



24 Hour Summary General and Plastic Surgery Devices Advisory Committee Meeting May 31, 2019

Introduction:

On May 31, 2019, the General and Plastic Surgery Devices Panel of the Medical Device Advisory Committee met to discuss and make recommendations regarding the reclassification of absorbable collagen-based hemostatic devices from class III to class II (special controls). These devices are considered transitional devices since they were in commercial distribution regulated as drugs prior to May 28, 1976, when the Medical Devices Amendments became effective.

Device Description:

As currently defined in 21 CFR 878.4490, the classification regulation for “Absorbable Hemostatic Agent and Dressing” states:

- (a) *Identification.* An absorbable hemostatic agent or dressing 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.

Absorbable hemostatic devices are primarily applied during surgical procedures 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.

A variety of accessories are currently approved for use with absorbable hemostatic devices. Since manual compression is the primary method of application, these accessories facilitate device delivery into confined spaces that would prohibit manual compression after application of the absorbable hemostatic devices. These accessories are typically syringe-like devices with short or long applicator tips to aid device delivery in open, endoscopic, or laparoscopic surgical procedures.

Currently, absorbable hemostatic devices regulated under 21 CFR 878.4490 are grouped under three product codes:

- LMF – Agent, Absorbable Hemostatic, Collagen Based
- PMX – Absorbable Collagen Hemostatic Agent with Thrombin
- LMG – Agent, Absorbable Hemostatic, Non-Collagen Based

The devices within these three product codes are discussed in greater detail below:

Absorbable Collagen-based Hemostatic Agents (Product Code: LMF)

Absorbable collagen-based hemostatic agents are manufactured from the following materials:

Gelatin Sponge: The gelatin sponge is an absorbable material created from porcine gelatin through which nitrogen has been bubbled to produce a porous device. 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. The United States Pharmacopeia (USP) includes a monograph for this device, USP29-NF24.

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.

Absorbable collagen-based hemostatic agents provide hemostasis through contact activation and the promotion of platelet aggregation, which occur as a direct result of contact between blood and the collagen. Gelatin-based products, a form of denatured collagen, also initiate clotting via contact activation. When held in place at the site of bleeding, gelatin will conform to the wound and swell. The swollen gelatin particles restrict blood flow and provide a stable matrix around which a clot can form. These devices do not promote clotting in a biologically active manner or work in combination with thrombin.

Absorbable Non-collagen-based Hemostatic Agents (Product Code: LMG)

Currently approved absorbable non-collagen based hemostatic agents are composed of plant-derived materials: oxidized cellulose, regenerated oxidized cellulose, and polysaccharides. These devices have been characterized to promote hemostasis via a passive, physical activation of clotting cascade. The biologic component is typically composed of purified thrombin to promote hemostasis through a direct biochemical activation of the factor(s) in the clotting cascade.

Absorbable Collagen-based Hemostatic Agents Containing Biologics (Product Code: PMX)

The devices in this category are regulated as combination products because they have a biologic component in addition to the device component. The device component is predominantly composed of gelatin or collagen-based materials, as described above, to promote hemostasis via

a passive, physical activation of clotting cascade. The biologic component is typically composed of purified thrombin to promote hemostasis through a direct biochemical activation of the factor(s) in the clotting cascade.

The Panel convened to discuss reclassification of absorbable collagen-based hemostatic devices currently designated under product code LMF. The scope of the Panel discussion excluded absorbable collagen-based hemostatic devices containing added biologics and non-collagen-based absorbable hemostatic devices currently designated under product codes PMX and LMG.

Summary of Presentations:

The committee heard presentations from FDA regarding clinical considerations of absorbable collagen-based hemostatic devices, including a review of the available literature. FDA presented a summary of medical device reports for absorbable collagen-based hemostatic devices. Additionally, FDA provided an overview of the current review practice for absorbable collagen-based hemostatic devices and discussed the risks, mitigations, and special controls that FDA proposed. One Industry speaker representing Ethicon expressed their desire to keep absorbable collagen-based hemostatic devices as Class III, stating that manufacturing modifications may affect the device and emphasizing that clinical data may be needed to demonstrate device safety and effectiveness. Following the presentations, the Panel proceeded to discuss FDA's questions listed below.

Panel Deliberations/FDA Questions:

1. FDA discussed the following risks to health for absorbable collagen-based hemostatic devices based on reports in the Medical Device Reporting database, information available to FDA under section 520(h)(4) of the FD&C Act (21 U.S.C. 360j(h)(4)), the published literature, and the recommendations of the 2002 and 2003 Panels:
 - a. *Uncontrolled Bleeding* – The absorbable collagen-based hemostatic device is intended for use during surgical procedures as an adjunct to hemostasis when conventional means fail to produce hemostasis or are impractical. Patients receiving antiplatelet or anticoagulation therapy have increased blood clotting times. This increase in blood clotting time occurs even when an absorbable collagen-based hemostatic device is used during the surgical procedure to control bleeding. Failure to completely control bleeding can lead to death or severe injury.
 - b. *Hematoma* – If small amounts of bleeding persist following the application of an absorbable collagen-based hemostatic device, the accumulation of blood behind the device will form a hematoma. The hematoma may press on soft tissue and cause soft tissue or nerve damage. A hematoma may also result in infection.
 - c. *Infection* – An absorbable collagen-based hemostatic device may serve as a nidus for infection and abscess formation. Absorbable collagen-based hemostatic devices are manufactured from materials derived from animal sources such as collagen and gelatin; bacteria can grow on these device materials. For example, the use of absorbable collagen-based hemostatic devices in nasal surgery has been associated with toxic shock syndrome.
 - d. *Wound Dehiscence* – The use of an absorbable collagen-based hemostatic device near sites of incision closures has interfered with the healing of the incision. This

interference is due to mechanical interposition of the device and is not due to intrinsic interference with the wound healing process.

- e. *Foreign Body Reactions* – The absorbable collagen-based hemostatic device has been associated with foreign body reactions involving fluid accumulation due to encapsulation of the device. Such encapsulated devices have resulted in granuloma formation, inflammation, and edema, which may require surgical removal. Encapsulated devices can also present as an image artifact mimicking residual or recurrent tumor or abscess resulting in additional diagnostic studies and surgical procedures.
- f. *Immunological Reactions* – Absorbable collagen-based hemostatic devices are made of collagen-based materials derived from animal-based sources such as porcine and bovine gelatin or collagen. Some patients are allergic to these animal-derived materials.
- g. *Adhesion Formation* – An absorbable collagen-based hemostatic device, in the presence of coagulated blood and tissue fluid, often leads to scarring and adhesion formation in the weeks and months following the surgical procedure. The surgical procedure itself may result in additional scarring and adhesion formation.
- h. *Failure to be Absorbed* – Absorbable collagen-based hemostatic devices are readily degraded by enzymatic and hydrolytic action. Occasionally, an absorbable collagen-based hemostatic device may be implanted in an area with low enzymatic and hydrolytic activity. In such instances, it may not be efficiently absorbed. Subsequently, it may become encapsulated and exert pressure or create a chronic granulomatous inflammatory reaction on surrounding soft tissue to cause necrosis or injury, requiring surgical intervention.
- i. *Interference with Methylmethacrylate Adhesives* – Some types of absorbable collagen-based hemostatic devices have been reported to reduce the strength of methylmethacrylate adhesives used to fixate orthopedic prosthetic devices to bone.
- j. *Aspiration into Blood Salvage System Filters* – Fragments of an absorbable collagen-based hemostatic device may pass through blood salvage system filters and occlude the systems or the patient's vasculature.
- k. *Embolization* – Absorbable collagen-based 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.
- l. *Paralysis/Nerve Damage/Tissue Necrosis* – Absorbable collagen-based hemostatic devices absorb fluids and swell to varying degrees, up to 40 times their weight in volume. This device swelling can encroach on surrounding nervous tissue to cause paralysis or tissue necrosis.
- m. *Disease Transmission* – Absorbable collagen-based hemostatic devices are composed of animal-derived collagen-based materials. Animal-derived materials may carry a risk of transmitting infectious disease when improperly collected, stored or manufactured.
- n. *Adverse tissue reaction* – Absorbable collagen-based hemostatic devices may result in local or systemic adverse tissue reaction due to material composition or interaction of

the material with the body.

- o. *Toxicity* - Absorbable collagen-based hemostatic devices may contain materials or ingredients that result in local or systemic toxicity.
 - i. Please comment on whether you believe FDA has identified a complete and accurate list of the risks to health presented by absorbable collagen-based hemostatic devices.
 - ii. Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of absorbable collagen-based hemostatic devices.

In general, the panel’s consensus was that the list of risks to health is accurate and comprehensive. Specific discussion clarified the risk of hematoma and reinforced the risk of foreign body reactions or image artifacts associated with device use. Some panel members also emphasized that embolization is a serious risk and is appropriately included. In addition, one panel member felt that asterixis could be removed from the adverse effects listed under embolization.

2. As defined in 21 CFR 860.7(d)(1), “there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury association with the use of the device for its intended uses and conditions of use.” As defined in 21 CFR 860.7(e)(1), “there is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

The panel consensus based upon the available valid scientific evidence, was there is a reasonable assurance of safety and effectiveness for absorbable collagen-based hemostatic devices. The available evidence is predominantly derived from the premarket clinical trials and the long history of safe and effective use for the currently approved absorbable collagen-based hemostatic devices.

3. FDA proposal for the following special controls would adequately mitigate the risks to health and provide reasonable assurance of safety and effectiveness for absorbable collagen-based hemostatic devices:
 - a. Materials characterization of the device must include the following:
 - o Material source information must be sufficient to demonstrate that the likelihood of the risk that the device is transmitting infectious diseases is minimized.
 - o Material processing information must detail all reagents used in the manufacture of the device, and residual amounts must be quantified.
 - o For crosslinked devices, the density of crosslinks must be provided.

- Device-related particulates must be characterized.
 - Collagen characterization information, including elemental analysis and de-cellularization efficiency determination, must demonstrate the identity, purity, and quality of the collagen.
- b. Biocompatibility evaluation of the device must include the following:
- Patient-contacting components of the device must be demonstrated to be biocompatible.
 - Residual reagents in the final product must be demonstrated to be safe for human exposure.
- c. Performance data must demonstrate the sterility of patient-contacting components and acceptable levels of endotoxins and material-mediated pyrogens.
- d. Performance data must support the shelf-life of the device by demonstrating continued sterility of the device, package integrity, and device functionality over the identified shelf-life.
- e. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, and must characterize:
- Amount of swelling, e.g., change in volume or change in weight, of the device;
 - In vitro clotting time;
 - Reliability of the delivery system mechanism and compatibility of the delivery system with the hemostatic device;
 - Absorption of the device under physiologically relevant conditions; and
 - Fragmentation of the device.
- f. For devices intended for use on bone surfaces, non-clinical performance testing must demonstrate that the device does not interfere with the bonding strength of methylmethacrylate adhesives.
- g. For devices intended to be used in applications that involve blood transfusion systems, non-clinical performance testing must demonstrate that the device does not impair the proper operation of the blood transfusion system.
- h. In vivo evaluation of the device must include the following:
- Usability testing and analysis must demonstrate that the device design and labeling are sufficient for the device to perform as intended.
 - In vivo performance data must demonstrate that the device controls bleeding and does not promote adverse local or systemic effects under anticipated conditions of use.
 - The in vivo models chosen for the intended application of the hemostatic device must represent the intended use, including type of bleeding and targeted tissue(s) of bleeding.
 - A validated bleeding scale tool for bleeding severity must be used for selection and evaluation of bleeding sites to support the intended use.
 - The following characteristic must be evaluated:
 - Reliability of deployment mechanism and anticipated compatibility issues of deployment, e.g. passage of device through trocars;

- Effectiveness of hemostasis at 10 minutes or less, and characterization of the following: re-bleeding potential, blood loss, thromboembolic risk;
 - Immunogenicity of non-mammalian collagens;
 - Inflammatory cell response/potential histotoxicities;
 - Time to complete absorption
 - Macroscopic and microscopic histology at implant site and sites distant from implant site; and
 - Hematological and clinical chemistry parameters.
- i. Labeling must include:
- Specific instructions for deployment by users;
 - Warnings, precautions, and limitations needed for safe use of the device. Unless available information indicates that the following do not apply, the labeling must provide appropriate warnings, precautions or limitations regarding how to avoid known hazards associated with device use including:
 - Interference with healing of wound edges;
 - Interference with methyl methacrylate adhesives; and
 - Use with autotransfusion systems.
- j. A contraindication for intravascular application of the device, unless clinical data demonstrating safe use in this area is provided.
- k. Information on how the device operates and the typical course of treatment;
- l. A detailed summary of the in vivo evaluation pertinent to use of the device;
- m. For devices intended for general surgical use, a hemostatic effectiveness table comparing device performance in multiple specialties of surgical procedures; and
- n. An expiration date/shelf life.

The panel was asked for consensus on whether the proposed special controls (or any other) are necessary to mitigate the risks to health and provide reasonable assurance of device safety and effectiveness or whether the panel disagrees with the inclusion of any of these special controls.

In general, the panel consensus was that the identified special controls were comprehensive.

In your deliberations, please include a discussion of the following questions:

- i. Are different special controls needed for different forms of the device (e.g., sheet form, powder form)?

The panel consensus was that different special controls are not needed for different forms of the device, e.g. sheet or powder forms.

- ii. Should a validated bleeding scale be used to demonstrate effectiveness of hemostasis? What should be considered as effective hemostasis?

The panel consensus supported the use of a validated bleeding scale to support the standardized assessment of premarket device effectiveness. The panel stated that effective hemostasis would have to be determined by experts in the field of clinical hemostasis.

- iii. Should effectiveness of hemostasis be evaluated at 10 minutes or less, or at a different time point?

The panel consensus deferred to the experts in the field of hemostatic devices to determine the appropriate time to evaluate device effectiveness in hemostasis.

- iv. Are clinical data necessary to demonstrate device safety and effectiveness for all absorbable collagen-based hemostatic devices?

The panel consensus determined that clinical data is not routinely necessary to demonstrate device safety and effectiveness. The panel stated that whether clinical data is necessary would depend on how similar it is to another legally marketed device. For example, the panel stated that clinical data would not be necessary if the device is identical in composition to another legally marketed absorbable collagen-based hemostatic device. In contrast, the panel stated that if the device is sufficiently different in composition compared to another legally marketed absorbable collagen-based hemostatic device, then clinical data would be necessary to demonstrate device safety and effectiveness. The Panel deferred to FDA's judgment during the review process on whether clinical data is necessary to demonstrate device safety and effectiveness.

- v. Are there additional special controls that could be implemented to mitigate risks associated with inappropriate device use (e.g., postmarket surveillance)?

The panel consensus did not believe that postmarket surveillance should be routinely performed for these devices. The panel felt that periodic reviews of literature and/or adverse events are not required to demonstrate device safety and effectiveness.

4. Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if:

- insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance, AND
- if, in addition, the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

A device should be Class II if:

- general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, AND
- there is sufficient information to establish special controls to provide such assurance.

A device should be Class I if:

- general controls are sufficient to provide reasonable assurance of the safety and effectiveness

OR

- insufficient information exists to:
 - determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness or
 - establish special controls to provide such assurance

BUT

- is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and
- does not present a potential unreasonable risk of illness or injury.

Please discuss the following questions:

- Please comment on whether the general controls, required for all medical devices, are insufficient to provide a reasonable assurance of safety and effectiveness for absorbable collagen-based hemostatic devices.
- Please comment on whether you agree or disagree with FDA's view that the application of general controls and special controls, are sufficient to provide reasonable assurance of safety and effectiveness for absorbable collagen-based hemostatic devices when intended to be placed in the body during surgery to produce hemostasis by accelerating the clotting process of blood.
- FDA does not believe that absorbable collagen-based hemostatic devices are life-supporting or life-sustaining. Do you agree with this assessment? If not, please explain why. Please comment on whether you believe that absorbable collagen-based hemostatic devices are for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury when intended to be placed in the body during surgery to produce hemostasis by accelerating the clotting process of blood.

The panel consensus, based upon the available valid scientific evidence and the proposed special controls, recommended Class II for absorbable collagen-based hemostatic devices when intended to be placed in the body during surgery to produce hemostasis by accelerating the clotting process of blood. The rationale for the panel's final classification recommendation took into account the available valid scientific evidence and the special controls proposed by FDA.

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