FDA Executive Summary

Prepared for the October 26 & 27, 2022 Meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Panel

Classification of Wound Dressings with Animal-derived Materials

Product Code: KGN

Table of Contents

List of Tables

List of Figures

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 wound dressings with animal-derived materials, a pre-amendments device type which remains unclassified. Specifically, the FDA will ask the Panel to provide recommendations regarding the regulatory classification of wound dressings with animal-derived materials that do not contain any antimicrobials, drugs, or biologics. Wound dressings with animal-derived materials that do not contain any antimicrobials, drugs or biologics, have primarily been cleared under the KGN product code. However, this device type may also have been cleared under other unclassified wound dressing product codes. 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 of these product codes are associated with a device classification regulation, some product codes, including "KGN," remain unclassified.

FDA is holding this panel meeting to obtain input on the risks to health and benefits of wound dressing with animal-derived materials that do not contain any antimicrobials, drugs, or biologics. The Panel will discuss whether these wound dressings with animal-derived materials should be classified into Class II (subject to General and Special Controls). If the Panel believes that classification into Class II is appropriate for this device type, the Panel will also be asked to discuss appropriate controls that would be necessary to mitigate the risks to health. FDA considers the risks to health for wound dressing with animal-derived materials to be similar regardless of the product code under which the device was cleared. FDA considers devices cleared under KGN to be representative of wound dressing with animal-derived materials that do not contain any antimicrobials, drugs, or biologics and intends to consolidate devices that fit into this device type during classification, notwithstanding the product code under which the device may have been originally cleared. FDA will therefore present information derived from its analyses of devices cleared under product code "KGN" to inform the panel's deliberations and recommendations to the Agency.

1.1 Current Regulatory Pathways

Wound dressings with animal-derived materials 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 wound dressing with animal-derived material(s) is a device consisting either entirely or in part of materials (e.g., decellularized extracellular matrix, collagen,

gelatin, keratin) derived from an animal (e.g., from bovine, porcine, ovine, equine, avian, amphibian, or fish, sources). There are also two dressings within KGN derived from human hair. Such dressing is intended to cover and protect a wound, to absorb exudate, and to maintain appropriate moisture balance within the wound. They may be derived from organs such as dermis, liver, tendon, intestine, as well as from extruded material such as wool or hair. Such wound dressings may be manufactured with other natural or synthetic materials to achieve the final physical state of the dressing (e.g., sheet, pad, gel, powder).

The animal-derived materials incorporated in these wound dressings are intended to support the intended use of the dressing as described above, or to provide or support the physical integrity of the dressings. The animal-derived materials in these dressings are not intended for biological actions related to wound healing (e.g., accelerate wound healing). A wound dressing with animal-derived material(s) does not contain any antimicrobials, drugs, or biologics.

Some dressings under the product code KGN are intended for one-time application only, while others may be suitable for multiple applications over the course of wound management.

2. Regulatory History

Wound dressings, including those containing animal-derived materials, are pre-amendments devices that have been in commercial distribution since prior to May 28, 1976.

To date, FDA has cleared over 120 wound dressings containing animal-derived materials through the 510(k) pathway under the KGN product code. Please refer to Table 4 in Appendix A for a listing of the manufacturers, device names, and associated 510(k) submission numbers for cleared wound dressings with animal-derived materials under product code "KGN".

2.1 Summary of Previous Classification Panel Meeting

On November 17, 1998, the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee met to discuss the classification of porcine wound dressings, cleared under product code "KGN", among other unclassified pre-amendment devices.[1] FDA presented information on porcine wound dressings, which are intended as temporary burn dressings made from pig skin, as well as the risks of use and potential mitigation measures for these products. Following the discussion, the panel voted unanimously to recommend that the Agency classify porcine wound dressings as Class I medical devices, although the majority of the panelists agreed that these products should not be exempt from 510(k) premarket notification due to risks associated with material sourcing and viral transmission.

[1] 1998 General and Plastic Surgery Devices Panel Meeting transcript, *available at* https://wayback.archive-it.org/7993/20170403222339/https://www.fda.gov/ohrms/dockets/ac/98/transcpt/3483t1.pdf

Since 1998, there have been significant developments, including new technologies and indications for use, in wound dressings cleared under the product code "KGN." Although the 1998 panel meeting only discussed wound dressings made from porcine skin and intended for burn wounds, more recent products cleared under the product code "KGN" have been composed of materials from many different sources and are indicated for a broader range of wounds. As such, these products under the product code "KGN" are now referred to as wound dressings with animal-derived materials. In addition, FDA's understanding and experiences with animal-derived materials have further developed since the 1998 panel meeting. This has led to issuance of the FDA guidance document in 2019, Medical Devices Containing Materials Derived from Animal Sources (except for in Vitro Diagnostic Devices).[2] Therefore, FDA is convening this classification panel to discuss the current landscape of product technology, indications of use, safety and effectiveness, and risks to health, on which to base classification of wound dressings with animal-derived materials.

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.

The wound dressings with animal-derived materials under the product code "KGN" have been cleared for the following prescription indications for use[3]:

- Prescription (Rx), management of wounds, including:
    - Partial- and full-thickness wounds
    - Pressure ulcers (stage I-IV)
    - Venous ulcers
    - Diabetic ulcers
    - Chronic vascular ulcers
    - Ulcers caused by mixed vascular etiologies
    - Tunneled/undermined wounds
    - Surgical wounds (e.g., incisions, donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence)
    - Trauma wounds (e.g., abrasions, lacerations, partial thickness burns and skin tears)
    - Traumatic wounds healing by secondary intention
    - Draining wounds
    - First- and second-degree burns
    - Severe sunburns
    - Superficial injuries

[2] Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices), *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-containing-materials-derived-animal-sources-except-in-vitro-diagnostic-devices

[3] In addition to use on general skin wounds, some wound dressings containing animal-derived materials have been previously cleared with other specific indications for use in other locations. Those other specific uses are outside of the scope for this panel discussion and the proposed classification action for wound dressings containing animal-derived materials.

    - Cuts
    - Abrasions
    - Blisters
    - Sores
    - Scrapes
    - Dry, light, and moderately exuding partial thickness wounds
    - Radiation dermatitis
- Over the Counter (OTC), Management of wounds, including:
    - Minor cuts
    - Minor scrapes
    - Minor bruises
    - Minor abrasions
    - Minor lacerations
    - Minor burns
- Maintain a moist wound environment
- Protective covering for meshed autograft

Wound dressings with animal-derived materials have not been cleared for indications such as wound treatment, promotion or acceleration of wound healing, or serving as a skin substitute. Such indications may pose a different intended use than the cleared indications and are outside of the scope for this panel meeting.

4. Clinical Background

4.1 Disease Characteristics

There is a wide variety of acute and chronic wounds. Acute wounds can affect anyone and usually occur suddenly and heal at a predictable and expected rate; these include cuts, post-surgical wounds, burns, and traumatic wounds. Chronic wounds develop over time and do not heal at an expected rate. The most common chronic wounds are venous ulcers, diabetic ulcers, and pressure ulcers. An acute wound can sometimes develop into a chronic wound.

The pathophysiology of wounds varies greatly and depends on the wound type and many other factors, including blood supply, blood pressure, infection, and other comorbidities (e.g., diabetes).

4.2 Patient Outcomes

Patient history, physical examination, and laboratory studies including 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 are a wide variety of wound types, there are 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. In addition, there are a variety of other wound care modalities available including compressive dressings, bioengineered dressings, wound dressings with antimicrobials, grafts, negative pressure wound therapy, pressure relief devices, hyperbaric oxygen, and topical drugs.

Various national and international organizations (e.g., The Wound Healing Society, American Academy of Dermatologists, American Burn Association, Infectious Diseases Society of America, American Society of Plastic Surgeons) have published clinical guidelines providing wound care recommendations.[4,5,6,7,8] Some of these organizations may be corporate-sponsored.

Although these clinical guidelines target different types of wounds, they generally recommend debridement, rinsing, and providing a moist wound environment as part of wound care. Most guidelines do not specify the use of a particular type of wound dressing as recommendations for dressing selection are based on patient-specific wound care needs such as the need for exudate management or prevention of fluid loss.

4.4 Risks

FDA has identified the following risks to health associated with wound dressings with animal-derived materials:

Table 1: Risks to Health and Descriptions/Examples for Wound Dressings with Animal-derived Materials

Identified Risk	Description/Examples
Adverse Tissue Reaction	This can result from the use of device materials that are not biocompatible. For devices intended to degrade in the wound, delayed tissue response or toxicity can result from the degradants, such as crosslinking agents used to crosslink the animal-derived materials.
Infection	This can result from inadequate device sterilization, inadequate viral inactivation, or inadequate packaging integrity.

[4] American Academy of Dermatologists: Wound healing and treating wounds: Chronic wound care and management (2016), *available at* https://www.jaad.org/action/showPdf?pii=S0190-9622%2815%2902183-0

[5] The Wound Healing Society: Chronic Wound Care Guidelines: Diabetic Foot Ulcers, Pressure Ulcers, Venous Ulcers, Arterial Ulcers (2015), *available at* https://woundheal.org/Publications/WHS-Wound-Care-Guidelines.cgi

[6] ABA Guidelines for Burn Care Under Austere Conditions: Surgical and Nonsurgical Wound Management (2016), *available at* http://ameriburn.org/wp-content/uploads/2017/05/guidelines_for_burn_care_under_austere_conditions_.98589-2.pdf

[7] Infectious Diseases Society of America: Clinical Practice Guideline for Diagnosis and Treatment of Diabetic Foot Infections (2012), *available at* https://academic.oup.com/cid/article/54/12/e132/455959

[8] American Society of Plastic Surgeons: Clinical Practice Guideline – Chronic Wounds of Lower Extremity (2007), *available at* https://www.plasticsurgery.org/documents/medical-professionals/quality-resources/ASPS-Evidence%E2%80%90Based-Clinical-Practice-Guideline-Methodology.pdf

Immunological reaction	This can result from a device derived from a new animal source or protein denaturation/modification due to the manufacturing conditions.
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.
Delays in wound healing	This can result from the use of device materials which may interfere with the wound healing process.

The Panel will be asked whether this list is a complete and accurate list of the risks to health presented by wound dressings with animal-derived materials and whether any other risks should be included in the overall risk assessment of the device type.

5. Literature Review

5.1 Methods

A systematic literature review was conducted in an effort to gather any published information regarding the safety and effectiveness of wound dressings with animal-derived materials.

On May 16, 2022 and July 18-19, 2022, literature searches were performed to identify all published articles for wound dressings with animal-derived materials 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 hemostatic wound dressings with or without thrombin. 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

The search yielded 1727 initial literature references. After duplicate articles were removed between databases, a total of 1677 articles remained. Following a review of the titles and abstracts, a total of 125 articles remained for full text review. Of these, five articles were determined to be relevant to the safety and effectiveness of wound dressings with animal-derived materials. The number of articles

meeting inclusion and exclusion criteria is summarized in the flow diagram in Appendix D. Out of the five selected studies, two studies consisted of randomized control trials (RCTs)[9,10], and three studies consisted of retrospective study design.[11,12,13] Of the selected studies, one study was conducted outside of the United States (OUS), four studies in the United States. One study reported both safety and effectiveness[9], while another study reported safety only.[11] Three other studies reported only effectiveness.[10,12,13] The animal-derived materials used in these studies were bovine, porcine, or ovine-derived.

Table 7 in Appendix C provides full details on the individual selected studies.

5.3 Adverse Events Associated with Wound dressings with Animal-Derived Material

Two studies assessing wound dressings with animal-derived materials reported mild, unspecified, local adverse tissue reactions.[9,11] One study found no differences in adverse events between standard of care (SOC) treatment, which consisted of sharp debridement, infection elimination, use of dressings and offloading, and wound dressings with animal-derived materials.[9] None of the five studies reported systemic adverse tissue reactions.

5.4 Effectiveness Associated with Wound Dressings with Animal-Derived Material

All five studies of wound dressings with animal-derived materials reported wound healing time.[9-13] One study found no difference in median time to wound closure between SOC treatment and wound dressings with animal-derived materials.[9] Another study compared a wound dressing containing animal-derived material (i.e., fetal bovine collagen dressing (FBCD)) with a bioengineered skin substitute (i.e., bilayered living cellular construct (BLCC)). They found that BLLC-treated patients experienced faster median wound closure rates than the FBCD-treated patients (BLLC 19 weeks vs. FBCD 30 weeks, p=0.01), which is expected as bioengineered skin substitutes are intended to accelerate the wound healing process whereas wound dressings containing animal-derived materials are intended to support the natural wound healing process. The study also reported on

[9] Lantis, John C., et al. "Fetal bovine acellular dermal matrix for the closure of diabetic foot ulcers: a prospective randomised controlled trial." *Journal of wound care* 30.Sup7 (2021): S18-S27.
[10] Yu, Qian, Fang-Jing Han, and De-Sheng Lv. "To compare the healing of pressure sores by the use of combination therapy with platelet rich plasma and gelatin hydrogel versus platelet rich plasma and collagen." *Biomedical Research* 28.3 (2017): 12-22.
[11] Griffin, Leah, et al. "Comparative Effectiveness of Two Collagen-containing Dressings: Oxidized Regenerated Cellulose (ORC)/Collagen/Silver-ORC Dressing Versus Ovine Collagen Extracellular Matrix." *Wounds: A Compendium of Clinical Research and Practice* 31.11 (2019): E73-E76.
[12] Sabolinski, Michael L., and Gary Gibbons. "Comparative effectiveness of a bilayered living cellular construct and an acellular fetal bovine collagen dressing in the treatment of venous leg ulcers." *Journal of Comparative Effectiveness Research* 7.8 (2018): 797-805.
[13] Marston, William A., et al. "Comparative effectiveness of a bilayered living cellular construct and a porcine collagen wound dressing in the treatment of venous leg ulcers." *Wound Repair and Regeneration* 22.3 (2014): 334-340.

the median interval between applications, which favored FBCD (BLCC 14 days vs. FBCD 21 days, p<0.01).[12] Another study compared a different wound dressing with animal-derived material (i.e., small intestine submucosa collagen dressing (SIS)) with BLCC. The reported median interval between applications (BLCC 24.5 days vs. SIS 8.5 days, p<0.0001) and median time to wound closure (BLCC 24 weeks vs. SIS 43 weeks, p=0.01) both favored the BLCC-treated group.[13] Although both wound dressings with animal-derived materials (i.e., FBCD and SIS) resulted in slower wound closure rate than BLLC, they nonetheless led to wound closure and were shown to be effective at supporting wound healing. Another study compared an oxidized regenerated cellulose (ORC) wound dressing, which contains collagen and silver, with a wound dressing with animal-derived material, which was composed of extracellular matrix (ECM). The study reported median time to 75%-100% granulation favored ORC (ORC 42 days vs. ECM 60 days, p=0.0109), and that fewer patients treated with ORC had a worsening diabetic foot ulcer than patients treated with ECM (ORC 15.2% vs. ECM 23.9%, p=0.0013) when the rates of antibiotic use between groups were similar (ORC 12.1% vs. ECM 9.0%, p=0.1451).[11] Even though ECM appeared to be less effective than ORC, which contains collagen and silver, ECM was still shown to be effective at supporting wound healing. Finally, one study compared two types of wound dressings with animal-derived materials, one with collagen and one with gelatin, and reported no difference in wound healing time.[10]

5.5 Overall Literature Review Conclusions

The published, peer-reviewed clinical evidence considering use of wound dressings with animal-derived materials consisted of five studies. All five studies reported on wound healing time. None of the studies reported any systemic adverse tissue reactions, while two studies reported local tissue reactions. None of the studies reported on mortality (all-cause).

The evidence base for wound dressings with animal-derived materials consisted of two studies with higher-quality study designs (e.g., RCTs)[9,10], while the remaining three studies used a retrospective design.[11,12,13] The funding source was not reported in one study[10], and in the other four studies the manufacturer of the device being studied funded the research.[9,11,12,13] On the whole, the strength of this evidence base is rated low, given the high potential for bias in retrospective study designs and in studies funded by device manufacturers.

Overall, wound dressings with animal-derived materials were shown to be effective at supporting wound healing, even though they may have slower wound closure rates than bioengineered skin substitutes, which is expected. The adverse events associated with wound dressings with animal-derived materials, as reported in these studies, were mild and limited to local reactions.

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: Wound Dressings with Animal-derived Materials

Individual MDRs for wound dressings with animal-derived materials 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 using the product code "KGN" returned a total of 119 reports from the start of the database through April 1, 2022. MDRs that met the criteria for serious injury totaled 103, and the remainder 16 reports were labeled as malfunction. The reporting country for 72 reports was the United States, and 47 reports did not have information on the reporting country. Manufacturers submitted 112 reports, and the remaining 7 reports were voluntary submissions. Table 2 lists the top 20 adverse events described in the 119 MDRs.

Table 2: Adverse Events Described in MDRs for Wound Dressings with Animal-derived Materials

Adverse Events	Count
Unspecified Infection	22

Swelling	13
No Known Impact Or Consequence To Patient	10
Bacterial Infection	10
No Code Available	9
Itching Sensation	8
Injury	8
Rash	7
Pain	7
No Consequences Or Impact To Patient	6
Hypersensitivity/Allergic reaction	6
No Clinical Signs, Symptoms or Conditions	6
Necrosis	5
Wound Dehiscence	5
Impaired Healing	5
Fever	4
Fluid Discharge	3
Discomfort	3
Edema	3
Cellulitis	3

Systematic review of the MDRs submitted for product code “KGN” revealed complications thought to be associated with various wound dressing with animal-derived materials. Health professionals reported 10 cases of wound infection that occurred after placement of wound dressing with animal-derived materials as well as failure of the dressing to incorporate into the wound. There was one report of a female patient developing Stevens-Johnson syndrome after the application of a wound dressing with animal-derived material to the dorsum of foot. The patient experienced moderate symptoms that resolved with treatment. Fourteen patients experienced certain allergic reactions that included redness, lumps, rash, systemic urticaria, itching and localized blanching. There were nine reports from health professionals that detailed unintentional application of expired products. The MDR events observed are expected for this device type and consistent with the risks found in the literature.

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: Wound Dressings with Animal-derived Materials

A total of eight (Class II[14]) recalls have been reported to date for devices with the product code "KGN", and are described below:

- Z-2109-2021: This recall was initiated due to products that failed dose audit after sterilization.
- Z-1338-2019: This recall was initiated due to products that failed to meet the stability testing acceptance criteria after 6 months.
- Z-1243-2019: This recall was initiated due to intermittent heat seal failures on the outer pouch of some products.
- Z-0379-2019, Z-0377-2019, Z-0378-2019: These recalls were initiated due to the potential for pouch seal failure.
- Z-0383-2018: This recall was initiated due to missing pages or extra pages in device labeling.
- Z-1452-2015: This recall was initiated due to one lot of products not meeting stability acceptance criteria for the attributes of visual appearance and force needed for product to be extruded from the syringe.

The recalls identified above are related to manufacturing errors and do not suggest additional risks related to wound dressings with animal-derived materials as a product class.

8. Summary

In light of the information available, the Panel will be asked to comment on whether wound dressings with animal-derived materials:

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

[14] 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 device is purported or represented to be for used 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 wound dressings with animal-derived materials 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 wound dressings with animal-derived materials. Following is a risk/mitigation table, which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks:

Table 3: Summary of Risks to Health and Proposed Mitigations for Wound Dressings with Animal-derived Materials

Identified Risk	Recommended Mitigation Measure
Adverse tissue reaction	Biocompatibility evaluation Pyrogenicity testing Performance testing and descriptive information Risk management assessment for animal-derived materials Labeling
Infection	Sterilization testing/validation/information Shelf-life validation Labeling Risk management assessment for animal-derived materials
Immunological reaction	Performance testing Material characterization Risk management assessment for animal-derived materials 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
Delays in wound healing	Performance testing and descriptive information Biocompatibility evaluation 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 wound dressings with animal-derived materials:

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. The device, including any degradants, must be demonstrated to be biocompatible, non-pyrogenic and contain endotoxin level within acceptable limits.

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 device degradation, if applicable, and evaluation of expected worst-case conditions.

6. If the device contains materials derived from a new animal species or from manufacturing processes which cause structural changes (i.e., denaturation, modification) to the animal protein, performance data (e.g., patch and prick testing, human repeat insult patch testing) must demonstrate that the device is not immunogenic.

7. The following information must be provided to support the safety of the animal-derived material(s):
   i) Documentation of the processing methods, including animal species, origin, 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 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. 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) A list of each ingredient or component within the finished device, including the functional role of that ingredient or component within the device.
iv) If the device is non-resorbable, a warning statement for the potential retention of material in the wound or the surrounding area.
v) A contraindication for any known sensitivity to components within the device.
vi) A contraindication if there are incompatibilities with other therapies.
vii) A shelf life.
viii) A statement regarding when to discontinue use of the device after multiple reapplications based on biocompatibility and performance testing, if applicable.
ix) 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.
x) Any statements in the labeling must be clear such that they may be understood by the end user, supported by appropriate evidence, and consistent with the intended use of covering and protecting a wound, absorbing exudate, and maintaining appropriate moisture balance within the wound.
xi) Disposal instructions.

If the panel believes that Class II is appropriate for the wound dressings with animal-derived materials, 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 wound dressings with animal-derived materials indicated for use to cover and protect the wound, to absorb exudate, and to maintain appropriate moisture balance within the wound be regulated as Class II devices.

878.4024 Wound dressing with animal-derived material(s).
(a) *Identification.* A wound dressing with animal-derived material(s) consists either entirely, or in part, of materials (such as collagen, gelatin) sourced from an animal and is intended to cover and protect a wound, to absorb exudate, and to maintain appropriate moisture balance within the wound. Such wound dressings may be manufactured with other natural or synthetic materials to achieve the final physical state of the dressing (including sheet, gel, powder). The animal-derived materials incorporated in these wound dressings are intended to provide or

support the physical structure of the dressings and are not intended for biological actions related to wound healing (e.g., to accelerate wound healing). A wound dressing with animal-derived material does not contain any antimicrobials, drugs, or biologics.

(b) *Classification.*
Class II (special controls). The special controls for this device are:

1. Performance testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and chemical characteristics of the device. The following must be provided:
    i) Identity, quantification, and purpose of each component in the finished product;
    ii) Specification and characterization of each component in the finished product; and
    iii) Final release specifications for the finished product.
2. Performance data must demonstrate the sterility of the device.
3. The device, including any degradants, must be demonstrated to be biocompatible, non-pyrogenic and contain endotoxin level within acceptable limits.
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 device degradation, if applicable, and evaluation of expected worst-case conditions.
6. If the device contains materials derived from a new animal species or from manufacturing processes which cause structural changes (i.e., denaturation, modification) to the animal protein, performance data (e.g., patch and prick testing, human repeat insult patch testing) must demonstrate that the device is not immunogenic.
7. The following information must be provided to support the safety of the animal-derived material(s):
    i) Documentation of the processing methods, including animal species, origin, 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 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. 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) A list of each ingredient or component within the finished device, including the functional role of that ingredient or component within the device.
   iv) If the device is non-resorbable, a warning statement for the potential retention of material in the wound or the surrounding area.
   v) A contraindication for any known sensitivity to components within the device.
   vi) A contraindication if there are incompatibilities with other therapies.
   vii) A shelf life.
   viii) A statement regarding when to discontinue use of the device after multiple reapplications based on biocompatibility and performance testing, if applicable.
   ix) 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.
   x) Any statements in the labeling must be clear such that they may be understood by the end user, supported by appropriate evidence, and consistent with the intended use of covering and protecting a wound, absorbing exudate, and maintaining appropriate moisture balance within the wound.
   xi) Disposal instructions.

Based on the available scientific evidence, the FDA will ask the Panel for their recommendation on the appropriate classification of the wound dressings with animal-derived materials.

Appendix A: A listing of the manufacturers, device names, and associated 510(k) submission numbers for cleared wound dressings with animal-derived materials

Table 4: 510(k) clearances for wound dressings with animal-derived materials under product code "KGN"

510(k) Number	Trade Name	Sponsor
K790496	BIOBRANE BRAND TEMPORARY WOUND DRESSING	WOODROOF LABORATORIES INC.
K843788	CUSTOM BURN DRESSING KIT	HERMITAGE HOSPITAL PRODUCTS INC.
K893647	COPOLYESTER FILM DRESSING	TRI-STATE HOSPITAL SUPPLY CORP.
K910944	MEDIFIL	BIOCORE
K913023	SKINTEMP	BIOCORE
K914024	VIADERM	ABS LIFE SCIENCES
K925545	SKINTEMP MODIFICATION	BIOCORE
K935189	E-Z DERM BIOSYNTHETIC WOUND DRESSING	BRENNEN MEDICAL INC.
K950281	MESH MATRIX WOUND DRESSING	BRENNEN MEDICAL INC.
K950032	MEDISKIN(R) SS ZENODERM BIOLOGICAL WOUND DRESSING	BRENNEN MEDICAL INC.
K955506	HYCURE	THE HYMED GROUP CORP.
K970266	KENDALL HYDROPHILIC POWDER WOUND DRESSING	KENDALL HEALTHCARE PRODUCTS CO. DIV.OF TYCO HEALTH
K973170	SIS WOUND DRESSING	COOK BIOTECH INC.
K982597	FIBRCOL PLUS COLLAGEN WOUND DRESSING WITH ALGINATE	JOHNSON & JOHNSON MEDICAL INC.
K984388	HA ABSORBENT WOUND DRESSING	CONVATEC A DIVISION OF E.R. SQUIBB & SONS
K990964	SIGNADRESS DUODERM DRESSING	CONVATEC A DIVISION OF E.R. SQUIBB & SONS
K993948	SIS WOUND DRESSING II	COOK BIOTECH INC.
K000054	FOAM CALCIUM ALGINATE TOPICAL	ADRI

	WOUND DRESSING WITH COLLAGEN	
K002443	COLLAGEN WOUND DRESSING	OASIS RESEARCH LLC.
K011026	FORTADERM WOUND DRESSING	ORGANOGENESIS INC.
K012990	COLLATEK POWDER	BIOCORE MEDICAL TECHNOLOGIES INC.
K020732	SS MATRIX	COOK BIOTECH INC.
K021792	BILAYER MATRIX WOUND DRESSING	INTEGRA LIFESCIENCES CORP.
K022127	AVAGEN WOUND DRESSING	INTEGRA LIFESCIENCES CORP.
K021637	ACELL UBM LYOPHILIZED WOUND DRESSING	ACELL INC
K022854	ACELL UBM HYDRATED WOUND DRESSING	ACELL INC
K030921	COLLAGEN TOPICAL WOUND DRESSING	COLLAGEN MATRIX INC.
K023778	DRESSSKIN	TEI BIOSCIENCES INC.
K040211	MODIFICATION TO: COLLAGEN TOPICAL WOUND DRESSING	COLLAGEN MATRIX INC.
K040558	MODIFICATION TO: COLLAGEN TOPICAL WOUND DRESSING	COLLAGEN MATRIX INC.
K030774	STIMULEN COLLAGEN	SOUTHWEST TECHNOLOGIES INC.
K040314	HEALICOLL	ENCOLL CORP.
K050177	COLACTIVE COLLAGEN WOUND DRESSING	COVALON TECHNOLOGIES INC.
K060456	MEDLINE COLLAGEN WOUND DRESSING	MEDLINE INDUSTRIES INC.
K060888	ACELL POWDER WOUND DRESSING	ACELL INC
K061407	PRIMATRIX DERMAL REPAIR SCAFFOLD	TEI BIOSCIENCES INC.
K061474	COLLAWOUND DRESSING	COLLAMATRIX CO. INC.
K061711	OASIS WOUND MATRIX	COOK BIOTECH INC.
K061494	DERMADAPT WOUND DRESSING	PEGASUS BIOLOGICS INC.
K061746	COLLAGUARD MODEL FCIAFCIBFCICAND FCID	INNOCOLL PHARMACEUTICALS

K070269	MODIFICATION TO COLLAWOUND DRESSING	COLLAMATRIX CO. INC.
K071425	UNITE BIOMATRIX	PEGASUS BIOLOGICS INC.
K072113	INTEGRA FLOWABLE WOUND MATRIX MODEL FWD301	INTEGRA LIFESCIENCES CORP.
K081782	COLLIEVA	INNOCOLL PHARMACEUTICALS
K082103	LTM WOUND DRESSING	LIFECELL CORP.
K081724	HYDROLYZED COLLAGEN WITH 10% CHONDROITIN SULFATE (PSGAG POLYSULFATED GLYCOSAMINOGLYCAN) WOUND GEL	APPLIED NUTRITIONALS
K081635	INTEGRA MESHED BILAYER WOUND MATRIX	INTEGRA LIFESCIENCES CORP.
K083440	PRIMATRIX DERMAL REPAIR SCAFFOLD	TEI BIOSCIENCES INC.
K082869	AWBAT-S AWBAT-D AWBAT-M	AUBREY INC.
K080868	AONGEN COLLAGEN MATRIX	AEON ASTRON EUROPE B.V.
K090812	THERAFORM STANDARD/SHEET	SEWON CELLONTECH CO. LTD.
K090954	ATLAS WOUND MATRIX	WRIGHT MEDICAL TECHNOLOGY INC.
K091338	COLLASORB COLLAGEN WOUND DRESSING	HARTMANN-CONCO INC.
K092926	ACELL MATRISTEM WOUND SHEET	ACELL INC
K092096	ENDOFORM DERMAL TEMPLATE	MESYNTHES LTD
K092805	COLLAGEN SPONGE	INNOCOLL PHARMACEUTICALS
K101546	ENDOFORM DERMAL TEMPLATE	MESYNTHES LTD
K100574	COLLEXA	INNOCOLL PHARMACEUTICALS
K100927	SURGIAID	MAXIGEN BIOTECH INC.
K102946	CORELEADER COLLA-PAD MODEL CS 03030	CORELEADER BIOTECH CO. LTD.
K112409	MATRISTEM WOUND MATRIX	ACELL INC

K112399	UNITE BIOMATRIX	SYNOVIS ORTHOPEDIC & WOUNDCARE
K103648	COLLAGEN POWDER	INNOCOLL PHARMACEUTICALS LTD
K110318	EXCELLAGEN	TISSUE REPAIR COMPANY
K113104	INTEGRA WOUND MATRIX (THIN)	INTEGRA LIFESCIENCES CORPORATION
K112888	MESO WOUND MATRIX	KENSEY NASH CORPORATION
K113866	PORCINE DERMAL XENOGRAFTS PORCINE DERMAL MATRIX	BRENNEN MEDICAL LLC
K112580	COLLAGEN WOUND DRESSING	DALIM TISSEN CO. LTD.
K120339	PROCOLL	INNOCOLL PHARMACEUTICALS
K122325	SKINTEMP II	HUMAN BIOSCIENCES INC.
K122502	BRIDGE EXTRACELLULAR COLLEGEN MATRIX	HARBOR MEDTECH INC.
K120250	FIBRILLAR COLLAGEN WOUND DRESSING	COLLAFIRM LLC
K131286	PRIMATRIX DERMAL REPAIR SCAFFOLD	TEI BIOSCIENCES INC.
K123756	COVAGEN	COVALON TECHNOLOGIES LTD.
K132343	MARIGEN WOUND DRESSING	KERECIS LIMITED
K140510	MIROMATRIX WOUND MATRIX	MIROMATRIX MEDICAL INC.
K140456	BIO-CONNEKT WOUND MATRIX	MLM BIOLOGICS INC.
K134037	PREMVIA	BIOTIME INC.
K140367	ARCHITECT PX EXTRACELLULAR COLLAGEN MATRIX	HARBOR MEDTECH INC.
K143426	Wound Matrix TF	MIROMATRIX MEDICAL INC.
K141738	MEDEOR MATRIX WOUND DRESSING	KENSEY NASH CORPORATION DBA DSM BIOMEDICAL
K140820	XENOMEM WOUND MATRIX	VISCUS BIOLOGICS LLC
K152033	Cook ECM Powder	Cook Biotech Incorporated
K152721	Cytal Wound Matrix	ACELL INC

K153690	PriMatrix Dermal Repair Scaffold	TEI BioSciences Inc.
K153754	MicroMatrix	ACELL INC
K160136	Flowable Wound Matrix	COOK BIOTECH INCORPORATED
K162348	ABCcolla Collagen Matrix	ACRO BIOMEDICAL CO. LTD
K162759	KeraStat(R) Gel	KeraNetics LLC.
K171231	Endoform Topical Matrix	Aroa Biosurgery
K171645	CoMatryx Collagen Wound Dressing 1 gram pouch CoMatryx Collagen Wound Dressing 1 gram vial CoMatryx Collagen Wound Dressing 10 gram bottle	Strukmyer Medical
K172399	MicroMatrix	ACell Inc.
K171842	Geistlich Wound Matrix	Geistlich Pharma AG
K173223	ologen Collagen Matrix	Aeon Astron Europe B.V.
K172593	XCelliStem Wound Powder	StemSys
K180776	Cytal Wound Particulate	ACell Inc.
K181330	NeoMatriX Wound Matrix	NeXtGen Biologics Inc.
K182838	Geistlich Derma-Gide	Geistlich Pharma AG
K182010	ProgenaMatrix	Cell Constructs I LLC
K190528	MariGen Wound Extra	Kerecis Limited
K192725	Cytal Wound Matrix 3-Layer	ACell Inc.
K192346	Scaffolene CL100 Bioresorbable Collagen Matrix	Freudenberg Technology Innovation SE & Co. KG
K191992	PELNAC Bilayer Wound Matrix	Gunze Limited
K192386	KeraStat Cream	KeraNetics
K200413	Symphony	Aroa Biosurgery Ltd.
K193552	InnovaMatrix	Triad Life Sciences Inc.
K201577	MatriDerm	MedSkin Solutions Dr. Suwelack AG
K200502	Myriad Particles	Aroa Biosurgery Ltd.
K210580	InnovaMatrix FS	Triad Life Sciences Inc.
K210024	NeoMatriX Wound Matrix	NeXtGen Biologics Inc.
K210128	INTEGRA Wound Matrix (Macro-Channels)	Integra LifeSciences Corporation
K213092	Cellusheet Cellufil	Human Biosciences Inc.
K213573	PELNAC Wound Matrix	Gunze Limited

Appendix B: Literature Search Terms and Filters for Wound Dressing with Animal-derived Materials

On July 18-19, 2022, literature searches were performed to identify all published articles for wound dressings with animal-derived materials between April 1, 2012 to April 1, 2022 in two databases: PubMed, and EMBASE.

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

Table 5: 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

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

Table 6: 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 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	6,425
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

The articles identified from PubMed and EmBase search were screened and reviewed for eligibility to be included in the review. The searches were limited to publications in English. Only comparative studies on human subjects, with a minimum of 75 patients per study arm, were included in the review. Studies were excluded if they did not report any of the specified outcomes:

- Mortality (all-cause)
- Adverse tissue reactions (local)
- Adverse tissue reactions (systemic)
- Duration of use

The abstracts/titles were first screened to remove irrelevant articles and assessed in detail regarding their eligibility for inclusion/exclusion. The flowchart of article retrieval and selection are detailed in Appendix D.

Appendix C: Literature Evidence Table

Table 7: Studies Included in the Systematic Literature Review for Wound Dressings with Animal-Derived Materials

Study Characteristics	Patient Characteristics	Device Brand/ Manufacturer	Safety Outcomes
Collagen and/or Animal-Derived Wound Dressings (KGN)			
Reference: Lantis et al. 2021[9] Country: USA Study Design: multicenter RCT Purpose: The purpose of this clinical trial was to evaluate the safety and efficacy of a fetal bovine acellular dermal matrix (FBADM) plus standard of care (SOC) for treating hard-to-heal diabetic foot ulcers (DFUs). Length of follow-up: 12 weeks; early termination sue to COVID-19 pandemic Funding Source: Integra LifeSciences Inc., manufacturer of PriMatrix®	Patients (N): 207 patients SOC: 104 patients, FBAMD: 103 patients Age mean (SD): SOC: 58.5 (11.92), FBAMD: 57.6 (11.49) Sex (% male): SOC: 83 (80.6%), FBAMD: 80 (76.9%) Diagnosis: Diabetic foot ulcer Inclusion criteria: ≥18 years of age with Type I or II diabetes; with Investigator-confirmed glycosylated hemoglobin (HbA1c) of ≤12% within 3 months prior to screening visit; at least one diabetic foot ulcer that meets all of the following criteria: • Ulcer has been in existence for a minimum of two weeks, prior to signing Informed Consent for trial participation • Ulcer has been diagnosed as either a partial or full thickness diabetic foot ulcer without tunneling, undermining, sinus tracts or capsule/tendon/bone exposure • Ulcer is either located on the foot or ankle (with no portion above the top of the malleolus)	Intervention: Acellular dermal tissue matrix derived from fetal bovine dermis (FBADM) (PriMatrix, Integra LifeSciences, Princeton, US) plus SOC Comparator: SOC alone All: SOC consisted of sharp debridement, infection elimination, use of dressings and offloading, which is consistent with the treatment guideline that addresses DIME (devitalized tissue, infection/ inflammation, moisture balance and edge preparation). Sharp debridement was mandated in this study during the first week of the screening visit; it was accomplished by removal of all surrounding	Mortality (all-cause): NR Adverse tissue reactions (local): Any AE, n (%): SOC 52 (44.8%), FBAMD 51 (46.4%), p=0.817 Target wound infection: SOC 16 (13.8%), FBAMD 19 (17.2%), p=0.122 Product-related SAE: SOC 0, FBAMD 0 Amputation: SOC 2 (1.9%) FBAMD 2 (1.9%) p=1.000 Adverse tissue reactions (systemic): NR Duration of use, reported as: Median time to closure, days (min, max): SOC 57 (16, 88), FBAMD 43 (22, 93) p=0.362

	• Ulcer size (area) ≥1cm2 and ≤12cm2 post debridement • There is a minimum 1cm margin between the qualifying study ulcer and any other ulcers on the specified foot, post debridement • Subject has adequate vascular perfusion of the affected limb, as defined by at least one of the following: • Ankle–brachial Index (ABI) ≥0.65 or ≤1.2 • Toe pressure (plethysmography) >50mmHg • TcPO2 >40mmHg • Subject or responsible caregiver is willing and able to maintain required applicable dressing changes as well as off-loading for the location of the ulcer. Exclusion criteria: Major exclusion criteria include suspected or confirmed signs/symptoms of gangrene or wound infection as evidenced by redness, pain and purulent drainage on any part of the affected limb; suspected or confirmed osteomyelitis of the foot; history of hypersensitivity to bovine collagen; history of bone cancer or metastatic disease on the affected limb, radiation therapy to the foot, or has had chemotherapy within 12 months of the study Comorbidities, % (n):	callus and non-viable tissue from the base and periphery of the wounds, as evidenced by punctate bleeding. This was followed by the application of moist wound therapy consisting of 0.9% sodium chloride gel. Wounds were then dressed with a non-adherent foam dressing and an outer gauze wrap. An off-loading device (Deluxe Pneumatic Ankle Walker, Medline, US) was dispensed to all patients with their DFUs located on either plantar or lateral surfaces of the foot (i.e., any location experiencing weight-bearing or shear forces). The patient was instructed to wear this device at all times, except during sleeping, bathing or showering. Patients were instructed to wear either the off-loading device or other form of protective wear recommended by the site	

	Cardiovascular: SOC 61 (58.7%), FBAMD 67 (65.1%) Neurological (including neuropathic foot): SOC 68 (65.4%), FBAMD 62 (60.2%) Previous ulcer, amputation, Charcot deformity: SOC 38 (36.5%,) FBAMD 37 (35.9%) Previous history of infection SOC 17 (16.4%), FBAMD 18 (17.5%) Renal disease SOC 10 (9.60%), FBAMD 16 (15.5%)	investigator if the wound was on non-weight-bearing surfaces, such as the dorsum of the foot. Patients whose study ulcer had not healed by more than 30% after the 2-week run-in period were then randomized to either the FBADM plus SOC or the SOC alone groups.	
Reference: Griffin et al. 2019[11] Country: USA Study Design: Retrospective review of the U.S. Wound Registry with propensity score matching Purpose: To evaluate the value proposition of ORC/collagen/silver-ORC dressing and ovine collagen ECM in matched cohorts of patients undergoing treatment for diabetic foot ulcers Length of follow-up: 16 weeks Funding Source: KCI	Patients (N): 844 DFUs ORC: 422 DFUs, ECM: 422 DFUs Age mean (SD): ORC: 59.8 years (12.2), ECM: 59.2 years (12.0) p=0.5238 Sex (% male): ORC: 74.2, ECM: 72.3, p=0.5340 Diagnosis: Diabetic foot ulcers Initial wound area, ORC vs. ECM, median (IQR): 1.5 cm (0.6-6.0) vs. 1.5 cm (0.6-5.6), p=0.8796 Initial granulation score, ORC vs. ECM, n (%): ≥75% and no depth: 39 (9.2) vs. 28 (6.6) ≥75%: 7 (1.7) vs. 4 (1.0) 25%-75% or has red moist tissue: 4 (1.0) vs. 7 (1.7) <25% or dry dark red/pink/poor quality red tissue: 349 (82.7) vs. 358 (84.8) ~0%: 23 (5.5) vs. 25 (5.9) p=0.4569	Intervention: ORC/collagen/silver-ORC dressing (Promogran Prisma Matrix, Systagenix Wound Management Ltd.) Comparator: Ovine collagen ECM dressing (Endoform Natural Dermal Template, Aroa Biosurgery Limited)	Mortality (all-cause): NR Adverse tissue reactions (local): Worsening of DFU, ORC vs. ECM: 15.2% vs. 23.9%, p=0.0013*, favoring ORC Antibiotic use, ORC vs. ECM, n (%): 51 (12.1) vs. 38 (9.0), p=0.1451 Note: Antibiotic use can be a proxy for infection. Adverse tissue reactions (systemic): NR Duration of use: Median time to 75%-100% granulation, ORC vs. ECM: 42 days vs. 60 days, p=0.0109*, favoring ORC Proportion achieving time to 75%-100% granulation, ORC vs. ECM: 4 weeks: 35.0% vs. 32.9%, p=0.05942 8 weeks: 49.1% vs. 43.5%, p=0.1774 12 weeks: 59.7% vs. 50.2%, p=0.0225*, favoring ORC 16 weeks: 63.6% vs. 54.8%, p=0.0325*, favoring ORC Time between first and last application, ORC vs. ECM, median (IQR): 21 days (4.9-63) vs. 21 days (6.0-49.1), p=0.5772

(part of 3M), San Antonio, TX	Inclusion criteria: DFUs with complete data records treated with either ORC/collagen/silver-ORC or oven collagen ECM Exclusion criteria: Cases that could not be propensity score matched Comorbidities, ORC vs. ECM, % (n): Arterial vascular disease: 33.7 (142) vs. 31.5 (133), p=0.5086 Hypertension: 84.8 (358) vs. 82.9 (350), p=0.4539 Peripheral vascular disease: 20.6 (87) vs. 20.9 (88), p=0.9323 Endovascular treatment: 28.4 (120) vs. 26.1 (110), p=0.4395		
Reference: Sabolinski & Gibbons 2018[12] Country: USA Study Design: Retrospective review of a large wound care-specific electronic medical record database (WoundExpert, Net Health) between January 2015 and January 2017 Purpose: To compare the effectiveness of BLCC and acellular FBCD for the treatment of venous leg ulcers	Patients (N): 927 BLCC: 805 (893 wounds), FBCD: 122 (128 wounds) Age mean (SD): BLCC: 69.0 years (14.2), FBCD: 68.3 years (14.9) p=0.80 Sex (% male): NR BLCC: 47.4, FBCD: 54.2 Diagnosis: Venous leg ulcers Number of wounds per patient, BLCC vs. FBCD: Mean (SD): 1.62 (1.13) vs. 1.48 (0.90), p=0.21 Single wound, n (%): 529 (65.7) vs. 87 (71.3) Multiple wounds, n (%): 276 (34.3) vs. 35 (28.7) p=0.21 Inclusion criteria: Received at least one treatment of either BLCC or FBCD on a partial or full thickness venous	Intervention: BLCC (Apligraf, Organogenesis, Inc.) Comparator: Acellular FBCD (Primatrix, Integra)	Mortality (all-cause): NR Adverse tissue reactions (local): NR Adverse tissue reactions (systemic): NR Duration of use: Interval between applications, BLCC vs. FBCD, days: Mean (SD): 20.1 (22.8) vs. 25.2 (19.7) Median: 14.0 vs. 21.0 p<0.01*, favoring FBCD Time to wound closure, BLCC vs. FBCD, weeks: Median: 19 vs. 30, p=0.01*, favoring BLCC Difference between median time: 37%

Length of follow-up: 36 weeks Funding Source: Organogenesis, Inc.	ulcer with location coded as ankle, lower leg, shin, pretibial, or calf; first treatment of BLCC or FBCD received between January 2015 and January 2017; baseline wound areas 1-40 cm2; ulcer duration >1 month prior to first treatment of BLCC or FBCD Exclusion criteria: Ulcers that achieved >40% closure within 4 weeks prior to first treatment with BLCC or FBCD; wounds without baseline or follow-up area measurements; unknown BLCC or FBCD treatment date; wounds that received skin substitute treatments (Apligraf, Primatrix, Dermagraft, Epifix, Theraskin, Grafix, Graftjacket) on or within 28 days of the first treatment with BLCC or FBCD Comorbidities, % (n): NR		
Reference: Yu et al. 2017[10] Country: China Study Design: Open-label, randomized, multiple dose, comparative Purpose: To evaluate the efficacy of a combination therapy of platelet-rich plasma and gelatin hydrogel versus platelet-rich plasma and collagen in	Patients (N): 320 Gelatin: 160, Collagen: 160 Age mean (range): Gelatin: NR years (20-82) Collagen: NR years (23-90) Sex (% male): Gelatin: 63.8, Collagen: 75.0 Diagnosis: Pressure sores Regions of sores, n (%): Sacrum: 108 (33.7) Heel: 90 (28.12) Buttock: 40 (12.5) Lower back: 24 (7.5) Back of head and ear: 20 (6.2)	Intervention: Platelet-rich plasma + Gelatin hydrogel sheet Comparator: Platelet-rich plasma + Collagen ointment (bovine-derived; majority type I collagen and small amount of type III and type V fibers) Note: Calcium chloride and thrombin were added to the platelet-rich	Mortality (all-cause): NR Adverse tissue reactions (local): None observed Adverse tissue reactions (systemic): None observed Duration of use: Healing time, weeks, mean (CI): Gelatin: 6 (96%) Collagen: 5 (96%), p=0.230

wound healing of pressure sores Length of follow-up: 7 weeks Funding Source: NR	Shoulder: 18 (5.6) Elbow: 15 (4.6) Inner knee: 5 (1.5) Inclusion criteria: Sore that has not healed in 6 months, sore that has been unresponsive to conventional treatment in 2 months, 20-90 years old, 1-2 ulcers together whose area ≤20 cm2 Exclusion criteria: Pregnant or breastfeeding, bleeding disorder, uncontrolled sugar levels, ulcers with active infection and saphenofemoral incompetency, continued corticosteroid therapy (prednisone dosage >20mg/day), current anticoagulant therapy and antithrombotics, unwilling to sign consent, discontinued by investigators after developing signs and symptoms of infection Comorbidities, % (n): NR	plasma in each treatment group	
Reference: Marston et al. 2014[13] Country: USA Study Design: Retrospective review of a national wound-specific electronic medical record database (WoundExpert, Net Health) Purpose: To compare the effectiveness of BLCC and an acellular porcine	Patients (N): 1489 BLCC: 1187 (1451 wounds) SIS: 302 (350 wounds) Age mean (SD): BLCC: 69.5 years (13.9), SIS: 69.1 years (14.4) p=0.655 Sex (% male): BLCC: 47.2, SIS: 43.1, p=0.217 Diagnosis: Refractory venous leg ulcer Number of wounds per patient, BLCC vs. SIS: Mean (SD): 1.22 (0.6) vs. 1.16 (0.5), p=0.041* Single wound, n (%): 988 (83.2) vs. 261 (86.4) Multiple wounds, n (%): 199 (16.8) vs. 41 (13.6) p=0.189	Intervention: BLCC (Apligraf, Organogenesis, Inc.) Comparator: SIS (Oasis, Healthpoint)	Mortality (all-cause): NR Adverse tissue reactions (local): NR Adverse tissue reactions (systemic): NR Duration of use: Interval between applications, BLCC vs. SIS, days: Mean (SD): 31.7 (24.1) vs. 12.6 (12.3) Median: 24.5 vs. 8.5 P<0.0001*, favoring BLCC Time to wound closure, BLCC vs. SIS, weeks: Median: 24 vs. 43, p=0.01*, favoring BLCC Difference between median time: 44%

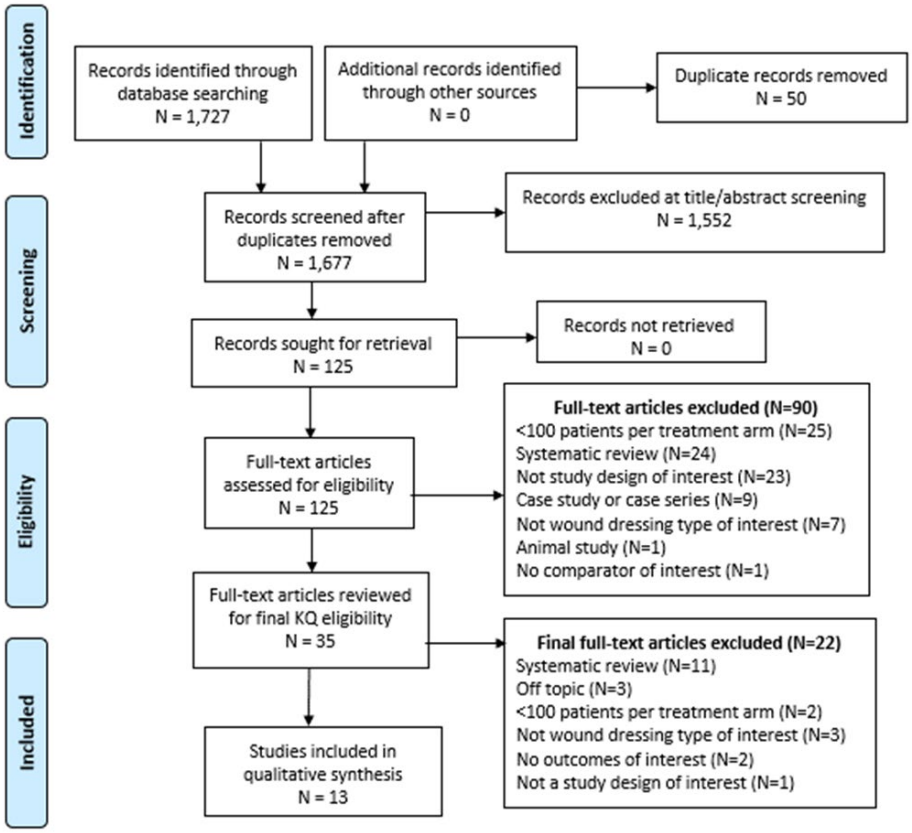
SIS in patients with refractory venous leg ulcers treated between July 2009 and July 2012 Length of follow-up: 36 months Funding Source: Organogenesis, Inc.	Inclusion criteria: Patients who received at least one treatment of BLCC or SIS on a venous ulcer (partial or full thickness) with location coded as ankle, lower leg, shin, pretibial, or calf; baseline wound area 1-150 cm2; ulcer duration >1 month prior to first treatment with BLCC or SIS; wounds closed ≤40% within 4 weeks prior to first treatment with BLCC or SIS Exclusion criteria: Wounds without baseline or follow-up measurements; wounds where date of BLCC or SIS treatment unknown; received either SIS or HFDS on or within 28 days of the first treatment with BLCC; received BLCC or HFDS on or within 28 days of the first treatment with SIS Comorbidities, % (n): NR		

*Statistically significant

Abbreviations: BID: twice per day; BLCC: bilayered living cellular construct; CI: confidence interval; DFU: diabetic foot ulcer; ECM: extracellular matrix; ESR: erythrocyte sedimentation rate; FBCD: fetal bovine collagen dressing; HBsAg: Hepatitis B surface antigen; HFDS: human fibroblast-derived dermal substitute; HIV: human immunodeficiency virus; NR: not reported; ORC: oxidized regenerated cellulose; SD: standard deviation; SIS: small intestine submucosa collagen dressing; TLC: total leukocyte count; USA: United States of America

Appendix D: Flow Diagram of Systematic Literature Review Search Results

Figure 1: Wound Dressing PRISMA



Of the 13 studies resulted from the search for wound dressings, which included hemostatic wound dressings and absorbable synthetic wound dressing, five studies were relevant to wound dressings with animal-derived materials.