

# Use of Unapproved Products, Off-Label Use, and Black-Box Warning ... A Variation of Newton's Third Law or the Practical Application of the Rule of Unintended Consequences ... Considerations in Military Operational Medicine

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**Executive Editors Note:** As multiple medical research and development efforts (both in SOF and in conventional research units) offer new drugs and medical equipment to the battlefield, we need to understand the rules of engagement for use, which, are different for individual providers versus military health care systems.

## ABSTRACT

This article discusses the regulatory requirements for the use of unapproved drugs and off-label use of drugs and provides specific examples for military medicine. Additionally, it explains issues associated with standardization by the Service as a designated set, kit, or outfit as opposed to a general guidance. The former situation can be interpreted as a de facto policy whereas the latter is an adaptation of practice of medicine.

Recent news stories brought to light the challenges facing military medicine in an environment where dramatic life-saving measures have become the expected rather than the exception.<sup>1,2</sup> However, many of these same life-saving measures have the potential to place a practitioner in situations of “damned if you do, damned if you don’t” with regard to adherence to various regulatory and legal hurdles.

This paper is intended to help explain the regulatory issues associated with unapproved (investigational new drug – IND) products, off-label use of approved products, and the practical implications of black-box warnings on drug labels. Furthermore, specific examples will be described with regard to the application of the respective regulations. Finally, practical considerations will be discussed to guide practitioners as they wade through the medical-legal environment.

The Food and Drug Administration (FDA) regulatory processes for approval of new pharmaceuticals, biologics, and medical devices focus on the evaluation of these products from well-controlled clinical trials. The approval process for a new product or a labeling change to an approved product requires several years and several hundred million dollars.<sup>3</sup> Furthermore, regardless of the exhaustive nature of the approval process, it is not perfect and has been

assaulted from many sides to include consumer groups who at times advocate for greater safety and at other times demand quicker access to therapeutic breakthroughs as well as the pharmaceutical industry which faces demands from stockholders for return on investment. Reliance upon results from controlled clinical trials is problematic in that it is difficult to derive a robust safety profile of a product due to the tight inclusion/exclusion criteria involved with an efficacy study. The FDA is well aware that when a product is introduced into the market place, the patient population will be anything but homogenous and the manner in which prescribers use the product will not necessarily reflect the labeled indications. In recent years, the FDA has addressed the potential blind spot associated with limited safety data through the requirement for additional post-marketing studies, also known as Phase IV studies, and reliance upon MedWatch reports submitted from practitioners.<sup>4</sup> Regardless of these initiatives, the introduction of a pharmaceutical, biological, or medical device into a human host can be viewed as an application of Newton's Third Law: For every action, there is an equal and opposite reaction. The problem with the introduction of that pharmaceutical, biologic, or medical device is that it is difficult to know how that opposite reaction will manifest itself. Therefore, managing

medication related adverse events is often an exercise in the application of the law of unintended consequences. Consequently, various laws and regulations have been implemented over the years to address some of the potential problems that can arise when the best intentions of prescribing by policy can result in unintended consequences.

#### **APPLICABLE LAWS, REGULATIONS AND POLICIES**

Department of Defense policy regarding unapproved medical products (investigational new drugs – INDs) and off-label use of medical products in military operations emanate from 10 United States Code (USC) 1107,<sup>5</sup> 21 Code of Federal Regulations (CFR) 50.23,<sup>6</sup> and Department of Defense Directive 6200.2.<sup>7</sup> For most practitioners, the laws and regulations are somewhat nebulous numbers that do not pertain to their practice environments. However, while the specific numbers associated with these laws and regulations may represent relatively low priority information in the context of required knowledge in order to treat patients, an orientation to the precepts of these documents will help the practitioner understand the basis for why the laws/regulations exist.

10 USC 1107 describes the basic legal requirements for the use of unapproved, investigational products in military operations. These requirements center around the need to inform recipients of the investigational or unapproved nature of the product provided, the reasons for prescribing, and the respective risks and benefits associated with the product. Furthermore, regarding any exception from informed consent requirements, the President is the approval authority. 10 USC 1107 reflects a Congressional recognition that when an IND product is the only means available to protect against a lethal chemical or biological weapon, the lives of individual members, the safety of their comrades who rely on them, and the success of the military operation may require uniform use of the medical protection. 21 CFR 50.23 (an FDA regulation) describes the procedures for review of the use of force health protection investigational products by the FDA and requirements for an Institutional Review Board (the Army Human Subjects Research Review Board – HSRRB). These reviews are required prior to implementation of any usage and prior to any requests through the Secretary of Defense to the President if a waiver of consent is requested.

In the BioShield legislation of 2004, Congress provided some relief to the many stringent requirements associated with investigational products and created a category known as the Emergency Use Authorization (EUA).<sup>8</sup> The EUA allows the FDA to authorize the use of products that have not been fully approved in the event of a real or potential public health or military emergency if there is sufficient evidence to demonstrate safety and effectiveness. A

key consideration for the FDA is the balancing of the seriousness of the emergency against the body of knowledge of the risks and benefits of the proposed product. For example, EUA approval for a product with a known safety profile that is in Phase III clinical trials for use in a fatal disease pandemic represents one end of a spectrum for FDA evaluation as compared to a novel product that has yet to be introduced in humans. Of note with the EUA is that the FDA also evaluates the information to be provided to healthcare providers on how to use the product and the information to be provided to recipients of the product. Furthermore, in the absence of a Presidential waiver, recipients are to provide consent approved by the FDA to receive the product. However, the consent does not necessarily need to be approved by an institutional review board as the FDA research rules do not typically apply for EUAs.

The EUA is different from an emergency use of an investigational product for the treatment of an individual patient or for the conduct of emergency research. The FDA has specific provisions to allow for an investigational product to be used in an emergency situation when that product represents the only potential life-saving intervention.<sup>9,10</sup> These are distinctly different situations where in one case, an unapproved drug or device may represent an intervention of last resort. The other situation involves a deliberate effort to conduct a well controlled trial with an investigational product where the study involves enrolling research participants who cannot provide their own consent due to the nature of their illness or injury.<sup>11</sup> Both of these situations will be briefly discussed later in this paper.

Another consideration for healthcare providers is the language in Department of Defense Directive (DoDD) 6200.2. DoDD 6200.2 states that “DoD Components shall make preferential use of products approved by the FDA for general commercial marketing, when available, to provide the needed medical countermeasure.” DoDD 6200.2 goes on to describe the requirements for using unapproved products and off-label products for force health protection. Key in this description is the definition of force health protection, “an organized program of healthcare preventive or therapeutic treatment, or preparations for such treatment, designed to meet the actual, anticipated, or potential needs of a group of military personnel in relation to military missions.” The practical take home point from DoDD 6200.2 is the differentiation between practice of medicine and force health protection when it comes to off-label prescribing. Practice of medicine is the interaction between a provider and his/her patient based on a personal knowledge of the medical history and needs of a specific patient. Off-label use of prescription products in the practice of medicine is not regulated by the Food and Drug Administration. The FDA regulation on investigational products specifically

states that the document “does not apply to the use in the practice of medicine for an unlabeled indication of a new drug approved under part 314 or of a licensed biological product.”<sup>12</sup> However, misadventures associated with off-label prescribing in the practice of medicine are open game to the legal community.

The practice of medicine often evolves faster than the capacity of the regulatory-laden approval process for prescription products. The practice of medicine often advances after publication of research results from randomized controlled trials reporting new ways in which approved products can be effective. In organized settings, these research results are often collated and organized into clinical practice guidelines as evidence-based medicine in an attempt to provide the best possible healthcare solutions for patients and reduce variation in the delivery of care. However, in most institutions, the clinical practice guideline is not viewed as a rote policy, but as a guide to allow the practitioner to assess the needs of the specific patient according to guidance derived from the current knowledge on that particular condition and the available products to treat that condition. Clinical practice guidelines are written for a particular disease or injury set, and it is often difficult to identify the constellation of co-morbid conditions that can accompany the guideline, thereby requiring the practitioner to exercise clinical judgment when assessing the evidence when prescribing to their patients according to guidelines.

An additional term that has more of a medical-legal basis for consideration is the “black-box warning.” A black box warning means that the FDA has determined that the drug carries a significant risk of serious or even life-threatening adverse effects. In addition to seeing an actual black box enclosing the warning on the approved package insert, the FDA usually requires the pharmaceutical company to send out a “Dear Doctor” letter to warn prescribers of the potential risk and any cautions with regard to patient monitoring. The reason this term has more of a medical-legal connotation is that if a patient has a medical misadventure with such a product, and the prescriber was not following the cautions listed within the black box, than the patient’s lawyer will have little difficulty in justifying a malpractice claim made on behalf of that patient.

#### **SPECIFIC EXAMPLES AND PRACTICAL CONSIDERATIONS**

Several examples will illustrate the application of the terms described above.

First, with regard to force health protection, the array of vaccinations provided to Service members at entry to active duty represents the classic example of the prescribing by policy an organized program of preventive medicine. When the anthrax vaccine experienced legal challenges to the FDA approval status a few years ago, the

FDA pulled the approval status. The DoD went through the process of identifying the potential emergency situation that existed for the use of anthrax as a biological weapon and submitted an EUA request to the FDA. The FDA allowed the use of the anthrax vaccine on a voluntary basis for those individuals who consented to receive the product. Fortunately, the controversy surrounding the approval status of the anthrax vaccine was resolved and the product is available for administration.

Regarding off-label use of an approved product, media attention was drawn to the use of recombinant factor VIIa for the treatment of severe bleeding in trauma casualties in Iraq.<sup>1</sup> The product, also known commercially as Novo-Seven®, is approved for the treatment of bleeding in hemophilia.<sup>13</sup> While the use of the product was outside the labeled indications, the introduction of the product into the military trauma environment was not based on a DoD policy position. Trauma surgeons in theater who were familiar with the most recent literature documenting positive results from the use of recombinant factor VIIa in trauma used a practical evidence-based medicine approach to establish local clinical practice guidelines for damage control resuscitation that were consistent with the austere nature of the environment and the recognition that early use in the trauma facility was associated with less need for massive transfusions and consistent with more positive outcomes.<sup>14-17</sup> Regardless of the complexity of the cases treated with recombinant Factor VIIa, the use of the product was open game for media attention (and subsequently the sub-title of the application of Newton’s Third Law). However, the same undesirable media attention provided an avenue to explain to the Congressional leadership the challenges associated with military medicine and the shortcomings associated with over-interpretation of well intended laws and regulations.

Related to the question of off-label use is the relationship of the black-box warning and the labeled indication for fentanyl lozenges (Actiq®). The fentanyl lozenge is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.<sup>18</sup> A request for stockage of this product in Special Forces aide bags resulted in considerable discussion regarding two aspects of the use of the product. These were the specific nature of the approved label and the intended level of prescribing. Regarding the limited indication, the approved label is a function of the environment for which clinical trials were conducted to obtain product approval. Conducting research in chronic pain to get a product onto the market is much more straightforward with regard to the regulatory burden of conducting research in the acute care environment, where obtaining

consent is a difficult proposition. Furthermore, the economic incentive for a company to obtain the kind of clinical data to justify the expanded labeling represents another hurdle as the clinical experience of practitioners with a product like fentanyl is substantial, as the product has been on the market for decades in the injectable dosage form. This means that studying the specific use of fentanyl (lozenges) by Special Operations Medics in the field represents little to no incentive to the company. Regardless, the therapeutic ratio with the product is relatively narrow and a substantial number of medication misadventures have been associated with its use resulting in the black box warning on the package insert that states:

including this product in the aide bag. Special consideration in the area of troops has to be with the training and experience of each medic with regard to the anticipated clinical experience they would need in making use of this product, as well as any other non-standard product added to the bag. Furthermore, in addition to the normal clinical planning/decision making factors, the organization does need to recognize that the product requires substantial accountability / control procedures to minimize the risk of diversion and abuse.

With regard to the use of an unapproved product in an emergency situation, U.S. Army physicians in Iraq have used a German made product, the Novalung interventional

**WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE**

**ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to that of other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.**

**ACTIQ is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60mg morphine/day, at least 25mcg transdermal fentanyl/hour, at least 30mg of oxycodone daily, at least 8mg oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

**Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. All units must be kept out of the reach of children and opened units properly discarded.**

The concomitant use of ACTIQ with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Such a strongly worded label represents a considerable challenge to any exercise in rationalizing the standardized use of the product. However, the Special Forces medicine environment is different from any clinical setting that can be envisioned by representatives from industry, the FDA, and most of the other providers in military medicine.

As such, the relationships that exist between the Special Forces surgeon and the physician extenders under their responsibility are drastically different from traditional military medicine organizations. Furthermore, by regulation, the Special Forces Medic may be indirectly supervised by their respective medical officer. The Special Forces surgeon and the patients under his or her responsibility would be best served through the evaluation of the situation under a METT-T type planning factor where a standard evaluation on a case by case basis is made for each mission before

lung assist device, as a measure of last resort in a few patients with acute respiratory distress syndrome subsequent to concussive lung injury. The use of this product followed procedures outlined by the FDA which include:

- Informed consent from the patient or a legal representative when feasible. The consent of the patient may not be possible, and the consent of a legal representative may be a function of the reliability of communication channels.
- Clearance from the institution as specified by their policies. An a priori determination by the respective medical leadership in theater was provided.
- Concurrence of the IRB chairperson within five-days of the use of the device. For the use of the device in Army facilities in Iraq, the Brooke Army Medical Center served as the IRB of record and current com-

munication channels should suffice.

- An independent assessment from an uninvolved physician. This occurred prior to use of the product and was documented in the patient medical record.
- Authorization from the IDE sponsor. Novalung® GmbH has provided the Department of Defense with authorization to use the product as an emergency IDE.

These regulatory requirements may appear to represent a hurdle to overcome the use of an unapproved product in an emergency situation. However, there are offices within the U.S. Army Medical Research and Materiel Command (USAMRMC) that have sufficient expertise to facilitate the appropriate use should the need arise. The USAMRMC Office of Research Protections and the Force Health Protection Office of the U.S. Army Medical Materiel Development Activity can help the practitioner reduce the labyrinth of regulations into an exercise in the appropriate documentation of clinical care.<sup>19,20</sup>

The FDA hurdles for use of an investigational product in an emergency setting for one specific patient are not as high as they are with the conduct of clinical research. Furthermore, it is important to recognize that the FDA does not look at these regulations as an avenue to provide early access to an investigational product for more than one patient. If a practitioner anticipates needing a product for several patients, they are required to go through the process of obtaining an investigational drug approval or an investigational device exemption from the FDA. This situation leads to the discussion of the practical limitations of conducting research under the FDA regulations for emergency research. The conduct of emergency research under FDA regulations during military operations is not a practical reality for obtaining data to support the marketing application of a drug or device.<sup>21</sup> The concept of conducting a controlled-clinical trial under the FDA's good clinical practice standards is counter-intuitive to the nature of the provision of care in the relatively uncontrolled environment of military medicine in a combat setting. While there is no absolute prohibition from conducting such a study, there are several practical considerations for the well-intentioned researcher. First, the personnel resources required to conduct the study, collect the data, monitor the data, and maintain control over the investigational product goes outside the normal staffing of a healthcare facility engaged in the provision of care. Adding these personnel has the potential to create undue stress on an already challenging environment and creates additional burdens for the theater of operations with regard to security, transportation, and housing to name just a few. Furthermore, before such a study can begin, the approval process could require more than a year to obtain the appropriate Service Secre-

tary approval.

The last example describes a situation in which a patient requires the use of a foreign anti-venom for treatment of either snake or scorpion venom poisoning. The U.S. Army Medical Research and Materiel Command (USAMRMC) filed a blanket IND with the FDA for the use of foreign anti-venoms. Additionally, the FDA basically views this IND as a pseudo-emergency IND and requests in-turn from the Army reports of very basic information such as the name of the anti-venom used, the source of the anti-venom (i.e., name of manufacturer, lot number) and outcome information from the use of the product. The Central Command established a procedure for reporting such episodes to the USAMRMC to assist in the regulatory compliance with the minimal FDA requirements.<sup>22</sup>

### TARGET FOCUS

Special operations medics are often the end-users of the medications that are being studied for off-label use. Therefore it is incumbent on the researchers keep this in mind at the outset of a study or examination of a product. Unlike civilian, and to some extent typical military medicine, Special Operations medicine is continually pushing the envelope on what can be done by non-physician medical personnel. Many times this occurs in environments that would have been considered impossible in the past. Therefore, when determining the safety of a medication used for applications other than that for which it was approved, strict adherence to closely observed protocols is of paramount importance. Without this, there is no way to evaluate the effectiveness of the medication.

For instance, in the observational study regarding the use of the fentanyl lozenge noted above, the clinicians supervising the use of this drug maintained a strict adherence to the protocols set forth before it was used. The black box warning given by the FDA was clearly daunting but all involved recognized that the warning did not directly apply to the population being studied. Fentanyl is a drug that causes respiratory depression at a given blood level and could become a very real concern if used by patients of their own accord while not being supervised. Rarely is this the case in special operations medicine since patients often have some form of observation following an injury. During the initial study, if observation was not possible, the study protocol indicated that the drug should not have been used.

At the end of the day, novel use of medications and medical devices are examined with a focus on saving lives. Medics at the point of injury are critical in the success of this endeavor and all clinicians considering the off-label use of a medication need to assume that, eventually, it will make it into the hands of a medic and craft the protocol accordingly.

## FOR THE MEDICS

This article is salient for non-physician medical providers in that it illustrates the complexity of the approval process that is taken by providers when using a drug for a condition other than that for which it was intended. Every medic dispensing medications to a patient should have a clear understanding of the pharmacology of that medicine. This is especially true in the case of off-label or novel uses.

Current Special Operations medical personnel are faced with an FDA black-box warning for the use of Actiq lozenges, This should not be taken as a mandate for preventing its use, rather it should be used to reinforce that the medic understand the potential problems and thus, be prepared. In doing so, there is a heightened awareness that will certainly lead to a minimal amount of complications.

## TAKE HOME POINTS

This paper scratches the surface with regard to the many issues associated with the regulatory and legal challenges associated with investigational and off-label use of products. A constant that can be applied to these situations is that there is no constant – each application represents a unique and differing aspect of military medicine. Therefore, the following generalized take home points that equip the practitioner to appropriately discern the complexities of these issues may represent a more useful tool than specific advice or guidance.

- The FDA approval process provides evaluation of product efficacy and safety in the intended population stated on the label. Therefore, much of what is known about a product is discovered in the post-marketing phase when it becomes available to a larger, more heterogeneous population of patients from across all age ranges, ethnic groups, and comorbid conditions. Industry needs appropriate incentives to conduct the expensive clinical trials necessary to support expanded indications. Fortunately, Novo-Nordisk is in the process of evaluating the efficacy of recombinant Factor VIIa in trauma in an international multi-center trial. Unfortunately, it will take several years to complete this complex study.
- Physicians have a personal responsibility for keeping current in the practice of medicine and for using critical evaluation of information from literature from randomized controlled trials. Care should be taken with regard to generalization of results from well-controlled trials and especially from anecdotal reports. Therefore, establishing consensus panels to establish general clinical practice guidelines represents a deliberate, orderly approach of evi-

dence-based medicine to expanding the use of a product in a controlled fashion without making the use part of a larger policy dictating what every patient should receive. Under the clinical practice guideline approach, the practitioner has the leverage to apply the guideline based on their experience and the unique characteristics of what each patient presents.

- Special operations medics undergo extensive screening and training before being allowed to act as medical extenders in the austere and/or combat environments. We expect them to act with a high level of maturity and with a full understanding of the medications they are using. It is up to the unit surgeons and physician assistants to ensure that the medics are qualified to use any drug, especially one with potentially serious adverse effects.
- Adding products for an unapproved use to sets, kits, and outfits represents a defacto policy and should be avoided as the approval process is long and challenging. If a product is needed for off-label use, the military medical supply channels are capable of providing a non-standard basis and furthermore, the non-standard acquisition shows the American public that it was the clinician who actively asked for the product to be available rather than a universal policy that made that product available for the care of the patient.

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**HEADQUARTERS  
MULTI-NATIONAL CORPS - IRAQ  
BAGHDAD, IRAQ  
APO AE 09342**

FICI-MD

7 July 2006

MEMORANDUM FOR See Distribution

SUBJECT: CENTCOM / MNC-I Policy for Antivenins Lacking U.S. Food and Drug Administration Approval

1. REFERENCES.

JCS Campaign Analysis Report U-145,017-02, 8 October 2002, "Venomous Snakes and Scorpions in Iraq, and Their Antivenin Sources"

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AR 40-7, Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances, 4 January 1991

AR 40-38, Clinical Investigation Program, 1 September 1989

21 U.S. Code, Chapter 9, The Federal Food, Drug, and Cosmetic Act of 1938 with amendments.

10 U.S. Code, Subtitle A, Part II, Chapter 55, Section 1107, Notice of Use of an Investigational New Drug or a Drug Unapproved for its Applied Use, 5 Jan 99.

21 CFR 50, Protection of Human Subjects, April 1, 2004.

Executive Order 13139, Improving Health Protection of Military Personnel Participating in Particular Military Operations, September 30, 1999.

21 CFR 50 & 312, Human Drugs and Biologics; Determination That Informed Consent is NOT Feasible or is Contrary to the Best Interests of Recipients, October 5, 1999.

DoD Directive 6200.2, Use of Investigational New Drugs for Force Health Protection, August 1, 2000.

2. **PURPOSE.** Establish the theater policy for the management, use, and reporting requirements of investigational antivenins.

3. **APPLICABILITY.** All military and civilian personnel under the operational or tactical control of CENTCOM & MNC-I.

4. **Background.** Highly poisonous pit vipers, cobras, and scorpions can be found in almost every habitat in the CENTCOM region. Military forces deployed to Iraq are at risk for venomous snakebites and scorpion stings. Seven venomous snake species and four venomous scorpion species found in Iraq are capable of inflicting life-threatening wounds. The snakes are well-camouflaged and when cornered or stepped on, these snakes are remarkable for the speed with which they strike. Their bites are responsible for many deaths throughout the region. Untreated snakebites can cause convulsions, paralysis, hemorrhage, and death. Scorpions hide in protected places. Favored sites are under rocks, wooden boards, in old tires, utility boxes, tentage, laundry piles, and debris piles. Their venom affects the nervous system. The most appropriate treatment for significant snake or scorpion envenomation is species-specific antivenin administered by trained medical personnel. Because the venomous snakes and scorpions found in Iraq are geographically different from other species the unique antivenins used to treat envenomation are not U.S. Food and Drug Administration (FDA) approved products. They are therefore classified as investigational new drugs by the FDA. Normally this classification would require the development of an investigational protocol directing the explicit conditions and manner of use of these agents in patient care. Their use would also require informed consent. The FDA has granted a "blanket waiver" of the IND requirements on the use of these antivenins and has instead placed some unique reporting requirements on their use.

## 5. Policy and Procedures.

a. **Stocking.** The unique, non-FDA approved antivenins required for treatment of snake or scorpion envenomation will only be stocked by Level 3 facilities within the CENTCOM AOR. Exceptions to this policy must be requested and justified to the CENTCOM Surgeons Office delegated to the P& T Committee. If a snakebite or scorpion envenomation occurs, identify the snake or scorpion if possible (kill it, do not attempt to capture it) and transport the victim immediately to the nearest Level 3 medical facility. Proper treatment of envenomation victims can only be provided by a physician and patients must be closely monitored during this treatment. Patients are at high risk for hypovolemic shock, renal impairment, and bleeding due to envenomations as well as immediate and delayed hypersensitivity reactions from the antivenins.

(1) These antivenins should be ordered and stocked only by the pharmacy service of the Level 3 MTF. The pharmacy services have personnel trained in the management of investigational new drugs (INDs) and proper preparation of doses.

(2) The pharmacy services in theater operate a communications network to ensure rapid replacement of used or expiring antivenin products.

b. **Ordering.** The investigational antivenins must be ordered only through USAMMC-SWA or USAMMCE. The pharmacy staff officers in these units have the data on each unique product and its source of supply. The following products are INDs that may be required for use in SWA:

(1) 6505-08-139-1423, Polyvalent Snake Antivenin, 10ml, 10s (FAVIREPT) for puff adder (*Bitis arietans*), whitebelly saw-scaled viper (*Echis leucogaster*), Egyptian cobra (*Naja haje*), black-necked spitting cobra (*Naja nigricollis*), desert-horned viper (*Cerastes cerastes*), and Sahara viper (*Microviper deserti*). Due to the limited coverage, Favirept will be procured as the **alternate** snake antivenom when other products are not available.

(2) 6505-08-139-1452, Polyvalent Snake Antivenom (Equine), 10ml, 10s from the National Antivenin & Vaccine Production Center in Saudi Arabia, for Desert Black Snakes and Cobras including *Bitis arietans*, *Cerastes cerastes*, *Echis carinatus*, *Echis coloratus*, *Naja haje*, *Walterinnesia aegyptia*. The antivenom also neutralizes hemorrhagic and myonecrotic activities of viper venoms and the neuromuscular blocking and cardiotoxic effects of elapid venoms. It has a wide spectrum of activity and can neutralize venom of many Middle East and North African snakes including *Bitis caudalis*, *Bitis gabonica*, *Naja melanoleuce*, *Naja naja*, and *Naja nigricollis*.

(3) Razi Polyvalent Snake Antivenin, 10ml, 10s from RAZI Vaccine & Serum Research Institute, Tehran, IRAN for *Echis carinatus*, *Vipera lebetina*, *Vipera albicornuta*, *Pseudocerastes persicus*, *Naja naja oxiana*, and *Agkistrodon halys* venom with phenol as preservative. Razi Antivenin contains the most commonly shared venomous snake in this geographic region and should be the first line of antivenin therapy.

(4) 6505-08-139-1255, Polyvalent Scorpion Antivenin, 1ml, 20s (SCORPIFAV) for fattailed scorpion (*Androctonus australis hector*), death stalker (*Leiurus quinquestriatus*), no common name (*Buthus occitanus mardachei*).

(5) 6505-08-140-1520, Polyvalent Scorpion Antivenom (Equine), 1ml, 10s from the National Antivenin & Vaccine Production Center in Saudi Arabia, for Saudi yellow scorpion (*Leiurus quinquestriatus*) and black scorpion (*Androctonus crassicauda*). The antivenom also has a wide spectrum of activity and can neutralize the venoms of many middle East and North African scorpions including *Buthus arenicola*, *Buthus minax*, *Buthus occitanus*, *Leiurus quinquestriatus hebraus*, and *Androctonus amoreuxi*.

c. **Distribution and Storage.** These antivenins must be distributed under cold chain managed, refrigeration conditions and must never be frozen. All persons involved in the storage or distribution of these antivenins must ensure maintenance of refrigeration cold chain at all times. The Cold Chain Management Guide should be consulted for information on packing and shipping if movement of these products is required. The authorized stock levels are described in Table 1.

**TABLE 1**

Antivenin Stockage List by Treatment Facility	Facility Name												
	CSH Bucca	CSH Abu	CSH Mosul	CSH Tikrit	CSH Baghdad	CSH Tallil/ AIA sad	332d Balad	Navy Kuwait	ROK Irbil	14th Bagram	376 Kyrgyzstan	British	Jordanian
Scorpifav Scorpion Species Anti Venom	20	20	20	20	20	20	20	20	0	20	0	20	20
Polyvalent Scorpion Antivenin Equine Serum	4	10	20	20	20	20	20	20	10	20	0	0	0
Polyvalent Snake Antivenin Equine Serum	20	20	20	20	20	20	20	20	10	20	0	0	0
Favirept Fragments Equine Antivenin	0	0	0	0	0	0	0	0	0	0	0	0	0
Razi Polyvalent Snake Anti-venin	20	20	20	20	20	20	20	20	0	20	10	10	0
Affinity Purified, European Viper Antivenom (Viper Tab)	0	0	0	0	0	0	0	0	0	0	0	0	0
Polyvalent Snake Antivenin (different NSN)	0	0	0	0	0	0	0	0	0	0	0	0	0

d. **Control and Accountability.** Because these antivenins are IND products they must be managed in the same manner as controlled substances. Each vial or ampoule is an accountable unit of issue. All receipts and expenditures must have justifying documentation (either an MRO for a receipt or a physician’s order or a turn-in document for dispensed or expired product). Maintain a perpetual inventory and provide documents to the monthly controlled substances inventory officer during routine inspections.

e. **Dispensing and Preparation.** When known envenomations occur and one of these products is ordered by a physician the pharmacy service will dispense the required amounts for patient administration. If product preparation is required follow the product labeling instructions. Pharmacy will sign doses over to the administering nursing or physician personnel using appropriate documentation.

f. **Administration.**

(1) **General.** Nursing or physician personnel administering one of these products must ensure total dose is documented in the patient record and matches the dose ordered by the physician, and prepared and dispensed by the pharmacy.

(2) **Supportive Therapy.** IV fluid administration to support hemodynamic stability (i.e., normal blood pressure and maintain urine output) is an essential element of treatment.

(3) **Monitoring.** The patient’s coagulation status must be monitored due to hemotoxicity of some venoms. When severe envenomation is suspected based on signs and symptoms, treatment with antivenin should be initiated. Before initiation of antivenin therapy educate the patient on the indication for antivenin treatment and document the patient’s consent to treatment in the medical record.

(4) **Antivenin administration.** Administration of antivenins must be closely monitored due to potential for hypersensitivity reactions. Greater than 10% of patients treated with antivenin may develop immediate allergic reactions. Keep epinephrine 1:1000 injection, 1ml and diphenhydramine 50mg/ml injection, 1ml available for anaphylactic shock. Consider administration of a TRIAL DOSE of antivenin (0.2ml of antivenin intradermally and observe for 30 minutes) to assess likelihood of anaphylaxis. Also consider prophylactic administration of diphenhydramine 50mg IV to reduce or prevent the likelihood of reactions to antivenin administration. Patients must be closely monitored for appropriate physiologic responses to the antivenin use.

(5) **Adjunctive therapy.**

- (a) Blood products may be required if severe coagulopathies develop.
- (b) Provide analgesics (NO NSAIDS or steroids) to reduce pain and inflammation.
- (c) Update patient’s tetanus vaccination status.

(d) Educate the patient about the possibility of delayed serum sickness.

g. **Reporting.** Use of one of these IND antivenins requires specific reporting. To ensure reporting can be easily completed ensure treatment is fully documented in the patient record. For each case when one of these products is ordered the following information must be provided to the Pharmacy Service:

- (1) Full Name and Rank of the patient.
- (2) Branch of service of the patient.
- (3) Last 4 of the SSN of the patient
- (4) Antivenin product used.
- (5) Quantity of product used (number of vials and total number of ml or total dose).
- (6) Patient's clinical outcome from the treatment.
- (7) Provider name, rank, last 4 of the SSN, and unit identification.

This data must be forwarded by the pharmacy service to the USAMMC-SWA or USAMMCE pharmacy staff officer. It is essential to provide these data as justification for reordering. These organizations will not provide additional stocks of these products to MTFs unless either this report is provided or stocks of one of these antivenins have expired. The USAMMC-SWA or USAMMCE pharmacy staff officers have the responsibility to pass these reports to the U.S. Army Medical Research and Materiel Command's Chief of Regulatory Affairs. The Chief of Regulatory Affairs is required to report all use of these products to the FDA.

h. USAMMCE pharmacy staff officer: MAJ Jorge Carrillo, DSN 314-495-7230, e-mail: [jorge.carrillo@us.army.mil](mailto:jorge.carrillo@us.army.mil).

i. USAMMC-SWA Pharmacy Staff Officer: CPT Joseph Taylor, DSN 318-432-2883, e-mail: [joseph.r.taylor@qatar.army.mil](mailto:joseph.r.taylor@qatar.army.mil)

6. The point of contact for this policy is LTC Guillermo Quiles, MNC-I Pharmacy Consultant, DSN 318-822-2416, e-mail: [guillermo.quiles@iraq.centcom.mil](mailto:guillermo.quiles@iraq.centcom.mil).

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