) *Date PMA or notice of completion of a PDP is required.* As of May 28, 1976, an approval under section 515 of the act is required before this device may be commercially distributed. See § 878.3.

PROPOSED IDENTIFICATION for THE ABSORBABLE HEMOSTATIC AGENT, SURGICAL (note new name):

§ 878.4490 – Absorbable hemostatic agent, surgical

(a) Identification. An absorbable hemostatic agent, surgical is an absorbable device intended to produce hemostasis by accelerating the clotting process of blood during surgical procedures.

(b) Classification.

(1) Class II (special controls) if it does not contain any drug or biological component. The special control for the class II device is FDA's "Class II Special Controls Guidance Document: Absorbable Hemostatic Agent, Surgical Device; Draft Guidance for Industry and FDA."

(2) Class III if it does contain a drug and/or biologic component, including thrombin.

(3) *Date PMA or notice of completion of a PDP is required.* As of May 28, 1976, an approval under section 515 of the act is required for any absorbable hemostatic agent described in paragraph (b)(2) of this section before the device may be commercially distributed. See § 878.3.

Summary of July 8, 2003 General and Plastic Surgery Devices (GPS) Panel Meeting:

Last year this Panel met to vote on this reclassification proposal. The GPS panel members heard from representatives of the manufacturers (Johnson & Johnson Wound Management Worldwide, Ferrosan A/S, and Integra LifeSciences) of absorbable hemostatic agents and from the FDA. The industry representatives and the FDA provided information attesting to the safe and effective use of the absorbable hemostatic agents for over 60 years. After these presentations, members of GPS panel discussed the proposed reclassification of the absorbable hemostatic agents from Class III to Class II. The consensus of opinion of the panel was that the product was appropriate for reclassification to Class II, but that they did not feel comfortable recommending reclassification without reviewing the proposed special control, a guidance document, developed to assure the continued safety and effectiveness of these products. Therefore, the panel voted 4 to 3 to table the vote on the proposed reclassification of absorbable hemostatic agents.

At the panel meeting, representatives of the manufacturers of some absorbable hemostatic agents pointed out that the manufacture of their product required careful purification of native fibers, controlled oxidation reactions, defined chemistry, dehydration, etc. The industry's central argument was that a special controls guidance document might be insufficient to address the complex nature of the processing that is involved in the manufacture of this type of product. FDA agrees that the manufacture of these products can be complex, however, FDA believes that we understand how to evaluate the performance of the finished product in order to evaluate whether they are safe and effective.

Special Controls Guidance Document:

When the Office of Device Evaluation (ODE) reclassifies a medical device from regulatory Class III to regulatory Class II, such reclassifications are accompanied by what the Agency refers to as "Special Controls". In the vast majority of cases, the special control has been in the form of a guidance document. The guidance document: "*Class II Special Controls Guidance Document: Surgical Sutures; Draft Guidance for Industry and FDA*", issued on June 3, 2003, is provided as an example of a Class II special controls guidance document for a transitional device that was reclassified from Class III to Class II. The Class II special controls guidance document for the absorbable surgical hemostatic agent devices would be very similar to the example special controls guidance document provided with the exception that specific product information would be different. The suture special control is also relevant because when FDA reclassified surgical sutures from Class III to Class II, one of the concerns mentioned by the industry was that suture manufacturing was technically complex. FDA agreed but felt that the performance characteristics needed to evaluate the safety and effectiveness of the finished sutures were well understood and could, therefore, be appropriately regulated as Class II.

While the agency has not provided you with a copy of a draft proposed special controls guidance document for absorbable hemostatic agents, this memo includes the sections for such a guidance document for your review. At present, a special controls guidance document is comprised of 11 chapters. For a proposed absorbable surgical hemostatic agent devices document, chapters 1 through 4 would be mostly boilerplate language except for references to the device type and regulation numbers. For your information and review we are providing the information that is

proposed for Chapters 5 through 11 of a special controls guidance document for the absorbable surgical hemostatic agents. Please note that the information presented in this memorandum is in draft form and, therefore, the exact format and information contained in the final guidance document is subject to change.

Chapter 5, "Risks to Health":

This chapter would include information quite similar to the table above, which discusses the risks to health associated with the use of the absorbable surgical hemostatic agents. The information to be placed in that chapter is proposed as follows:

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

Identified risk	**Recommended mitigation measures**
Uncontrolled bleeding due to device failure	Sections 6, 7, and 8
Hematoma from continued bleeding following device application	Sections 7, 8, and 11
Potentiation of bacterial growth leading to increased infections and Fever	Sections 7, 9, and 11
Wound dehiscence at the wound edge	Section 11
Inflammation and/or edema due to foreign body reaction	Sections 7, 10, and 11
Adhesion formation	Section 7
Failure to be absorbed	Sections 6, 7, and 10
Reduced strength of methylmethacrylate adhesion when used to attach prosthetic devices to bone surfaces	Sections 7 and 11
Aspiration into blood transfusion filters may activate coagulation inside the filtering device	Section 11
Concomitant antiplatelet drug therapy, systemic heparinization and cardiopulmonary bypass may increase risk for hemostatic agent failure	Sections 7 and 11
Application in closed spaces may exert pressure causing nerve damage or tissue necrosis	Section 11
Accidental injection into the intravascular space may result in embolization	Section 11
Paralysis due to swelling of the product and exertion of pressure onto nerves	Section 11
Infection due to improper sterilization	Sections 6 and 9

Chapter 6, "Material and Performance Characterization":

This chapter would include the types of bench top, material characterization and manufacturing information that the Agency would be looking for. The proposed chapter would read as follows:

We recommend that the information below be performed to establish the material and performance characteristics of the device.

Material Information
We recommend that you provide all material components of the device. 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 and/or a Materials Safety Data Sheet(s) can also greatly simplify review of components.

If collagen or other animal-derived material is a device component, we recommend that you also provide the following information:

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

- How is the herd's health maintained and monitored? For example:
  - Is the herd closed?
  - What vaccinations are standard for the herd (e.g., focus on live modified viruses)?
  - Are veterinarian inspections performed and if so how frequently?
  - What is the composition of the animal feed?
  - Is the abattoir USDA approved or inspected?
  - If the animal material is of bovine origin, certification that the herd is from a bovine spongiform encephalopathy-free country.

- How is each animal's health maintained and monitored? For example:
  - What is the age of the animal at sacrifice?
  - Are pre- and/or post-mortem inspections performed?
  - What tests are performed to determine that the material is acceptable for further processing or pooling with material from other animals?

If the product contains synthetic (e.g., polymeric) components, we recommend that you provide 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.

Manufacturing Information
We recommend that the product manufacturing process be briefly described and

compared to the standard methods for this device. Any innovations or deviations from the accepted methods must be supported with data that justify the modifications since any modifications from standard techniques could effect time to hemostasis, absorption properties or other important characteristic of the device.

We recommend that you provide the final product release specification for relevant in-process and final product tests, including identification of the test method and time of testing during manufacture. Examples of final product release specifications include:

- Specific amino acid content for protein devices
- Residual levels of manufacturing reagents
- Residual levels of heavy metals
- Pyrogen levels, and
- Sterility.

Final Product Information

We recommend that you provide the following information regarding your final absorbable hemostatic agent:

- Cross-linking agent material identification and toxicity
- Initial cross-linking agent concentration and any residual concentration
- The time to complete device absorption determined in animal studies. Animal studies should be performed in a manner expected to accurately predict product decomposition (e.g., in comparable cellular and proteolytic environments at 37°C).

Shelf Life Information

FDA recommends that you provide shelf life data supporting an expiration date for the labeling of your absorbable hemostatic agent. Shelf life testing should consist of both stability testing of the agent and packaging testing.

We recommend that you collect stability data from at least three production lots. The stability data should include the critical parameters of the absorbable hemostatic agent that are required to ensure it will perform consistently during its entire shelf life.

With regard to packaging testing, we recommend that you provide data for the final finished package for initial integrity and maintenance of integrity after selecting the appropriate materials and qualifying the package configuration. We recommend that you use test methods that are either validated or standardized.

Accelerated testing should be supported/validated by real-time shelf life testing. 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 will not support claims for product stability.

Chapter 7, "Animal Testing":

This chapter discusses the animal testing the Agency would recommend. The information proposed for inclusion into this chapter is as follows:

FDA recommends that you provide animal studies modeling each surgical application for which the absorbable hemostatic agent is to be indicated. For example, for general surgical use, we recommend that the animal testing include arteriolar, venous and capillary bleeding from various tissues and organs. For the arterial bleeding, we recommend that you provide specific data to support this indication.

FDA recommends that your animal study evaluates the time to hemostasis, time to resorption of the hemostatic agent, and any complications. The complications monitored should include infections, hematomas, coagulopathies, increased wound healing times, etc.

FDA also recommends that your animal study include testing of an approved/cleared device of similar components and manufacture so that observations can be made as to the substantial equivalence of the two devices in reference to the evaluations outlined in the paragraph above.

Chapter 8, "Clinical Testing":

This chapter of the special controls guidance document discusses clinical data. The information proposed for this chapter is as follows:

In accordance with the Least Burdensome provisions of the FDA Modernization Act of 1997, FDA will rely upon well-designed bench 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 will not be needed for most absorbable hemostatic agent devices, FDA may recommend that you collect clinical data for an absorbable hemostatic agent device with:

- New technology, i.e., technology different from that used in legally marketed absorbable hemostatic agent device); or
- Indications for use dissimilar from an absorbable hemostatic agent device of the same type.

FDA will always consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale.
Absorbable hemostatic agents 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 agent may be applied due to the inaccessibility of a site to conventional hemostatic methods. Accordingly, FDA recommends that a clinical study address the following:

- A study should be designed to compare the safety and effectiveness of the new device to a legally marketed predicate device. In most cases, such comparisons should be made between absorbable hemostatic agents manufactured from similar materials and with similar indications for use.

- A study should be conducted at enough institutions to assure that the observations made regarding the safety and effectiveness of the devices will be significant in spite of technical and procedural differences likely to be encountered when the product is marketed.

- Patients should be followed for a reasonable length of time to assess any after effects of device use.

- Safety and effectiveness should be demonstrated for each surgical specialty for which the device is to be indicated beyond the general surgery indication. As in the animal studies, device absorption and or migration are likely to vary from site to site and specific data should be provided.

- The primary effectiveness endpoint for the clinical study should assess the products ability to achieve hemostasis in a reasonable amount of time.

- The primary safety endpoints should be 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.

The Plastic and Reconstructive Surgery Devices Branch is available to discuss any questions you may have about clinical studies and alternatives.

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 812. FDA has determined that the absorbable hemostatic agent device addressed by this guidance document is a significant risk device as defined in 21 CFR 812.3(m)(4). In addition to the requirement of 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).

After FDA determines that the device is substantially equivalent, clinical studies conducted in accordance with the indications reviewed in the 510(k), including clinical design validation studies conducted in accordance with the quality systems regulation, are exempt from the IDE requirements. However, such studies must be performed in conformance with 21 CFR 56 and 21 CFR 50.

Chapter 9, "Sterility":

This is a chapter that is fairly boilerplate for most medical devices. The information to be included in this chapter is as follows:

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. The device should be sterile with a sterility assurance level (SAL) of 1×10^{-6}.

Chapter 10, Biocompatibility:

This is another chapter where the language and content is virtually identical from guidance document to guidance document. The proposed information to be placed into this chapter is as follows:

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 are used in a predicate device with the same type and duration of patient contact, you may identify the predicate device in lieu of biocompatibility testing.

Chapter 11, Labeling:

This last chapter of the special controls guidance document gives recommendations of the general content of the labeling for a medical device. I am providing a specific example of the information ODE recommends for the labeling of an absorbable surgical hemostatic agent in the labeling for the Surgifoam product attached to this memo. The proposed information for this chapter is as follows:

The 510(k) should 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 807.87(e).

Prescription Use:
In accordance with 21 CFR 801.109, this device must bear the following caution statement: "Caution: Federal law restricts this device to sale by or on the order of a physician."

Instructions for Use:

Instructions for Use" should include adequate information regarding the contraindications, warnings, and precautions in order to address the identified risks to health and a clear explanation of the device technological features and how it is to be used.

The Least Burdensome Provisions of FDAMA:

A central purpose of the Food and Drug Administration Modernization Act of 1997 (FDAMA) is "to ensure the timely availability of safe and effective new products that will benefit the public and to ensure that our Nation continue to lead the world in new product innovation and development. Congress' goal was to streamline the regulatory process (i.e., reduce burden) to improve patient access to drugs and devices that could benefit the public.

One of the concepts central to this "least burdensome" approach to the regulation of medical devices is to review devices at the Class level (Class I, Class II, Class III) where they will receive an appropriate level of oversight in accordance with what is known about the safety and effectiveness of the device type. Since absorbable hemostatic agents have been on the market since the 1940s, the Agency believes that they can be appropriately regulated at the Class II, Special Controls, regulatory level because how to assess their effectiveness and what the known complications are, from the use of these devices, is well understood. More than just risk is taken into account when devices are classified. An understanding of the methods to assess safety and effectiveness is a central factor in the classification of medical devices. Other Class II devices that are considered to have high risks associated with their use are dura replacements, surgical meshes and sutures. Sutures were Class III transitional devices that were reclassified in the early 1990s.

The Guidance Document: *The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final guidance for FDA and Industry*, is provided as a reference for your convenience.

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