FDA Executive Summary

Prepared for the Meeting of the
General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee

Classification of Topical Hemostatic Wound Dressings

Device Types:
Topical Hemostatic Wound Dressing without Thrombin
and
Topical Hemostatic Wound Dressing with Licensed Thrombin

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1. Introduction

Per Section 513(b) of the Food, Drug, and Cosmetic Act (the Act), the Food and Drug Administration (FDA) is convening the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Panel (the Panel) for the purpose of obtaining recommendations regarding the classification of topical hemostatic wound dressings, a pre-amendments device type which remains unclassified. Specifically, the FDA will ask the Panel to provide recommendations regarding the regulatory classification of two types of topical hemostatic wound dressings: 1) topical hemostatic wound dressings *without* thrombin and 2) topical hemostatic wound dressings *with* licensed thrombin. These are a subset of devices currently cleared under product code "FRO." The device names and associated product codes are developed by the Center for Devices and Radiological Health (CDRH) in order to identify the generic category of a device for FDA. While most product codes are associated with a device classification regulation, some product codes, including "FRO," remain unclassified.

FDA is holding this panel meeting to obtain input on the risks to health and benefits of the topical hemostatic wound dressings. The Panel will discuss whether the topical hemostatic wound dressings should be classified into Class II (subject to General and Special Controls). If the Panel believes that classification into Class II is appropriate for topical hemostatic wound dressings, the Panel will also be asked to discuss appropriate controls that would be necessary to mitigate the risks to health.

1.1 Current Regulatory Pathways

Topical hemostatic wound dressings are a pre-amendments, unclassified device type. This means that this device type was marketed prior to the Medical Device Amendments of 1976, but was not classified by the original classification panels. 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.

1.2 Device Description

A topical hemostatic wound dressing *without* thrombin is intended for external use, often as an adjunct to manual compression, to control bleeding and absorb wound exudate. These dressings generally help achieve hemostasis through physical means, such as creating a physical barrier to stop blood flow, leveraging the absorptive properties of the dressing material to support rapid dehydration and to concentrate platelets and clotting factors at the wound site to aid the natural coagulation cascade.[1] These dressings can be manufactured from a variety of natural materials, including animal-derived materials, such as collagen and

[1] In addition to products containing thrombin, some products in this category are currently considered combination products based on claims that a constituent part achieves its primary intended purpose through chemical action rather than the modes of action FDA describes here. FDA may re-evaluate the classification and jurisdiction of these products based on the claims being made. FDA is requesting panel input on the risks to health and proposed mitigations for these products, but does not intend to ask the panel to opine on issues regarding classification of products as drugs, devices, or combination products.

chitosan from shellfish, as well as other natural materials, such as calcium alginate from seaweed, cellulose, zeolite, and kaolin. These dressings can also be manufactured from synthetic materials (e.g., synthetic polymers). Many of these dressings are formulated into solid pads or sponges or granules (e.g., powder, beads); while some are formulated as gel, and others combine structural material (e.g., gauze) with the hemostatic component (e.g., calcium alginate, chitosan, kaolin). When exposed to blood or wound exudate, solid or granular topical hemostatic wound dressings may transform into an adhesive gel which expands and adheres to the wound to control bleeding. Topical hemostatic wound dressings *without* thrombin 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. Considerations relating to antimicrobials included in these products are similar to the considerations discussed for other products grouped under product code "FRO" that were discussed at the September 20-21, 2016 meeting of this panel.[2]

A topical hemostatic wound dressing *with* licensed thrombin is 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. Such dressing contains thrombin which has been approved through a Biologic License Application (BLA).[3] The licensed thrombin in these dressings facilitates hemostasis by enhancing the surface-activated clotting cascade through enzymatic cleavage and conversion of fibrinogen to fibrin. When applied directly over the source of bleeding, these dressings also create a physical barrier to blood flow that may be accompanied by the application of adjunctive manual compression to control the bleeding. Some topical hemostatic wound dressings *with* licensed thrombin 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.

In general, topical hemostatic wound dressings are not intended to be implanted, or be in contact with arteries, veins, nerves, or any other internal organ or tissue. These products should not be used to control organ space bleeding. They are not intended for internal use; hemostatic devices for internal use are outside of the scope of this classification panel.[4]

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[2] 2016 General and Plastic Surgery Advisory Panel Meeting materials and transcript, *available at* https://www.fda.gov/advisory-committees/general-and-plastic-surgery-devices-panel/2016-meeting-materials-general-and-plastic-surgery-advisory-panel

[3] Biologics License Applications (BLA) Process (CBER), *available at* https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biologics-license-applications-bla-process-cber

[4] Hemostatic devices for internal use are outside of the scope for this classification panel. Many of those devices have already been classified, which include Absorbable hemostatic agents (21 CFR 878.4490), Hemostatic device for endoscopic gastrointestinal use (21 CFR 878.4456), Non-absorbable, hemostatic gauze for temporary internal use (21 CFR 878.4454), Non-absorbable expandable hemostatic sponge for temporary internal use (21 CFR 878.4452).

2. Regulatory History

Wound dressings, including topical hemostatic wound dressings, are pre-amendments devices that have been in commercial distribution since prior to May 28, 1976.

FDA has cleared over 100 topical hemostatic wound dressings *without* thrombin and 18 topical hemostatic wound dressings *with* licensed thrombin. Please refer to Table 6 and Table 7 in Appendix A for listings of the manufacturers, device names, and associated 510(k) submission numbers for cleared topical hemostatic wound dressings *without* thrombin and topical hemostatic wound dressings *with* licensed thrombin, respectively.

3. Indications for Use

The Indications for Use (IFU) statement identifies the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.

Topical hemostatic wound dressings *without* thrombin have been cleared for the following indications for use[5]:

- 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
- 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
- For use on the following types of wounds:
    - Partial and full thickness wounds
    - Pressure ulcers

[5] In addition to controlling bleeding in general skin wounds, some topical hemostatic wound dressings *without* thrombin have been previously cleared with other specific indications of controlling bleeding in other locations. Those other specific uses are outside of the scope for this panel discussion and the proposed classification action for topical hemostatic wound dressings *without* thrombin.

- Arterial ulcers
- Venous ulcers
- 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 and pins

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

4. Clinical Background

4.1 Disease Characteristics

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. Moderate and severe bleeding can lead to hemodynamic instability and typically lead to American College of Surgeons (ACS) Class 3 or 4 hemorrhagic shock. Fifty percent (50%) of combat mortality is attributed to uncontrolled hemorrhage. This clinical condition is the second leading cause of civilian trauma related mortality. A third of such bleeding is compressible and treated with temporary hemostats, which are also used as wound dressing, and two thirds of such bleeding are not compressible. Twenty four percent (24%) of deaths may be prevented with prompt effective treatment. Uncontrolled bleeding can result in the lethal triad: hypothermia, coagulopathy and acidosis. Prolonged

bleeding can result in multisystem organ failure secondary to hypotension, sepsis and excessive transfusions.[6]

4.2 Patient Outcomes

History, physical examination, and laboratory studies to include bloodwork, cultures, and radiologic imaging may be used to ascertain the wound diagnosis. Depending on the wound type, the patient may be asked about pain, functional status, and quality of life.

4.3 Currently Available Treatment

As there is a wide variety of wound types, 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. The selection of a specific wound product is made by the surgeon based on surgical judgment, the operative approach, and the severity of bleeding at the target bleeding site. 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.

Many topical hemostatic wound dressings are non-absorbable and intended for temporary control of moderate to severe external bleeding used as an adjunct to compression and must be removed when the patients reach a center for definitive surgical treatment. These devices are not for use in the organ space, next to internal tissues, veins, arteries, or nerves. These hemostatic dressings swell by absorbing water and adhere to the target bleeding site to provide mechanical tamponade. They also provide a surface for clot formation and can non-chemically activate the intrinsic clotting system by concentrating platelets and clotting factors through rapid absorption. Typically, chitosan-based hemostats work primarily by adherence to the target bleeding site. They do not accelerate the rate of clot formation or strength on the clot when evaluated in vitro with thromboelastography.[7] Conversely, topical hemostats that are synthetic mineral-based (e.g., quartz, zeolite, kaolin) act by tamponade. Dressings which act purely by tamponade and adhesion to the target bleeding site without inducing a rapid strong clot may be effective for slow, low pressure, mild severity bleeding;

[6] Kheirabadi BS, Scherer MR, Estep JS, Dubick MA, Holcomb JB. Determination of efficacy of new hemostatic dressings in a model of extremity arterial hemorrhage in swine. J Trauma. 2009 Sep;67(3):450-9; discussion 459-60. doi: 10.1097/TA.0b013e3181ac0c99. PMID: 19741385.

[7] Zhang W, Zhong D, Liu Q, Zhang Y, Li N, Wang Q, Liu Z, Xue W. Effect of chitosan and carboxymethyl chitosan on fibrinogen structure and blood coagulation. J Biomater Sci Polym Ed. 2013;24(13):1549-63. doi: 10.1080/09205063.2013.777229. Epub 2013 Mar 14. PMID: 23848448.

however, when mean arterial pressure is restored to normal, many of these topical hemostats are displaced from the bleeding site and re-bleeding may occur. Powder, granular, and bead-like hemostats may conform more easily to broad surface area bleeding unlike hemostats impregnated on gauze, which depending on their flexibility may not conform as well to bleeding sites of different geometries and may have compromised effectiveness. However, granular hemostats are more difficult to handle and may not accurately reach a target bleeding sites, especially in austere environmental conditions (e.g., cold, poorly lit, windy).

Similar to topical hemostatic wound dressings *without* thrombin, topical hemostatic wound dressings *with* thrombin are intended to improve hemostasis as an adjunct to compression control of a bleeding site. The added thrombin directly activates the intrinsic coagulation system by enzymatically cleaving fibrinogen into fibrin monomers, which are the building blocks of clot formation.

4.4 Risks

FDA has identified the following risks to health associated with topical hemostatic wound dressings, with licensed thrombin and without thrombin:

Table 1: Risks to Health and Descriptions/Examples 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.
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 animal sources 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.

The Panel will be asked whether this list is a complete and accurate list of the risks to health presented by topical hemostatic wound dressings, with licensed thrombin and without thrombin, and whether any other risks should be included in the overall risk assessment of the device type(s).

5. Literature Review

5.1 Methods

A systematic literature review was conducted to gather any published information regarding the safety and effectiveness of topical hemostatic wound dressing *without* thrombin and topical hemostatic wound dressing *with* thrombin.

On May 16, 2022 and July 18-20, 2022, literature searches were performed to identify all published articles for topical hemostatic wound dressings in two databases (PubMed and EMBASE) with two search periods (April 1, 2012 – April

1, 2022 for the first search and April 1, 2012 – July 18, 2022 for the second search).

The searches were performed together with other wound dressings being presented at this classification panel, including absorbable synthetic wound dressings and wound dressings with animal-derived materials. The literature searches were performed using multiple search terms related to wound dressing, with hedges for study design and publication years, and the searches were limited to publications in English. Detailed methods, search terms and filters are provided in Appendix B.

5.2 Results

In total, the original search identified 1,677 unique records for screening at the title/abstract level. After excluding 1,552 records that were not relevant to the review at this level, there were 125 full-text articles assessed for eligibility. The most common reasons references were excluded at the abstract level were completely off topic (n=354), animal study (n=296), and fewer than 100 patients per study arm (n=202). All 125 articles were retrieved and screened. Thirteen of the 125 articles published between April 1, 2012 and April 1, 2022 were retained for analysis.

The second search identified an additional 3,341 unique records for screening at the title/abstract level. After excluding 3,305 records that were not relevant to the review at this level, there were 36 full-text articles assessed for eligibility. The most common reasons references were excluded at the abstract level were pre-clinical study and other study type not of interest (n=2,246), completely off topic (n=533), and animal study (n=157). All 36 full-texts record were retrieved and screened. Two of the 36 articles published between April 1, 2012 and July 18, 2022 were retained for analysis.

The number of articles meeting inclusion and exclusion criteria is summarized in the flow diagrams in Appendix C.

Of the 15 included studies from the combined searches (13 from the original search, two from the second search), four studies examined topical hemostatic wound dressings *without* thrombin, and none of the studies examined topical hemostatic wound dressings *with* thrombin. Of these four studies, there were two studies for treatment of severe bleeding[8,9] and two studies for an unspecified level

[8] Schauer SG, April MD, Naylor JF, et al. QuikClot® Combat Gauze® Use by Ground Forces in Afghanistan The Prehospital Trauma Registry Experience. J Spec Oper Med. Summer 2017;17(2):101-106.
[9] Winstanley M, Smith JE, Wright C. Catastrophic haemorrhage in military major trauma patients: a retrospective database analysis of haemostatic agents used on the battlefield. J R Army Med Corps. Dec 2019;165(6):405-409. doi:10.1136/jramc-2018-001031

of bleeding.[10,11] Two studies used a retrospective study design[8,8] and two studies were randomized controlled trials (RCTs).[10,11]

Of the four studies assessing topical hemostatic wound dressings *without* thrombin, one study was conducted in the US[8] and one study each was conducted in the UK,[9] Italy,[7] Poland[11] and Japan.[10] These four studies each enrolled between 200[10,11] and 3792[9] patients. Duration of follow-up ranged from <1 hour[10] to 6 months.[11] Patients ranged in age from 25[9] to 71 years[10].

Of the four studies assessing topical hemostatic wound dressings *without* thrombin, reported outcomes included survival (n=2),[8,9] time to clot (n=1),[10] systemic adverse reactions (n=1),[10] and local adverse tissue reaction (n=2).[10,11]

Table 13 in Appendix B provides additional details on the individual selected studies.

5.3 Adverse Events Associated with Topical Hemostatic Wound Dressings

One study of topical hemostatic wound dressings reported on systemic adverse reactions including allergic reaction and anaphylactic shock and found no statistically significant differences compared to control (non-drug sheet).[10]

Two studies[10,10] of topical hemostatic wound dressings reported on local adverse tissue reactions, including large hematoma, iatrogenic pseudoaneurysm, total artery occlusion, or rebleeding, and found no statistically significant differences compared to control (non-drug sheet, standard mechanical compression).

5.4 Effectiveness Associated with Topical Hemostatic Wound Dressings

One study of topical hemostatic wound dressings reported time to clot.[10] Calcium alginate (CA) was favored over no CA at 5 minutes for clotting (CA 57% vs. no CA 39%, p = 0.01) in one study and no difference in clotting was found between diabetic and non-diabetic patients.[10]

Two studies of topical hemostatic wound dressing use in combat situations reported survival.[8,9] Winstanley 2019 found the use of hemostatic dressings led to a 7% increase in survival when compared to no hemostatic dressing patients with combat trauma.[8] Schauer 2017 compared use of a particular hemostatic dressing

[10] Matsubara M, Banshodani M, Takahashi A, et al. Vascular access management after percutaneous transluminal angioplasty using a calcium alginate sheet: a randomized controlled trial. Nephrol Dial Transplant. Sep 1 2019;34(9):1592-1596. doi:10.1093/ndt/gfy143

[11] Pawel L, Dagmara GL, Pawel M, Bogumil R, Andrzej B, Sebastian S. Efficacy and safety of kaolin-based hemostatic pad vs. standard mechanical compression following transradial and transulnar access for elective coronary angiography and PCI: RAUL trial substudy. Heart Vessels. Apr 2020;35(4):502-508. doi:10.1007/s00380-019-01520-z

to no use of that hemostatic dressing and found no statistically significant difference in survival between the two treatment arms.[8]

5.5 Overall Literature Review Conclusions

The evidence base for topical hemostatic wound dressings included two studies[10,10] with high quality study designs (i.e., RCT) and two studies[8,8] with a retrospective design. Observational study designs (e.g., retrospective studies, case-control studies, cohort studies), even those that included age- and sex-matched patient groups, are prone to a number of biases (e.g., confounding and selection) because patient and provider characteristics are not balanced across study arms. The funding source was not reported in two studies,[8,10] there was no funding in one study,[9] and in the final study, the funding source was unbiased.[11] On the whole, the strength of this evidence base is low to moderate.

The published literature did not indicate any significant difference in safety between topical hemostatic wound dressings *without* thrombin and controls (e.g., non-drug sheet[10] and standard mechanical compression[11]). 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.

6. Risks to Health Identified through Medical Device Reports (MDRs)

6.1 Overview of the MDR System

The MDR system provides FDA with information on medical device performance from patients, health care professionals, consumers and mandatory reporters (manufacturers, importers and device user facilities). The FDA receives MDRs of suspected device-associated deaths, serious injuries, and certain malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDRs 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

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the submission of incomplete, inaccurate, untimely, unverified, duplicated or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about the frequency of device use. Finally, the existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Because of these limitations, MDRs comprise only one of the FDA’s tools for assessing

device performance. As such, MDR numbers and data should be taken in the context of the other available scientific information.

6.2 MDR Data: Topical Hemostatic Wound Dressing without Thrombin

Individual MDRs for topical hemostatic wound dressings *without* thrombin are reported through FDA's Manufacturer and User Facility Device Experience (MAUDE) Database, which houses mandatory reports from medical device manufacturers, importers and user facilities, as well as voluntary reports from entities such as health care professionals, patients and consumers.

A search of MDRs for topical hemostatic wound dressings that do not contain thrombin was conducted using date range of January 1, 1986 (year of first clearance) to April 1, 2022. The results were filtered for products designated as topical hemostatic wound dressings that do not contain thrombin. The filtering resulted in 68 unique MDRs.

Of the 68 MDRs identified for topical hemostatic wound dressings *without* thrombin, MDRs that met the criteria for serious injury totaled 50, and 15 reports were labeled as malfunction. Manufacturers submitted 48 of the reports, and 13 were submitted voluntarily, and the remaining 7 reports were submitted by user facilities.

Eleven reports discussed 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 appeared to be a chemical burn that led to necrosis.

Table 2: Top 30 Adverse Events Described in MDRs for Topical Hemostatic Wound Dressings *without* Thrombin

Adverse Events	Count
Injury	12
Hemorrhage/Bleeding	8
Patient Problem/Medical Problem	8
Hematoma	6
Ulcer	6
Bleeding	5
Swelling	4
Tissue Damage	4
Therapy/non-surgical treatment, additional	4
No Known Impact or Consequence to Patient	4

Adverse Events	Count
Bacterial Infection	4
Treatment with medication(s)	3
Tissue Breakdown	3
Pseudoaneurysm	3
Allergic reaction	3
Unspecified Infection	3
Abscess	3
Skin Erosion	2
Necrosis	2
Localized Skin Lesion	2
Other (for use when an appropriate patient code cannot be identified)	2
No Information	2
Pain	2
Death	2
Burn, Thermal	2
Missing Value Reason	2
Pressure Sores	2
Foreign Body In Patient	2
Hospitalization required	2
Burn(s)	2

Of the 68 MDRs that were reported, three were labeled as death. In one report, due to the severity of the patient's condition (medication-induced toxic epidermal necrolysis) prior to the use of the hemostatic wound dressing, it is not possible to determine that the device caused the patient's death. The remaining 2 death MDRs did not include any event narratives but reported adverse events including bleeding, weakness, septic shock.

6.3 MDR Data: Topical Hemostatic Wound Dressing with Licensed Thrombin

A search of MDRs for topical hemostatic wound dressings that contain licensed thrombin was conducted using date range of January 1, 1986 (year of first clearance) to April 1, 2022. This resulted in 15 unique MDRs.

Of the 15 MDRs identified for topical hemostatic wound dressings *with* licensed thrombin, 13 MDRs met the criteria for serious injury, and 2 reports were labeled as malfunction. Manufacturers submitted 10 reports, 4 reports were submitted voluntarily, and the remaining 1 report was submitted by a user facility.

Table 3: Adverse Events Described in MDRs for Topical Hemostatic Wound Dressings *with* Licensed Thrombin

Adverse Events	Count
Hematoma	3
Treatment with medication(s)	2
Tachycardia	2
Allergic reaction	2
Foreign Body In Patient	2
Breathing difficulties	1
Burning Sensation	1
Bruise/Contusion	1
No Consequences Or Impact To Patient	1
Air Embolism	1
Rash	1
No Information	1
Foreign body, removal of	1
Reaction	1
Seizures	1
Skin Discoloration	1
Swelling	1
Hemorrhage/Bleeding	1
Therapeutic Response, Decreased	1
Hives	1
Unspecified Infection	1
Impaired Healing	1
Itching Sensation	1

The MDRs for topical hemostatic wound dressings that contain licensed thrombin were analyzed in their entirety for data relating to patient injury. 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, but no additional information was provided. Therefore, it is unclear whether this was caused by the wound dressing. In another report, a pediatric patient required a debridement procedure when the dressing components formed a hard foreign body that interfered with the healing process.

7. Recall History

7.1 Overview of Recall Database

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 may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall. Therefore, the recall information posting date ("create date") identified on the database indicates the date FDA classified the recall, it does not necessarily mean that the recall is new.

7.2 Recall Results: Topical Hemostatic Wound Dressing without Thrombin

Eight Class II[12] recalls have been reported for topical hemostatic wound dressing *without* thrombin, and are described below:

- Z-0211-2022: This recall was initiated due to the lack of packaging seal integrity, which may result in a sterile barrier breach.
- Z-0925-2018: This recall was initiated due to the wrong products being packaged together.
- Z-2612-2017: This recall was initiated due to packaging breach, which may compromise product sterility.
- Z-0298-2017, Z-0293-2016, Z-0318-2016: These recalls were initiated due to product being mis-labeled with inappropriate claims.
- Z-1697-2015: This recall was initiated due to promotion of inappropriate claims on customer literature and web sites.
- Z-0493-2015: This recall was initiated due to non-sterile products being shipped instead of sterile products.

7.3 Recall Results: Topical Hemostatic Wound Dressing with Licensed Thrombin

Four Class II recalls have been reported for topical hemostatic wound dressing *with* licensed thrombin, and are described below:

- Z-0142-06, Z-0143-06, Z-0144-06, Z-0003-06: These recalls were initiated due to packaging defect, which may compromise product sterility.

[12] Recalls are classified into a numerical designation (I, II, or III) by the FDA to indicate the relative degree of health hazard presented by the product being recalled. A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. A Class II recall is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. A Class III recall is a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

The recalls identified above for topical hemostatic wound dressings without thrombin and with licensed thrombin are related to manufacturing errors or promotional issues, and do not suggest additional risks related to topical hemostatic wound dressings as a product class.

8. Summary

In light of the information available, the Panel will be asked to comment on whether topical hemostatic wound dressing *without* thrombin and topical hemostatic wound dressing *with* licensed thrombin:

meet the statutory definition of a Class III device in accordance with section 513 of the Food, Drug, and Cosmetic Act (FD&C Act):

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

- 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

or would be more appropriately regulated as Class II, in which:

- general and special controls, which may include performance standards, postmarket surveillance, patient registries and/or development of guidelines, are sufficient to provide reasonable assurance of safety and effectiveness;

or as Class I, in which:

- the device is subject only to general controls, which include registration and listing, good manufacturing practices (GMPs), prohibition against adulteration and misbranding, and labeling devices according to FDA regulations.

For the purposes of classification, FDA also considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;

2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;

3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and

4. The reliability of the device.

The Panel will be asked whether they believe topical hemostatic wound dressings, with licensed thrombin and without thrombin, would be appropriately regulated as Class II. If the Panel does not agree with FDA's proposed classification, the Panel will be asked to provide their rationale for recommending a different classification.

8.1 Special Controls

FDA believes that special controls, in addition to general controls, can be established to mitigate the risks to health identified, and provide a reasonable assurance of the safety and effectiveness of topical hemostatic wound dressings. Following is a risk-mitigation table, which outlines the FDA identified risks to health for these device type(s) and the recommended and necessary controls to mitigate the identified risks to health:

Table 4: Summary of Risks to Health and Proposed Mitigations 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, 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

Based on the identified risks and recommended mitigation measures, FDA believes that the following special controls would provide reasonable assurance of safety and effectiveness for the topical hemostatic wound dressings *without* thrombin:

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.

If the Panel believes that Class II is appropriate for the topical hemostatic wound dressing without thrombin, the Panel will be asked whether the identified special controls appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.

Table 5: Summary of Risks to Health and Proposed Mitigations 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

Based on the identified risks and recommended mitigation measures, FDA believes that the following special controls would provide reasonable assurance of safety and effectiveness for the topical hemostatic wound dressings *with* licensed thrombin:

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.

If the panel believes that Class II is appropriate for the topical hemostatic wound dressing with licensed thrombin, the panel will be asked whether the identified special controls appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.

8.2 Overview of Proposed Classification/FDA Recommendation

Based on the safety and effectiveness information gathered by the FDA, the identified risks to health and recommended mitigation measures, we recommend that topical hemostatic wound dressing indicated for use to temporarily stop or control bleeding from external wounds be regulated as Class II devices.

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.

(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.

(b) *Classification*.
Class II (special controls) for a topical hemostatic wound dressing without thrombin. 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. 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:
   (c) Identification of each antimicrobial, proposed mechanism of action and justification of its status as not medically important.
   (d) 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.

(c) *Classification*.
Class II (special controls) for a topical hemostatic wound dressing with licensed thrombin. 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.

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.

Based on the available scientific evidence, the FDA will ask the Panel for their recommendation on the appropriate classification of the topical hemostatic wound dressings with licensed thrombin or without thrombin.

Appendix A: Listings of the manufacturers, device names, and associated 510(k) submission numbers for cleared topical hemostatic wound dressings

Table 6: 510(k) clearances for topical hemostatic wound dressings *without* thrombin

510(k) number	Trade Name	Sponsor
K893123	ADHESIVE BANDAGES & PADS FOR MINOR CUTS/SCRAPES	LES LABORATORIRES BROTHIER, S.A.
K904488	KALTOSTAT WOUND DRESSING	CALGON VESTAL DIV.
K910059	KALTOSTAT WOUND DRESSING	CALGON VESTAL DIV.
K910080	KALTOSTAT WOUND PACKING	CALGON VESTAL DIV.
K965034	SORBASTACE	HEMOSTACE LLC.
K982638	3M TEGAGEN HI ALGINATE DRESSING	INNOVATIVE TECHNOLOGIES LTD.
K010933	SEAL-ON TOPICAL HEMPSTATIC POWDER SPRAY	ALLTRACEL PHARMA LTD.
K013390	QUICKCLOT	ON SITE GAS SYSTEMS, INC.
K021581	HEMOSORB	ON SITE GAS SYSTEMS, INC.
K021678	HEMADERM COTAINING HEMADEX CLOTTING BEADS	MEDAFOR, INC.
K021062	CHITO-SEAL	ABBOTT VASCULAR INC.
K023298	HEMCON BANDAGE	HEMCON, INC.
K030334	T-SCIENTIFIC T-PAD	T-SCIENTIFIC, INC.
K030946	HEMCON BANDAGE OTC; HEMCON CATH/AID	HEMCON, INC.
K033666	HEMADERM	MEDAFOR, INC.
K032986	CLO-SURPLUSP.A.D.	SCION CARDIO-VASCULAR, INC.
K033291	TOPSEAL HEMOSTATIC DRESSING	RADI MEDICAL SYSTEMS AB
K040208	NEPTUNE PAD, NEPTUNE DISC, NEPTUNE COMFORT-BAND, COMFORT-BAND	TZ MEDICAL, INC.

K050769	QUIKCLOT BRAND HEMOSTATIC AGENT - ADVANCED BEADED FORMULATION	Z-MEDICA CORPORATION
K043050	HEMCON BANDAGE AND HEMCON BANDAGE OTC	HEMCON, INC.
K040283	BIOPAD	EURORESEARCH S.R.L.
K051955	QUICKCLOT ACS - ACCELERATED CLOTTING SPONGE	Z-MEDICA CORPORATION
K060409	HEMOHALT HEMOSTASIS PAD	VANSON-HALOSOURCE, INC.
K061079	MEDTRADE PRODUCTS CELOX TOPICAL HEMOSTATIC GRANULES, MEDTRADE PRODUCTS CELOX 762 HEMOSTATIC GRANULES	MEDTRADE PRODUCTS LTD.
K061767	QUIKCLOT 1ST RESPONSE & QUIKCLOT ACS+	Z-MEDICA CORPORATION
K061722	BLOXX RAPID CLOTTING AGENT	CROSSLINK-D, INC
K070010	QUIKCLOT SPORT AND QUIKCLOT SPORT SILVER	Z-MEDICA CORPORATION
K070211	TRAUMARREST AND BLEEDARREST HEMOSTATIC PARTICLES AND FOAM	HEMOSTASIS, LLC
K070175	AQUANOVA SUPER-ABSORBENT GELLING DRESSING, OTC	MEDTRADE PRODUCTS LTD.
K071519	HEMCON CHITOFLEX-SURGICAL DRESSING	HEMCON, INC.
K063190	SILVERSEAL WOUND PACKING STRIPS WITH X-STATIC	NOBLE FIBER TECHNOLOGIES, INC.
K071936	WOUNDSTAT, MODEL TC1001	TRAUMACURE INC.
K071578	BLOODSTOP AND BLOODSTOP IX HEMOSTATIC GAUZE	LIFESCIENCE PLUS, INC.
K072474	QUIKCLOT EX	Z-MEDICA CORPORATION
K070520	PRO QR (QUICK RELIEF) POWDER (FOR MINOR EXTERNAL BLEEDING FROM WOUNDS & PROCEDURES)	BIOLIFE, LLC

K072900	EXCELARREST FOAM	HEMOSTASIS, LLC
K072681	BLOODSTOP HEMOSTATIC GAUZE; IX HEMOSTATIC GAUZE	LIFESCIENCE PLUS, INC.
K072890	STASILON FR	ENTEGRION, INC.
K072328	MEDTRADE PRODUCTS CELOX SOLBAG, ANTI - COAGULANT	MEDTRADE PRODUCTS LTD.
K080648	TRAUMASTAT RAPID HEMOSTATIC WOUND DRESSING BANDAGE	ORE-MEDIX, LLC
K080818	HEMCON BANDAGE, HEMCON BANDAGE OTC, HEMCON CHITOFLEX-SURGICAL DRESSING	HEMCON MEDICAL TECHNOLOGIES, INC.
K081183	WOUNDSTAT	TRAUMACURE INC.
K080097	MEDTRADE PRODUCTS CELOX HEMOSTATIC GRANULES ON SHEET	MEDTRADE PRODUCTS LTD.
K072486	MODIFICATION TO HEMCON BANDAGE AND HEMCON BANDAGE OTC	HEMCON MEDICAL TECHNOLOGIES, INC.
K082601	INSTA-CLOT, INSTA-CLOT OTC	EMERGENCY MEDICAL DEVICES, LLC
K080532	BENACEL, MODELS C-001, C-002 AND C-005	UNICARE BIOMEDICAL, INC.
K080210	PRO QR ADVANCED FORMULA POWDER	BIOLIFE, LLC
K090100	SOFTSEAL-STF	CHITOGEN, INC.
K090026	CHITOGAUZE, MODELS 130, 131, 263, 264, 265, 266	HEMCON MEDICAL TECHNOLOGIES, INC.
K090620	QUIKCLOT INTEVENTIONAL, MODEL P/N 182	Z-MEDICA CORPORATION
K091194	ALGISEAL PAD	EVOLUTION MEDICAL TECHNOLOGIES LLC
K092357	CHITOGAUZE	HEMCON MEDICAL TECHNOLOGIES, INC.
K092552	CLO-SURPLUS P.A.D.	SCION CARDIO-VASCULAR, INC.
K090780	MEDTRADE PRODUCTS CELOX TOPICAL HEMOSTATIC PASTE	MEDTRADE PRODUCTS LTD.

K091795	MEDTRADE PRODUCTS CELOX TRAUMA GAUZE	MEDTRADE PRODUCTS LTD.
K093519	MEDTRADE PRODUCTS CELOX VASCULAR TOPICAL HEMOSTATIC GRANULES ON SHEET	MEDTRADE PRODUCTS LTD.
K093593	CELOX PRO, CELOX PRO OTC, CELOX HEMOSTATIC GRANULES, CELOX PRO HEMOSTATIC GRANULES, OMNI STAT PRO	MEDTRADE PRODUCTS LIMITED
K093729	GUARDIVA ANTIMICROBIAL HAEMOSTATIC IV DRESSING, 1 IN/ 4MM, STERILE, GUARD IVA ANTIMICROBIAL HAEMOSTATIC IV DRESSING	HEMCON MEDICAL TECHNOLOGIES EUROPE LTD
K101097	CALGAESEAL	BZ MEDICAL INC
K102546	CHITOGAUZE	HEMCON MEDICAL TECHNOLOGIES, INC.
K102459	NEXSTAT (TM) TOPICAL HEMOSTAT POWDER; NEXFOAM (R) TOPICAL SPONGE	HEMOSTASIS, LLC
K102965	CELOX TRAUMA GAUZE AG, CELOX HEMOSTATIC ANTIBACTERIAL TRAUMA GAUZE, OMNI-STAT TRAUMA GAUZE AG, OMNI-STAT HEMOSTATIC ANTI	MEDTRADE PRODUCTS LTD.
K102742	NASAL CEASE	CATALINA, INC.
K103245	CELSTAT	BAXTER HEALTHCARE CORP.
K110386	CELOX RAPID GAUZE	MEDTRADE PRODUCTS LTD.
K111163	CHITOGAUZE FUSION	HEMCON MEDICAL TECHNOLOGIES, INC.
K103641	GUARDACARE	HEMCON MEDICAL TECHNOLOGIES, INC.
K112961	CLO-SURPLUS P.A.D.	SCION CARDIO-VASCULAR INC.
K120782	INTERVENTIONAL HEMOSTATIC BANDAGE	Z-MEDICA CORPORATION

K112215	HEMCON HEMOSTATIC GEL	HEMCON MEDICAL TECHNOLOGIES EUROPE LTD.
K112800	SUNTOUCH TOPICAL HEMOSTATIC DRESSING	HUIZHOU FORYOU MEDICAL DEVICES CO LTD
K102944	CORELEADER HEMO-PAD MODEL CPII 02030	CORELEADER BIOTECH CO. LTD.
K120958	POSISEP AND POSISEP X HEMOSTAT DRESSINGS	HEMOSTASIS LLC
K113560	CELOX GAUZE PRO	MEDTRADE PRODUCTS LTD.
K101257	ADVANCED TRAUMA DRESSING (ATD)	NANOSYS INC.
K112864	SOFTSEAL-C	CHITOGEN INC.
K121485	GUARDIVA ANTIMICROBIAL HAEMSTATIC IV DRESSING	HEMCON MEDICAL TECHNOLOGIES EUROPE LTD
K122886	NEXSTAT PLUS AND NEXFOAM PLUS TOPICAL HEMOSTAT DRESSING	HEMOSTASIS LLC
K123387	QUIKCLOT HEMOSTATIC DRESSING	Z-MEDICA LLC
K130324	Statseal Disc	BIOLIFE, LLC
K132105	PERCLOT TOPICAL	CRYOLIFE, INC.
K133121	CHITO-SAM 100,4IN X4IN,CHITO-SAM, 3IN X6FT, CHITO-SAM 100,3IN X10FT, CHITO-SAM ACTIVE, 4INX4IN,CHITO-SAM ACTIVE, 3INX6FT	SAM MEDICAL PRODUCTS
K132333	BONDILOXS TOPICAL HEMOSTATIC DRESSING	MEDTRADE PRODUCTS LTD.
K140757	D2 Hemostatic Dressing	Z-Medica
K140313	STOPSBLEEDING TOPICAL HEMOSTAT POWDER AND FOAM	COAG MEDICAL LLC
K140573	Woundclot Hemostatic Gauze	Core Scientific Ltd.
K142363	NUSTAT, NUSTAT XR	Beeken Biomedical

K143462	AnsCare ChitoClot Gauze (prescription use), AnsCare ChitoClot Gauze (over-the-counter use)	BENQ MATERIALS CORPORATION
K143466	Hemogrip Patch	REMEDIUM TECHNOLOGIES, INC.
K151204	HEMO-Bandage	CORELEADER BIOTECH CO., LTD.
K150963	AnsCare ChitoClot Pad	BENQ MATERIALS CORPORATION
K150916	HemCon Bandage PRO HemCon Patch PRO HemCon Strip PRO HemCon Strip First Aid PRO ChitoFlex PRO	HemCon Medical Technologies Inc.
K153582	Prometheus ChitoGauze XR PRO	HEMCON MEDICAL TECHNOLOGIES INC.
K160130	BloodSTOP iX Battle Matrix	LifeSciencePLUS Inc.
K160578	Nustat XR	Beeken Biomedical LLC
K160679	WoundClot9	CORE SCIENTIFIC CREATION LTD
K161013	InnoSEAL Hemostatic Pad	InnoTherapy Inc.
K161274	Bondiloxs Topical Hemostatic Granules	MEDTRADE PRODUCTS LTD.
K172324	Axiostat Chitosan Hemostatic Dressing	Advamedica Inc.
K172155	StatGuard Hemostatic Patch, StatGuard Hemostatic Dressing	StatGuard, Llc
K180152	Gel-E Flex	Gel-E, Inc.
K180893	IHM Technology Bandage	Protege Biomedical
K181641	QuikClot Radial	Z-Medica, LLC
K182811	gel-e Flex+	gel-e, Inc.
K192667	gel-e Flex+ gel OTC	gel-e Inc.
K183622	NasalCEASE and BleedCEASE	Les Laboratoires Brothier S.A.
K190012	OMNI-STAT Vascular (Rapid); CELOX Vascular Rapid	Medtrade Product Ltd
K192671	Hemostatic Xerogel Sponge	Solaplus Biotech Co. Ltd.
K202830	Axiostat Patch	Advamedica Inc.

K211570	Zeolite Hemostatic Gauze	Hangzhou Zeo-Innov Life Technology Co., Ltd.

Table 7: 510(k) clearances for topical hemostatic wound dressings *with* licensed thrombin

510(k) Number	Trade Name	Sponsor
K012293	VASCULAR SOLUTIONS DUETT FLOWABLE HEMOSTAT	VASCULAR SOLUTIONS, INC.
K030836	D-STAT-DRY HEMOSTATIC BANDAGE; D-STAT RADIAL HEMOSTATIC BANDAGE	VASCULAR SOLUTIONS, INC.
K033709	VASCULAR SOLUTIONS D-STAT 2 DRY HEMOSTATIC BANDAGE	VASCULAR SOLUTIONS, INC.
K040118	VASCULAR SOLUTIONS D-STAT DRY HEMOSTATIC BANDAGE, THE D-STAT RADIAL HEMOSTATIC BAND AND THE D-STAT 2 DRY HEMOSTATIC	VASCULAR SOLUTIONS, INC.
K040510	VASCULAR SOLUTIONS D-STAT DRY 3X3 HEMOSTATIC PAD	VASCULAR SOLUTIONS, INC.
K050133	D-STAT RADIAL HEMOSTATIC BAND	VASCULAR SOLUTIONS, INC.
K050511	THROMBIGEL THROMBIN/GELATIN FOAM HEMOSTAT	VASCULAR SOLUTIONS, INC.
K053054	THROMBIX 3X3 HEMOSTATIC PAD	VASCULAR SOLUTIONS, INC.
K053644	THROMBIGEL THROMBIN/GELATIN FOAM HEMOSTAT	VASCULAR SOLUTIONS, INC.
K061219	D-STAT DRY HEMOSTATIC BANDAGE	VASCULAR SOLUTIONS, INC.
K063860	THROMBIGEL THROMBIN/GELATIN FOAM HEMOSTAT	VASCULAR SOLUTIONS, INC.
K070938	THROMBI-PASTE THROMBIN/GELATIN POWDER PASTE HEMOSTAT	VASCULAR SOLUTIONS, INC.
K072117	THROMBIX PATCH THROMBIN HEMOSTASIS PATCH	VASCULAR SOLUTIONS, INC.
K073264	D-STAT DRY CLEAR HEMOSTATIC BANDAGE, MODEL 3005	VASCULAR SOLUTIONS, INC.

K083190	D-STAT DRY WRAP HEMOSTATIC BANDAGE, MODEL: 3015	VASCULAR SOLUTIONS, INC.
K092612	D-STAT RAD-BAND, RAD-BAND, MODELS 3501, 3505	VASCULAR SOLUTIONS, INC.
K102212	D-STAT DRY SILVER; D-STAT DRY CLEAR SILVER; D-STAT DRY WRAP SILVER; THROMBIX SILVER	VASCULAR SOLUTIONS, INC.
K200720	D-Stat Radial Topical Hemostat	Vascular Solutions LLC

Appendix B: Literature Search Terms and Filters for Topical Hemostatic Wound Dressings

On July 18-20, 2022, literature searches were performed to identify all published studies for topical hemostatic wound dressings with the search periods of April 1, 2012 to April 1, 2022 and April 1, 2012 to July 18, 2022 in two databases: PubMed and EMBASE.

The search terms used for the PubMed search are presented in the table below.

Table 8: Wound Dressing PubMed Literature Search Strategy (July 18, 2022)

Wound Dressings		
Set	**Query**	**Results**
Filters: English, Human, 2012-2022		
6	#3 OR #4	1,557
5	#4 NOT #2	47
4	((Wound[tiab] or "Wounds and Injuries"[Mesh]) AND (dressing*[tiab] OR bandage*[tiab] or "Bandages"[Mesh])) AND (hemostat[tiab] OR hemostatic[tiab] OR "Collagen"[Mesh] AND "Hemostatics"[Mesh])	74
3	#1 NOT #2	1,510
2	(("negative pressure"[tiab]) OR (comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR "Book Illustrations"[pt] OR congress[pt] OR annual[tiab] OR book[tiab] OR comment[tiab] OR chapter[tiab] OR note[tiab] OR review[tiab] OR symposium[tiab] OR poster[tiab] OR abstract[tiab] OR "conference paper"[tiab] OR "conference proceeding"[tiab] OR "conference review"[tiab] OR congress[tiab] OR editorial[tiab] OR erratum[tiab] OR letter[tiab] OR note[tiab] OR meeting[tiab] OR sessions[tiab] OR "short survey"[tiab] OR symposium[tiab] OR animal[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR goat[tiab] OR goats[tiab] OR pig[tiab] OR pigs[tiab] OR cadaver[tiab] OR dog[tiab] OR dogs[tiab] OR monkey[tiab] OR monkeys[tiab] OR ape[tiab] OR apes[tiab]))	1,967,773
1	(Wound[tiab] or "Wounds and Injuries"[Mesh]) AND ((dressing*[tiab] OR bandage*[tiab] or "Bandages"[Mesh]) AND ("animal derived"[tiab] or "absorbable synthetic*"[tiab] or "wound dressing*"[tiab] or Biologic[tiab] or "Biologic* dressing*"[tiab] or "Biological Dressings"[Mesh] or collagen[tiab] or "Collagen"[Mesh] or "contact layer"[tiab] or "Acellular dermal matrix"[tiab] or "porcine dermal matrix"[tiab] or "decellularized extracellular matrix"[tiab] or "decellularized dermal graft"[tiab] or "decellularized xenograft"[tiab] or "porcine dermis"[tiab] or "bovine dermis"[tiab] or "skin substitute*"[tiab] or (dermal[tiab] and scaffold*[tiab]) or (synthetic[tiab] and "hybrid-scale"[tiab] and matrix[tiab]) or (resorbable[tiab] and "glass fiber"[tiab] and matrix[tiab]) or (biodegradable[tiab] and "temporizing matrix"[tiab]) or (synthetic[tiab] and "skin substitute*"[tiab])))	1,510

Table 9: PubMed Search Strategy, Trade Names (July 20, 2022)

Wound Dressings		
Set	**Query**	**Results**

Filters: English, Human, 2012-2022		
3	#1 OR #2	277
2	hemostat* and ("quickclot"[tiab] or hemosorb[tiab] or "chito-seal"[tiab] or "hemcon bandage"[tiab] or "neptune pad"[tiab] or "comfort-band"[tiab] or biopad[tiab] or "quikclot acs+"[tiab] or (bleedarrest[tiab] and (particles[tiab] or foam[tiab])) or woundstat[tiab] or bloodstop[tiab] or "softseal-stf" or "chitogauze"[tiab] or celstat[tiab] or posisep[tiab])	3
1	("animals"[MeSH] OR "animal"[Title/Abstract]) AND ("biobrane"[Title/Abstract] AND "temporary wound dressing"[Title/Abstract])) OR "medifil"[Title/Abstract] OR "skintemp"[Title/Abstract] OR "viaderm"[Title/Abstract] OR "collagen wound dressing"[Title/Abstract] OR "bilayer matrix wound dressing"[Title/Abstract] OR ("animals"[MeSH Terms:noexp] OR "animal"[All Fields])) AND ("wound dressing"[Title/Abstract] OR "oasis wound matrix"[Title/Abstract] OR ("hydrolyzed collagen"[Title/Abstract] AND "chondroitin sulfate"[Title/Abstract]) OR "polysulfated glycosaminoglycan"[Title/Abstract] OR "awbat"[Title/Abstract] OR "collagen sponge"[Title/Abstract] OR "matristem wound matrix"[Title/Abstract] OR "collagen powder"[Title/Abstract] OR "porcine dermal matrix"[Title/Abstract] OR "collagen wound dressing"[Title/Abstract] OR "procoll"[Title/Abstract] OR "covagen"[Title/Abstract] OR "flowable wound matrix"[Title/Abstract] OR "ologen collagen matrix"[Title/Abstract] OR "symphony"[Title/Abstract] OR "matriderm"[Title/Abstract] OR "macro-channels"[Title/Abstract])	274

The search terms used for the EMBASE search are presented in the table below.

Table 10: Wound Dressings EMBASE Literature Search Strategy (July 19, 2022)

Wound Dressings		
Set	**Query**	**Results**
Filters: English, Human, 2012-2022		
6	#3 OR #5	3,910
5	#4 NOT #2	1,572
4	(('bandages and dressings'/mj OR 'bandages and dressings' OR bandage*:ab,ti OR dressing*:ab,ti) AND (absorbable:ab,ti OR synthetic:ab,ti OR 'hemostatic agent'/mj OR hemostatic:ab,ti OR collagen:ab,ti OR 'animal derived':ab,ti OR 'extracellular matrix':ab,ti OR 'extracellular matrix'/mj) OR 'biological dressing'/mj OR 'collagen dressing'/mj OR 'hemostatic dressing'/mj)	
3	#1 NOT #2	3,202
2	'negative pressure':ab,ti OR 'editorial'/exp OR 'letter'/exp OR 'medical illustration'/exp OR 'book'/exp OR 'poster'/exp OR 'conference abstract'/exp OR 'conference paper'/exp OR 'conferences and congresses'/exp OR 'conference review'/exp OR 'erratum'/exp OR 'symposium'/exp OR 'short survey'/exp OR 'note'/exp OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR abstract:nc OR annual:nc OR conference:nc OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR	6,425

	meeting:nc OR sessions:nc OR symposium:nc OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR comment:ti OR book:pt OR comment:ab,ti OR annual:ab,ti OR 'conference proceeding':ab,ti OR note:ab,ti OR meeting:ab,ti OR sessions:ab,ti OR 'short survey':ab,ti OR animal:ab,ti OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR goat:ab,ti OR goats:ab,ti OR pig:ab,ti OR pigs:ab,ti OR cadaver:ab,ti OR dog:ab,ti OR dogs:ab,ti OR monkey:ab,ti OR monkeys:ab,ti OR ape:ab,ti OR apes:ab,ti	
1	('wound'/mj OR wound:ab,ti) AND ('bandages and dressings'/mj OR dressing*:ab,ti OR bandage*:ab,ti) AND ('animal derived':ab,ti OR 'absorbable synthetic*':ab,ti OR 'wound dressing*':ab,ti OR biologic:ab,ti OR 'biologic* dressing*':ab,ti OR 'biological dressing'/mj OR collagen:ab,ti OR 'collagen'/mj OR 'contact layer':ab,ti OR 'acellular dermal matrix':ab,ti OR 'porcine dermal matrix':ab,ti OR 'decellularized extracellular matrix':ab,ti OR 'decellularized dermal graft':ab,ti OR 'decellularized xenograft':ab,ti OR 'porcine dermis':ab,ti OR 'bovine dermis':ab,ti OR 'skin substitute*':ab,ti OR (dermal:ab,ti AND scaffold*:ab,ti) OR (synthetic:ab,ti AND 'hybrid-scale':ab,ti AND matrix:ab,ti) OR (resorbable:ab,ti AND 'glass fiber':ab,ti AND matrix:ab,ti) OR (biodegradable:ab,ti AND 'temporizing matrix':ab,ti) OR (synthetic:ab,ti AND 'skin substitute*':ab,ti))	9,274

Table 11: Embase Search Strategy, Trade Names (July 20, 2022)

Wound Dressings		
Set	**Query**	**Results**
Filters: English, Human, 2012-2022		
3	#1 OR #2	314
2	hemostat* AND (quickclot OR hemosorb OR 'chito-seal' OR 'hemcon bandage' OR 'neptune pad' OR 'comfort-band' OR biopad OR 'quikclot acs' OR (bleedarrest AND (particles OR foam)) OR woundstat OR bloodstop OR 'softseal-stf' OR chitogauze OR celstat OR posisep	25
1	animal AND (biobrane AND 'temporary wound dressing' OR medifil OR skintemp OR viaderm OR 'bilayer matrix wound dressing' OR 'oasis wound matrix' OR ('hydrolyzed collagen' AND 'chondroitin sulfate') OR 'polysulfated glycosaminoglycan' OR awbat OR 'collagen sponge' OR 'matristem wound matrix' OR 'collagen powder' OR 'porcine dermal matrix' OR 'collagen wound dressing' OR procoll OR covagen OR 'flowable wound matrix' OR 'ologen collagen matrix' OR symphony OR matriderm OR 'macro-channels')	289

The table below summarizes the patients, interventions, comparisons, outcomes, timing, and settings (PICOTS) elements that were used to inform the inclusion/exclusion criteria.

Table 12: PICOTS Eligibility of studies

PICOTS	**Inclusion Criteria**	**Exclusion Criteria**
Population	Patients requiring coverage/protection in the management of wound healing using wound dressings.	Patients that do not require wound management using wound dressings.

Intervention	Absorbable synthetic wound dressings (FRO) Hemostatic wound dressings with and without thrombin (FRO) Collagen and/or animal-derived wound dressings (KGN)	No wound dressing Other types of wound dressings
Comparison	• One wound dressing vs. another wound dressing • No use of a wound dressing	No exclusion
Outcomes	All wound dressing devices: 1. Mortality (all-cause) 2. Adverse tissue reactions (local) 3. Adverse tissue reactions (systemic) 4. Duration of use Hemostatic dressings: 5. Time to clot 6. Survival Subgroups: 1. Sterile vs. non-sterile products 2. With vs. without thrombin 3. Diabetics vs. non-diabetics 4. For hemostatic dressings: Minor, moderate, and severe bleeding	Studies will be excluded if they do not report any of the specified outcomes.
Timing	All	None
Setting	US and OUS	No exclusion
Study Design	• Randomized controlled trials (RCTs) • Cohort studies (prospective/retrospective)	Laboratory studies Nonclinical studies (e.g., narrative reviews, commentaries) Economic and cost effectiveness analyses Cross-sectional studies Case-control studies Systematic literature reviews (SLRs), meta-analyses Case series (≥10 patients) and case reports (≤9 patients) Animal studies), Original search: N <100 per arm Second search: N <75 per arm
Language	Articles published in English	Non-English language
Publication dates		Published outside of date ranges

Table 13: Studies included in the Systematic Literature Review for Topical Hemostatic Wound Dressings

Study Characteristics	Patient Characteristics	Device Brand/ Manufacturer	Safety Outcomes
Hemostatic Wound Dressings (FRO)			
Severe Bleeding			
Reference: Schauer et al. 2017[8] **Country:** USA **Study Design:** Retrospective review of the Prehospital Trauma Registry between January 2013 and September 2014 **Purpose:** To describe the use of QCCG by ground forces in Afghanistan and compare patients who received QCCG with the remaining population in the database who did not receive QCCG **Length of follow-up:** NR **Funding Source:** NR	**Patients (N):** 705 QCCG: 118, No QCCG: 587 Note: Outcomes data available for only 190 patients (28 QCCG, 162 No QCCG) **Age mean (SD, range):** NR **Sex (% male):** NR **Diagnosis:** Combat injuries, QCCG vs. No QCCG, n (%): Explosive: 26 (22.0) vs. 319 (54.3) Gunshot wound: 85 (72.0) vs. 176 (30.0) Gunshot wound + Explosive: 1 (0.9) vs. 6 (1.0) Other/Unknown: 6 (5.1) vs. 86 (14.7) p<0.001* **Inclusion criteria:** Patient casualties in Afghanistan during Operation Enduring Freedom within the Prehospital Trauma Registry database **Exclusion criteria:** Killed in action, dead	**Intervention:** QuikClot Combat Gauze (QCCG; Z-Medica) **Comparator:** No QCCG	**Mortality (all-cause):** NR **Adverse tissue reactions (local):** NR **Adverse tissue reactions (systemic):** NR **Duration of use:** NR **Time to clot:** NR **Survival, n (%):** QCCG vs. No QCCG: 25 (89.3) vs. 153 (94.4), p=0.300

	on arrival, enemy prisoners of war **Comorbidities, % (n):** NR		
Reference: Winstanley et al. 2019[9] **Country:** UK **Study Design:** Retrospective database review using the UK Joint Theater Trauma Registry from 2003-2014 **Purpose:** To analyze the use of hemostatic dressings in major trauma patients on the battlefield **Length of follow-up:** NR **Funding Source:** No grant nor funding agency in the public, commercial, or not-for-profit sectors declared	**Patients (N):** 3792 Hemostatic dressing: 317 • Celox: 212 • Hemcon: 87 • QuikClot: 18 No hemostatic agent: 3475 **Age mean (IQR):** 24.8 years (8) Hemostatic: 25.1 (SD: 7.6) None: 24.7 (SD: 8.6) p=0.52 **Sex (% male):** 97.2 Hemostatic vs. None: 98.7 vs. 97.0, p=0.08 **Diagnosis:** Major battlefield trauma NISS, Hemostatic vs. None, mean (SD): 43.4 (20.8) vs. 42.4 (22.2), p=0.39 **Inclusion criteria:** Patients with NISS ≥15, injured in the Iraq or Afghanistan conflicts **Exclusion criteria:** No NISS recorded, NISS <15, multiple hemostatic agents used **Comorbidities, % (n):** NR	**Intervention:** Hemostatic dressing (Celox, Hemcon, or QuikClot) **Comparator:** No hemostatic agent	**Mortality (all-cause):** NR **Adverse tissue reactions (local):** NR **Adverse tissue reactions (systemic):** NR **Duration of use:** NR **Time to clot:** NR **Survival, % difference (χ^2):** Hemostatic vs. None: 7 (10.86), p<0.00*, favoring Hemostatic Celox vs. None: 14 (26.53), p<0.00*, favoring Celox QuikClot vs. None: -6 (0.24), p=0.63, no difference Hemcon vs. None: -8 (2.27), p=0.13, no difference
Unspecified Level of Bleeding			

Reference: Matsubara et al. 2019[10] **Country:** Japan **Study Design:** Prospective, single center, open-label, randomized, controlled **Purpose:** To analyze the efficacy and safety of a hemostatic wound dressing made of calcium alginate (CA) at the puncture site of VA after PTA and evaluate other factors affecting hemostasis **Length of follow-up:** 5, 10, 15, and >15 minutes after start of hemostatic procedure **Funding Source:** NR	**Patients (N):** 200 CA: 100, Non-drug: 100 **Age mean (SD):** CA: 70.2 years (12.4), Non-drug: 71.1 (12.0) p=0.6 **Sex (% male):** CA: 60, Non-drug: 58, p=0.7 **Diagnosis:** End-stage kidney disease with VA dysfunction Stenosis (n): 164 Occlusion, CA vs. Non-drug, n (%): 20 (20) vs. 16 (16), p=0.5 **Inclusion criteria:** Hemodialysis patients who underwent PTA for VA dysfunction at the Tsuchiya General Hospital between November 1, 2016, and July 27, 2017; only first PTA cases in instances of multiple PTAs were eligible for inclusion **Exclusion criteria:** Did not provide consent, underwent arterial puncture, punctured by ≥3 sheaths, hematoma at the puncture site during PTA, had a technically unsuccessful PTA procedure **Comorbidities, CA vs. Non-drug, % (n):**	**Intervention:** Calcium alginate (CA) sheet (nepcell S, Alliance Medical Group) **Comparator:** Non-drug sheet	**Mortality (all-cause):** NR **Adverse tissue reactions (local):** Rebleeding after homeostasis, CA vs. Non-drug, n (%): 6 (6) vs. 7 (7), p=0.7 **Adverse tissue reactions (systemic):** "No serious complications, such as anaphylactic shock, bleeding refractory to manual compression, cutaneous allergy, or false aneurysm at the puncture site were identified in the two groups." **Duration of use:** NR **Time to clot:** Proportions of hemostasis after start of hemostatic procedure, CA vs. Non-drug, n (%): At 5 minutes: 57 (57) vs. 39 (39), p=0.01*, favoring CA At 10 minutes: 25 (25) vs. 28 (28) At 15 minutes: 8 (8) vs. 14 (14) >15 minutes: 10 (10) vs. 19 (19) Multivariate analysis of predictors for homeostasis: Diabetes vs. No diabetes: OR: 1.26 (95% CI: 0.72 to 2.21), p=0.4 **Survival:** NR

	Diabetes: 47 (47) vs. 49 (49), p=0.8 Chronic glomerulonephritis: 27 (27) vs. 26 (26), p=0.9 Nephrosclerosis: 13 (13) vs. 10 (10), p=0.5		
Reference: Pawel et al. 2020[11] **Country:** Poland **Study Design:** Prospective, single center, randomized **Purpose:** To compare the efficacy and safety of QuikClot and standard manual compression in patients scheduled for elective CAG with TRA and TUA between 2013-2017 **Length of follow-up:** 6 months **Funding Source:** Center of Postgraduate Medical Education, Warsaw, Poland (grant 501-1-10-14-15)	**Patients (N):** 200 QuickClot: 100 (60 TRA, 39 TUA, 1 TBA) Compression: 100 (60 TRA, 38 TUA, 2 TBA) **Age mean (SD):** QuikClot: 64 (9.1), Compression: 67 (10), p=0.01* **Sex (% male):** QuikClot: 49, Compression: 42, p=0.32 **Diagnosis:** Suspected coronary artery disease requiring diagnostic CAG **Inclusion criteria:** Patients ≥18 years old, hospitalized for first elective CAG **Exclusion criteria:** Patients with upper-limb anomalies, underwent prior vascular interventions (TRA or TUA), radial or ulnar artery <1.5mm per preprocedural ultrasound, positive Allen's test results **Comorbidities, QuikClot vs. Compression, % (n):**	**Intervention:** QuikClot Radial pad (Z-Medica Corporation) + 120 minutes of compression **Comparator:** Standard manual compression with 120 minutes of compression	**Mortality (all-cause):** NR **Adverse tissue reactions (local):** Composite TAO/IPA/large hematoma, QuikClot vs. Compression: 8% vs. 9%, p=0.8 TAO, at 3 months, QuikClot vs. Compression: 4% vs. 3% IPA, at 3 months, QuikClot vs. Compression: 2% vs. 2% Large hematoma, at 3 months, QuikClot vs. Compression: 5% vs. 3% Note: Large hematoma defined as grade 4 on the EASY scale. Small hematomas defined as grades 1-3 on the EASY scale and were noted as the most common complications (data not provided). **Adverse tissue reactions (systemic):** NR **Duration of use:** NR **Time to clot:** NR **Survival:** NR

	Hypertension: 81 (81) vs. 81 (81), p=1.00 Hypercholesterolemia: 71 (71) vs. 76 (76), p=0.42 Peripheral artery disease: 13 (13) vs. 6 (6), p=0.09 Diabetes: 33 (33) vs. 29 (29), p=0.54 Stroke: 6 (6) vs. 6 (6), p=1.00 Renal insufficiency: 2 (2) vs. 5 (5), p=0.25		

*Statistically significant

Abbreviations: CAG: coronary angiography; CI: confidence interval; IPA: pseudoaneurysm; IQR: interquartile range; NISS: New Injury Severity Score; OR: odds ratio; PTA: percutaneous transluminal angioplasty; QCCG: QuikClot Combat Gauze; SD: standard deviation; TAO: total artery occlusion; TBA: transbrachial approach; TRA: transradial approach; TUA: transulnar approach; UK: United Kingdom; USA: United States of America; VA: vascular access

Appendix C: Flow Diagram of Systematic Literature Review Search Results

Figure 1. Wound Dressing PRISMA, original search (April 1, 2012 – April 1, 2022)

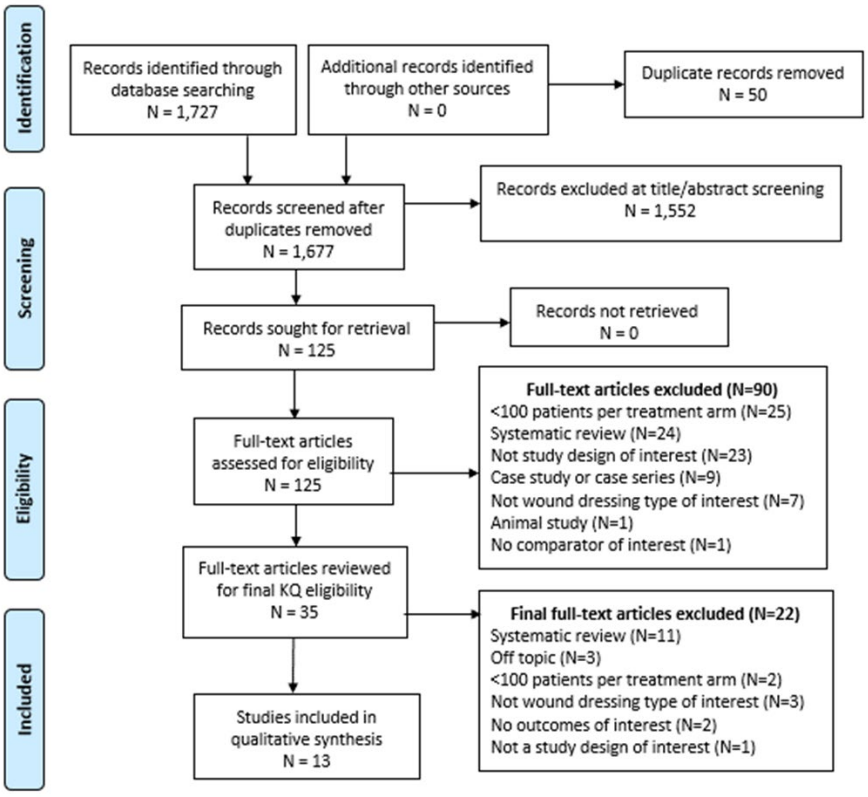

Figure 2. Wound Dressing PRISMA, second search (April 1, 2012 – July 18, 2022)