Healing the Warfighter With Mustard Gas Burns

First FDA Approved Product

Sulfur mustard vapor, commonly known as mustard gas, has racked up casualties during wars and military skirmishes worldwide since the German army first used it in WWI. The potent chemical weapon at first appears to have no effect on those exposed to it. However, severe skin blisters or other devastating symptoms appear within a day or two, or sometimes even in just a matter of hours, depending on the dose. It is so powerful that a single drop can cause skin burns on people within 10 cubic meters, according to the book, *Military History*.

Despite the 100-year history of mustard gas use, there was no medical product available to treat the skin burns caused by exposure. That is, until recently when MRIGlobal client Argentum Medical announced that its Silverlon burn and wound care products received Food and Drug Administration (FDA) clearance in the U.S. Silverlon products now can be used in a national emergency to treat the skin burns of victims exposed to the chemical and constitute the only approved medical countermeasure in the world for dermal sulfur mustard burns.

Path to FDA Approval

The path to FDA approval began when David Barillo, M.D., now a subject matter expert for Argentum and a retired U.S. Army Colonel, used a Silverlon bandage off-label at the U.S. Army Burn Center in San Antonio, Texas, to treat a patient who sustained a sulfur mustard burn in Iraq on his arm. Silverlon, a nylon fabric embedded with silver ions, is widely used on surgery sites in hospitals for its immediate, profound microbial effect, which helps prevent infection and promote wound healing. Later while discussing this case with colleagues at a Biomedical Advanced Research and Development Authority (BARDA) Industry Days meeting, the idea for a research contract for Silverlon use on either radiation or chemical vesicant (sulfur mustard) burns came about.

Silverlon products contain 50 to 100 times more metallic silver ions than other silver-impregnated dressings. They have been highly effective in treating sulfur mustard burns in hostile and austere military environments, as they were for Dr. Barillo's patient in Iraq. Dr. Barillo subsequently recommended that Argentum develop a program to add the bandage to the U.S. government's medical

countermeasures stockpile. This stockpile is the repository of medical material from which state and local public health agencies can be resupplied in the event of a national emergency. Inclusion in the national stockpile requires FDA approval.

Dr. Barillo prepared a proposal for BARDA, which is part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services. BARDA supports the progression of medical countermeasures from research to advanced development, toward consideration for FDA approval and inclusion in the strategic national stockpile. The agency agreed to fund the studies necessary to show that Silverlon was appropriate for use on sulfur mustard dermal wounds.

MRIGlobal's Role in the Approval Process

MRIGlobal is one of only four companies in the country that operates chemical containment laboratories required to study Silverlon's efficacy. Claire Croutch, Ph.D., a toxicologist and member of MRIGlobal's Medical Countermeasures division, served as the program's principal investigator, working with Argentum to optimize the study's design by anticipating how the FDA might require the research to be structured. During that process, the FDA recommended that the team change its approach for the final definitive study. Flexibility was critical, Dr. Croutch said, in redesigning the study in accordance with the FDA's recommendations.

After BARDA awarded the contract to Argentum and Argentum subcontracted the work to MRIGlobal, Dr. Croutch directed the series of eight required Silverlon studies, each of which built upon its predecessor studies. The first study, which began in 2013, involved determining how best to create a sulfur mustard wound on the animal subjects' skin and identify the injury's optimal depth. Subsequent studies involved debriding the wound to eliminate the bound sulfur mustard, verifying the frequency with which the Silverlon bandage should be changed and establishing the moisture level that would allow the bandage's silver ions to work most effectively.

After the first few studies were complete, Argentum and MRIGlobal met with representatives of BARDA, the FDA, and other government agencies. The federal officials reviewed data generated by the initial studies, confirmed that the research was working and awarded option years for completion of the program.

Along the way, Dr. Croutch and her team encountered and overcame certain challenges. A major hurdle occurred when the FDA recommended that the final pivotal study should be a non-inferiority study, rather than an efficacy study. A non-inferiority study's purpose is to show that the product being tested is equal to or better than an existing FDA approved product. In this case, however, there was no other FDA approved product on the market to treat mustard gas burns. Dr. Croutch and the Argentum research team and BARDA worked closely with the FDA to redesign and fine tune the study protocol and to choose a product to compare to Silverlon.

The Importance of Silverlon's FDA Approval and of Continued Research

The threat of chemical weapons is not going away. Sulfur mustard, used in at least 11 regional conflicts since WWI, is estimated to have exacted more than 100,000 casualties in the Iraq war and has been

used as an ISIS weapon in Syria since 2016. In a post-9/11 world, it has become increasingly vital to add products to the national stockpile that can mitigate the effects of chemical weapons and treat the mass casualties they can inflict. Silverlon products are among the first BARDA has added to prepare the nation to address a chemical agent – in this case, mustard gas – and save as many lives as possible in a national emergency and to protect warfighters.

In addition to burning skin, sulfur mustard damages eyes and, if inhaled, harms the lungs and respiratory tract. MRIGlobal is working on research programs for products that will address these injuries, as well. Dr. Croutch and her team also run more than 10 programs for CounterAct, a National Institutes of Health program that supports research to identify therapeutic medical countermeasures against chemical threat agents. Many of MRIGlobal's other BARDA-funded clients are commercial businesses/pharmaceutical companies looking for cross-licensure of their existing products for chemical agent medical countermeasures. All medical countermeasures clients rely on the company's chemical agent research capabilities, including its chemical agent containment labs and animal models.

"There is no animal model we haven't run here," Dr. Croutch said. "MRIGlobal has the ability to help clients design studies and run successful medical countermeasure programs that will gain FDA approval. We work with our clients as one team, and we are just as invested in the success of the client's products as they are."