FDA Executive Summary

Classification of Wound Dressings Combined with Drugs

Prepared for the Meeting of the
General and Plastic Surgery Devices
Advisory Panel
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SECTION I: Introduction / Background

Introduction

Human skin wounds pose substantial risks to patients and increasing challenges to the U.S. public health. The prevalence rate for chronic non-healing wounds is ~2% of the general population (Sen et al., 2009). This prevalence rate is similar to that of heart failure, but unlike heart failure, little is known regarding the outcome of these patients or the comparative effectiveness of the treatment they receive (Berry et al., 2001). An aging population and its requisite medical interventions, the continuing rise in diabetes and obesity, and the increase in traumatic wounds all translate to large increases in skin wounds needing treatment. Patients with the hardest to heal wounds include those with diabetes, sickle cell ulcers, vasculitis, scleroderma, as well as those who are obese (Sen et al., 2009; Carter et al., 2009). Cost of caring for these wounds in the US alone exceeds $50 billion annually, which is 10 times more than the annual budget of the World Health Organization (Kuhn et al., 1992; Hess, 2004; Driver et al., 2010; Gordon et al., 2004). Often, these wounds become infected, interrupting and delaying wound healing and leading to increased treatment times, suffering, risk of severe complications, and expenses (European Wound Management Association (EWMA) 2013). Guo and Di Pietro (2010) estimate that non-healing wounds affect 3-6 million people in the United States (Guo and Di Pietro, 2010). Non-healing wounds are implicated in increased healthcare expenditures estimated at greater than $3 billion per year (Mathieu et al., 2006; Menke et al., 2007). There are a wide variety of dressings available for treating both acute wounds and chronic non-healing wounds. The wound dressing market alone is predicted to reach over $10 billion in 2020 (Wound Dressing Market, 2016) which demonstrates the magnitude of their impact on public health.

Purpose of Meeting

As required by section 513(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Food and Drug Administration (FDA) is convening the General and Plastic Surgery Devices Advisory Panel (the Panel) for the purposes of obtaining recommendations about the classification of devices that are wound dressings combined with drugs (also referred to in this document as "wound dressings containing drugs"), which FDA has grouped under product code[1] "FRO." These products include solid wound dressings, gels, creams, ointments, and liquid wound washes and collectively may be referred to as wound dressings in this document (see Appendix 2 for a list of drugs).

[1] FDA's Center for Devices and Radiological Health (CDRH) uses product codes to help categorize and assure consistent regulation of medical devices. A product code consists of 3 characters which are assigned at the time a product code is generated and is unique to a product type. The 3 characters carry no other significance and are not an abbreviation.

FDA is holding this panel meeting to obtain input on the risks and benefits of wound dressings that are combined with drugs as well as the clinical relevance of certain indications. The Panel will be asked to recommend to FDA whether such wound dressings that are combined with drugs should be classified into Class III (subject to Premarket Approval), Class II (subject to General and Special Controls), or Class I (subject only to General Controls). More than one classification can be considered and recommended for different sub-categories of products within this category. For example, products within this category with different intended uses and/or technology (e.g., composition) may have different risks and benefits and warrant different classifications. The Panel will be asked to discuss the types of evidence (including clinical evidence) that would be helpful to support certain indications as well as appropriate controls necessary to mitigate the risks to health and assure the safety and effectiveness of these wound dressings.

Structure of Meeting

The panel meeting will be held over a period of two consecutive days. The **first day** of the panel meeting will focus on current clinical practice for wound care and a discussion around the available scientific evidence regarding clinical practice. This discussion will broadly cover the range of wound types (both acute and chronic) and variety of wound dressing products that are commercially available. The discussion will primarily focus on the scientific evidence concerning the risks and benefits of wound dressings that are combined with drugs, with special focus on those that use antimicrobials, given the risk of antimicrobial resistance and applicability of antimicrobial stewardship practices to wound care (Core Elements of Hospital Antibiotic Stewardship Programs, 2016; CMS Issues Proposed Rule that Prohibits Discrimination, Reduces Hospital-Acquired Conditions, and Promotes Antibiotic Stewardship in Hospitals, 2016; and Nursing Home Antimicrobial Stewardship Modules, 2014). For the purposes of this document, the term *antimicrobials* is used broadly to capture antibacterials, antifungals and antiseptics, although in general, antiseptics are used to clean skin. The **second day** of the panel meeting will focus on specific sub-categories of wound dressing products under product code “FRO” and classification recommendations. Risks and benefits of wound dressings combined with drugs as well as potential methods for evaluating safety and effectiveness will be an essential part of the discussion. The Panel will be asked to provide classification recommendations for wound dressings combined with drugs, in light of their risk/benefit profiles.

SECTION II: Regulatory History and Background

A. Classification History

1. Wound Dressings Combined With Drugs

Wound dressings that are combined with drug(s)[2] together are generally regulated as combination products. A combination product is comprised of two or more constituent parts (i.e., drug/device[3], biologic/device, drug/biologic, or drug/device/biologic (21 CFR 3.2(e)). A combination product is assigned to an FDA center that will have primary jurisdiction for the combination product's premarket review and regulation based on its "primary mode of action" (PMOA). PMOA is the single mode of action of a combination product that provides the most important therapeutic action of the combination product (21 CFR 3.2(m)). CDRH generally has primary jurisdiction over the combination wound care dressings.

Wound dressings that are combined with drugs are a pre-amendment, unclassified device type.[4] This means that this device type was marketed before the Medical Device Amendments of 1976, but has not yet been affirmatively classified by FDA. These devices have generally been subject to premarket review through the 510(k) pathway and have been cleared for marketing if their indications for use and technological characteristics are "substantially equivalent" to a legally marketed predicate device.

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[2] Section 201(g)(1) of the FD&C Act defines *drugs*, in part, by their intended use, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals."

[3] Section 201(h) of the FD&C Act defines medical devices (devices), in part, as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part of accessory, which is…intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals (ref. 201(h)(2)), or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes (ref. 210(h)(3), emphasis added). Under this definition, a product (or a constituent part of a combination product) is not a device if it "achieve[s] its primary intended purpose through chemical action within or on the body.

[4] Some products in this category may be regulated only as "devices" and not combination products, even though they contain components that are regulated as "drugs" in other contexts. FDA may also re-evaluate whether some wound dressings, such as certain washes or gels, are properly regulated as device-led combination products, or instead only meet the statutory definition of a drug in the FD&C Act, and whether other wound dressings should be regulated as drug-led combination products instead of device-led combination products. Considerations regarding such would be discussed in the future (e.g., in a proposed rule). FDA does not intend to ask the Panel to opine on these issues regarding classification of products as drugs, devices, or combination products.

2. Other Wound Dressing Devices Classified by FDA

Following enactment of the Medical Device Amendments of 1976, FDA issued a proposed rule for classification of several wound dressing types in the *Federal Register* of January 19, 1982 (47 FR 2810). While preparing the final rule to classify these devices, FDA found that the device names, identifications, and classifications of these wound dressing devices needed further clarification and issued a second proposed rule on September 19, 1989 (54 FR 38600). Based on the comments received to a proposed rule published on September 19, 1989, recommendations of a classification panel held on November 17, 1998, and wound care and product use current at that time, on October 5, 1999, FDA published final rules for regulation of four types of wound dressings as Class I medical devices (64 FR 53927). These are:

- Nonresorbable gauze/sponge for external use
- Hydrophilic wound dressing
- Occlusive wound dressing
- Hydrogel wound dressing and burn dressing

The identification and classification of these wound dressings are published in the Title 21 of the Code of Federal Regulations (21 CFR) and provided in Attachment 1. The identification for these four wound dressing types specifically excludes wound dressings that contain added drugs such as antimicrobial agents. The final rules did not address wound dressings that contain added drugs such as antimicrobial agents, added biologics such as growth factors, or composed of materials derived from animal sources.

On October 16, 2009, FDA classified as Class II the wound dressing with poly(diallyl dimethyl ammonium chloride) (pDADMAC) additive through the de novo classification pathway. The identification and classification of this wound dressing is published in 21 CFR 878.4015 and provided in Attachment 1. As stated in the identification for this wound dressing and the associated special controls guidance document (Class II Special Controls Guidance, 2009), this is a dressing type where the pDADMAC additive is permanently bound to the textile substrate. The pDADMAC is a high-charge density cationic polymer with antimicrobial activity.

Wound dressings, whether combined with drugs or not, only fall within these classified types of wound dressings or within the unclassified pre-amendments type categorized under product code FRO if they have the same intended use as another device within these types; wound dressings that are not substantially equivalent to Class I, Class II, or unclassified wound dressings are automatically Class III under section 513(f)(1) of the FD&C Act. For example, FDA has determined wound dressings intended to accelerate the normal rate of wound healing, serve as a replacement for full-thickness skin grafting (e.g., artificial skin substitute), or treat

full-thickness (3rd degree) burns to be Class III medical devices. An example of a Class III wound dressing is the Integra Omnigraft Dermal Regeneration Matrix that was approved through premarket approval (PMA) (submission number P900033).[5]

3. Summary of Previous Classification Panel Meeting

The General and Plastic Surgery Devices Panel met on August 25 and 26, 2005, to provide advice and recommendations to FDA on the classification of five unclassified pre-amendment devices, including wound dressings that contain drug(s).[6] FDA presented information on wound dressings that contain drugs (e.g., silver, bismuth, or chlorhexidine containing wound dressings), including certain risks of use, and potential risk mitigation measures. Following discussion, the panel voted unanimously to recommend that FDA classify wound dressings with a drug as Class II medical devices with special controls, requiring 510(k) premarket notification.

FDA recognizes that there has been an evolution in wound care practices as well as in product technology, product composition, indications for use, and knowledge of risks to health (such as antimicrobial resistance) from those discussed at a 2005 panel meeting. Therefore, FDA is convening this classification panel to discuss the current landscape of product technology, indications for use, safety and effectiveness, and risks to health, on which to base classification of wound dressings that contain drug(s).

[5] Additional information on this PMA submission, including a Summary of Safety and Effectiveness Data, can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P900033S042.

[6] Additional information on this panel meeting, including executive summary and transcript, can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=552.

B. Product Overview and Scope

1. Introduction

Unclassified wound dressings that contain drug(s) that are under the product code FRO[7,8] have generally been regulated through the 510(k) pathway. More than 700 510(k) submissions have been cleared to date.[9] Listings of 510(k) submissions that have been cleared are available on the FDA website.[10] Wound dressings that contain drug(s) can be subcategorized into three broad categories based on their physical form:

- Solid wound dressings
- Gels, creams, ointments
- Liquid wound washes

The graphic below provides visual representation of the three subcategories of wound dressings that contain drug(s).

[7] Wound dressings with or without an added drug or biologic that are intended to provide hemostasis through accelerated blood clotting when combined with manual compression are unclassified wound dressings under product code FRO. These wound dressings are outside of the scope of this panel meeting. FDA intends to address these separately.

[8] Wound dressings composed of animal derived materials without added drug(s) or biologic(s) are unclassified wound dressings under product code KGN. These wound dressings are outside of the scope of this panel meeting. FDA intends to address these separately.

[9] These 700 510(k) submissions do not correlate to 700 individual wound dressing products as some submissions may regard multiple, similar wound dressings or be submissions for modifications to previously cleared wound dressings.

[10] See http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.

2. Product Description

Solid wound dressings are composed of various synthetic or naturally derived materials and can be biodegradable or non-biodegradable. They can be in the form of woven or non-woven fabric pad, foam, or as a hydrogel that has sufficient structural integrity to hold a physical form, such as a scaffold or matrix. Some dressings are multilayered, with each layer made of a different solid form, such as a four-layered dressing with a woven layer, foam layer, hydrocolloid layer, and occlusive adhesive backing layer. The types of materials used in dressings include polyester, nylon, poly(vinyl alcohol), alginate, collagen, poly(ethylene glycol), and poly(lactic-co-glycolic acid). Typically these dressings contain added antimicrobials such as silver, bismuth, chlorhexidine, polyhexamethylene biguanide (PHMB), and antimicrobials (e.g., bacitracin). In some cases, wound dressings containing antimicrobials have been cleared with claims that they "enhance the microbial barrier function of the wound dressing product by minimizing the passage of microbes through the dressing material" or are "intended to minimize microbial growth within the dressing while in use to cover a wound."

Wound gels, creams, and ointments are amorphous and can have high water content with thickening agents or consist of an oil-water emulsion. Many of these wound gels, creams, and ointments contain plant derived materials, such as shea butter, avocado oil, or aloe vera. These products typically contain added antimicrobials such as paraben based preservatives[11], silver, or PHMB. These products are generally packaged in tubes or containers that can be for single use only or labeled for multiple use after the package has been opened. These products are not typically terminally sterilized. Products have been cleared with antimicrobial preservatives to minimize microbial growth during shelf storage or from multiple uses after the package has been opened. Products that do not contain antimicrobials are sometimes terminally sterilized and labeled for single use.

Wound wash solutions are liquid in form and are typically water or saline based. These wound wash solutions may contain various salts or surfactants. These products typically contain added antimicrobials such as hypochlorous acid/sodium hypochlorite, silver, or PHMB. They are generally packaged in bottles with plain caps or pump sprays. These products are not typically

[11] In the context of wound dressings, the term *preservatives* has historically been used to prevent or retard the deterioration of the dressing or support the device function of the dressing. This is different than how preservatives are defined in the common pharmaceutical sense, which is a substance that prevents or inhibits microbial growth and may be added to pharmaceutical preparations for this purpose to avoid consequent spoilage by microorganisms. Nonsterile dosage forms may have preservatives added to protect them from growth of microorganisms inadvertently introduced during or subsequent to the manufacturing process. In the case of sterile articles packaged in multiple-dose containers, antimicrobial preservatives are added to inhibit the growth of microorganisms that may be introduced from repeatedly withdrawing individual doses.

terminally sterilized. Products have been cleared with antimicrobial preservatives to minimize microbial growth during shelf storage or multiple uses after the package has been opened. Products that do not contain antimicrobials are sometimes terminally sterilized and labeled for single use. Some products may contain antimicrobials but also be terminally sterilized.
The Panel will be asked to comment on the clinical relevance of the use of antimicrobials in these products to serve as a preservative during shelf storage, enhance bacterial barrier of the dressing product while in use on a wound, or minimize colonization of the dressing material while in use on a wound.

A listing of ingredients that have been present in cleared wound dressings under product code "FRO" can be found in Appendix 2. While the majority of wound dressing products under product code "FRO" contain antimicrobials, there are wound dressings under this product code that contain other types of drugs such as lidocaine and hydrocortisone. The ingredients presented in Appendix 2 may be generally categorized into drugs (e.g., bacitracin, chlorhexidine, iodine, hydrocortisone, lidocaine); chemicals that may be identified as "inactive ingredients" in drug products [12] (e.g., benzalkonium chloride, calcium carbonate, glycerol, methyl salicylate, parabens); chemicals with antimicrobial activity (e.g., crystal violet, hypochlorous acid, ozone, silver); plant derived materials (e.g., aloe vera, oak extract, tea tree oil); and other additive components (e.g., betaine, chromium chloride, ceramide, sodium tetraborate).[13]

[12] FDA Inactive Ingredient Search for Approved Drug Products: http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm.

[13] Please note that some products contain unapproved drugs.

3. Indications for Use

The Indications for Use (IFU) statement generally identifies the condition and patient population for which a device is to be used. The range of indications for use statements cleared through 510(k) submissions varies among the three subcategories of wound dressings that contain drugs under product code FRO.

Solid wound dressings have been cleared, for example to provide or support a moist wound environment, absorb wound exudate, and protect against external contamination. These dressings are typically cleared for use on a variety of wounds, including traumatic wounds, partial thickness burns, ulcers (e.g., venous stasis ulcers, diabetic foot ulcers, arterial ulcers), or surgical wounds. These wounds may or may not be colonized with microbes or be infected. Some dressings are cleared for use to cover and protect catheter insertion sites or other percutaneous device insertion sites (e.g., drains, orthopedic external pins). Some are cleared for management of infected wounds. Some are cleared to provide an antimicrobial "barrier to bacterial penetration of the dressing as this may help reduce infection" or for the "control of wound bacteria within [the dressing that] may help reduce the risk of wound infection".

Wound gels, ointments, and creams have been cleared for use, for example to provide or support a moist wound environment. These dressings are typically cleared for use on a variety of wounds, including traumatic wounds, partial thickness burns, ulcers (e.g., venous stasis ulcers, diabetic foot ulcers, arterial ulcers), or surgical wounds. Some products are cleared to relieve the symptoms of skin irritations, such as dryness, itching, and pain, by providing a moist wound environment. The types of skin irritations include various types of dermatoses (e.g., radiation dermatitis, seborrheic dermatitis). Some claim to "maintain a moist environment that is conducive to healing, by either absorbing wound exudate or donating moisture while delivering antimicrobials that inhibit the growth of microorganisms" and are intended for use in wounds such as stage I-IV pressure ulcers, partial and full thickness wounds, diabetic foot and leg ulcers, post-surgical wounds, first and second degree burns, and grafted and donor sites. Some claim to specifically "inhibit the growth of bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Serratia marcescens*, *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis*, and fungi such as *Candida albicans* and *Aspergillus niger*" within the gel, ointment or cream.

Wound wash solutions have been cleared for use, for example to rinse or irrigate a wound to remove foreign material, such as debris and wound exudate. Additionally, they have been cleared for irrigating away microbes, debris and exudate from the wound. These products are typically cleared for use on a variety of wounds, including traumatic wounds, partial thickness

burns, ulcers (e.g., venous stasis ulcers, diabetic foot ulcers, arterial ulcers), or surgical wounds. Some include broad-spectrum antimicrobials to "inhibit the growth of microorganisms within the product" such as "*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Escherichia coli*, methicillin-resistant *Staphylococcus aureus*, and *Candida albicans*." Within each of these three subcategories, for the indicated wound types described above, these products are typically indicated for prescription use. The same product may also be indicated for over-the-counter (OTC) use where OTC use is limited to use *only* for use on minor types of wounds, such as minor cuts, minor scalds and burns, minor abrasions, or minor lacerations. OTC use wound dressing products are not indicated for use on more serious acute and chronic wounds.

Some wound dressing products may be cleared for use on infected or colonized wounds to create a moist wound environment for these wounds, or rinse debris from these wounds. However, these products are not cleared for use as a treatment for wound infection.

The specific examples presented above are not necessarily representative of the most commonly cleared indications and claims, but are provided to illustrate the range of cleared statements. Example IFU statements that have been cleared for wound dressings under product code FRO can be found in Appendix 3.

FDA recognizes that science and clinical practice have evolved and indications for use that have been cleared for certain wound dressings containing drugs may not be clinically relevant or supported by available evidence. We also believe there are instances when the indications are too vague or broadly encompassing, and do not correlate to clinical practice.

The Panel will be asked to comment on the clinical benefits of these products and FDA will be seeking input from the Panel regarding appropriate indications for use for these products based on current science, clinical practice and available evidence.

C. Typical Content of 510(k) Submissions

Typical content for a 510(k) submission includes a complete device description, IFU statement, draft labeling, and testing to demonstrate substantially equivalent safety and effectiveness as compared to the identified predicate device. This does not necessarily include evidence that independently demonstrates the clinical benefit of a specific product.

The types of testing regarding safety include toxicological risk analysis and biocompatibility evaluation for potential cytotoxicity, irritation, and sensitization response. Depending on material composition and toxicological risk analysis, additional biocompatibility evaluation such as chronic toxicity, systemic toxicity, or genotoxicity testing may be necessary. Animal testing to demonstrate that wound healing is not delayed due to use of the wound dressing product may also be needed. Clinical studies to evaluate product safety are not typically necessary but can be conducted to evaluate biocompatibility response, such as irritation or sensitization, in human subjects.

Evidence regarding product performance typically consists of bench testing, such as tests demonstrating the ability of dressing material to absorb fluids or minimization of water loss through dressing material, or material strength testing. For products that contain antimicrobials, testing regarding antimicrobial effectiveness, including microbial barrier effectiveness, typically consists of quantitative *in vitro* assays. Data to support shelf stability has also generally been necessary to show substantial equivalence as the components in wound dressings are generally sensitive to degradation during shelf storage. Animal or clinical studies to evaluate product effectiveness are not typically needed to demonstrate substantial equivalence. Animal studies have typically been conducted to evaluate wound healing. Clinical studies may be needed to support substantial equivalence for certain indications, such as a reduction in the incidence of catheter related bloodstream infections.

SECTION III: Clinical Practice Guidelines

1. Clinical Practice Guidelines Regarding Wound Care

The wide variety of wound types is associated with a range of standard of care methods, depending on wound type and phase of wound healing progression. Various organizations have published clinical guidelines providing care recommendations. Some of these organizations may be corporate-sponsored. This section reports on the findings of wound care clinical guidelines published by national and international organizations. Representative clinical guidelines for wound care published by the following organizations are presented below:

A. American Burn Association (ABA)
B. American Society of Plastic Surgeons (ASPS)
C. Infectious Diseases Society of America (IDSA)
D. American Academy of Dermatologists (AAD)
E. The Wound Healing Society (WHS)
F. Center for Disease Control Guideline for the Prevention of Intravascular Catheter-Related Infections (CDC)

Although these guidelines target different types of wounds, in general, these guidelines recommend debridement, rinsing, and providing a moist wound environment as part of wound care. Recommendations for dressing selection are based on patient-specific wound care needs such as the need for exudate management or prevention of fluid loss. Topical antimicrobials/anti-infectives are ***not*** typically recommended for wounds that do not exhibit clinical signs of infection. Most guidelines do not specify the use of a particular type of wound dressing, and many conclude that there is little difference in effectiveness in terms of wound healing outcomes between dressing types (including comparison of dressings that do or do not contain antimicrobials). Excerpts from these guidelines as they relate to wound care with wound dressings are summarized below.

A. American Burn Association: Practice Guidelines (2001)

The American Burn Association (ABA) published in 2001 its evidence based practice guidelines for the management of acute burn injuries.[14] The ABA task force conducted a comprehensive literature search in this area, followed by review and grading of clinical literature. ABA adhered to level of evidence (LOE) review criteria for ranking review research in the development of the acute burn 'practice guidelines.' At the time of writing the 2001 guidelines, ABA reported that there were few objective studies that supported even the most widely practiced principles in

[14] See http://www.ameriburn.org/PracticeGuidelines2001.pdf.

burn care, so many of the recommendations as "options" instead of as guidelines or standards of care that indicate a higher LOE.

Worldwide there is in incidence of 11 million people per year with burn injuries sufficient to seek medical attention – placing burns as the fourth most common cause of injury and resulting in a significant utilization of health care (WHO, 2014). According to the national Center for Health Statistics 90% of the 1.25 million burn injuries occurring annually do not require hospitalizations (Brigham and McLoughlin, 1996). For partial-thickness burns being managed in an outpatient setting, ABA guidelines state that wound management includes gentle and periodic cleansing of the burn. Occlusive dressing should be used on the wound to provide a covering for the wound that mimics the barrier function of epithelium.

In patients with limited, partial-thickness burns (e.g., second degree burns) that are managed in an outpatient setting, the guidelines state that infection is uncommon. Guidelines recommend against use of prophylactic antibiotics to protect against cellulitis or sepsis. They also state that there is no evidence that use of topical antimicrobial agents in initial management of minor burns reduces the incidence of infection.

Reference to published literature is provided within the guidelines with the following conclusions:

- No significant difference in overall wound healing rates between non-antibacterial and antibacterial impregnated dressings
- Infection rate was not influenced by use of topical penetrating antibacterial agents or topical non-penetrating antibacterial agent when compared to fine mesh gauze with petrolatum

B. American Society of Plastic Surgeons: Clinical Practice Guideline – Chronic Wounds of Lower Extremity (2007)

American Society of Plastic Surgeons (ASPS) guidelines[15] provide general advice that chronic wounds of the lower extremity be treated with a protocol emphasizing debridement, pressure relief, infection control, and management of exudates. ASPS graded the clinical practice recommendations based on the level of evidence present in literature consensus of the ASPS Health Policy Committee. The practice guideline was based on a critical appraisal of the studies

[15] See http://www.plasticsurgery.org/Documents/medical-professionals/health-policy/evidence-practice/Evidence-based-Clinical-Practice-Guideline-Chronic-Wounds-of-the-Lower-Extremity.pdf.

the literature represented, and each study was assigned a corresponding level of evidence depending on the quality and type of each study: diagnostic, prognostic or therapeutic research.

ASPS guidelines recommend that following wound debridement, irrigation with saline should be considered. In terms of wound dressings, it is recommended that dressings should ensure a moist wound environment while readily absorbing wound exudate. Dressing removal should be atraumatic and minimally painful. Dressing care should be patient centered and individualized. These guidelines conclude that, when compared to traditional moist saline gauze, no dressing or device has yet been proven as superior. The types of dressings cited as being available to the wound care practitioner include gauze, foam, hydrocolloid, and hydrogels, bioactive dressings (e.g., topical antimicrobials, bioengineered composite skin equivalent, bilaminar dermal regeneration template, and recombinant human growth factor).

ASPS guidelines state that there is insufficient evidence to support the routine use of topical antimicrobials in wound dressings, note the risks of antimicrobial resistance and contact dermatitis when using antimicrobials, and recommend close monitoring of wounds for any adverse response. ASPS point to the dearth of evidence directly examining the benefit of oral versus parenteral antimicrobial strategies (i.e., topical administration) in treating infected chronic wounds. Additionally, while numerous studies have reported that common microorganisms exist and can be cultured from chronic wounds, there is little evidence regarding the deleterious effects of colonization on wound healing. This lack of evidence and the risk of antimicrobial resistance and contact dermatitis suggest that judicious use of antimicrobial topical applications should be exercised. Appropriate antimicrobial intervention (such oral antimicrobials) is recommended in situations when infection is confirmed or highly suspected. For mild to moderate infections, surgical debridement and narrow-spectrum antimicrobials are recommended. Wound infections that are severe and/or complicated by critical limb ischemia are generally considered to need hospitalization, parenteral broad-spectrum antimicrobial, and surgical intervention.

C. Infectious Diseases Society of America: Clinical Practice Guideline for Diagnosis and Treatment of Diabetic Foot Infections (2012)

In its guidelines[16] regarding wound care for diabetic ulcers, the Infectious Diseases Society of America (IDSA) recommends a goal of creating a moist wound environment to promote

[16] See http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/2012%20Diabetic%20Foot%20Infections%20Guideline.pdf.

granulation, autolytic processes, angiogenesis, and more rapid migration of epidermal cells across the wound base. Selection of wound dressing is based on the wound bed characteristics, and due to their heterogeneous nature, no single dressing is suitable for all types of diabetic foot wounds. The guidelines include the following list of commonly used dressing types:

- Continuously moistened saline gauze: for dry or necrotic wounds to aid in mechanical debridement
- Hydrogels: for dry and or necrotic wounds and to facilitate autolysis
- Films: occlusive or semiocclusive for moistening dry wounds
- Alginates: for drying exudative wounds
- Hydrocolloids: for absorbing exudate and to facilitate autolysis
- Foams: for exudative wounds

IDSA guidelines caution that currently, there is insufficient evidence to recommend one specific dressing type over another, although some data support the effectiveness of hydrogels, and clinicians should base dressing selection on wound location, size, and depth, amount of exudate, presence of infection or necrosis, and the condition of the surrounding tissue. Diabetic foot ulcers to heal properly require patient–specific wound dressing and off-loading of pressure.

IDSA noted in its 2012 *Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections* that the limited available evidence does not support using antibacterial therapy for treating clinically uninfected wounds, either to enhance healing or as prophylaxis against clinically overt infection. Wounds without evidence of soft tissue or bone infection do not require antimicrobial therapy. Infected wounds should be treated after debridement with targeted antimicrobials selected for sensitivity based on a tissue aerobic and anaerobic culture. With respect to topical antimicrobials, the IDSA Guidelines also state that the controversial concept of excess wound bioburden has led to the increasing use of antimicrobials, particularly topical antiseptics (e.g., cadexomer iodine) and silver-based dressings, despite a lack of evidence demonstrating an advantage for these dressings over conventional therapy, and that, in addition to their expense and potential for causing local adverse effects, use of these antimicrobials may promote the emergence of bacterial resistance (IDSA, 2012).

D. American Academy of Dermatologists: Clinical Guidelines - Atopic Dermatitis: Nonpharmacologic Interventions Recommendations (2014)

American Academy of Dermatologists (AAD) guidelines[17] state that the application of moisturizers should be an integral part of the treatment of patients with atopic dermatitis (AD) as there is strong evidence that their use can reduce disease severity and the need for pharmacologic intervention. Topical moisturizers are recommended for use when the varying amounts of emollient, occlusive, and/or humectant ingredients provide the main benefits to combat xerosis and transepidermal water loss. The types of ingredients found in these topical moisturizers include emollients (e.g., glycol and glyceryl stearate, soy sterols), occlusive agents (e.g., petrolatum, dimethicone, mineral oil), and humectants (e.g., glycerol, lactic acid, urea). In addition, a number of clinical trials are cited to have shown that these topical moisturizers lessen symptoms and signs of AD, including pruritus, erythema, fissuring, and lichenification.

Prescription emollient devices (PEDs) are identified as a class of topical agents designed to target specific defects in skin barrier function observed in AD. They include preparations containing palmitoylethanolamide, glycyrrhetinic acid, or other hydrolipids. Although there is some evidence that PEDs also lessen symptoms and signs of AD, including xerosis and inflammation, they have only been tested in a small number of controlled studies. Moisturizers containing ceramides and/or filaggrin breakdown products that are available over the counter are also mentioned. Head-to-head trials between specific moisturizing products are noted to be few in number, and those performed to date have not demonstrated one to be superior to others, including the PEDs.

E. The Wound Healing Society: Chronic Wound Care Guidelines (2006)

The Wound Healing Society (WHS) guidelines[18] recommend the use of dressings that maintain a moist wound healing environment for venous ulcer, pressure ulcer, diabetic ulcer, and arterial insufficiency ulcer. These guidelines are based on a panel consensus that reviewed scientific literature on wound management and treatment and provides recommendations with three grades of LOE to demonstrate the weight of the evidence found in the literature. These guidelines state that dressing selection should take into consideration the amount of exudate management needed and the need for dressings that can stay in place to minimize shear stress and damage to fragile tissues.

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[17] See https://www.aad.org/practice-tools/quality-care/clinical-guidelines/atopic-dermatitis.

[18] See http://woundheal.org/documents/final_pocket_guide_treatment.aspx.

Wound debridement and cleansing is recommended with use of neutral, non-irritating, non-toxic cleansing solutions that results in minimal chemical and/or mechanical trauma, such as sterile saline or water (non-toxic surfactant solution may also be helpful). The guidelines state that wound antiseptic agents (e.g., hydrogen peroxide, hypochlorite solution, acetic acid, chlorhexamide, povidone/iodine, cetrimide) have antibacterial properties, but are all considered toxic to healthy granulation tissue.

Beyond maintaining moist wound healing environment, the guidelines provide the following information for consideration when deciding on treatment options:

- For venous ulcers, bilayered artificial skin with compression therapy is better than compression and simple dressing.
- For diabetic ulcers, selective use of adjuvant agents (topical, device and/or systemic) is recommended after evaluating a patient and their ulcer characteristics, and when there is a lack of healing progress in response to more traditional therapies. Platelet-derived growth factor (PDGF) is effective for diabetic neurotrophic foot ulcers.
- For arterial insufficiency ulcers, topical antimicrobial dressings may be beneficial in management of chronically/heavily colonized wounds, decreasing their bacterial load and helping wound healing.
- For arterial insufficiency ulcers, there is evidence that autografts, allografts, and extracellular matrix replacement can accelerate the closure of wounds, but further study is required.

F. Center for Disease Control (CDC): Guidelines for the Prevention of Intravascular Catheter-Related Infections (2011)

CDC guidelines (O'Grady et al., 2011) list several strategies for prevention of catheter-related infections. With respect to catheter site dressing regimens, the guidelines recommend use of a povidone iodine antiseptic ointment or bacitracin/gramicidin/polymyxin B ointment for dialysis catheter exit sites (only if the ointment does not interact with the material of the catheter per manufacturer's recommendation). However the guidelines recommend use of a chlorhexidine-impregnated sponge dressing for temporary short-term catheters in patients older than 2 months of age if the central line associated blood stream infection rate is not decreasing despite adherence to basic prevention measures, including education and training, appropriate use of chlorhexidine for skin antisepsis, and maximal sterile barrier precautions. No recommendation for other types of antimicrobial wound dressings are made. The guideline also recommends using a chlorhexidine-impregnated sponge dressing for certain situations based

Category 1B evidence; no recommendations are made for other types of chlorhexidine dressings (O'Grady et al., 2011).

2. Clinical Practice Guidelines Regarding Topical Antimicrobial Use

Some clinical guidelines suggest that topical antimicrobials may be beneficial in certain situations, including in non-healing wounds when the classic signs and symptoms of infection are absent but when there is a clinical suspicion of increased bacterial bioburden (Wound Management in Diabetic Foot Ulcer, 2013; Harding et al., 2015; Robson et al., 2006). In general, the guideline states that in such situations, topical antimicrobials (either alone or as an adjunctive therapy to systemic therapy) have the potential to reduce bacterial load (or bioburden) and may protect the wound from further contamination and prevent spread of infection to deeper tissues. They further state that when the bacteria in a wound cause problems, intervention is required to prevent deterioration and facilitate wound healing.[19] There are similar reports for iodine dressings, which may be used as adjunctive antimicrobial agents when other options are limited (Broussard et al., 2013).

General consensus is lacking in clinical guidelines as to whether to use antimicrobial dressings (and topical antimicrobials in general) in uninfected wounds. Some guidelines recommend against the use of antimicrobial dressings in uninfected wounds. The International Working Group on the Diabetic Foot (IWGDF) issued a guidance in 2015 stating: "Do not select a specific type of dressing for a diabetic foot infection with the aim of preventing an infection or improving its outcome (Lipsky et al., 2016)." This view is consistent with recommendations 43 and 19 of the 2012 IDSA clinical practice guidelines for diabetic foot infections, which state: "We do not advocate using topical antimicrobials for treating most clinically uninfected wounds" (IDSA, 2012).

Although the advantages of topical therapy include the ability to deliver a high local concentration with small doses of the agent while reducing risks of systemic side effects, it is not clear whether antimicrobial agents impregnated in a dressing applied to an infected wound can deliver the concentrations needed to effectively treat the infected wound (Abbas et al., 2015). For more discussion on concentration, see the section on Complicating Wound Treatment below) (EWMA, 2013). Additionally, the 2012 IDSA clinical guidelines for diabetic foot infection note that the available evidence does not demonstrate any benefit to using silver-based dressings for clinically infected wounds (IDSA, 2012).

[19] See also http://www.wuwhs.org.

For venous leg ulcers (VLUs), the clinical practice guidelines published in 2014 by the Society for Vascular Surgery and the American Venous Forum (Clinical Practice Guidelines on the Management of Venous Leg Ulcers) state that “we recommend against the routine use of topical antimicrobial-containing dressings in the treatment of noninfected venous leg ulcers.”

SECTION IV: Assessment of Data on Antimicrobial Clinical Effectiveness

Assessment of Data of Antimicrobial Clinical Effectiveness

This section contains a review of published literature to provide a general understanding of the types of effectiveness information that has been published on the use of antimicrobial wound dressing products in treating specific types of wounds. Evidence related to specific wound types and wound care methods (diabetic foot ulcers, venous leg ulcers, burns, surgical wounds, catheter insertion sites, chronic wounds, and wound irrigation) is discussed.

Data to Evaluate Clinical Benefit: Focus on Antimicrobial Wound Dressings

FDA undertook a review of the scientific literature available via PubMed, focusing on publications that systematically assessed randomized controlled clinical trials (RCTs) in human subjects that compared the use of antimicrobial dressings with non-antimicrobial controls and reviewed clinical practice guidelines on wound dressings.[20] The goals of this review were to assess the clinical evidence supporting the use of antimicrobial dressings over non-antimicrobial dressings to (1) prevent or treat wound infections and/or (2) improve wound healing.

The wounds discussed in the reviewed literature included diabetic foot ulcers, VLUs, burns, pressure ulcers, and surgical wounds. In some cases, studies compared topical antimicrobial drugs (e.g., creams and ointments) with non-antimicrobial controls (not combined with dressings). These findings are discussed and included, where relevant.

We looked for studies evaluating the use of antimicrobial dressings over non-antimicrobial dressings in wound care, such as well-designed, randomized controlled clinical trials (RCTs) that (1) compare a dressing impregnated with an antimicrobial drug with the same dressing but without the antimicrobial and (2) show whether the antimicrobial dressing provides meaningful clinical advantage over the non-antimicrobial dressing in a specific wound-healing setting.

Only a small number of RCTs were identified that compared an antimicrobial dressing to a non-antimicrobial dressing, and many of these contained deficiencies in study design (see next section), reported conflicting results, and/or generally did not allow a definitive conclusion regarding the relative efficacy of the different dressings. Examples of study design limitations identified in these clinical trials included:

[20] Although the focus of the Panel meeting is on wound dressings containing drugs under procode "FRO", this literature review was not limited to this product category. In addition, studies reported below may contain information about uses that are not consistent with the FDA-cleared or approved indications.

- Not defining the types of patients and wounds included in the study
- Inappropriate control groups selected
- Inadequate sample sizes
- Failing to use consistent definitions and classifications of infection
- Dressings being compared were often made with different materials

These design deficiencies made it difficult to assess the efficacy of wound dressings combined with topical antimicrobials for chronic wounds and to compare results across studies (Lipsky and Hoey, 2009). Many systematic reviews of available published trials (e.g., Cochrane Database of Systematic Reviews (CDSR)) concluded that there are a lack of appropriate randomized trials evaluating the effects of wound dressing combined with topical antimicrobials in wound care and further good quality research is needed before definitive conclusions can be reached about the effectiveness of these topical antimicrobials (including antimicrobial dressings)products (Storm-Versloot et al., 2010; Vermeulen et al., 2007; O'Meara et al., 2014).

Many of the trials we reviewed do not clearly indicate the infection status of the wounds being studied, and few RCTs were available that compare the efficacy of antimicrobial dressings vs. non-antimicrobial dressings on treating/preventing wound infections when the primary outcome measure is the cure of infection or some related measure. Even when appropriate trials have been conducted, it is sometimes difficult to determine the effectiveness of topical antimicrobials used to treat infected wounds or prevent infections.

An expert working group issued a consensus statement on the use of silver-containing wound dressings, noting that in certain Cochrane reviews that concluded that silver dressings do not improve healing rates, the use of the silver dressings was not always as indicated by the manufacturers and that in some cases they were used for extended periods and sometimes on wounds that were not infected or did not show evidence of heavy bioburden (Wounds International, 2012). Nevertheless, the working group noted that the aim of silver dressings is to reduce wound bioburden, treat local infection and prevent systemic spread, and that the main purpose of silver dressings is not to promote wound healing directly.

The following sections discuss in more detail the findings from FDA's literature review of the effectiveness of antimicrobial dressings versus non-antimicrobial dressings in infected versus uninfected wounds.

A. ***Diabetic Foot Ulcers***

With respect to wound dressings with or without antimicrobials, it has been noted that available data to support the use of the different dressings and adjunctive measures for the management of diabetic foot wounds are "weak," and that the fundamental problem with studies regarding the benefits of various measures is that they are "small in size and suboptimal in design and execution" (IDSA, 2012; Toy and Macera, 2011).

B. Venous Leg Ulcers

With respect to VLUs, some studies suggest that antimicrobial dressings improve wound healing while other studies suggest that they do not. Some studies found inconclusive results. Table 1 below is a summary of these types of findings.

A 2013 systematic review by the European Wound Management Association (EWMA) described two studies on the use of antimicrobial wound dressings in diabetic foot ulcers (EWMA, 2013). One study in 229 patients reported no statistically significant differences among three dressings (a dressing containing povidone-iodine, a simple non-adherent dressing, and a hydrofiber dressing) in wound healing outcomes (i.e., percentage healed by 24 weeks, 55.2% vs. 59.4% vs. 63.0%) and the mean time to healing (118.1 vs. 110.7 vs. 108.5 days) (Jeffcoate et al., 2009). The other study, in 134 patients, compared an alginate dressing and a silver-impregnated dressing and found no difference in the velocity of healing, time to complete healing, proportion of complete healing during study, or reduction in ulcer area (Jude et al., 2007). The authors of the EWMA review (Gottrup et al., 2013) concluded that there was little evidence to support the choice of any one dressing or wound application in preference to any other in attempts to promote healing of chronic ulcers of the foot in diabetic patients.

Authors of a 2015 review echoed this conclusion, noting that many studies have assessed topical disinfectants or antiseptics for the treatment of diabetic foot infection (e.g., silver, povidone iodine), and the majority of these studies used ulcer healing as the primary outcome. None of these agents has demonstrated superior outcomes compared to non-antiseptic dressings (Uckay et al., 2015).

Silver-containing dressings and topical agents for treating diabetic foot ulcers were evaluated in a systematic review published in 2006 (Bergin et al., 2006); the authors found no RCTs that reported a study of a silver dressing or topical agent to treat diabetic foot ulcers, although the use of such products is common for these wounds.

A 2015 review (Abbas et al., 2015) noted that as topical agents are typically applied in mild diabetic foot infection (or uninfected diabetic foot ulcer), it is difficult to distinguish their

clinical benefits from those of local wound care alone (Abbas et al., 2015). This review also noted that the eradication or reduction of microorganisms in the wound alone is not a sufficient endpoint for their efficacy.

A randomized, open-label, multicenter study of 99 patients (71 VLUs; 28 pressure ulcers) compared silver-releasing hydroalginate dressing with a pure calcium alginate dressing and found that fewer wounds in the silver dressing group developed a clinical infection over the four-week follow-up compared with the control group (33% vs. 46%), but the difference was not statistically significant (p=0.223) (Meaume et al., 2005). In an RCT (N=38) cited by Storm et al., (2010), an activated-charcoal dressing containing silver was compared with conventional topical agents (e.g., granulating ointments; zinc paste). The difference in infection rate was not significant (Wunderlich and Orfanos, 1991).

A 2014 systematic review evaluated the effect of antimicrobials and antiseptics (including topical agents) in venous leg ulcers (O'Meara et al., 2014). The review found 45 RCTs with 4486 subjects; dressings evaluated included honey-containing dressings and silver-containing dressings. The review found no difference in time to healing or complete healing between honey-containing dressings and standard of care; no difference was found between complete healing rates between silver-containing dressings and non-antimicrobial dressings or different brands of silver-containing dressings. Table 1 presents the mixed findings related to wound dressings and results from two additional studies (Michaels et al., 2009; and Senet et al., 2014).

Table 1. Findings Related to Wound Dressings

Author, Year (sample size)	Antimicrobial Dressing (vs. comparator dressing)	Findings (antimicrobial vs. non-antimicrobial dressings) in Patients with Venous Leg Ulcer
<u>Antimicrobial Dressings Improved Wound Healing</u>*:*		
Dimakakos et al., 2009 (n=42)	Silver foam dressing (vs. non-adhesive foam)	• Healing rate at week 9: 81% (17 of 21 patients) vs. 48% (10 of 21 patients)
Lazareth et al., 2008 (n=102)	Contact layer silver dressing (vs. contact layer dressing)	• Wound size reduction at week 4: 4.2 vs. 1.1 cm^2 • Wound size reduction at week 8: 5.9 vs. 0.8 cm^2 • Wound closure rate at week 4: 0.145 vs. 0.044 cm^2/day
Jørgensen et al., 2005 (n=129)	Silver-releasing foam dressing (vs. hydrocellular foam dressing)	• Wound size reduction at week 4: 45% vs. 25% • Percentage of complete healing at week 4: no difference (5 of 64 vs. 5 of 65)
Meaume et al.,	Silver-releasing hydroalginate	• Wound closure rate at week 4: 0.32 vs. 0.16

Table 1. Findings Related to Wound Dressings		
Author, Year (sample size)	**Antimicrobial Dressing (vs. comparator dressing)**	**Findings (antimicrobial vs. non-antimicrobial dressings) in Patients with Venous Leg Ulcer**
2005 (n=99)	dressing (vs. calcium alginate dressing)	cm^2/day • Wound size reduction at week 4: 32% vs. 25%
Wunderlich and Orfanos, 1991 (n=38)	Silver-impregnated activated charcoal dressing (vs. conventional agents, such as zinc paste)	• Wound size reduction at week 6: silver group was significantly better • Percentage of wounds healed at week 6: in favor of silver group (6 of 19 vs. 2 of 19) but the difference was not significant
No Difference in Wound Healing		
Kerihuel, 2010 (n=60)	Activated charcoal impregnated with silver (vs. non-silver dressing)	• Wound size reduction at week 4: 4.5 vs. 3.5 cm^2 • Percentage reduction in size at week 4: 35.6% vs. 40.9% • But week 1 results were in favor of silver: wound reduction (2.2 vs. 0.1 cm^2; 16.4% vs. 0.9%)
Michaels et al., 2009 (n=213)	Silver-donating low-adherence dressing (vs. non-silver dressing)	• Percentage of wounds healed at week 12: 59.6% vs. 56.7% • Time to healing at week 12: 67 vs. 58 days (median)
Blair et al., 1988 (n=120)	Silver sulfadiazine-containing dressing (vs. non-adherence dressing vs. occlusive dressing)	• Percentage healed at week 12: 63% vs. 78% vs. 73%
Uncertain Results		
Senet et al., 2014 (n=181)	Silver-releasing foam dressing (vs. same dressing without silver)	• Wound size reduction at week 6: 42% vs. 35% (p=0.0853) • Healing rate at week 6: 0.67 vs. 0.053 mm/week (p=0.0852) • Confounding effect was found: significant country effect (French patients had different parameters and the silver group showed more healing advantage in this group)

Some researchers are of the view that there is little data from appropriate clinical studies to suggest significantly improved outcomes from the use of antimicrobials in wound dressings for VLUs. It has been noted by others that a systematic review of iodine in wound healing showed that a majority of trials showed no substantial difference between iodine and other methods of wound care (e.g., Broussard et al., 2013). The same researchers who found moderate strength of evidence in cadexomer iodine for wound healing also noted that silver dressings did not

improve wound healing compared with non-silver dressings, and that "[c]learly, more studies are needed to further explore the role of antimicrobial dressings in the management of CVUs [chronic venous ulcers] (Valle et al., 2014)."

C. Burns

A 2013 systematic review assessed the results of 30 RCTs on the effects of burn wound dressings on wound healing of superficial and partial thickness burns (Wasiak et al., 2013). The products assessed within the RCTs included silver sulfadiazine (SSD), silver-containing dressings, chlorhexidine-impregnated paraffin gauze, biosynthetic skin substitute dressings, hydrocolloid dressings, and silicon-coated dressings.

In three RCTs comparing hydrocolloid dressings with chlorhexidine-impregnated paraffin gauze dressings, no difference was demonstrated between the two dressings (although the evidence was poor quality); evaluated parameters included time to complete wound healing and incidence of infection. One RCT compared calcium alginate with silver sulfadiazine dressings in 59 patients with partial thickness burns and found no significant difference in time to healing (Costagliola, 2002).

The review found five RCTs of 331 patients total comparing silver-impregnated dressings to SSD cream, and noted that although the evidence was of low quality, the data overall indicated that silver-impregnated dressings heal burns more quickly than SSD. The parameters evaluated that demonstrated better results for silver dressings overall than SSD included time to complete wound healing, level of pain, and number of wound dressings. No significant difference was found between silver-impregnated dressings and SSD for healing rate, need for surgery, length of hospital stay, incidence of infection, and nursing time.

Other reviews analyzing randomized controlled trials in patients with burn wounds found silver-based topical agents had longer wound healing time compared to non-silver treatments (Rashaan et al., 2014; Aziz, 2012). One of these systematic reviews (Aziz et al., 2012) of silver-containing products discussed studies that evaluated silver-containing dressings or topical silver agents used with a dressing, compared to non-silver dressings (including dressings containing honey, biologics, and povidone-iodine). Of the 14 studies with 877 patients included in the review, only two of the studies evaluated a silver-containing dressing; all other studies evaluated SSD. The review found a lack of evidence to suggest any difference between silver-containing dressings and SSD cream in preventing wound infection; however, the majority of the trials included SSD and not silver-containing dressings.

One non-blinded clinical trial demonstrated that silver-containing dressings resulted in faster healing of superficial and partial thickness burns compared to Vaseline-coated gauze control dressings (Chen et al., 2006). Another study (Innes et al., 2001) that evaluated silver-containing dressings did not assess the effectiveness of the dressings on burn wounds, but rather on split-thickness skin graft donor sites; the authors report that wounds covered with the silver-containing dressing healed significantly slower than those covered with a polyurethane foam non-antimicrobial dressing. Similarly, a systematic review focused on one brand of silver-containing dressing in burn wounds (Khundkar et al., 2010) found only two studies of RCTs of the silver-containing dressing in comparison to SSD or silver nitrate (Huang et al., 2007, Tredget et al., 1998). These two studies suggest that wounds managed with silver-containing dressing had significantly lower burn healing times and significantly higher bacterial clearance than those treated with SSD, and lower frequency of burn wound sepsis and secondary bacteremia compared to those treated with silver nitrate.

Various reviews examining the effects of topical antimicrobials on prevention of infections in burns concluded that overall there is no evidence that the use of topical antimicrobials reduces the risk of wound infections, although the interventions used in the reviewed trials were mostly topical antimicrobial drugs (e.g., creams and ointments), not dressings (Barajas-Nava et al., 2013). This conclusion is in broad agreement with those of other reviews (e.g., Avni et al., 2010).

Several additional studies compared antimicrobial dressings with non-antimicrobial dressings in burn patients. For example, in a study of 48 patients with small, partial skin-thickness burns, a chlorhexidine-containing dressing plus silver sulfadiazine was compared with a hydrocolloid dressing. One of 24 patients in the chlorhexidine dressing group developed an infection vs two of 24 in the hydrocolloid dressing group, a difference that is not statistically significant (Afilalo et al., 1992). Another study of 124 patients with 20%-50% second- and third-degree burns compared silver sulfadiazine dressing with human amniotic membrane and found that incidences of both wound infection and sepsis were higher in the antimicrobial dressing group (65.6% vs. 46.9% and 24.6% vs. 6.1%, respectively). These differences were reported to be statistically significant (Mohammadi et al., 2009).

The American Burn Association's 2001 guidelines for burn care cited a prospective study (Nance et al., 1972) of 145 patients with partial-thickness burns treated in an outpatient environment that showed no significant difference in overall wound healing rates between non-antibacterial and antibacterial-impregnated dressings. In addition, a 2013 Cochrane review (Wasiak et al., 2013) described five studies of patients with superficial and partial thickness burns that compared chlorhexidine-impregnated dressing with hydrocolloid dressings (Thomas, 1995;

Wright, 1993; Afilalo, 1992; Phipps, 1988; and Neal, 1981); none of the studies showed a difference in time to healing between the two groups. The authors of the review concluded that there is no evidence of a difference between hydrocolloid dressings and chlorhexidine-impregnated paraffin gauze, although the evidence is of poor quality.

In summary, based on the results and design limitations of studies of wound dressings in diabetic foot ulcers, VLUs, and burns, it cannot be concluded that antimicrobial dressings provide a clinically or statistically meaningful difference in clinical outcomes in preventing wound infection in these wound types as compared to non-antimicrobial dressings. This is consistent with systematic reviews of RCTs evaluating antimicrobials (including cream, ointment, and dressings) in wound care. Examples of these reviews' conclusions are presented in Table 2.

Table 2. Conclusions Reached in Studies of Diabetic Foot Ulcers, Venous Leg Ulcers, and Burns

Author, Year (studies reviewed)	Wound Type	General Conclusion: Topical Antimicrobials (Including Drugs and Dressings)
Uckay et al., 2015 (not specified)	Diabetic foot ulcer	• None of the topical disinfectants or antiseptics (such as silver and povidone) has demonstrated superior outcomes in ulcer healing or resolution or prevention of infection compared to nonantiseptic dressings. Thus, as was true three decades ago, dressing changes with simple gauze and saline solution alone appears to be sufficient for most patients.
O'Meara et al., 2014 (45 studies)	Venous leg ulcer	• Some evidence supports the use of cadexomer iodine (but it is associated with more frequent adverse effects than standard of care). • Current evidence does not support the routine use of honey- and silver-based preparations.
Barajas-Nava et al., 2013 (36 studies)	Burn	• The available evidence is limited and, in general, does not demonstrate that antibacterial (including topical and systemic) prophylaxis reduces the risk of burn wound infection, invasive infections, or mortality associated with infection. • The use of topical antibacterials and, specifically, the use of silver sulfadiazine (SSD) in burn wounds needs to be reconsidered since the available evidence suggests that patients treated with topical SSD have a higher risk of burn wound infection and longer length of hospital stay than those treated with dressings.
Vermeulen et al., 2010 (26 studies)	Multiple wound types (e.g., burn)	• There is currently insufficient evidence that silver-containing dressings prevent wound infection or promote wound healing; the available evidence is low both in volume and quality. • There is some evidence from small, poor-quality trials suggesting that SSD does not reduce wound infection and slows down wound healing in

Table 2. Conclusions Reached in Studies of Diabetic Foot Ulcers, Venous Leg Ulcers, and Burns		
Author, Year (studies reviewed)	**Wound Type**	**General Conclusion: Topical Antimicrobials (Including Drugs and Dressings)**
		people with partial-thickness burns.

D. Surgical Wounds

Mixed results have been reported regarding the efficacy of antimicrobial dressings over non-antimicrobial dressing in preventing infections in surgical wounds. An RCT comparing silver ion-eluting dressings with soft paper cloth in 514 women undergoing cesarean section found no difference in incidence of post-cesarean section surgical site infection (SSI) rates: 25/239 patients (10.5%) in the silver dressing group developed infection vs. 19/236 patients (8.0%) in the cloth dressing group (Kellett et al., 2015). In a retrospective chart review of 72 patients undergoing cesarean delivery that compared the effectiveness of silver-impregnated dressings with traditional wound dressings (Connery et al., 2012), 2/36 patients in the silver dressing group and 2/36 patients in the gauze pad group developed an SSI requiring additional wound care visits. Silver dressings did not significantly reduce the rate of wound care-related postoperative visits; however, the silver dressing group had a higher rate of comorbidities.

A study of 112 patients undergoing elective colorectal cancer surgery compared a silver-containing dressing with a commonly used non-silver dressing and reported a numerically lower but nonsignificant overall rate of SSIs in the silver dressing group (15.5% vs. 20.4% in the control group; p=0.451) (Biffi et al., 2012). Another study of 110 patients undergoing elective colorectal surgery compared a silver-plated nylon dressing with standard gauze dressings and found that silver dressings significantly reduced the rate of SSIs from 30% to 13% (p=0.011) (Krieger et al., 2011). A third study on 160 colorectal surgery patients compared patients receiving an ionic silver dressing with patients treated without dressing. There was only 1 SSI in the silver group, vs. 8 SSIs in the control group (not statistically significant) (Siah et al., 2011).

A study comparing silver-nylon dressings in 365 patients undergoing coronary artery bypass graft or open valve replacement with 1,235 historical controls receiving a dry gauze dressing showed 13 mediastinal infections in the control group vs. no infections in the silver group ($p<0.05$) (Huckfeldt et al., 2008).

In 234 patients undergoing lumbar laminectomies with instrumented fusion, silver-nylon dressings were compared with routine dressings (iodine or alcohol swabs under dry gauze), and the results showed that there were 11 superficial and 3 deep SSIs in the routine dressing group

and no infections in the silver-nylon group. A detailed statistical analysis was not performed and the author recommended additional large-scale prospective trials (Epstein, 2007).

A prospective study of 59 patients investigating silver hydrogel dressings on postsurgical incisions in foot and ankle surgery reported 1 (3.5%) patient in the silver group experienced a superficial infection while the control group had 3 (10%) superficial infections and 1 (3.3%) deep infection (this difference was not statistically significant; p = 0.37) (Galli et al., 2013).

A study comparing a polyhexamethylene biguanide dressing with a non-occlusive dressing in 197 patients undergoing elective laparoscopic cholecystectomy reported that 1/96 patients (1.04%) in the antimicrobial dressing group had an SSI whereas 5/101 patients (4.95%) in the non-antimicrobial dressing group had infection (Martin et al., 2013). Although the study showed a numerical advantage for the antimicrobial dressing group, the study lacked sufficient statistical power to demonstrate significance for the difference.

In a systematic review of dressings for SSI prevention, Dumville et al., concluded that they "generally found insufficient evidence" that covering surgical wounds with any dressing compared with leaving them exposed influences the subsequent rate of SSIs and that "there was insufficient evidence" on which to base solid conclusions regarding whether any single type of dressing reduces rates of SSIs in surgical wounds (Dumville et al., 2014).

E. Catheter Insertion Sites

Some wound dressings containing drug(s) for use to cover catheter insertion sites have been cleared with an indication to reduce catheter-related bloodstream infections (CRBSI). A systematic review was published in 2016 on the effects of central venous access device (CVAD) dressings/securement devices on outcomes including CRBSI, catheter colonization, entry- and exit-site infection, skin colonization, skin irritation, catheter security, dressing condition, or mortality (Ullman et al., 2016). Twenty-two RCTs and controlled clinical trials were included in the qualitative and quantitative analyses. The analysis showed that there are data to show that medication-impregnated dressings reduce CVAD-related bloodstream infection incidence compared to other dressing types; however, there may be increased risk of skin irritation or damage. However, a similar systematic review (Lai et al., 2016) which focused on CRBSI in neonates found that antimicrobial dressings compared to control dressings did not result in a significant different in the risk of CRBSI or sepsis. No adverse skin reactions were reported in a study of a silver-alginate patch compared to control. In a study of chlorhexidine dressing with alcohol cleansing compared to polyurethane dressing with povidone-iodine cleansing, infants in

the chlorhexidine/alcohol cleansing group had a significantly higher rate of contact dermatitis (Garland et al., 1996, Garland et al., 2001).

G. Chronic Wounds

The role of antimicrobial agents (topical, oral, or systemic) in the healing of chronic wounds is unclear, partly because there is uncertainty about whether bacterial presence is an important factor in wound healing (O'Meara et al., 2000).

A systematic review published in 2008 (Lo et al., 2008) assessed the effectiveness of silver-releasing dressings in the management of infected chronic wounds, as shown in fourteen clinical studies of 1,285 patients. Wounds included pressure ulcers, venous ulcers, diabetic ulcers, and other chronic wound types. The review generally found that the data suggested positive wound healing effects and positive effects on infection and inflammation; however, variability in methodology and confounding factors such as antibiotic use limits the conclusion that may be drawn from the data.

A systematic review of antimicrobials for pressure ulcers published in 2016 (Norman et al., 2016) evaluated drugs as well as dressings and found only twelve studies (576 patients) on the use of topical products (no systemic antimicrobials). Most of the products in the studies were antiseptics. The products included povidone iodine, cadexomer iodine, polyhexanide dressing, silver-containing dressing, SSD, and honey. The data were deemed to be too limited in terms of study size, variations in study design, and study duration to draw any conclusions on the relative effects of antimicrobials on pressure ulcers.

H. Wound Irrigation Solutions and Honey Dressings

There are few published clinical studies on the effectiveness of wound wash and wound cleansing solutions. One small controlled study was conducted on 23 patients (Lindfors, 2004), comparing antimicrobial wound cleanser (containing sodium hypochlorite in saline) to normal saline control cleanser. The study found a reduction in wound bioburden in the wounds cleansed with antimicrobial solution compared to control, and the data suggested that there may have been a positive effect on wound size at two months. However, the small sample size and limitations due to study design and conduct preclude definitive conclusions. A systematic review on wound cleansing for pressure ulcers (Moore et al., 2013) evaluated the effect of wound cleansing solutions and techniques on the rate of healing for these wounds. Three RCTs (169 patients) were identified; two evaluated different wound cleansing solutions and one evaluated cleansing techniques. One trial found a statistically significant improvement in

healing with a cleansing solution (that is not cleared under 510(k) in the U.S.) compared to saline (Bellingeri et al., 2004); another trial showed no difference in healing between wounds cleansed with water compared to saline (Griffiths et al., 2001). The third study compared pulsatile lavage with sham (no lavage), and found a statistically significant decrease in ulcer volume at 3 weeks in the lavage group (Ho et al., 2012). However, due to the small sizes of the studies, the authors concluded that there were limited data available to support any specific wound cleansing solution or technique for pressure ulcers.

In 2015, a systematic review of RCTs on the use of honey in wounds (acute and chronic) was published (Jull et al., 2015). Twenty-six RCTs with 3011 subjects were found, with three trials on use of honey in minor acute wounds, eleven trials on honey in burn wounds, ten trials on honey in various chronic wounds, and two trials on a mixture of patients with acute and chronic wounds. There is a lack of high-quality data regarding the effectiveness of honey in other wound types. There is evidence based on 2 trials of 992 patients that wounds with honey dressings heal partial thickness burns faster than conventional dressings (Subrahmanyam, 1993; Subrahmanyam, 1996); however, there is little data on the difference in adverse event rates or infection rates. Additionally, one clinical trial showed that honey heals infected post-operative wounds faster than antiseptic washes followed by gauze (Al-Waili et al., 1999).

In summary, many experts in the wound care community have concluded that topical antimicrobials (including antimicrobial dressings) do not improve wound healing. Some example statements are as follows:

- “Do not use antimicrobial dressings with the goal of improving wound healing or preventing secondary infection.” (diabetic foot ulcer; International Working Group on the Diabetic Foot (IWGDF) 2015)
- “To date, there is no evidence that wound dressings containing silver lead to faster wound healing.” (VLU; European Dermatology Forum, 2014)
- “It is becoming more apparent that silver dressings are not rising to meet their claims but they are still very popular even without an evidence-base to support their increasing use.” (wounds in general; Sweeney et al., 2012)
- “There is insufficient evidence to establish whether silver-containing dressings or topical agents promote wound healing or prevent wound infection; some poor quality evidence for SSD [silver sulfadiazine] suggests the opposite.” (Storm-Versloot, 2010)
- Based on the limited published RCT data, no benefit was shown for the treatment of infected wounds with silver-containing dressings compared to non-antimicrobial controls (Vermeulen et al., 2007)

- Mixed results have also been reported on the effectiveness of antimicrobial dressings (over non-antimicrobial dressings) in promoting wound healing. Although some studies show improved wound healing in patients using antimicrobial dressings, other studies show no difference in wound healing between the two groups. Additionally, certain antimicrobial dressings (e.g., silver-based dressings) were reported to delay wound healing, and some researchers noted that one of the disadvantages of topical antimicrobial products for infected chronic wounds is they may interfere with wound healing processes (Lipsky and Hoey, 2009).

The available evidence does not appear to demonstrate improved clinical outcomes from the use of antimicrobial dressings over non-antimicrobial dressings for the prevention or treatment of local wound infections or to improve wound healing. Specifically with respect to the prevention of catheter-related bloodstream infections, there may be clinical benefit from the use of antimicrobial dressings. Given the apparently equivocal and low-quality data available in published literature, the Panel will be asked to comment on how available evidence is used to determine choice of dressing and course of wound care. As part of this discussion, the Panel will be asked to explore the characteristics (e.g., composition, indications) of wound dressings products that provide clinically meaningful benefit and what types of evidence (such as clinical evidence) would be helpful to support certain indications.

SECTION V: Information Pertaining to the Safety of Antimicrobial Wound Dressings

FDA conducted a survey of published literature using the Cochrane Database of Systematic Reviews (CDSR) and PubMed to gain a general understanding of the types of safety information that have been published regarding use of antimicrobial wound dressing products. This section reviews the available evidence concerning antimicrobial dressings and their potential to delay wound healing, cause toxicity or allergic reactions, induce drug resistance, and otherwise complicate antimicrobial selection and treatment of wound infections. Specific examples that highlight some of these risks are included. In addition, a summary of adverse event reports submitted to FDA concerning wound dressings is provided.

A. Delayed Healing

As already discussed, the available evidence does not appear to demonstrate improved clinical outcomes with the use of antimicrobial dressings over non-antimicrobial dressings for the prevention or treatment of local wound infections or to improve wound healing. In fact, in some cases, researchers have noted delayed wound healing may be associated with the use of antimicrobial dressings. For example, authors of a 2014 trial review (Rashaan et al.,) reported results of a meta-analysis of seven randomized controlled trials in 473 children with partial-thickness burns in the acute stage. The studies compared silver-containing dressings and silver topical agents with non-silver treatments. The studies found that non-silver treatment led to shorter wound healing time (a mean difference of 3.4 days in healing time) and shorter length of hospital stay compared with silver sulfadiazine treatment (Aziz et al., 2012). Rashaan et al., (2014) noted that these findings are in agreement with another systematic review of randomized controlled trials comparing silver dressings and topical silver to non-silver dressings, which also found a longer healing time for partial-thickness burns when silver dressings were compared with non-silver treatment in adults (a mean difference of 3.96 days in healing time).

When discussing the observed differences in healing time of donor sites wounds in a prospective, controlled matched pair study, some researchers (Innes et al., 2001) noted that the non-antimicrobial dressing did not particularly enhance re-epithelialization; rather the antimicrobial dressing (silver-based) appeared to specifically retard re-epithelialization. They believed the delay in wound healing might be related to the concentration of silver (released from the dressing) on the wound surface, although they acknowledged that the actual concentration of silver on the wound surface under the silver-containing dressings is unknown (nor is it known whether the silver concentration varies with the degree of moisture beneath the dressing); see also the discussion in section E.2 below.

Delayed healing has also been reported from the use of other topical antimicrobials, such as povidone-iodine. For example, a 1999 review (Kramer) noted that varied studies provide evidence that in most instances, povidone-iodine did not effectively promote good wound healing; in fact, most studies showed impaired wound healing.

B. Toxicity and Allergic Reactions

Toxicity to host tissues has been reported for some topical antimicrobials (Lipsky and Hoey 2009). For example, chlorhexidine and povidone-iodine have been shown to be toxic to wound environments and (particularly in the case of povidone-iodine) to fibroblasts and keratinocytes (Mertz and Ovington, 1993).

Similar findings have been reported for silver-based topical agents. In one study, Burd et al., (2007) found that three of the five commercially available silver-based dressings were likely to produce the most significant cytotoxic effects on both cultured keratinocytes and fibroblasts and that the cytotoxicity correlated with the silver released from the dressings as measured by silver concentration in the culture medium. They also observed that the silver dressings resulted in a significant delay of re-epithelialization in the tissue explant culture model, whereas in a mouse wound model, two silver dressings indicated a strong inhibition of wound re-epithelialization on the post-wounding day seven. The researchers concluded that these findings might partly explain the clinical observations of delayed wound healing or inhibition of wound epithelialization after the use of certain silver dressings.

Some topical antimicrobials are also considered common allergens. For example, Zug et al., (2009) from the North American Contact Dermatitis Group tested patients who have suspected allergic contact dermatitis with a broad series of screening allergens, and the 10 most frequently positive allergens during the 2005/2006 period included topical antimicrobials neomycin (with a positive reaction rate of 10.0%) and bacitracin (9.2%). This finding is consistent with the observation that one topical antimicrobial (neomycin) is part of the standard series of patch tests, which underscores the frequency of topical antimicrobials as allergens (Sheth and Weitzul, 2008).

One of the potential advantages of topical therapy is the ability to deliver a high local drug concentration and reduce the risk of systemic side effects with small doses of the agent (Abbas et al., 2015). However, it may be difficult to accurately deliver the intended dose of medication through the use of topical antimicrobial products (creams or ointments) or wound dressing containing antimicrobials for infected chronic wounds (Lipsky and Hoey, 2009). The local wound

environment (e.g., the degree of moisture beneath a dressing) might also affect the concentration and amount of antimicrobial reaching the wound site.

C. Narrowing Treatment Options

To the extent the antimicrobial component of a wound dressing is released or migrates to the skin or wound site, such component may complicate the antimicrobial selection and treatment of a wound infection by narrowing treatment options due to drug resistance concerns. For example, the 2012 IDSA guidelines for diabetic foot infections recommend targeting only aerobic gram-positive cocci for mild to moderate infections in patients who have not recently received antimicrobial treatment. Recent exposure of a patient to a wound dressings impregnated with an antimicrobial may necessitate broader spectrum antimicrobial treatment, should systemic therapy become necessary.

Other guidelines caution against the topical use of certain antimicrobials in order to reserve them for oral/IV use. For example, the Canadian Association of Wound Care Best Practice Recommendations for Treatment of Pressure Ulcers (2006a) recommends that gentamicin should be reserved for oral/IV use because topical use may encourage resistance. It has also been suggested that, with certain exceptions, it is preferable to avoid using topical antimicrobials that are available for systemic therapy when treating wound infections because such topical antimicrobials may provoke delayed hypersensitivity reactions, favor superinfections, and select for resistant pathogens (Lipsky and Hoey, 2009).

D. Growing Concerns About Development of Antimicrobial Resistance

The development of antimicrobial resistance is widely recognized as a serious public health concern. An Executive Order was issued on September 18, 2014, (Combating Antibiotic-Resistant Bacteria, 2014) which recommended antimicrobial stewardship measures to reduce the emergence and spread of antimicrobial-resistant bacteria and help ensure the continued availability of effective therapeutics for the treatment of bacterial infections. According to the U.S. Centers for Disease Control and Prevention (CDC), drug-resistant bacteria cause 23,000 deaths and 2 million illnesses each year (Antibiotic / Antimicrobial Resistance, 2016).

According to a recent report on Antibiotic Stewardship by the National Quality Forum (2016), overuse and misuse of antibacterials have contributed to the cultivation of an abundance of drug-resistant organisms that are becoming increasingly difficult to treat. Studies indicate that 30% to 50% of antibacterials prescribed in hospitals are unnecessary or inappropriate. Misuse occurs in healthcare settings for a variety of reasons, including use of antimicrobial when not needed, continued treatment when no longer necessary, wrong dose, use of broad-spectrum

agents to treat very susceptible bacteria, and wrong antimicrobial to treat an infection. Changes to clinical practice patterns to promote appropriate use of antibiotics are now essential.

On June 2, 2015, the White House hosted the Forum on Antibiotic Stewardship to bring together more than 100 key human and animal health leaders involved in antimicrobial stewardship—the development, promotion, and implementation of activities to promote optimal use of antimicrobials nationwide. The leaders represented hospitals and healthcare systems, human and animal health, diagnostic and diagnostic pharmaceutical companies, agriculture organizations, and more who committed to taking part in antibiotic stewardship to change the way antibiotics are currently prescribed and used to slow the spread of drug-resistant infections (Federal Engagement in Antimicrobial Resistance, 2015).

Public health agencies in the Department of Health and Human Services (HHS) are engaged in efforts to promote antimicrobial stewardship practices and curb antimicrobial resistance. This includes recommending a more judicious use of antimicrobials to reduce the amount that are unnecessary or inappropriately prescribed (consisting of 20-50% of antimicrobials in U.S. acute care hospitals) (Core Elements of Hospital Antibiotic Stewardship Programs, 2016). In July 2016, HHS announced an International Public-Private Partnership to fight antimicrobial resistance. This is a joint effort to speed up efforts to discover and develop new antimicrobials to combat antimicrobial resistance, titled, Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), by creating “one of the world’s largest public-private partnerships focused on preclinical discovery and development of new antimicrobial products” (Sun, 2016).

Numerous classes of antimicrobials have been developed and utilized to attack bacterial targets such as cell wall synthesis (e.g., penicillins, bacitracin), DNA and RNA synthesis (e.g., rifampin, metronidazole), and protein synthesis (e.g., gentamicin, clindamycin) mechanisms. However, each antimicrobial is effective only for a limited segment of the microbial world. Some species of bacteria are naturally resistant to a given antimicrobial, while others may eventually acquire resistance (e.g. via random mutation or acquisition of a resistance gene). After decades of antimicrobial usage, this applied therapeutic pressure has contributed to the selection of bacteria that have developed a vast array of antimicrobial resistance mechanisms, including the expression of hydrolytic enzymes such as Beta-lactamases, activation of efflux pump systems, and the alteration of cell wall permeability (to name a few). Many antimicrobial resistance genes are found on plasmids, which not only play an integral role in the horizontal transfer of resistance between organisms, but can also stack multiple resistance genes together on a single mobile element. As a result, it is not uncommon for today’s hospital acquired infections to involve bacteria that are resistant to multiple classes of antimicrobials.

Antimicrobials commonly incorporated as a component in wound dressings fall under the following categories:

- Metal based antimicrobials (e.g., silver, bismuth)
- Polymer based antimicrobials (e.g., PHMB)
- Quaternary ammonium compounds (e.g., benzalkonium chloride)
- Oxidizing agents (e.g., hydrogen peroxide, hypochlorous acid/sodium hypochlorite)

Unlike antibiotics which may be prescribed for systemic delivery of a targeted antimicrobial, these four categories of antimicrobials have been used in combination with medical devices for a localized antimicrobial effect. In addition, most of these categories of antimicrobials are currently used as part of the recommended cleaning, disinfecting, and sterilization in healthcare facilities. Published studies evaluating resistance mechanisms to these antimicrobials are limited. Although some resistant strains have been noted, it is difficult to draw any conclusions regarding the prevalence of antimicrobial resistance to these types of antimicrobials without results of a surveillance study.

Moist chronic skin ulcers are an ideal medium for bacterial growth, and a variety of micro-organisms can be cultured from these lesions (O'Meara et al., 2000). The polymicrobial nature of chronic wounds is likely to provide an appropriate environment for genetic exchange among bacteria, leading to resistance (Howell-Jones et al., 2005; Gottrup et al., 2013). In fact, the first two cases of vancomycin-resistant *Staphylococcus aureus* in the United States were both isolated from chronic wound patients (Howell-Jones et al., 2005; *Staphylococcus aureus* Resistant to Vancomycin, 2002). In their 2005 literature review, Howell-Jones et al., described a number of publications that have found antibacterial-resistant organisms may colonize and infect chronic wounds; examples are presented below (Tentolouris et al., 1999; Dang et al., 2003):

- A study in a diabetic foot clinic found 40% of S. aureus isolated from infected foot ulcers to be methicillin-resistant *Staphylococcus aureus* (MRSA); giving MRSA a prevalence of 15% in all diabetic foot ulcer patients with infected ulcers.
- There were significantly more MRSA isolates from patients who had received prior antibacterial therapy, compared with those who had not.
- A follow-up study, in the same clinic, identified a similar proportion of methicillin resistance in the *Staphylococcus aureus* isolates, but showed that the prevalence of MRSA in foot ulcers had almost doubled over a three-year period to 30% of all diabetic foot ulcer patients with ulcer infection.

Other instances of developing resistance to antimicrobials have been reported in wound treatment (EWMA, 2013). Certain topical antibacterials (e.g., neomycin) are linked to relatively frequent development of resistance and long-term use of mupirocin can lead to resistance among staphylococci (Lipsky and Hoey, 2009). For example, in a study of patients with medium-sized burns, topical antibacterials (neomycin plus bacitracin) were associated with rapid emergence of drug-resistant organisms (Livingston et al., 1990). Another study of wound patients reported that gentamicin iontophoresis (electrically inducing the drug in solution to migrate into target tissues) appeared to offer no additional benefit beyond those that are provided by routine care and may encourage the development of antibacterial resistance (Desai et al., 1991).

Some recent guidelines advise against the use of antimicrobial dressings or topical antimicrobial drugs due to concerns about drug resistance.

- Indiscriminate use of antimicrobial dressings should be discouraged because of concerns over bacterial resistance and toxicity (National Institute for Health and Care Excellence (NICE) Advice, 2015).
- [Advise] against the use of topical antibiotics in venous leg ulcer because of the development of resistance and contact allergy (European Dermatology Forum, 2014).
- Use topical antibiotics judiciously in managing venous leg ulcers as there is a concern that their use is associated with antibiotic resistance and sensitivities (Australian and New Zealand Clinical Practice Guideline, 2011).
- Use of topical antibiotics in the management of infected wounds should generally be avoided to minimize the risk of allergy and the emergence of bacterial resistance (World Union of Wound Healing Societies, 2008).

The more frequently an antimicrobial is used, the greater the opportunity to select for resistant mutants and for transmission to susceptible individuals (EWMA, 2013). The combination of increasing numbers of the population who are at risk of developing chronic wounds, together with the increasing prevalence of antibacterial resistance, make this a highly important issue (Howell-Jones et al., 2005).

As antimicrobial resistance has become a major public health concern, the Panel will be asked to discuss how risks of antimicrobial resistance should influence the selection of wound care products and its impact when considering the overall benefit and risk profile of wound care products. The Panel will be asked to comment on the evidence available to support the use of these products.

E. Examples to Highlight Concerns about Antimicrobial Resistance

In the following section, we highlight selected wound care products with antimicrobials. These include bacitracin and polymyxin B sulfate, hypochlorous acid/sodium hypochlorite and silver, and chlorhexidine. Each example highlights potential risks which the panel should discuss as part of their assessment of the benefit–risk profile of certain wound dressings with drugs. We also include other risks of these drugs as part of the discussion.[21]

1. Bacitracin or polymyxin B sulfate

Products in this category may be used in the management of partial and full-thickness wounds, including diabetic ulcers, venous stasis ulcers, pressure ulcers, surgical wounds, ischemic ulcers, traumatic wounds, superficial burns, donor sites, and abrasions and lacerations.
Bacitracin is an antibacterial that disrupts both Gram-positive and Gram-negative bacteria by interfering with cell wall and peptidoglycan synthesis. Polymyxin B sulfate is an antibacterial that interacts with the outer membrane of the Gram-negative cell wall and destroys bacterial membranes with a detergent-like mechanism that is used topically in the treatment of infections of the eye caused by susceptible strains of *P. aeruginosa*. It also inhibits the activity of endotoxins (Glasser et al., 2010).

Polymyxins consist of polymyxins A-E, of which polymyxin B and polymyxin E (colistin) are currently used as clinical medicines. In general, they have a narrow antibacterial spectrum mainly against the Gram-negatives. Polymyxin B and colistin have re-emerged as drug of last resort in treatment of carbapenem-resistant Enterobacteriaceae (Morrill et al., 2015). Different mechanisms of polymyxin-resistance have been found in bacteria and resistance to the current polymyxins could become an increasing global health challenge, because few antibacterials are available to treat polymyxin-resistant organisms (Yu et al., 2015).

Use of both bacitracin and polymyxin B sulfate poses risks of allergic reaction and systemic absorption. Bacitracin has been shown to act as a dermatological irritant and may impede healing. In addition, bacitracin may cause renal damage if used if used internally (Miller et al., 1950).

[21]Please note that some of these uses may not be cleared or approved.

2. Hypochlorous Acid/Sodium Hypochlorite and Silver[22]

A number of wound care products contain antimicrobials such as hypochlorous acid/sodium hypochlorite and silver. These products are generally used in the management of wounds such as stage I-IV pressure ulcers, partial and full thickness wounds, venous and arterial ulcers, diabetic foot and leg ulcers, postsurgical wounds, first and second degree bums, trauma wounds, and grafted and donor sites to moisten the wound bed and facilitate autolytic debridement of acute and chronic dermal lesions. The hypochlorous acid/sodium hypochlorite or silver are broad spectrum antimicrobials that inhibit the growth of microorganisms and control the microbial contamination of the product. Dressings that include either hypochlorous acid/sodium hypochlorite or silver as broad spectrum antimicrobial preservatives may contribute to drug resistance (Suwantarat et al., 2014; Horner et al., 2012; Higgins et al., 2001; Percival et al., 2005; Atiyeh et al., 2007). These products target multiple sites on or within bacterial cells which likely contributes to their broad-spectrum activity. This type of resistance can be acquired via mutations in normal cellular genes, plasmids or transposons.

Percival et al. (2005) in their review article state that plasmid-mediated biocide resistance has been documented as occurring in *Staphylococcus aureus*, coagulase-negative staphylococci, members of the Enterobacteriaceae and *Pseudomonas spp*. The vast majority of these broad spectrum antimicrobials act on cell surface components of the bacteria and/or the cytoplasmic membrane. Therefore, intrinsic resistance would involve natural resistance via the structure of the cell surface and its chemical composition (Percival et al., 2005). Plasmid-mediated mechanisms of resistance to antiseptics and increased minimum inhibitory concentration are documented for staphylococci, and several laboratory studies have raised concerns that emergence of biocide nonsusceptibility may result in cross-resistance to antimicrobials (Suwantarat et al., 2014).

Specific risks of hypochlorous acid/sodium hypochlorite use include systemic absorption and toxicity. Sodium hypochlorite solution causes moderate mucosal irritation, the extent of which depends very much on the volume ingested and the viscosity and concentration of the preparation and the duration of contact. The main toxic effect is due to release of chlorine gas. Studies of silver-containing dressings compared to non-antimicrobial dressings for the treatment of infection have generally not demonstrated significant differences in the rates of adverse events.

[22] The most common compound currently in use is silver sulfadiazine (SSD), although silver metal, silver acetate, silver nitrate, and silver protein all of which have antimicrobial properties, are listed in Martindale, The Extra Pharmacopeia (McDonnell and Russell, 1999). Please note that only SSD is an FDA-approved drug.

Data concerning the absorption, metabolism, tissue distribution, accumulation, excretion, and pharmacodynamics (effect of the drug at its action site) of silver in the body, when applied externally, and of the effect of the particle size of the silver on these systemic effects is limited. Because of the acknowledged differences in silver content and particle size of the silver in various products, it is difficult to draw conclusions from clinical studies conducted on different silver products.

Finally, argyria[23] is a permanent ashen-gray discoloration of the skin, conjunctiva, and internal organs results from the long-continued use of silver salts. Argyria occurs because a small amount of the silver compound is absorbed and deposited in the skin, where it is reduced by light to metallic silver; the resulting skin discoloration persisting almost indefinitely.

3. Chlorhexidine Gluconate

There are many wound care products that contain the antimicrobial chlorhexidine gluconate. These products are generally used to cover and protect catheter sites and to secure devices to the skin (e.g., securing and covering IV catheters, other intravascular catheters and percutaneous devices) and to cover the peri-wound area of a wound caused by the use of vascular and non-vascular percutaneous medical devices (e.g., IV catheters, central venous lines, arterial catheters, dialysis catheters, midline catheters, drains, chest tubes, externally placed orthopedic pins, epidural catheters).

Chlorhexidine acts by binding to the negatively charged bacterial cell wall and affecting the osmotic equilibrium of the cell. At higher in-use concentrations, binding of chlorhexidine causes the membrane to lose structural integrity, which results in cell death. Chlorhexidine is most active against Gram-positive bacteria, but also has activity against Gram-negative bacteria, anaerobes, fungi, and some enveloped viruses (Horner et al., 2012).

As a broad spectrum antimicrobial, it also raises concerns about resistance. Clinical bacterial isolates with reduced chlorhexidine susceptibility, especially in coagulase-negative *Staphylococcus spp*. and *S. aureus*, have been reported. In addition, studies have found high chlorhexidine minimum inhibitory concentration from isolates of multidrug-resistant bacteria, including VRE, MRSA, methicillin-resistant coagulase-negative *Staphylococcus spp*., and resistant Gram-negative bacteria (Suwantarat et al., 2014). The clinical impact of *in vivo*

[23] In 21 CFR § 369.20, under Silver, it states: "Caution – Frequent or prolonged use of this preparation may result in permanent discoloration of skin and mucous membranes."
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=369

reduced susceptibility to chlorhexidine is not well understood. Increased clinical use of chlorhexidine may lead to the emergence of new clones with reduced susceptibility, but until more is known, indiscriminate chlorhexidine use in the absence of efficacy data has been discouraged (Horner et al., 2012).

Other risks of chlorhexidine uses include allergic reaction, systemic absorption, and toxicity. Hypersensitivity reactions to chlorhexidine have included allergic contact dermatitis, pruritus, vesicle formation, urticaria, dyspnea, and anaphylactic shock. Chlorhexidine dressings have been associated with increased rates of localized contact dermatitis when placed over catheter insertion sites in infants (Garland et al., 2001, Levy et al., 2005).

On March 11, 1998, FDA issued a public health notice about the potential hypersensitivity reactions to chlorhexidine-impregnated medical devices (Potential Hypersensitivity Reactions 1998). Hypersensitivity reactions, including allergic contact balanitis and anaphylactic shock, have been reported after the use of products containing chlorhexidine as a preservative or devices coated with chlorhexidine. Patch testing using chlorhexidine has revealed positive reactions in more than 2% of patients tested and in eczema patients, the rate may be as high as 5% (Chlorhexidine topical Side Effects, n.d.). Some have recommended against using chlorhexidine routinely in wounds that involve more than the superficial layers of the skin (Chlorhexidine Gluconate topical, 2016).

F. Medical Device Adverse Event Reports

The FDA receives medical device reports (MDRs) of suspected device-associated deaths, serious injuries, and certain malfunctions. MDRs are submitted by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters, such as health care professionals, patients and consumers. 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:

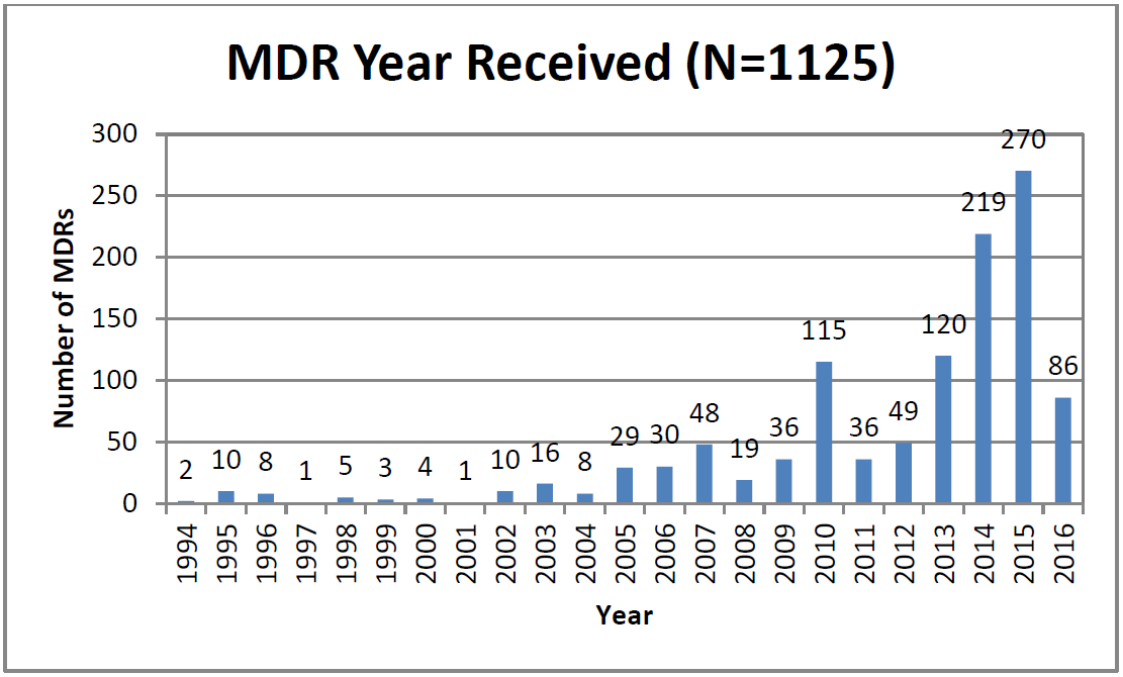
- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a “real world” setting/environment

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the submission of incomplete, inaccurate, untimely, unverified, 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.

FDA conducted a query of the MDR database to identify adverse events related to use of wound dressings that contain drug(s). The search was conducted on July 28, 2016 using the parameter of device product code FRO, with no date restrictions. A total of 1,125 reports for product code FRO were identified. There were 17 Deaths, 725 Serious Injuries, and 383 Malfunctions (170 reports with Event Types reported as "other" or "blank" were corrected by referencing the event texts and patient problem descriptions provided). There were 1,010 Manufacturer/Distributer reports, 78 Voluntary reports, and 37 User Facility reports. There were 623 MDRs reported from the US and 502 MDRs reported from outside the US. The oldest MDR was received by the FDA in 1994. The number of reports received by FDA each year is shown in Figure 1.

Figure 1. Number of Reports Received by Year



Each report was individually reviewed for patient problems. Table 3 shows the top 10 patient problems.

Table 3. Top 10 Patient Problems.

Patient Problem	Count
Erythema	159
Infection	100
Blister(s)	86
Allergic Reaction (including anaphylaxis)	82
Skin tear/Skin Breakdown/Tissue Damage	76
Discharge/Drainage	71
Rash	50
Skin Irritation	47
Burn/Chemical Burn/Burning sensation	50
Dermatitis/Cellulitis	37

Each report was individually reviewed for device problems. Table 4 shows the top 5 device problems.

Table 4. Top 5 Device Problems

Device Problem	Count
Packaging Issue	114
Foreign Material	104
Difficult to Remove	84
Improper Use	35
Poor Adhesion	22

NOTE: Throughout the Results section the total number of occurrences may differ from the total number of records identified in the above query when there are multiple occurrences of a data item on a record (which results in more occurrences than records), or when a value for a data item is missing (which results in fewer occurrences than records).

Death Reports

Seventeen death reports were received in the past 22 years. Five of the deaths were deemed by the manufacturer as not likely related to the device. It could not be determined by the manufacturer if the patient's cause of death was related to the reported device in the remaining 12 MDRs.

SECTION VI: Wound Dressings With Other Drugs

Two additional products, dressings with lidocaine and corticosteroids, highlight the risk of systemic absorption and local toxicity. These dressings are used on partial and full-thickness wounds, including diabetic ulcers, venous stasis, pressure, and ischemic ulcers, surgical and traumatic wounds, superficial burns, donor sites, and abrasions and lacerations.

Lidocaine, a local anesthetic, works by blocking nerve signals. System toxicity can occur through excessive absorption, especially with large open wounds (Nicks et al., 2010). Systemic absorption can cause methemoglobinemia, cardiac arrest, idiosyncratic reaction; and death (FDA Alerts Public, 2009; Improper use of, 2009). When applied to the skin surface, lidocaine can be absorbed into the bloodstream and, if used improperly, may cause life-threatening side effects, such as irregular heartbeat, seizures, breathing difficulties, coma, even death. If skin temperature increases, for example as a result of bandaging, the amount of anesthetic reaching the bloodstream is unpredictable, and the risk of life-threatening side effects increases with greater amounts of lidocaine in the blood. FDA (2009) has advised consumers against:

- making heavy application of topical anesthetic products over large areas of skin,
- using formulations that are stronger or more concentrated than necessary,
- applying these products to irritated or broken skin,
- wrapping the treated skin with plastic wrap or other dressings, or
- applying heat from a heating pad to skin treated with these products.

Corticosteroids can affect all phases of wound healing (Treadwell, 2013). Recent studies have shed additional light on the negative wound healing qualities of corticosteroids. For example, glucocorticoids, which are contained in corticosteroids, decrease the steady state levels of procollagen messenger ribonucleic acids (mRNAs) and mRNA synthesis in unwounded cells, thereby decreasing type I procollagen synthesis. The treated wound heals with incomplete granulation tissue and reduced wound contraction. Corticosteroids also reduce collagen production as well as transforming growth factor beta (TGF-β) and insulin-like growth factor 1 (IGF-1) production in wounds, both of which are vital during normal wound healing. Moreover, corticosteroids increase the chance of a localized wound infection, retarding healing (Bosanquet et al., 2013).

SECTION VII: Device Classification

Device Classification

A. Statutory Definitions of Medical Device Classes

The Panel will be asked to recommend whether wound dressings that contain drug(s) meet the statutory definition of Class III, which means that:

- 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 life-supporting or life-sustaining or for a use which is of substantial importance in preventing impairment of human health, or 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.

B. Medical Device Classification Considerations

For the purposes of classification, FDA 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
4. The reliability of the device

Section (g)(1) of this regulation further states that it "is the responsibility of each manufacturer and importer of a device to ensure that adequate, valid scientific evidence exists, and to furnish such evidence to FDA to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to FDA adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into Class III."

According to 21 CFR 860.7(d)(1), "there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

According to 21 CFR 860.7(e)(1), "there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

To inform FDA's determination about the appropriate regulatory classification for wound dressings that contain drug(s), FDA identifies the risks to health associated with device use. After the risks to health have been identified, FDA must determine whether sufficient information exists to establish regulatory controls – known as special controls – to mitigate those risks. Special controls can include guidelines, labeling, device design requirements, conformance to performance standards, and other measures to provide a reasonable assurance of safety and effectiveness for the device type. Whether sufficient information exists to develop such controls will determine whether wound dressings that contain drug(s) should be classified into Class II or Class III.

<u>The panel will be asked to comment on the adequacy of the available scientific evidence with respect to safety and effectiveness for this device type, on whether the probable benefits to health from use of the device for the specific indications outweigh the probable risks (reasonable assurance of safety), and on whether the device will provide clinically significant results in a significant portion of the target population (reasonable assurance of effectiveness).</u>

If there is not a reasonable assurance of safety and effectiveness for this device type, or for subtypes with certain indications and/or technology, and special controls cannot be established at this time to assure such, PMAs (class III) would likely be required to establish safety and effectiveness.

If the Panel believes that Class II is appropriate, the Panel will be asked whether certain mitigation measure would serve as appropriate special controls and whether additional or different special controls are recommended. FDA has identified a number of risks and potential mitigation measures (Table 5). The Panel will be asked whether this list is a complete and accurate list of the risks to health presented by wound dressings that contain drug(s) and whether any other risks should be included in the overall risk assessment of the device type. Based on the available scientific evidence, FDA will ask the Panel for their recommendation on the appropriate classification of wound dressings that contain drug(s) under product code FRO.

Table 5: Risks and Potential Mitigation Measures

Dressing Type	Potential Risks to Health
Solid wound dressings	• Adverse tissue reaction (e.g., toxicity, allergic reaction) • Delay wound healing • Incompatible with other therapies • Increased risk of developing antimicrobial resistance • Infection • Loss of barrier function • Microbial growth within product due to ineffective antimicrobial activity and lack of “preservative” effectiveness • Product degradation during shelf storage • Retention of dressing material in wound
Creams, gels, ointments	• Adverse tissue reaction • Delay wound healing • Incompatible with other therapies • Increased risk of developing antimicrobial resistance • Infection • Microbial growth within product due to ineffective antimicrobial activity and lack of “preservative” effectiveness • Product degradation during shelf storage
Liquid wound washes	• Adverse tissue reaction • Delay wound healing • Inability to remove wound debris and foreign materials • Incompatible with other therapies • Increased risk of developing antimicrobial resistance • Infection

Dressing Type	Potential Risks to Health
	• Microbial growth within product due to ineffective antimicrobial activity and lack of "preservative" effectiveness • Product degradation during shelf storage

Identified Risk	Potential Mitigation Measure
Adverse tissue reaction	• Biocompatibility evaluation
Delay wound healing	• In vivo evaluation
Infection	• Labeling • Shelf-life validation • Sterilization validation • "preservative" effectiveness testing
Product degradation during shelf storage	• Labeling • Shelf-life validation
Retention of dressing material in wound	• Labeling
Incompatible with other therapies	• Labeling
Loss of barrier function	• Microbial barrier effectiveness testing • Water loss/moisture barrier effectiveness testing
Microbial growth within product due to ineffective antimicrobial activity and lack of "preservative" effectiveness	• Antimicrobial effectiveness testing
Inability to remove wound debris and foreign materials	Bench performance testing Labeling
Increased risk of developing antimicrobial resistance	Evaluation and identification of potential mechanisms for resistance development Labeling

SECTION VIII Appendices

Appendix 1 – Citations from 21 CFR for Classified Wound Dressings

Wound dressings regulated as Class I medical devices:

21 CFR 878.4014 Nonresorbable gauze/sponge for external use.

(a) Identification. A nonresorbable gauze/sponge for external use is a sterile or nonsterile device intended for medical purposes, such as to be placed directly on a patient's wound to absorb exudate. It consists of a strip, piece, or pad made from open woven or nonwoven mesh cotton cellulose or a simple chemical derivative of cellulose. This classification does not include a nonresorbable gauze/sponge for external use that contains added drugs such as antimicrobial agents, added biologics such as growth factors, or is composed of materials derived from animal sources.
(b) Classification. Class I (general controls). The device is exempt from the premarket notification procedures in part 807, subpart E of this chapter subject to the limitations in 878.9.

[64 FR 53929, Oct. 5, 1999]

21 CFR 878.4018 Hydrophilic wound dressing.

(a) Identification. A hydrophilic wound dressing is a sterile or non-sterile device intended to cover a wound and to absorb exudate. It consists of nonresorbable materials with hydrophilic properties that are capable of absorbing exudate (e.g., cotton, cotton derivatives, alginates, dextran, and rayon). This classification does not include a hydrophilic wound dressing that contains added drugs such as antimicrobial agents, added biologics such as growth factors, or is composed of materials derived from animal sources.
(b) Classification. Class I (general controls). The device is exempt from the premarket notification procedures in part 807, subpart E of this chapter subject to the limitations in 878.9.

[64 FR 53929, Oct. 5, 1999]

21 CFR 878.4020 Occlusive wound dressing.

(a) Identification. An occlusive wound dressing is a nonresorbable, sterile or non-sterile device intended to cover a wound, to provide or support a moist wound environment, and to allow the exchange of gases such as oxygen and water vapor through the device. It consists of a piece of synthetic polymeric material, such as polyurethane, with or without an adhesive backing. This classification does not include an occlusive wound dressing that

contains added drugs such as antimicrobial agents, added biologics such as growth factors, or is composed of materials derived from animal sources.
(b) Classification. Class I (general controls). The device is exempt from the premarket notification procedures in part 807, subpart E of this chapter subject to the limitations in 878.9.

[64 FR 53929, Oct. 5, 1999]

21 CFR 878.4022 Hydrogel wound dressing and burn dressing.

(a) Identification. A hydrogel wound dressing is a sterile or non-sterile device intended to cover a wound, to absorb wound exudate, to control bleeding or fluid loss, and to protect against abrasion, friction, desiccation, and contamination. It consists of a nonresorbable matrix made of hydrophilic polymers or other material in combination with water (at least 50 percent) and capable of absorbing exudate. This classification does not include a hydrogel wound dressing that contains added drugs such as antimicrobial agents, added biologics such as growth factors, or is composed of materials derived from animal sources.
(b) Classification. Class I (general controls). The device is exempt from the premarket notification procedures in part 807, subpart E of this chapter subject to the limitations in 878.9.

[64 FR 53929, Oct. 5, 1999]

Wound dressing regulated as a Class II medical device:

21 CFR 878.4015 Wound dressing with poly (diallyl dimethyl ammonium chloride) (pDADMAC) additive.

(a) Identification. A wound dressing with pDADMAC additive is intended for use as a primary dressing for exuding wounds, 1st and 2d degree burns, and surgical wounds, to secure and prevent movement of a primary dressing, and as a wound packing.
(b) Classification. Class II (special controls). The special control is: the FDA guidance document entitled "Class II Special Controls Guidance Document: Wound Dressing With Poly (Diallyl Dimethyl Ammonium Chloride) (pDADMAC) Additive." See 878.1(e) for availability of this guidance document.

[74 FR 53167, Oct. 16, 2009]

Appendix 2 – Listing of Ingredients in Wound Dressings

The following is a list of ingredients that are contained within unclassified cleared wound dressings with product code “FRO”. This is not an exhaustive list, but provides a list of ingredients that either have or potentially have "chemical activity" regardless of the intended function of the ingredient as described in the 510(k) submission. This list does not contain ingredients considered to serve as the "base" dressing material, such as carboxymethylcellulose, synthetic polymer, or collagen.

- Allantoin
- Bacitracin
- Behenyl alcohol (docosanol, Abreva)
- Benzocaine
- Cadexomer iodine
- Calamine
- Chlorhexidine
- Dimethicone
- Hydrocortisone
- Hydrogen peroxide
- Iodine
- Iodoform
- Lidocaine
- Manganese chloride
- Polymyxin B sulfate
- Potassium iodide
- Povidone iodine
- Povidone USP (Plasdone K 29-32)
- Salicylic Acid
- Silver sulfadiazine
- Sodium fluoride
- Thrombin
- Tromethamine USP
- White petroleum
- Acesulfame K
- Activated charcoal
- Aluminum hydroxide
- Aluminum oxide
- Aluminum sulfate
- Ammonium phosphate
- Ascorbyl palmitate (Vitamin C ester)
- Beeswax
- Benzalkonium chloride
- Benzoic acid
- Benzyl alcohol
- Bismuth subgallate
- Butylated Hydroxytoluene (BHT)
- Butylene glycol
- Calcium
- Calcium carbonate
- Calcium chloride
- Calcium oxide
- Calcium sulfate
- Candelilla wax
- Cetearyl alcohol (Cetostearyl alcohol)
- Ceteth-20
- Cetyl alcohol
- Cetyl palmitate
- Cholesterol
- Citric acid
- Copper
- Cyclodextrin
- Dehydroacetic acid
- Diazolidinyl urea
- Diisopropyl adipate
- DMDM hydantoin
- Ferric chloride Hexahydrate
- Ferric oxide
- Glycerin (glycerol)
- Glyceryl monostearate
- Glyceryl stearate
- Hydrochloric acid
- Hydrogenated castor oil
- Hydrogenated lecithin
- Hydroquinone
- Hydrous lanolin
- Iron sulfate
- Isopropyl alcohol
- Isopropyl myristate
- Kaolin
- Lactic acid
- Lecithin
- Light mineral oil
- Magnesium aluminum silicate
- Magnesium oxide
- Magnesium stearate
- Magnesium sulfate
- Malic acid
- Maltodextrin
- Mannitol
- Menthol
- Methyl salicylate
- Methylene blue
- Mineral oil
- Palmitic acid
- Parabens (various forms)
- Paraffin
- Pentalyn-H (Pentaerythritol ester of rosin)
- Petrolatum
- Phenoxyethanol
- Phosphoric acid
- Potassium sorbate
- Propyl gallate
- Propylene glycol
- Rubidium chloride
- Saccharin
- Sodium benzoate
- Sodium citrate
- Sodium lactate
- Sodium metabisulfite
- Sodium sulfate
- Sorbic acid
- Sorbitan sesquioleate (Arlacel C)
- Sorbitol
- Squalane
- Steareth-10
- Stearic acid
- Sucrose
- Sucrose laurate

- Tartaric acid
- Titanium dioxide
- Triethanolamine (TEA)
- Trolamine
- Vitamin C (ascorbic acid)
- Vitamin E (tocopherol)
- Xanthan gum
- Xylitol
- Zirconium oxide
- Acetic acid
- Alcohol
- Copper chloride (cupric chloride)
- Crystal violet
- Ethanol
- Gentian violet
- Germaben II
- Hypochlorous acid
- Liquid Germall Plus (propylene glycol, diazolidinyl urea, iodopropynyl butylcarbamate)
- Ozone
- Polyaminopropyl biguanide (PAPB)
- Polyhexamethylene biguanide (PHMB, polyhexanide)
- Polyvinyl pyrrolidone-iodine
- Quaternium 15
- Silver (various forms)
- Sulfur dioxide
- Triiodide resin
- Zinc (various forms)
- African palm oils
- Almond meal
- Aloe vera
- Angelica sp.
- Aqueous wheat extract
- Avocado oil
- Bisabolol (chamomile oil)
- Borneol
- Butyrospermum parkii
- Camella sinensis
- Carvacrol
- Centella asiatica
- Citris grandis extract
- Cocoamphodiacetate
- Cupuacu butter
- Eucalyptus oil
- Eugenol
- Extracts of licorice (deglycyrrhizinated)
- Fruit extract
- Glycyrrhetinic acid (licorice extract)
- Guar gum (Cyaiuopsis letragonolobus)
- Gum mastic
- Hydroxypropyl guar
- Karaya gum
- Konjac flour
- Lavender
- Lemon
- Meadowsweet extract
- Myristyl myristate
- Myrtillus extract
- Oak extract
- Oat glucan
- Olive oil
- Palm glycerides
- Piroctone olamine
- Polygonum cuspidatum
- Sandalwood oil
- Shea butter
- Solanum lycopersicum (tomato) extract
- Soy protein
- Styrax
- Tara Gum
- Tea tree oil
- Theobroma Grandiflorum seed butter
- Thymol
- Transcinnamaldehyde
- Vaccinium (blueberry)
- Vegetable oil
- Vitis vinifera (grape)
- Wintergreen fragrance
- Wood pulp core
- Acetamide MEA (monoethanolamine)
- Aluminum magnesium hydroxide stearate
- Aluminum pigment
- Arachidyl alcohol
- Ascorbyl tetraisopalmitate (Vitamin C ester)
- Betaines (various forms)
- Bismuth tribromophenate
- Capryloyl glycine
- Ceramide
- Ceteareth-10 phosphate
- Cetyl dimethicone copolyol
- Chlorine dioxide
- Chlorophyllin copper complex sodium
- Chromium chloride
- Cobalt chloride
- Colloidal silica
- Conjugated linoleic acid
- Cyclomethicone
- DEA Cetyl phosphate
- Decanoic acid (capric acid)
- Dialkyl carbamoyl chloride
- Dicetyl phosphate
- Dipolyhydroxystearate
- Dissolved oxygen
- EDTA
- Ethoxydiglycol
- Ethylene glycol monostearate
- Ethylhexyl glycerin
- Ethylhexyl palmitate
- Fumed silica
- Glyceryl monolaurate
- Hectorite clay
- Hexyl laurate
- Hydroxypropyl bispalmitamide MEA (ceramide)
- Iron (various forms)
- Isohexadecane
- Isopropyl sorbate
- Keratin
- L-glutamic acid

- Lyophilized formulate porcine plasma
- Manganese oxide
- Methyl triethoxysilane (MTES)
- Methylal
- Molybdenum chloride
- O-cymen-5-ol (Biosol)
- Palmitamide MEA
- Panthenol FCC (form of vitamin B)
- Pentylene glycol
- Phosphorus pentoxide
- Polyricinoleate
- Potassium ferrate
- Potassium iron oxyacid salt
- Pyroglutamic acid
- RADA-16 peptide
- Sarcosine
- Sodium selenite
- Sodium tetraborate (Borax)
- Sucralfate (sucrose octasulfate, aluminum hydrochloride)
- Telmesteine
- Titanium oxide
- Tonalin FFA 80
- Triglycerol (polyglycerol-3)

Appendix 3 – Example Indications for Use Statements

Representative indications for use and statements describing product performance for various cleared wound dressings within the FRO product code are provided below, subdivided based on wound dressing type and composition.

Dressings Containing an Antimicrobial such as Silver

Example 1: Prescription Use

"Under the supervision of a healthcare professional Brand X Dressings are intended for up to 7 day use for wounds such as vascular access or peripheral IV sites, orthopedic external pin sites, wound drain sites, surgical wounds (donor and graft sites, incisions), and partial to full thickness dermal ulcers (stage I-IV pressure sores, venous stasis ulcers, arterial ulcers, diabetic ulcers).

Brand X Dressing is indicated for the management of infected wounds, as the silver in the dressing provides an antimicrobial barrier that may be helpful in managing these wounds. In addition, the moist wound healing environment and control of wound bacteria within the Brand X Dressing may help reduce the risk of wound infection and support the body's healing process.

Brand X Dressing may be used for the management of painful wounds. Brand X Dressing's non-adherent wound contact layer reduces pain during dressing changes and evaporation of moisture in the dressing may soothe the wound."

Example 2: Prescription Use

"Brand X Dressing is indicated for use on partial and full thickness wounds up to 7 days.

This includes: first and second degree burns, as a protective covering for grafts, surgical sites, venous ulcers, pressure ulcers, diabetic ulcers."

Example 3: Prescription Use

"Under the supervision of a healthcare professional, Brand X Dressing may be used for the management of:

- Wounds as an effective barrier to bacterial penetration of the dressing as this may help reduce infection
- Partial thickness (second degree) burns
- Diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers and leg ulcers of mixed etiology) and pressure ulcers/sores (partial & full thickness)
- Surgical wounds left to heal by secondary intention such as dehisced surgical incisions

- Surgical wounds that heal by primary intent such as dermatological and surgical incisions (e.g., orthopedic and vascular)
- Traumatic wounds
- Wounds that are prone to bleeding such as wounds that have been mechanically or surgically debrided and donor sites
- Oncology wounds with exudate such as fungoides-cutaneous tumors, fungating carcinoma, cutaneous metastasis, Kaposi's sarcoma and angiosarcoma
- Management of painful wounds
- Infected Wounds"

Example 4: Over-the-Counter Use

"For Over-the-Counter Use, Brand X Dressing may be used for:

- Abrasions
- Lacerations
- Minor cuts
- Minor scalds and burns"

Catheter/Port Site Dressings

Example 5: Prescription Use

"Brand X Dressing is intended for use as a hydrophilic wound dressing that is used to absorb exudate and to cover a wound caused by the use of vascular and non-vascular percutaneous medical devices such as Vascular Devices, IV Catheters, Central Venous Lines, Arterial Catheters, Dialysis Catheters, Peripherally Inserted Coronary Catheters, Mid-Line Catheters, Non-vascular percutaneous devices, Drains, Chest Tubes, Externally Placed Orthopedic Pins, Epidural Catheters.

It is also intended to reduce local infections, catheter related bloodstream infections (CRBSI), and skin colonization of microorganisms commonly related to CRBSI, in patients with central venous or arterial catheters."

Example 6: Prescription Use

"Brand X Dressing can be used to cover and protect catheter sites and to secure devices to skin. Common applications include securing and covering intravascular catheters and percutaneous devices."

Creams for Managing Symptoms of Skin Disease

Example 7: Prescription Use

"Indicated to manage and relieve the signs and symptoms of seborrhea and seborrheic dermatitis such as itching, erythema, scaling and pain. Brand X Cream also aids to relieve dry, waxy skin by maintaining a moist wound and skin environment. A moist wound and skin environment is beneficial to the healing process."

Example 8: Prescription Use

Under the supervision of a healthcare professional, Brand X Wound Dressing is indicated to manage and relieve the burning, itching and pain experienced with various types of dermatoses, including radiation dermatitis, atopic dermatitis and allergic contact dermatitis. Brand X Wound Dressing may be used to relieve the pain of first and second degree burns. Brand X Wound Dressing helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process.

Products for Rinsing Wounds

Example 9: Prescription Use

"Brand X wound wash is intended for the removal of foreign material, such as debris and dirt, from dermal wounds."

Example 10: Prescription Use

"Brand X Wound Wash is intended for professional use for cleansing and removal of foreign material including micro-organisms and debris from wounds such as stage I-IV pressure ulcers, diabetic foot ulcers, post-surgical wounds, first and second degree burns, grafted and donor sites."

Example 11:

"Brand X Wound Wash is intended to cleanse, irrigate and externally manage dermal lesions such as lacerations, post-operative (surgical) wounds, grafts, partial and full thickness wounds, burns and ulcers (diabetic, venous stasis, pressure). It is meant to be used in conjunction with a sterile dressing that absorbs fluids (i.e. gauze, gel, alginate, foam, hydrocolloid)."

Appendix 4 – Recommendations on Use of Antimicrobial Dressings in Wounds

* The guidelines that *suggest* the use of antimicrobial dressings are shaded.

Type of wound	Recommendation/Conclusion	Source
Diabetic foot ulcer	• The available evidence does not support any benefit to using silver-based dressings for clinically infected wounds.	IDSA (2012)
	• Do not use antimicrobial dressings with the goal of improving wound healing or preventing secondary infection. • Do not select a specific type of dressing for a diabetic foot infection with the aim of preventing an infection or improving its outcome.	IWGDF (2015) and Lipsky et al., (2016)
	• Topical antimicrobial or antimicrobial-containing wound dressings are not recommended.	International Consensus on the Diabetic Foot (2007)
Venous leg ulcer	• We recommend against the routine use of topical antimicrobial-containing dressings in the treatment of noninfected venous leg ulcers.	Society for Vascular Surgery and American Venous Forum (2014)
	• No specific dressing product is superior for reducing healing time in VLUs. Select dressings based on clinical assessment of the ulcer, cost, access and patient/health professional preferences.	Australian Wound Management Association and New Zealand Wound Care Society (2011)
	• Simple non-adherent dressings are recommended in the management of venous leg ulcers. • Silver dressings are not recommended in the routine treatment of patients with venous leg ulcers.	Scottish Intercollegiate Guidelines Network (2010)
	• Antimicrobial dressings may be used short-term for the treatment of wound infection. • Use antimicrobial dressings for local infection or for prevention of infection in wounds at high risk.	Expert Working Group, Harding et al., (2015)
	• Topical antibacterial agents, such as antiseptics, topical antibiotics, and newer antimicrobial dressings as well as systemic antibiotics can be used to treat critically colonized or infected wounds.	Canadian Association of Wound Care (2006)
Pressure ulcer	• Consider using topical antimicrobial dressings to treat a pressure ulcer where clinically indicated in neonates, infants, children and young people, for example, where there is spreading cellulitis.	UK's NICE Guideline (2014)
	• In areas of high risk for contamination, the use of antimicrobial dressings may be useful in reducing the risk of infection.	Canadian Association of Wound Care (2006)
	• Consider using silver-impregnated dressings for pressure ulcers	National Pressure

Type of wound	Recommendation/Conclusion	Source
	that are: (1) clinically infected or heavily colonized; or (2) at high risk of infection. • Avoid prolonged use of silver-impregnated dressings. Discontinue silver dressings when wound infection is controlled.	Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel, and Pan Pacific Pressure Injury Alliance (2014)
	• Do not routinely use topical antiseptics or antimicrobials to treat a pressure ulcer in adults, or in neonates, infants, children and young people. • Consider using topical antimicrobial dressings to treat a pressure ulcer where clinically indicated in neonates, infants, children and young people, for example, where there is spreading cellulitis.	UK's NICE (2014). Clinical Guideline – Pressure ulcers: prevention and management
	Pressure ulcer in people with spinal cord injury: • Consider the use of antimicrobial dressings if signs of infection are present.	Canadian Association of Wound Care (2006)
Wound (general)	• Do not routinely choose antimicrobial (for example, silver, iodine or honey) dressings ahead of non-medicated dressings. • There is no robust clinical- or cost-effectiveness evidence to support the use of antimicrobial dressings (for example, silver, iodine or honey) over non-medicated dressings for preventing or treating chronic wounds. • Indiscriminate use should be discouraged because of concerns over bacterial resistance and toxicity. • Antimicrobial dressings may be considered to help reduce bacterial numbers in wounds, but should be avoided unless the wound is infected or there is a clinical risk of the wound becoming infected.	UK's NICE Advice (2015)
	• Consider a two-week trial of topical antimicrobials/antimicrobial dressings if the wound isn't healing despite optimal care (increased bacterial burden, covert infection, critical colonization suspected).	Canadian Association of Wound Care (2006)
	• There is insufficient evidence to support the routine use of topical antibiotics as a wound dressing. • Risks of antimicrobial resistance and contact dermatitis are noted when using antibiotics and recommend close monitoring of wounds for any adverse response. • Appropriate antimicrobial intervention (such oral antibiotics) is recommended in situations when infection is confirmed or highly suspected. • For mild to moderate infections, surgical debridement and narrow-spectrum antibacterials are recommended.	American Society of Plastic Surgeons: Clinical Practice Guideline – Chronic Wounds of Lower Extremity (2007)

Type of wound	Recommendation/Conclusion	Source
	• Wound infections that are severe and/or complicated by critical limb ischemia are generally considered to need hospitalization, parenteral broad-spectrum antibiotic, and surgical intervention.	
	• The guidelines state that wound antiseptic agents and others have antibacterial properties, but are all considered toxic to healthy granulation tissue. • For arterial insufficiency ulcers, topical antimicrobial dressings may be beneficial in management of chronically/heavily colonized wounds, decreasing their bacterial load and helping wound healing.	The Wound Healing Society: Chronic Wound Care Guidelines (2006)
Burn	• Guidelines recommend against use of prophylactic antibiotics to protect against cellulitis or sepsis. • There is no evidence that use of topical antimicrobial agents in initial management of minor burns reduces the incidence of infection.	American Burn Association: Practice Guidelines (2001)
Catheter Insertion Sites	• Do not use topical antibiotic ointment or creams on insertion sites, except for dialysis catheters, because of their potential to promote fungal infections and antimicrobial resistance. • Use a chlorhexidine-impregnated sponge dressing for temporary short-term catheters in patients older than 2 months of age if the CLABSI rate is not decreasing despite adherence to basic prevention measures, including education and training, appropriate use of chlorhexidine for skin antisepsis, and MSB. • No recommendation is made for other types of chlorhexidine dressings.	CDC Guidelines for the Prevention of Intravascular Catheter-Related Infections (2011)

SECTION IX: Bibliography

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