Classification of Topical Hemostatic Wound Dressings

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Device Description

A **topical hemostatic wound dressing *without* thrombin:**

- Intended for external use, often as an adjunct to manual compression, to control bleeding and absorb wound exudate.
- Generally helps achieve hemostasis through physical means.
- Can be manufactured from a variety of natural or synthetic materials in the form of solid pads, sponges, granules, or gel.
- Not for use in the organ space, next to internal tissues, veins, arteries or nerves
- May contain antimicrobials (e.g., chlorhexidine, silver), which serve to either prevent dressing deterioration (e.g., contamination) during shelf storage or to protect the dressing from microbial colonization during use.

Device Description

A **topical hemostatic wound dressing *with* licensed thrombin**

- Intended for external use for temporary control of moderate to severely bleeding wounds and for control of surface bleeding from vascular access sites and percutaneous catheters or tubes.
- Contains thrombin which has been approved through a Biologic License Application (BLA).
- The licensed thrombin facilitates hemostasis by enhancing the surface-activated clotting cascade through enzymatic cleavage and conversion of fibrinogen to fibrin.
- May additionally contain an antimicrobial (e.g., chlorhexidine, silver), which serves to either prevent dressing deterioration (e.g., contamination) during shelf storage or to protect the dressing from microbial colonization during use.

Indications for Use

Topical hemostatic wound dressings *without* thrombin have been cleared for the following indications for use:

- Help control minor bleeding
- Absorb body fluid in traumatic superficial lacerations or wounds
- Local management of bleeding wounds such as minor cuts, lacerations, and abrasions
- Temporary treatment of severely bleeding wounds such as surgical wounds (post-operative, donor sites, dermatological), traumatic injuries
- Temporary external use to stop bleeding of superficial wounds, minor cuts, and abrasions (Over the Counter use)
- Local management and control of bleeding from percutaneous needle access, vascular access sites and percutaneous catheters

Indications for Use

Topical hemostatic wound dressings *without* thrombin cleared indications for use (*continued*):

- Emergency use only as an external temporary traumatic wound treatment to achieve hemostasis for moderate to severe bleeding
- Rapid control of bleeding in patients following hemodialysis, or in patients on anticoagulation therapy
- Provide a barrier to bacterial penetration
- Control of local wound bleeding, to encourage draining by wicking fluids from a body cavity, infected area, or abscess, and to help remove necrotic tissue from ulcers or other infected wounds when used as a wet-to-dry packing
- Local management of moderately to heavily exuding wounds

Indications for Use

Topical hemostatic wound dressings *without* thrombin cleared indications for use (*continued*):

For use on the following types of wounds:

- Partial and full thickness wounds
- Pressure, arterial, venous, diabetic ulcers
- Donor sites
- Trauma wounds
- Dermal lesions
- Surgical incisions, including dehisced surgical incisions
- Draining wounds
- Lacerations
- Post-laser surgery
- Podiatric, surgical and traumatic wounds
- Other bleeding surfaces
- Abrasions
- Surgical debridement sites
- Skin surface puncture sites
- Vascular procedure sites
- Sites involving percutaneous catheters, tubes, pins

Indications for Use

Topical hemostatic wound dressings *with* licensed thrombin have been cleared for the following indications for use:

- Local management and control of surface bleeding from vascular access sites and percutaneous catheters and tubes
- Trauma dressing for temporary control of moderate to severely bleeding wounds
- An adjunct to manual compression
- Reducing the time-to-hemostasis in patients undergoing diagnostic endovascular procedures utilizing a 4-6 Fr. introducer sheath

Regulatory History

- Topical hemostatic wound dressings are a pre-amendments, unclassified device type (i.e., have been in commercial distribution since prior to May 28, 1976)
- Currently these devices are being regulated through the 510(k) pathway and are cleared for marketing if their intended use and technological characteristics are “substantially equivalent” to a legally marketed predicate device. Since these devices are unclassified, there is no regulation associated with the product code.
  - Topical hemostatic wound dressings are subset of devices currently cleared under product code "FRO.”
- To date, FDA has cleared over 100 topical hemostatic wound dressings *without* thrombin and 18 topical hemostatic wound dressings *with* licensed thrombin.

Clinical Background

- Topical hemostatic wound dressings with and without thrombin contribute to wound hemostasis and are especially important adjuncts to compression in the control of external hemorrhage.
- These dressings are used for temporary control of bleeding of a range of topical wounds, including minor cuts and lacerations through severe bleeding in traumatic wounds.
- They are commonly used in both military and civilian wounds to control bleeding. External bleeding can be mild, moderate or severe.

Clinical Background

Currently Available Treatment

- There is a range of standard of care methods, depending on the wound type and wound healing progression.
- Wounds are typically managed by applying a dressing to cover and protect the wound and maintain a moist wound environment. Many of these wound dressing devices also frequently serve as hemostatic agents.
- Traditional methods of attaining hemostasis include compression, suture ligation, clipping, and use of energy devices to cauterize bleeding sites. When conventional methods of hemostasis fail or are ineffective or impractical for any severity of external bleeding, topical hemostatic devices may be used as an adjunct to local compression. These include topical hemostatic wound dressings with and without thrombin.

Literature Review

- A systematic literature review was conducted to gather any published information regarding the safety and effectiveness of topical hemostatic wound dressing with and without thrombin.
- Literature searches were performed to identify all relevant articles for topical hemostatic wound dressings between April 1, 2012 - July 18, 2022.
- The literature searches were performed using multiple search terms related to wound dressings, with hedges for study design and publication years, and the searches were limited to publications in English.
- The searches yielded 15 articles that met the inclusion criteria at the title/abstract level and were retained for full text analysis.
- A total of four studies were determined to be relevant to the safety and/or effectiveness of topical hemostatic wound dressings without thrombin and none of the studies that met the inclusion criteria were relevant to topical hemostatic wound dressings with thrombin.

Literature Review

- Evidence base for topical hemostatic wound dressings:
  - One study evaluated time to clotting with and without a hemostatic wound dressing and found the hemostatic wound dressing resulted in significantly shorter time to clot. The same study found no serious complications, such as anaphylactic shock, bleeding refractory to manual compression, cutaneous allergy, or false aneurysm at the puncture site
  - 2 studies reported mixed results on whether use of topical hemostatic wound dressing improves chance of survival in combat situations when compared to no hemostatic wound dressing.
- Overall, the literature review did not indicate any significant difference in safety between topical hemostatic wound dressings *without* thrombin and controls. The use of topical hemostatic wound dressings appears to generally improve clotting time when compared to use of non-hemostatic wound dressings. However, the impact on survival was inconclusive.

Medical Device Reports

- Medical Device Reporting (MDR): the mechanism for the FDA to receive significant medical device adverse events from:
  - mandatory reporters (manufacturers, importers and user facilities)
  - voluntary reporters (health care professionals, patients, consumers)

Medical Device Reports

- MDR reports can be used effectively to:
  - Establish a qualitative snapshot of adverse events for a specific device or device type
  - Detect actual or potential device problems used in a “real world” setting/environment, including:
    - rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - off-label use
    - user error

Medical Device Reports

- Limitations
  - Under reporting of events
  - Potential submission of incomplete, inaccurate, untimely, unverified, or biased data
  - Incidence or prevalence of an event cannot be determined from this reporting system alone
  - Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report
  - MAUDE data does not represent all known safety information for a reported medical device

Medical Device Reports

- MAUDE (Manufacturer And User Facility Device Experience) Database reviewed for Topical Hemostatic Wound Dressing With or Without Thrombin, from January 1, 1986 to April 1, 2022.

Topical Hemostatic Wound Dressings *without* Thrombin

- 68 MDRs
- Manufacturers submitted reports: 48
- Voluntarily submitted: 13
- User facilities reported: 7
- Serious injury: 50
- Malfunction: 15

Medical Device Reports

Topical Hemostatic Wound Dressings *without* Thrombin

- Of the 68 MDRs, the most commonly reported event was unintentional off-label use on internal bleeding with multiple patients requiring re-operation or debridement.
- Associated with these MDRs were complaints that the dressings did not contain enough radiopaque material to be definitively identified on x-ray.
- Multiple patients experienced skin irritation and blistering that resulted in infection
- One patient suffered what appears to be a chemical burn that led to necrosis

Medical Device Reports

Topical Hemostatic Wound Dressings *with* Licensed Thrombin

- 15 MDRs
- Manufacturers submitted reports: 10
- Voluntarily submitted: 4
- User facilities reported: 1
- Serious injury: 13
- Malfunction: 2

Medical Device Reports

Topical Hemostatic Wound Dressings *with* Licensed Thrombin

- Multiple patients experienced allergic reactions that included redness and disseminating rash that resolved after treatment with antihistamine medication.
- Multiple patients reacted with severe symptoms like tachycardia, facial oedema, airway constriction, and itching, that required steroid and antihistamine treatment.
- In one case, the patient had a seizure and required emergency care (no additional information to determine causation).
- A pediatric patient required a debridement procedure when the dressing components formed a hard foreign body that interfered with the healing process.

Recall History

- The Medical Device Recall database contains medical device recalls classified since November 2002.
- Since January 2017, it may also include correction or removal actions initiated by a firm prior to review by the FDA.
- The status is updated if the FDA identifies a violation and classifies the action as a recall and again when the recall is terminated.
- FDA recall classification (resulting in the posting date) may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall.

Recall History

- The Medical Device Recall Database was queried for product code “FRO” (not time restricted).

- Eight (8) topical hemostatic wound dressings *without* thrombin have been recalled. Reasons for recall include:
  - package seal integrity
  - wrong products packaged together
  - packaging breach (sterility)
  - inappropriate claims
  - shipping non-sterile product instead of sterile product

Recall History

- Four topical hemostatic wound dressings *with* licensed thrombin have been recalled.
- These recalls were initiated due to packaging defects, which may compromise product sterility.
- The recalls for topical hemostatic wound dressings *without* thrombin and *with* licensed thrombin are related to manufacturing errors and do not suggest additional risks related to topical hemostatic wound dressings as a product class.

Risks and Examples

Topical hemostatic wound dressing *without* thrombin and *with* licensed thrombin

Identified Risk	Description/Examples
Uncontrolled bleeding	This occurs when the device does not effectively stop bleeding under anticipated conditions of use. This can also result when the device is used incorrectly.
Infection	This can result from inadequate device sterilization, inadequate viral inactivation (for devices containing animal-derived materials), or inadequate packaging integrity.
Adverse tissue reaction	This can result from the use of device materials that are not biocompatible.
Delay in wound healing	This can result from the use of device materials which may interfere with the wound healing process.
Transmission of pathogens and parasites *(e.g., bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents)*	This can result from contaminated animal sources, feed, inadequate processing and viral inactivation of the animal-derived materials.
Immunological reaction	This can result from a device derived from a new animal source or protein denaturation/modification due to the manufacturing conditions. Also, this occurs in certain patients who may be allergic to animal-derived materials.

Risks and Examples

Topical hemostatic wound dressing without thrombin and with licensed thrombin (*Cont.*)

Identified Risk	Description/Examples
Microbial growth within the product during use	This occurs when the antimicrobial in the dressing does not adequately reduce microbial growth during dressing use.
Contribution to the spread of antimicrobial resistance (AMR)	This occurs when the antimicrobial in the dressing contribute to the selection of antimicrobial resistance organisms and/or limit a clinician's therapeutic options to treat infections.
Foreign body reaction due to retained device	This occurs when nonabsorbable hemostats are not completely removed from the external target bleeding site, resulting in a sustained inflammatory response. The end result of such a response is pseudo mass formation requiring invasive diagnostic procedures to rule out tumor or abscess. Such an event can also result in chronic pain, obstruct blood vessels or compress nerves and compromise function of an extremity.
Rebleeding after attaining hemostasis	This can result when there is inadequate adhesive capacity of the hemostat. Precise coverage of the target bleeding site, especially in austere environments, may be compromised by temperature extremes, poor lighting and wind.
Arterial or venous embolism	This may occur if granular, powder or reduced dimension hemostat enters a blood vessel.
Thrombosis (e.g., deep vein thrombosis (DVT))	This may occur if granular, powder or reduced dimension hemostat enters a blood vessel.

Risks and Mitigations

Topical hemostatic wound dressing *without* thrombin and *with* licensed thrombin

Identified Risk	Recommended Mitigation Measure
Uncontrolled bleeding	Material characterization, Performance testing Shelf-life validation, Labeling Biologics License Application (BLA) approval for thrombin*
Infection	Sterilization testing/validation information, shelf-life validation, labeling, risk management assessment for animal derived materials, Biologics License Application (BLA) approval for thrombin*
Adverse tissue reaction	Biocompatibility evaluation, performance testing and descriptive information, labeling, Biologics License Application (BLA) approval for thrombin*
Delays in wound healing	Performance testing and descriptive information, Biocompatibility evaluation, Labeling
Transmission of pathogens (e.g., bacteria, mycoplasma, fungi, viruses and TSE agents)	Risk management assessment for animal-derived materials, performance testing, labeling, Biologics License Application (BLA) approval for thrombin*

** Applies only to topical hemostatic wound dressings with licensed thrombin*

Risks and Mitigations

Topical hemostatic wound dressing without thrombin and with licensed thrombin

Identified Risk	Recommended Mitigation Measure
Immunological reaction	Risk management assessment for animal-derived materials Performance testing and descriptive information Biologics License Application (BLA) approval for thrombin* Labeling
Microbial growth within the product during use	Antimicrobial characterization and performance testing Sterilization validation
Contribution to the spread of antimicrobial resistance (AMR)	Antimicrobial characterization and performance testing, AMR risk assessment, Labeling
Foreign body reaction due to retained device	Performance testing, Labeling
Rebleeding after attaining hemostasis	Performance testing, Labeling
Arterial or venous embolism	Performance testing, Labeling
Thrombosis (e.g., deep vein thrombosis (DVT))	Performance testing, Labeling

** Applies only to topical hemostatic wound dressings with licensed thrombin*

Proposed Classification

878.4021 Topical hemostatic wound dressing

(a) Identification: A topical hemostatic wound dressing is a device that is placed externally on skin wounds to temporarily stop or control minor, moderate or moderate-to-severe bleeding. This device is not to be implanted, in contact with arteries, veins, nerves, or used on any internal organ or tissue. A topical hemostatic wound dressing does not contain drugs.

(1) Topical hemostatic wound dressing without thrombin. A topical hemostatic wound dressing without thrombin is intended for external use to temporarily control bleeding and absorb wound exudate. This device helps achieve hemostasis through only physical (i.e., not chemical) means, such as creating a physical barrier to stop blood flow and absorbing moisture. A topical hemostatic wound dressing without thrombin may contain animal-derived materials (e.g., collagen) for structural or moisture retention purposes. Additionally, a topical hemostatic wound dressing without thrombin may contain an antimicrobial of low or medium antimicrobial resistance (AMR) risk as a preservative (e.g., to prevent contamination or deterioration of the dressing during shelf storage) or a protectant (e.g., to protect the dressing from microbial colonization during use). Such dressing does not contain any biologics (including thrombin) or antimicrobials of high AMR risk.

Proposed Classification

(2) Topical hemostatic wound dressing with licensed thrombin. A topical hemostatic wound dressing with licensed thrombin is intended for external use to temporarily control bleeding. The device creates a physical barrier to blood flow through the application of adjunctive manual compression, and the thrombin in the device facilitates hemostasis by enhancing the surface-activated clotting cascade through enzymatic cleavage and conversion of fibrinogen to fibrin. A topical hemostatic wound dressing with licensed thrombin may additionally contain an antimicrobial of medium or low AMR risk as a preservative (e.g., to prevent contamination or deterioration of the dressing during shelf storage) or a protectant (e.g., to protect the dressing from microbial colonization during use). Such dressing does not contain any biologics other than licensed thrombin or antimicrobials of high AMR risk.

(a) Classification. Class II (special controls)

Special Controls

The special controls for this device are:

1. Performance testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and chemical characteristics of the device. The following must be provided:
    i. Identity, quantification, and purpose of each component in the finished product;
    ii. Specification and characterization of each component in the finished product; and
    iii. Final release specifications for the finished product.
2. The thrombin component in the device must be licensed through an approved Biologics License Application (BLA) and must function in the device consistent with the BLA-approved indications and usage.*

** Applies only to topical hemostatic wound dressings with licensed thrombin*

Special Controls

3. Performance data must demonstrate the sterility of the device.
4. Device must be demonstrated to be biocompatible.
5. Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.
6. Performance data must demonstrate that the device performs as intended under anticipated conditions of use, including evaluation of expected worst-case conditions, and must characterize:
    i. Amount of swelling (i.e., change in volume or change in weight of the device);
    ii. In vitro clotting time;
    iii. Absorption of the device under physiologically relevant conditions, if the device is resorbable;
    iv. In vivo time to hemostasis, rate of rebleeding, failed hemostasis, effectiveness of hemostasis in the presence of coagulopathy, effectiveness in patients on anticoagulation therapy if indicated, uniform definition of hemostasis;
    v. Amount of device retained in the wound;
    vi. Reliable adhesion to the target bleeding site for different bleeding severities; and
    vii. Risk of thrombosis and embolization if the product contains powder or granules.

Special Controls

7. For devices containing animal-derived material(s), the following information must be provided to support the safety of the non-thrombin animal-derived material(s):
    i. Documentation of the processing methods, including animal husbandry and tissue selection as well as methods for tissue storage, transport, and quarantine, that mitigate the risk of parasites and pathogens.
    ii. Performance data which demonstrates adequate removal (i.e., clearance or inactivation) of parasites and pathogens (including bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents) from the final finished device.
    iii. A risk management assessment for the inclusion of animal-derived material(s) which considers any probable risk associated with the presence of the animal tissue in the final finished solid wound dressing (including pathogen and parasite infection and immunological reaction). The risk management assessment must describe how these risks are controlled and mitigated by:
        a) The methods of animal husbandry, tissue selection, and tissue handling;
        b) Manufacturing and process controls; and
        c) Data documenting the ability of the manufacturing and sterilization procedures to ensure adequate removal (i.e., clearance or inactivation) of parasites and pathogens from the final finished device.

Special Controls

8. For devices containing antimicrobial(s), antimicrobial characterization and performance data must include the following:

i. Performance data must demonstrate that each antimicrobial has a purpose and is present in appropriate amounts to perform as intended under anticipated conditions of use and storage conditions, including evaluation of worst-case conditions. If the antimicrobial is present as a microbial barrier, microbial barrier testing must be conducted to demonstrate inhibition of passage of microorganisms through the product. If the antimicrobial is present to inhibit microbial growth within the product during use, antimicrobial effectiveness testing must be conducted to demonstrate inhibition of microbial growth within the product during use.

This testing must include:

a. Establishment of the Minimum Effective Concentration (MEC) of the final product under worst-case conditions.

b. Identification of the period of effectiveness (maximum product use-life) based on concentration of antimicrobial, leachability data, and performance under worst-case simulated use conditions.

Special Controls

c. For solid topical hemostatic wound dressings (e.g., pads, gauze) containing antimicrobials, performance evaluation should be conducted with clinically relevant strains including available strains of challenge organisms containing specific antimicrobial resistance mechanisms as part of worst-case scenario performance testing. For topical hemostatic wound dressings containing antimicrobials and formulated as gel, cream, ointment, powder, or granules, preservative effectiveness testing must be conducted on at least three different manufactured lots of the final, finished device that has been real-time aged for the stated shelf-life. If the dressing is a multiple-use product, the test articles should also be conditioned based on worst-case simulated use for maximum use-life.

ii. Evaluation and identification of any probable risk for potential contribution to the development and spread of antimicrobial resistance (AMR) must include:

a. Identification of each antimicrobial, proposed mechanism of action and justification of its status as not medically important.

b. An AMR risk assessment for each antimicrobial, including the following characterization elements: known resistance mechanisms, transmissibility of resistance, list of resistant microbial species and location of isolation, or contribution to medically important antimicrobial resistance.

Special Controls

9. The labeling must include:
   i. A description of the intended user population.
   ii. Specific instructions regarding the proper placement, sizing, duration of use, frequency of dressing change, maximum use life per application of the dressing, maximum total use life of the dressing, and removal of the dressing or approximate resorption rate, if applicable.
   iii. Instruction to inspect the wound after dressing removal to remove any residual dressing material that may be left in the wound.
   iv. A list of each ingredient or component within the finished device, including the functional role of that ingredient or component within the device.
   v. If the device is non-resorbable, a warning statement for the potential retention of material in the wound or the surrounding area.
   vi. The concentration or amount of thrombin present in the product.*
   vii. Warnings, precautions, and contraindications associated with the thrombin as stated in the approved BLA.*

** Applies only to topical hemostatic wound dressings with licensed thrombin*

Special Controls

viii. A warning that for severe bleeding or when vasculature is exposed, caution should be taken when using dressings in powder or granular form at the bleeding site as there is a risk of causing embolization.
ix. A contraindication for any known sensitivity to components within the device.
x. A contraindication if there are incompatibilities with other therapies.
xi. A warning that the device is not intended for control of internal bleeding.
xii. A shelf life.
xiii. Storage conditions.
xiv. A statement regarding when to discontinue use of the device after multiple reapplications based on biocompatibility and performance testing, if applicable.
xv. For devices indicated for over-the-counter use, the indications must specify conditions, uses, or purposes for which the product may be safely administered by a lay user without the supervision of a licensed practitioner.
xvi. Disposal instructions.

Special Controls

10. For devices containing antimicrobial(s), the labeling must also include:
    i. Statement of the role of the antimicrobial(s) in the product.
    ii. Specific instructions regarding how and when to properly dispose of the product.
    iii. A statement of general effectiveness, such as “antimicrobial,” “antibacterial” or “microbial barrier” without listing specific test organisms or log reduction values.
    iv. A statement explaining that the effectiveness of the antimicrobial in affecting wound bioburden has not been evaluated or established

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Thank You

Questions to Panel - Topical Hemostatic Wound Dressings

Sam Arepalli, PhD OHT4

Question 1 to Panel

FDA has identified the following risks to health for topical hemostatic wound dressings:

Identified Risk	Description/Examples
Uncontrolled bleeding	This occurs when the device does not effectively stop bleeding under anticipated conditions of use. This can also result when the device is used incorrectly.
	This can result from inadequate device sterilization, inadequate viral inactivation (for devices containing animal-derived materials), or inadequate packaging integrity.
Transmission of pathogens and parasites (e.g., bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents)	This can result from contaminated animal sources, feed, inadequate processing and viral inactivation of the animal-derived materials.
Immunological reaction	This can result from a device derived from a new animal source or protein denaturation/modification due to the manufacturing conditions. Also, this occurs in certain patients who may be allergic to animal-derived materials.
Microbial growth within the product during use	This occurs when the antimicrobial in the dressing does not adequately reduce microbial growth during dressing use.
Contribution to the spread of antimicrobial resistance (AMR)	This occurs when the antimicrobial in the dressing contribute to the selection of antimicrobial resistance organisms and/or limit a clinician's therapeutic options to treat infections.
Foreign body reaction due to retained device	This occurs when nonabsorbable hemostats are not completely removed from the external target bleeding site, resulting in a sustained inflammatory response. The end result of such a response is pseudo mass formation requiring invasive diagnostic procedures to rule out tumor or abscess. Such an event can also result in chronic pain, obstruct blood vessels or compress nerves and compromise function of an extremity.
	This can result when there is inadequate adhesive capacity of the hemostat. Precise coverage of the target bleeding site, especially in austere environments, may be compromised by temperature extremes, poor lighting and wind.
Arterial or venous embolism	This may occur if granular, powder or reduced dimension hemostat enters a blood vessel.
Thrombosis (e.g., deep vein thrombosis (DVT))	This may occur if granular, powder or reduced dimension hemostat enters a blood vessel.

Question 1 to Panel

Please comment on whether you agree with inclusion of all the risks in the overall risk assessment of topical hemostatic wound dressings, **without thrombin and with licensed thrombin**.

In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these topical hemostatic wound dressings, without thrombin and with licensed thrombin.

Question 2 to Panel

- Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if:
  - insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, AND
  - if the device is 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, 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.

Question 2 to Panel

- 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.

Question 2 to Panel

FDA believes general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risks to health and provide reasonable assurance of device safety and effectiveness for this device type.

As such, FDA believes that Class II is the appropriate classification for topical hemostatic wound dressings.

Question 2a to Panel

The following table outlines the identified risks to health for topical hemostatic wound dressing devices **without thrombin** and the recommended controls to mitigate the identified risks.

Question 2a to Panel

Identified Risk	Recommended Mitigation Measure
Uncontrolled bleeding	Material characterization, Performance testing, Shelf-life validation, Labeling
Infection	Sterilization testing/validation information, Shelf-life validation, Labeling, Risk management assessment for animal-derived materials
Adverse tissue reaction	Biocompatibility evaluation, Performance testing and descriptive information, Risk management assessment for animal-derived materials, Labeling
Delays in wound healing	Performance testing and descriptive information, Biocompatibility evaluation, Labeling
Transmission of pathogens and parasites (e.g., bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents)	Risk management assessment for animal-derived materials, Performance testing, Labeling
Immunological reaction	Risk management assessment for animal-derived materials, Performance testing and descriptive information, Labeling
Microbial growth within the product during use	Antimicrobial characterization and performance testing Sterilization validation
Contribution to the spread of antimicrobial resistance (AMR)	Antimicrobial characterization and performance testing, AMR risk assessment, Labeling
Foreign body reaction due to retained device	Performance testing, Labeling
Rebleeding after attaining hemostasis	Performance testing, Labeling
Arterial or venous embolism	Performance testing, Labeling
Thrombosis (e.g., deep vein thrombosis (DVT))	Performance testing, Labeling

Question 2a to Panel

Please discuss whether the identified special controls for topical hemostatic wound dressings *without* thrombin appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.

Proposed Special Controls

1. Performance testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and chemical characteristics of the device. The following must be provided:
    i. Identity, quantification, and purpose of each component in the finished product;
    ii. Specification and characterization of each component in the finished product; and
    iii. Final release specifications for the finished product.

Question 2a to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *without* thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

2. Performance data must demonstrate the sterility of the device.
3. Device must be demonstrated to be biocompatible.
4. Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.
5. Performance data must demonstrate that the device performs as intended under anticipated conditions of use, including evaluation of expected worst-case conditions, and must characterize:
    i. Amount of swelling (i.e., change in volume or change in weight of the device);
    ii. In vitro clotting time;
    iii. Absorption of the device under physiologically relevant conditions, if the device is resorbable;
    iv. In vivo time to hemostasis, rate of rebleeding, failed hemostasis, effectiveness of hemostasis in the presence of coagulopathy, effectiveness in patients on anticoagulation therapy if indicated, uniform definition of hemostasis;
    v. Amount of device retained in the wound;
    vi. Reliable adhesion to the target bleeding site for different bleeding severities; and
    vii. Risk of thrombosis and embolization if the product contains powder or granules.

Question 2a to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *without* thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

6. For devices containing animal-derived material(s), the following information must be provided to support the safety of the non-thrombin animal-derived material(s):
    i. Documentation of the processing methods, including animal husbandry and tissue selection as well as methods for tissue storage, transport, and quarantine, that mitigate the risk of parasites and pathogens.
    ii. Performance data which demonstrates adequate removal (i.e., clearance or inactivation) of parasites and pathogens (including bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents) from the final finished device.
    iii. A risk management assessment for the inclusion of animal-derived material(s) which considers any probable risk associated with the presence of the animal tissue in the final finished solid wound dressing (including pathogen and parasite infection and immunological reaction). The risk management assessment must describe how these risks are controlled and mitigated by:
        a) The methods of animal husbandry, tissue selection, and tissue handling;
        b) Manufacturing and process controls; and
        c) Data documenting the ability of the manufacturing and sterilization procedures to ensure adequate removal (i.e., clearance or inactivation) of parasites and pathogens from the final finished device.

Question 2a to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *without* thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

7. For devices containing antimicrobial(s), antimicrobial characterization and performance data must include the following:

i. Performance data must demonstrate that each antimicrobial has a purpose and is present in appropriate amounts to perform as intended under anticipated conditions of use and storage conditions, including evaluation of worst-case conditions. If the antimicrobial is present as a microbial barrier, microbial barrier testing must be conducted to demonstrate inhibition of passage of microorganisms through the product. If the antimicrobial is present to inhibit microbial growth within the product during use, antimicrobial effectiveness testing must be conducted to demonstrate inhibition of microbial growth within the product during use. This testing must include:
   a. Establishment of the Minimum Effective Concentration (MEC) of the final product under worst-case conditions.
   b. Identification of the period of effectiveness (maximum product use-life) based on concentration of antimicrobial, leachability data, and performance under worst-case simulated use conditions.

Question 2a to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *without* thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

c. For solid topical hemostatic wound dressings (e.g., pads, gauze) containing antimicrobials, performance evaluation should be conducted with clinically relevant strains including available strains of challenge organisms containing specific antimicrobial resistance mechanisms as part of worst-case scenario performance testing. For topical hemostatic wound dressings containing antimicrobials and formulated as gel, cream, ointment, powder, or granules, preservative effectiveness testing must be conducted on at least three different manufactured lots of the final, finished device that has been real-time aged for the stated shelf-life. If the dressing is a multiple-use product, the test articles should also be conditioned based on worst-case simulated use for maximum use-life.

ii. Evaluation and identification of any probable risk for potential contribution to the development and spread of antimicrobial resistance (AMR) must include:

a. Identification of each antimicrobial, proposed mechanism of action and justification of its status as not medically important.

b. An AMR risk assessment for each antimicrobial, including the following characterization elements: known resistance mechanisms, transmissibility of resistance, list of resistant microbial species and location of isolation, or contribution to medically important antimicrobial resistance.

Question 2a to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *without* thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

8. Labeling must bear all information required for the safe and effective use of the device, specifically including the following:

i. A description of the intended user population.
ii. Specific instructions regarding the proper placement, sizing, duration of use, frequency of dressing change, maximum use life per application of the dressing, maximum total use life of the dressing, and removal of the dressing, if applicable.
iii. Instruction to inspect the wound after dressing removal to remove any residual dressing material that may be left in the wound.
iv. A list of each ingredient or component within the finished device, including the functional role of that ingredient or component within the device.
v. If the device is non-resorbable, a warning statement for the potential retention of material in the wound or the surrounding area.
vi. A contraindication for any known sensitivity to components within the device.
vii. A contraindication if there are incompatibilities with other therapies.
viii. A warning that the device is not intended for control of internal bleeding.
ix. A warning that for severe bleeding or when vasculature is exposed, caution should be taken when using dressings in powder or granular form at the bleeding site as there is a possibility of causing embolization.
x. A shelf life.

Question 2a to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *without* thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

xi) A statement regarding when to discontinue use of the device after multiple reapplications based on biocompatibility and performance testing, if applicable.
xii) For devices indicated for over-the-counter use, the indications must specify conditions, uses, or purposes for which the product may be safely administered by a lay user without the supervision of a licensed practitioner.
xiii) Disposal instructions.

9. For devices containing antimicrobial(s), the labeling must also include:
i) Statement of the role of the antimicrobial(s) in the product.
ii) Specific instructions regarding how and when to properly dispose of the product.
iii) A statement of general effectiveness, such as “antimicrobial,” “antibacterial” or “microbial barrier” without listing specific test organisms or log reduction values.
iv) A statement explaining that the effectiveness of the antimicrobial in affecting wound bioburden has not been evaluated or established.

Question 2b to Panel

The following table outlines the identified risks to health for topical hemostatic wound dressing devices **with licensed thrombin** and the recommended controls to mitigate the identified risks.

Question 2b to Panel

Identified Risk	Recommended Mitigation Measure
Uncontrolled bleeding	Material characterization, Performance testing, Biologics License Application (BLA) approval for thrombin, Shelf-life validation, Labeling
Infection	Sterilization testing/validation information, Shelf-life validation, Labeling, Risk management assessment for animal-derived materials, Biologics License Application (BLA) approval for thrombin
Adverse tissue reaction	Biocompatibility evaluation, Performance testing and descriptive information, Labeling, Biologics License Application (BLA) approval for thrombin
Delay in wound healing	Performance testing and descriptive information, Biocompatibility evaluation, Labeling
Transmission of pathogens and parasites (e.g., bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents)	Risk management assessment for animal-derived materials, Performance testing Biologics License Application (BLA) approval for thrombin, Labeling
Immunological reaction	Risk management assessment for animal-derived materials, Performance testing and descriptive information, Biologics License Application (BLA) approval for thrombin, Labeling
Microbial growth within the product during use	Antimicrobial characterization and performance testing, Sterilization validation
Contribution to the spread of antimicrobial resistance (AMR)	Antimicrobial characterization and performance testing, AMR risk assessment, Labeling
Foreign body reaction due to retained device	Performance testing, Labeling
Rebleeding after attaining hemostasis	Performance testing, Labeling
Arterial or venous embolism	Performance testing, Labeling
Thrombosis (e.g., deep vein thrombosis (DVT))	Performance testing,Labeling

Question 2b to Panel

Please discuss whether the identified special controls for topical hemostatic wound dressings *with* licensed thrombin appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.

Proposed Special Controls

1. Performance testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and chemical characteristics of the device. The following must be provided:
    i. Identity, quantification, and purpose of each component in the finished product;
    ii. Specification and characterization of each component in the finished product; and
    iii. Final release specifications for the finished product.
2. For hemostatic wound dressings with licensed thrombin, the thrombin component in the device must be licensed through an approved Biologics License Application (BLA) and must function in the device consistent with the BLA-approved indications and usage.

Question 2b to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *with* licensed thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

3. Performance data must demonstrate the sterility of the device.
4. Device must be demonstrated to be biocompatible.
5. Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.
6. Performance data must demonstrate that the device performs as intended under anticipated conditions of use, including evaluation of expected worst-case conditions, and must characterize:
    i. Amount of swelling (i.e., change in volume or change in weight of the device);
    ii. In vitro clotting time;
    iii. Absorption of the device under physiologically relevant conditions, if the device is resorbable;
    iv. In vivo time to hemostasis, rate of rebleeding, failed hemostasis, effectiveness of hemostasis in the presence of coagulopathy, effectiveness in patients on anticoagulation therapy if indicated, uniform definition of hemostasis;
    v. Amount of device retained in the wound;
    vi. Reliable adhesion to the target bleeding site for different bleeding severities; and
    vii. Risk of thrombosis and embolization if the product contains powder or granules.

Question 2b to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *with* licensed thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

7. For devices containing animal-derived material(s), the following information must be provided to support the safety of the non-thrombin animal-derived material(s):
    i. Documentation of the processing methods, including animal husbandry and tissue selection as well as methods for tissue storage, transport, and quarantine, that mitigate the risk of parasites and pathogens.
    ii. Performance data which demonstrates adequate removal (i.e., clearance or inactivation) of parasites and pathogens (including bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents) from the final finished device.
    iii. A risk management assessment for the inclusion of animal-derived material(s) which considers any probable risk associated with the presence of the animal tissue in the final finished solid wound dressing (including pathogen and parasite infection and immunological reaction). The risk management assessment must describe how these risks are controlled and mitigated by:
        a) The methods of animal husbandry, tissue selection, and tissue handling;
        b) Manufacturing and process controls; and
        c) Data documenting the ability of the manufacturing and sterilization procedures to ensure adequate removal (i.e., clearance or inactivation) of parasites and pathogens from the final finished device.

Question 2b to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *with* licensed thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

8. For devices containing antimicrobial(s), antimicrobial characterization and performance data must include the following:

i. Performance data must demonstrate that each antimicrobial has a purpose and is present in appropriate amounts to perform as intended under anticipated conditions of use and storage conditions, including evaluation of worst-case conditions. If the antimicrobial is present as a microbial barrier, microbial barrier testing must be conducted to demonstrate inhibition of passage of microorganisms through the product. If the antimicrobial is present to inhibit microbial growth within the product during use, antimicrobial effectiveness testing must be conducted to demonstrate inhibition of microbial growth within the product during use. This testing must include:

   a. Establishment of the Minimum Effective Concentration (MEC) of the final product under worst-case conditions.

   b. Identification of the period of effectiveness (maximum product use-life) based on concentration of antimicrobial, leachability data, and performance under worst-case simulated use conditions.

Question 2b to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *with* licensed thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

c. For solid topical hemostatic wound dressings (e.g., pads, gauze) containing antimicrobials, performance evaluation should be conducted with clinically relevant strains including available strains of challenge organisms containing specific antimicrobial resistance mechanisms as part of worst-case scenario performance testing. For topical hemostatic wound dressings containing antimicrobials and formulated as gel, cream, ointment, powder, or granules, preservative effectiveness testing must be conducted on at least three different manufactured lots of the final, finished device that has been real-time aged for the stated shelf-life. If the dressing is a multiple-use product, the test articles should also be conditioned based on worst-case simulated use for maximum use-life.

ii. Evaluation and identification of any probable risk for potential contribution to the development and spread of antimicrobial resistance (AMR) must include:

a. Identification of each antimicrobial, proposed mechanism of action and justification of its status as not medically important.

b. An AMR risk assessment for each antimicrobial, including the following characterization elements: known resistance mechanisms, transmissibility of resistance, list of resistant microbial species and location of isolation, or contribution to medically important antimicrobial resistance.

Question 2b to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *with* licensed thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

9. The labeling must include:
    i. A description of the intended user population.
    ii. A statement that the device is intended for topical, temporary (less than 24 hours) control of bleeding.
    iii. Specific instructions regarding the proper placement, sizing, duration of use, frequency of dressing change, maximum use life per application of the dressing, maximum total use life of the dressing, and removal of the dressing or approximate resorption rate, if applicable.
    iv. Instruction to inspect the wound after dressing removal to remove any residual dressing material that may be left in the wound.
    v. A list of each ingredient or component within the finished device, including the functional role of that ingredient or component within the device.
    vi. If the device is non-resorbable, a warning statement for the potential retention of material in the wound or the surrounding area.
    vii. The concentration or amount of thrombin present in the product.
    viii. Warnings, precautions, and contraindications associated with the thrombin as stated in the approved BLA.

Question 2b to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *with* licensed thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

ix. A warning that for severe bleeding or when vasculature is exposed, caution should be taken when using dressings in powder or granular form at the bleeding site as there is a risk of causing embolization.
x. A contraindication for any known sensitivity to components within the device.
xi. A contraindication if there are incompatibilities with other therapies.
xii. A warning that the device is not intended for control of internal bleeding.
xiii. A shelf life.
xiv. Storage conditions.
xv. A statement regarding when to discontinue use of the device after multiple reapplications based on biocompatibility and performance testing, if applicable.
xvi. For devices indicated for over-the-counter use, the indications must specify conditions, uses, or purposes for which the product may be safely administered by a lay user without the supervision of a licensed practitioner.
xvii. Disposal instructions.

Question 2b to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for topical hemostatic wound dressings *with* licensed thrombin. Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

10. For devices containing antimicrobial(s), the labeling must also include:
    i) Statement of the role of the antimicrobial(s) in the product.
    ii) Specific instructions regarding how and when to properly dispose of the product.
    iii) A statement of general effectiveness, such as “antimicrobial,” “antibacterial” or “microbial barrier” without listing specific test organisms or log reduction values.
    iv) A statement explaining that the effectiveness of the antimicrobial in affecting wound bioburden has not been evaluated or established.

Question 3 to Panel

Please discuss whether you agree with FDA's proposed classification of Class II with special controls for topical hemostatic wound dressing *without* thrombin and topical hemostatic wound dressing *with* licensed thrombin.

If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

End of Panel Questions for Topical Hemostatic Wound Dressings

Sam Arepalli, PhD OHT4