Classification of Topical Hemostatic Wound Dressings
FDA Questions

General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee

October 26-27, 2022

1. FDA has identified the following risks to health for topical hemostatic wound dressings, 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.
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.

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.

2. 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 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.

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
    I. 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
    II. does not present a potential unreasonable risk of illness or injury.

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. Following are the risk/mitigation tables which outline the identified risks to health for these devices and the recommended controls to mitigate the identified risks.

Risk/mitigation recommendations for topical hemostatic wound dressing *without* thrombin

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,	Risk management assessment for animal-derived materials

mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents)	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

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:

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. 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 (e.g., 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, incidence of rebleeding, failed hemostasis, effectiveness in patients with 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.

6. For devices containing animal-derived material(s), the following information must be provided to support the safety of the 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.

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.
(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.

8. 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, 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.
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.

Risk/mitigation recommendations for topical hemostatic wound dressing *with* licensed thrombin

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

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:

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.

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 (e.g., 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.

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.

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.
(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.

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.
   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.

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.

3. **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.**