Classification of Wound Dressings with Animal-derived Materials Under Product Code "KGN"

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Device Description

- Wound dressings with animal-derived material(s) are intended to cover and protect a wound, to absorb exudate, and to maintain appropriate moisture balance within the wound.
  - The dressing consists either entirely or in part of materials (e.g., decellularized extracellular matrix, collagen, gelatin, keratin) sourced from an animal (e.g., from bovine, porcine, ovine, equine, avian, amphibian or fish sources).
  - The dressing may be derived from organs such as dermis, liver, tendon, intestine as well as from extruded material such as wool or hair.
  - The dressing may be manufactured with other natural or synthetic materials to achieve the final physical state of the dressing

- Wound dressings with animal-derived material (s) are typically present in sheet, pad, gel or powder form.

Device Description

- The animal-derived materials support the intended use of the dressing or to provide or support the physical integrity of the dressings.

- The animal-derived materials 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.

Indications for Use

These devices have been cleared as both prescription and OTC use devices for the following representative indications for use:

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
- 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

Regulatory History

- Wound dressings with animal derived material(s) are a pre-amendments, unclassified device type (i.e., have been in commercial distribution prior to May 28, 1976)

- Currently these devices are being regulated through the 510(k) pathway and are cleared for marketing if their intended use and technological characteristics are “substantially equivalent” to a legally marketed predicate device. Since these devices are unclassified, there is no regulation associated with the product code.

- To date, the FDA has cleared more than 120 devices under the KGN product code.

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.

- 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.

- Since 1998, there have been significant developments, including new technologies and indications for use, and 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.

- In addition, FDA's understanding and experiences with animal-derived materials have further developed since the 1998 panel meeting. 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.

Clinical Background

Disease Characteristics

- There are a 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).

Clinical Background

Currently Available Treatment

- There is a range of standard of care methods, depending on the wound type and wound healing progression.
  - Dressing to cover and protect the wound and maintain a moist wound environment.
  - Compressive dressings, bioengineered dressings, wound dressings with antimicrobials, grafts, negative pressure wound therapy, pressure relief devices, hyperbaric oxygen, and topical drugs.
- Debridement, rinsing, and providing a moist wound environment are generally recommended as part of wound care.

Literature Review

- 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 material(s) under product code “KGN.”
- Literature searches were conducted to identify any relevant articles published between April 1, 2012 and July 18, 2022.
- The searches were limited to publications in English and excluded conference proceedings and abstracts.
- The searches yielded 1727 initial literature references. After duplicate articles were removed, the literature search of the above electronic databases yielded 1677 literature references.
- A total of **five** studies were determined to be relevant to the safety and/or effectiveness of wound dressings with animal derived material(s).

Literature Review – Safety Assessment

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

Literature Review – Effectiveness Assessment

- The first study found no difference in median time to wound closure time between standard of care (SOC) treatment and wound dressings with animal-derived materials.
- In the second and third study, they compared wound dressings with animal derived materials with a bioengineered cellular product (BLLC), which is intended to accelerate the wound healing. Even though BLLC was found more effective than wound dressings with animal derived materials, they are still effective at supporting wound healing.
- The fourth study compared the use of collagen with oxidized regenerated cellulose (ORC). While the data still favored the ORC product, the wound dressing with animal derived material still supported wound healing.
- In the fifth study, they compared wound healing time between collagen and gelatin, which are both animal-derived wound dressings, and found that the healing time is comparable.

Literature Review – Summation

- 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. None of the five studies reported any systemic adverse tissue reactions.
- On the whole, the strength of the evidence base for the literature review is low, given only five studies met the inclusion criteria, and the high potential for bias in retrospective study designs and in studies funded by device manufacturers.

Medical Device Reports

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

Medical Device Reports

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

Medical Device Reports

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

Medical Device Reports

- MAUDE (Manufacturer And User Facility Device Experience) Database reviewed for product code “KGN” from the start of the database through April 01, 2022.
  - The search returned a total of 119 reports. 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.

Medical Device Reports

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

Adverse Events (cont.)	Count
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

Recall History

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

Recall History

Medical Device Recall Database reviewed for product code “KGN”.
Eight (8) recalls (Class II) have been reported to date:

- **Z-2109-2021:** products that failed dose audit after sterilization.
- **Z-1338-2019:** products that failed to meet the stability testing acceptance criteria after 6 months.
- **Z-1243-2019:** intermittent heat seal failures on the outer pouch of some products.
- **Z-0379-2019, Z-0377-2019, Z-0378-2019:** potential for pouch seal failure.
- **Z-0383-2018:** missing pages or extra pages in device labeling.
- **Z-1452-2015:** 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.

Risks

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.
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.

Risks and Mitigations

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

Proposed Classification

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).

Proposed Special Controls

1. Performance testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and chemical characteristics of the device. The following must be provided:
    i. Identity, quantification, and purpose of each component in the finished product;
    ii. Specification and characterization of each component in the finished product; and
    iii. Final release specifications for the finished product.
2. 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.

Proposed Special Controls

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.

Proposed Special Controls

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 medical 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.

Thank You

Questions to Panel - Wound Dressings with Animal-derived Material(s) Under Product Code “KGN”

Tek Lamichhane, Lead Reviewer, OHT4

Question 1 to Panel

FDA has identified the following risks to health 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.
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.

Question 1 to Panel

- Please comment on whether you agree with inclusion of all the risks in the overall risk assessment of wound dressings with animal-derived materials under product code “KGN”.
- In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these wound dressings with animal-derived materials.

Question 2 to Panel

Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if:

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, AND
- the device is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

A device should be Class II if:

- general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, AND
- there is sufficient information to establish special controls to provide such assurance.

Question 2 to Panel

A device should be Class I if:

- general controls are sufficient to provide reasonable assurance of the safety and effectiveness, OR
- insufficient information exists to:
  - determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness, OR
  - establish special controls to provide such assurance, BUT
    - is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, AND
    - does not present a potential unreasonable risk of illness or injury.

Question 2 to Panel

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

As such, FDA believes that Class II is the appropriate classification for wound dressings with animal-derived material(s) cleared under product code “KGN.”

Question 2 to Panel

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

Question 2 to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for wound dressings with animal-derived material(s). Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

1. Performance testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and chemical characteristics of the device. The following must be provided:
   i. Identity, quantification, and purpose of each component in the finished product;
   ii. Specification and characterization of each component in the finished product; and
   iii. Final release specifications for the finished product.
2. 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.

Question 2 to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for wound dressings with animal-derived material(s). Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

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.

Question 2 to Panel

Please discuss whether the identified special controls appropriately mitigate the identified risks to health for wound dressings with animal-derived material(s). Please also discuss whether additional or different special controls are recommended.

Proposed Special Controls

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 medical 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.

Question 3 to Panel

Please discuss whether you agree with FDA's proposed classification of Class II with special controls for wound dressings with animal-derived material(s). If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

End of Panel Questions for Wound Dressings with Animal-derived Materials Under Product Code “KGN”

Tek Lamichhane, Lead Reviewer, OHT4