General and Plastic Devices Advisory Panel Meeting

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Disclosures

• Consultant to Argentum Medical, LLC

• Co-principal Investigator on BARDA Contract # HSSO1002013000019C developing silver-based burn dressings for radiation, mustard gas and other mass casualty use
Background

• 25+ years of experience as burn surgeon & chronic wound surgeon

• Board Certification in General Surgery, Plastic & Reconstructive Surgery and Surgical Critical Care

• Retired Colonel, USAR with 5 tours / 12 years at US Army Burn Center

• Former Professor of Surgery / Chief of Wound Center, U of Florida

• Former Associate Professor of Surgery / Chief of Plastic Surgery MUSC

• Involved in development of Southern Region and National Burn Disaster Plans

• Research in use of silver products for wound healing and burn care
Concern: Effect of regulatory changes on burn care

- The United States has barely sufficient resources to manage the day-to-day care of burn patients

- There are 123 burn centers, approximately 1700 burn beds and approximately 350 experienced burn surgeons in the US. Recruitment of nurses and physicians into the specialty is very difficult

- The Federal Government recognizes that there is insufficient surge capacity to manage a WMD or burn mass casualty incident in the US

- Burn care is tremendously resource-intensive and difficult to provide. Multiple dressing techniques and materials are often necessary. Several of the antimicrobials in daily use date back to the 1960’s.

- Many of the newer dressings come from small businesses that cannot afford the regulatory burden of device reclassification / PMA application or post-marketing studies
Silver: A naturally-occurring element

- Silver ion is normally present in humans from natural ingestion (blood levels of <2.3 ug/L, urine excretion 2 ug/day)

- Silver has been used for jewelry, currency and food handling for > 5000 years (mentioned in the First Book of the Old Testament)

- Alexander the Great used silver vessels to keep water pure (335 BC)

- Ambrose Pare (1590) used silver clips in surgery.

- Crede in 1880 first applied silver nitrate to eyes of newborns to prevent ophthalmia neonatorum – in US required by law for most of the 20th century

- Halstead (Johns Hopkins, 1889) used silver foil to prevent surgical infection

- A mainstay of burn treatment since the 1960’s

REF: Marx et al - Burns 2014; 40s: 9-18
Barillo et al - Burns 2014; 40s: 3-8
Microbial Resistance to Silver is Extremely Uncommon

- Silver ion has 4 antimicrobial mechanisms of action and all 4 need to be overcome to induce resistance – difficult to do even intentionally in the lab

- There are 3 known silver-resistance genes but the presence of these genes does not protect bacteria against high levels of silver ion

- Warriner: “silver does not induce bacterial resistance if used at adequate concentrations”

- Chopra: fewer than 20 cases of silver resistance found in a 32-year literature review-some were intentionally induced and 1 *Pseudomonas* strain found in a silver mine

- No clinical problems in 60+ years of burn experience with silver nitrate and silver sulfadiazene

REF: Marx- Burns 2014; 40s: 9-18
Chopra- J Antimicrobial Chemotherapy 2007;59:587-90
Warriner- Adv Skin Wound Care 2005; 18 (suppl): 2-12
Silver Dressings = Less Antibiotic Use

- Appropriate use of topical silver dressings provides high antimicrobial effect at site of infection (wound)

- High and sustained levels of silver ion at the wound PREVENT the development of microbial resistance

- With Silver-Nylon Dressings, silver ion is not absorbed into systemic circulation or found in solid organs, even after long-term use:
  This effect has been demonstrated in at least three species (minipig, rat, hairless guinea pig); in three depths of burn injury (superficial partial thickness, deep partial thickness, full thickness); and in 2 different mechanisms of injury (thermal burns and chemical burns)

- Silver based dressings allow local control of wound infection rather than using oral / intravenous systemic antibiotics


Barillo et al  -The Toxicologist, Supplement to Toxicological Sciences, 2016; Abstract # 2111.
Microbial Resistance is a Valid Concern

• For those of us in intensive-care unit practice, this is a daily problem

• Responsible stewardship of systemic antibiotics is advocated by many medical societies

• Topical antibiotics, however, are not the problem
Animal Use of Antibiotics As Growth-Promoting Agents

- In 2011, 13.6 million kilograms of antimicrobials were sold for use in food-producing animals, representing ~80% of all antibiotics sold in the United States (US FDA Data)

- Khachatourians: ‘About 90% of the antibiotics used in agriculture are given as growth-promoting & prophylactic agents rather than to treat infection’

- Union of Concerned Scientists: ‘Nontherapeutic livestock use accounts for 70% of total antimicrobial use. When all agricultural uses are considered, this share could be as high as 84%.’


Khachatourians – CMAJ 1998;159 (9):1129-1136

Union of Concerned Scientists: Hogging it!: Estimates of Antimicrobial Abuse in Livestock, April 2004
Guidance for Industry

New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209

Submit comments on this guidance at any time. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All written comments should be identified with the Docket No. FDA-2011-D-0889.

For further information regarding this document, contact William T. Flynn, Center for Veterinary Medicine (HFV-1), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 240-276-9084. E-mail: william.flynn@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
December 2013
Summary

• Antimicrobial resistance is a major concern for all of us

• Silver ion, with several millennia of human experience, is not causing antimicrobial resistance

• Topical wound therapies allow targeted therapy at the site of infection and decrease the use of systemic antibiotics

• It makes no sense to further hinder the difficult work of burn care providers by unnecessary over-regulation of products that we already know are working

• Reclassification of *Wound Dressings Combined with Drugs* will likely put small medical device companies out of business and further restrict the limited therapeutic options available to practicing clinicians

• Further regulation? Let's reconsider the 80% of antibiotics sold in the US that now are used in agriculture rather than to treat human disease