FDA Questions
May 31, 2019 meeting of the
General Surgery Devices Panel of the Medical Devices Advisory Committee
Absorbable Collagen-Based Hemostatic Device Reclassification

Please refer to the Regulatory Reference Sheet for additional information regarding classification procedures and definitions.

1. FDA has identified 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:

- *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.
- *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.
- *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.
- *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.
- *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.
- *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.
- *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.

- *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.
- *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.
- *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.
- *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.
- *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.
- *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.
- *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.
- *Toxicity* - Absorbable collagen-based hemostatic devices may contain materials or ingredients that result in local or systemic toxicity.

   a. **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.**

   b. **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.**

2. As defined in 21 CFR 860.7(d)(1), "there is reasonable assurance that a device is <u>safe</u> 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."

Please comment on whether, based on the available scientific evidence, there is a reasonable assurance of safety and effectiveness for absorbable collagen-based hemostatic devices.

3. FDA proposes that 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:

- Materials characterization of the device must include the following:
    - Material source information must be sufficient to demonstrate that the likelihood of the risk that the device is transmitting infectious diseases is minimized.
    - Material processing information must detail all reagents used in the manufacture of the device, and residual amounts must be quantified.
    - 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.

- 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.

- Performance data must demonstrate the sterility of patient-contacting components and acceptable levels of endotoxins and material-mediated pyrogens.

- 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.

- 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.

- 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.

- 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.

- 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.

- 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.

- A contraindication for intravascular application of the device, unless clinical data demonstrating safe use in this area is provided.

- Information on how the device operates and the typical course of treatment;

- A detailed summary of the in vivo evaluation pertinent to use of the device;

- For devices intended for general surgical use, a hemostatic effectiveness table

comparing device performance in multiple specialties of surgical procedures; and

- An expiration date/shelf life.

Please comment on whether you believe any other special controls are necessary to mitigate the risks to health and provide reasonable assurance of device safety and effectiveness or whether you disagree with the inclusion of any of these special controls.

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

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

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

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

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

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

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:

a. **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.**

b. **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.**

c. **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.**

5. **Based upon the available scientific evidence and special controls proposed in Question 3, do you recommend Class II or Class III 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. Please provide a rationale for your final classification recommendation, taking into account the available scientific evidence and your responses to Question 4 above.**