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Current Limitations of the Emergency Use Authorization: The Need to Strengthen All-Hazards Preparedness for Medical Products to Support US Military Forces

Terry M. Rauch

School of Arts and Sciences

History and Military Studies

The thesis for the master's degree submitted by

Terry Michael Rauch

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has been read by the undersigned. It is hereby recommended

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(Signed, first reader) Samer Koutoubi (Date) 1/25/2015

(Signed, second reader, if required) Ebun Ebunlomo (Date) 1/30/2015

Recommended for approval on behalf of the program

(Signed) James Forton (Date) 2/3/2015

Recommendation accepted on behalf of the

program director

(Signed) B. Freeland (Date) 2/5/2015

Approved by academic dean

CURRENT LIMITATIONS OF THE EMERGENCY USE AUTHORIZATION: THE NEED TO STRENGTHEN ALL-HAZARDS PREPAREDNESS FOR MEDICAL PRODUCTS TO SUPPORT US MILITARY FORCES

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DEDICATION

I dedicate this thesis to all who have served in the United States Armed Forces and their families.

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ABSTRACT OF THE THESIS

CURRENT LIMITATIONS OF THE EMERGENCY USE AUTHORIZATION: THE NEED TO STRENGTHEN ALL-HAZARDS PREPAREDNESS FOR MEDICAL PRODUCTS TO SUPPORT US MILITARY FORCES

by

Terry Michael Rauch

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Charles Town, West Virginia

Professor Samer Koutoubi, Thesis Professor

The purpose of this study is to present an argument for the expansion of the Emergency Use Authorization beyond the current scope of threats that cover chemical, biological, radiological, or nuclear agents and to include instruments of war or terrorism (explosive devices or agents), or hazards which cause or threaten to cause massive physical trauma. A literature search using PubMed, the Defense Technical Information Center, and Google Scholar identified 26 articles from January 1982 to December 2014 that examined the effects of blast as an instrument of war on combat casualty care. An assessment was made of each article that included a medical product in either pre-clinical or clinical trial status, a medical product that the Food and Drug Administration approved for another indication other than a particular trauma indication, or a product approved by a foreign regulatory entity. The results show a major gap in the Emergency Use Authorization that requires expansion to allow the Food and Drug Administration to grant authorization for an unapproved medical product (or unapproved use of an approved product) that is the best available medical countermeasure for trauma care.

EXPANDING THE EMERGENCY USE AUTHORIZATION

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Introduction

Protecting the health of United States (U.S.) service members is vital to US national security interests. Significant progress has been made in increasing the survival rate of U.S. forces in the Iraq and Afghanistan wars following combat injury; nevertheless, there are combat fatalities with wounds that were potentially survivable if U.S. military medical forces had better medical products and more operational control of those products. The U.S. Department of Defense has mandated preferential use of medical products approved by the U.S. Food and Drug Administration for general commercial marketing, when available, to treat U.S. forces in theaters of combat operations (U.S. Department of Defense, 2008). Such policy was mandated by Executive Order 13139 (1999) that requires the United States Government to provide military personnel with safe and effective vaccines, antidotes, and treatments that will negate or minimize the effects of health threats and that the United States Government will administer products approved for their intended use by the Food and Drug Administration.

There are provisions for the use of medical products not yet approved by the Food and Drug Administration; however, it is arguable that such provisions, as they exist, fail to provide the essential protection of the health and safety of US forces in theaters of combat. It becomes even more problematic when in the recent wars in Iraq and Afghanistan, due to multi-national military forces acting in a collation, US combat casualties may be treated in multi-national medical facilities, by foreign military providers, and with the most efficacious products not approved by the Food and Drug Administration but approved by foreign regulatory entities.

Under section 564 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360bbb-3), an Emergency Use Authorization grants the Food and Drug Administration authority to permit the emergency use of a medical product that, although not approved for use generally or not

approved for the particular use in question, is the best available product to deal with the emergency (Nightingale, Prasher, & Simonson, 2007). The emergency is restricted to events caused by chemical, biological, radiological, or nuclear agents. There, nonetheless, exists a critical and unfortunate limitation in the Food and Drug Administration's authority to permit emergency use of medical products in prevention, diagnosis, or treatment during major public health emergencies that goes beyond the spectrum of chemical, biological, radiological, or nuclear agents. Specifically, section 564 permits the Food and Drug Administration, under the principle of the best available product, to intervene with that product in a chemical, biological, radiological, or nuclear emergency; nevertheless, this section does not extend to all hazards in medical emergencies. Instead, the authority is expressly available and delimited to medical intervention to deal with mass casualties that result from chemical, biological, radiological, or nuclear disasters.

Therefore, there is a current exclusion, or gap in section 564, that does not include instruments of war or terrorism that consists of explosive devices which cause or threaten to cause massive physical and/or psychological trauma. Does this gap in the Emergency Use Authorization lead to unfortunate health consequences and a heightened risk to the medical readiness of US military forces? In certain cases, the Emergency Use Authorization is an essential tool which permits the Secretary of Defense to make a determination that a certain chemical, biological, radiological, or nuclear agent threat on a particular occasion presents a heightened risk to U.S. military forces. However, is the scope of the Emergency Use Authorization statute too limited and thereby creates unnecessary risk to U.S. force health protection and readiness? Among such agents of war are improvised explosive devices, which have claimed many lives in the current conflicts in Iraq and Afghanistan. Principal examples

where an Emergency Use Authorization could save lives in catastrophic and battlefield emergency casualty care would include use of blood products to stop uncontrolled bleeding and use blood products for resuscitation in trauma patients.

The purpose of this study is to present an argument for the expansion of section 564 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360bbb-3) beyond the current threat scenario of chemical, biological, radiological, or nuclear agents to include instruments of war or terrorism (explosive devices or agents), or hazards which cause or threaten to cause massive physical trauma. The specific objectives of this study are to determine: (1) if a gap in the Emergency Use Authorization results in potential risk for increased mortality among U.S. military forces subject to combat trauma from blast forces beyond chemical, biological, radiological, or nuclear agents; and (2) if there is a need for including a "all hazard" condition which includes "instruments of war" to enhance National Security and enhance public health preparedness.

Literature Review

Governing Authorities Regulating the Use of Medical Products

Health care providers have long recognized that there are promising drugs, biologic products and devices that are not approved by the Food and Drug Administration, as well as promising off-label uses of drugs, biologic products, and devices that are approved by the Food and Drug Administration for other indications (Nightingale et al., 2007). Some unapproved or off-label medical products may be the best therapeutic option available and a physician in practice can prescribe an approved drug for an off-label use or an unapproved drug on a patient-

by-patient basis (Nightingale et al., 2007). Large-scale use of unapproved drugs or off-label use of approved drugs could only be provided under an Investigational New Drug status prior to the availability of Emergency Use Authorizations. Hence, the only instrument initially available for making products that were not Food and Drug Administration approved and available in an emergency was an Investigational New Drug protocol or an Investigational Device Exemption (Nightingale et al., 2007).

Currently, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360bbb-3), the Food and Drug Administration may approve medical products for use generally, or for a particular use. Similarly, section 564 authorizes the Food and Drug Administration to grant an Emergency Use Authorization for a medical product which, although not approved for use generally, or not approved for the particular use in question, is the best available product to address the emergency. More precisely for national security purposes, the Emergency Use Authorization is an essential tool which permits the Secretary of Defense, to render a determination that a specified chemical, biological, radiological, or nuclear agent or agents, prompts a heightened risk to U.S. military forces. Such a determination provides the opportunity for timely, practical medical use of the best available product for treatment and prevention under emergency conditions. It also fills the void in the case of an absent Food and Drug Administration approval, or where Food and Drug Administration approval does not cover in terms of particular emergency use (Nightingale, et al., 2007).

Section 564 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb-3) was amended by the Project BioShield Act of 2004. As amended, the Commissioner of the Food and Drug Administration is authorized to override the unapproved status of a medical product, or to override the limitations placed upon an approved medical product, in order to strengthen the

public health protections against chemical, biological, radiological, or nuclear agents that may be used to attack the American people or the U.S. armed forces (Nightingale, et al., 2007). The exercise of authorization allows medical countermeasures to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by such agents, when there are no adequate, approved, and available alternatives. Such Emergency Use Authorization candidates include products and uses that are not approved, cleared, or licensed under sections 505, 510(k), and 515 of the FD&C Act.

Procedurally, Section 564(b)(1) of the Food, Drug and Cosmetic Act requires, as a prerequisite to issuance of an Emergency Use Authorization, either the Secretary of Homeland Security, the Secretary of Defense, or the Secretary of Health and Human Services, must declare an emergency based on one of various criteria. Specifically, the Secretary of Homeland Security must have declared the existence of or significant potential for a domestic emergency involving a heightened risk of a specified chemical, biological, radiological, or nuclear agent(s) attack (Food and Drug Administration, 2007). In like manner, as reported by Nightingale et al. (2007), the Secretary of Defense bears the duty of determining the existence of or significant potential for a military emergency, involving a heightened risk to United States military forces of attack with a specified chemical, biological, radiological, or nuclear agent(s). Likewise, the Secretary of Health and Human Services under section 319 of the Public Health Service Act can recognize the existence of or significant potential for national security to be affected by a specified chemical, biological, radiological, or nuclear agent or agents, or by a specified disease or condition that may be attributable to such agent or agents (Nightingale et al., 2007).

Upon the declaration of an emergency sufficient to justifying a section 564 authorization to use an unapproved medical product or an approved product for an unapproved use, the

Assistant Secretary for Preparedness and Response under the Secretary of Health and Human Services may convene the Emergency Use Authorization Working Group to provide expert consultation and input on the information and data submitted to the Food and Drug Administration, including eligible products and uses that may be effective to mitigate a disease or condition caused by chemical, biological, radiological, or nuclear agents (Food and Drug Administration, 2007). In such cases, a Food and Drug Administration regulated product, including an Emergency Use Authorization product, or an approved, cleared, or licensed product used to diagnose, treat, or prevent a disease or condition caused by such agent is evaluated under the “effective” standard. It should be noted that the "may be effective" standard for Emergency Use Authorizations requires a lower level of evidence than the "effectiveness" standard that Food and Drug Administration uses for product approvals (Food and Drug Administration, 2007).

The Assistant Secretary for Preparedness and Response will review the exigencies of feasibility and propriety of the emergency circumstances and in consultation with the Director of the National Institutes of Health and the Director of the Centers for Disease Control and Prevention, form the basis for deeming issuance of an Emergency Use Authorization to be the appropriate action, assuming all other statutory criteria and conditions are satisfied (Institute of Medicine, 2010). Thereafter, the Food and Drug Administration Commissioner determines whether the specified product may be efficacious in diagnosing, treating, or preventing the serious or life-threatening disease or condition referenced in the declaration of emergency. The determination is based upon the totality of the scientific evidence, in that it can reasonably be believed to be efficacious in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by an agent authorized under section 564 (Institute of Medicine, 2010).

An affirmative conclusion would form the basis upon which the Food and Drug Administration Commissioner issues an Emergency Use Authorization, introducing into interstate commerce the drug, device, or biological product, to be warranted in pursuit of remedy and relief of the serious or life-threatening disease or condition caused by the chemical, biological, radiological, or nuclear agent(s). Coupled with this evaluation is the determination by the Food and Drug Administration Commissioner that the known and potential benefits of using the product to diagnose, prevent, or treat the serious or life-threatening disease or condition (the subject of the declaration), outweigh the known and potential risks of the product. In addition, the Commissioner certifies that there is no adequate, approved, available alternative for the identified serious or life-threatening disease or condition (Food and Drug Administration, 2007).

It should be noted that an Emergency Use Authorization has a one year, renewable lifespan. On the other hand, the Emergency Use Authorization may be terminated at an earlier point in time, upon consultation with the Secretary of Homeland Security or the Secretary of Defense. Early termination of the authorization is based on whether the circumstances that precipitated the declaration of an actual or potential emergency have ceased and sufficient advance notice is provided to allow for disposition of product, labeling, or other information related to an unapproved use of an approved product (Nightingale et al., 2007).

Comparison of the Emergency Use Authorization to the Investigational New Drug, Investigational Device Exception Protocol, and Off-Label Usage

Nightingale et al. (2007) report that in addition to the Emergency Use Authorization, unapproved products may be available in an emergency through an Investigational New Drug protocol or an Investigational Device Exemption. Then again, the Emergency Use Authorization and Investigational New Drug and Investigational Device Exemption protocols are different mechanisms, each with its own distinct statutory and regulatory requirements that vary with particular circumstances such as the nature of the medical product or the size of the population to be treated. Unlike the Emergency Use Authorization, the objective of the Investigational New Drug and Investigational Device Exemption is to assess the safety and efficacy of an investigational drug/biologic/device product while ensuring that human subjects are protected during the research study of the investigational product (Pierson, 2007).

Investigational protocols specify requirements to ensure participant protection and the validity of the data collected during the clinical trial. Hence, under the Investigational New Drug and Investigational Device Exemption mechanism, the Food and Drug Administration must review the protocol and agree that the study may proceed. Each protocol requires Institutional Review Board review and approval; written, signed, and witnessed informed consent; all investigators must be trained on the investigational protocol and research ethics and data reporting requirements; monitoring and reporting of adverse events associated with the product is required; and recordkeeping and access to distribution and administration records is required (Nightingale et al., 2007).

The duration of approval of an Investigational New Drug or Investigational Device Exemption protocol is usually the length of the clinical trial. On the other hand, the Emergency

Use Authorization permits the public health system access to a larger array of medical products during a declared emergency. The Emergency Use Authorization is intended to permit more rapid utilization of a product compared to the Investigational New Drug or Investigational Device Exemption approach. The Food and Drug Administration is required to review and approve the request for Emergency Use Authorization; yet, an Institutional Review Board is not required. Furthermore, written, signed and witnessed informed consent may or may not be required at the discretion of the Food and Drug Administration Commissioner. Nonetheless, distribution of information for healthcare professionals and recipients that contains product safety, available alternative products, and the right to refuse administration of the Emergency Use Authorization product is required. On the other hand, investigator training is at the discretion of the Food and Drug Administration Commissioner as well as adverse event monitoring and reporting and recordkeeping and access to product distribution and administration records (Food and Drug Administration, 2007). The duration of approval for an Emergency Use Authorization is up to one year from the date of the declaration of emergency or for as long as the §564 emergency declaration is in effect, whichever is shorter.

Food and Drug Administration regulations governing the use of unapproved or off-label new pharmaceuticals, biologics, and medical products, sets forth the prerequisite that such products demonstrate their efficacy via randomized, placebo controlled, clinical trials (Pierson, 2007). Conversely, the Food and Drug Administration recognizes the imperfection of this process and addresses the limited clinical safety data acquired through various vehicles. Such vehicles include requiring post-marketing (Phase IV) studies in conjunction with practitioner submitted MedWatch reports, by making an Investigational New Drug product available as medical protection for life and safety in face of a lethal chemical, biological, radiological, or

nuclear agent under the Emergency Use Authorization category, and by evaluating the labelling information regarding the precise indications which govern the manner in which the devices, drugs, or biologics can be safely and effectively used. Compliance with the precise labeling instructions is considered by the Food and Drug Administration to be essential to safe and effective utilization of the product for the exact medical indications.

As reported by Pierson (2007), off-label use refers to use of medical products in a manner that is different and distinguishable from that specified in the labeling and is under a condition where there is the potential for serious risk to health, safety, or welfare of a patient. The Food and Drug Administration provides mechanisms for expansion to off-label use to address life threatening or serious diseases or conditions, where no alternative exists and where there is no time to obtain Food and Drug Administration approval (Pierson, 2007). Likewise, off-label use is permissible for compassionate purposes, meaning where patients do not meet the clinical investigation inclusion criteria and no alternative exists in face of serious diseases or conditions which may be benefitted by the product (Pierson, 2007). It should be clear that it does not mean the Food and Drug Administration has determined the off-label use to be adverse, improper, illegal, or contraindicated. Thus, off-label uses cannot be considered unapproved, as they simply have not been reviewed at all. Likewise it does not mean the use is investigational or experimental use; thus it is not subject to the informed consent regulations governing investigational drugs and devices. In fact, it should be noted that off-label use of medical devices is an accepted part of the practice of medicine, and off-label Investigational New Drug uses have resulted in discovery of new applications for existing drugs. Most treatment modalities that can be used off-label are outside of the normally encountered situations. Nevertheless, off-label can have both desirable and non-desirable results ranging from discomfort to a serious consequence.

Thus solid medical rationale should support the off-label use, and a plan of action should be executed for implementation in the event of a non-desirable situation. Nonetheless, Investigational Device Exemption and Investigational New Drug trials are exempt from off-label use.

Black-Box warnings indicate that the Food and Drug Administration has determined that use of the drug carries adverse effects ranging from a significant risk of serious injury to potential life threatening consequences (Pierson, 2007). The Food and Drug Administration Black-Box warning should not be taken as a prohibition against its use, but should be used to reinforce the need for the combat medic understand the potential problems and proceed with heightened awareness and vigilance. Additionally, it should be noted that the approved label is a function of the environment for which clinical trials were conducted to obtain product approval.

The Military Use of Investigational Products in the Deployed Setting

Current regulations preclude the military use of products with Investigational New Drug status without adherence to extant regulations applicable to clinical research with experimental products as specified under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 50, subpart B dated 2001. Additionally, as a prerequisite, the sponsor of the Investigational New Drug for military use must submit to the Food and Drug Administration certain information pertaining to the product and to the proposed clinical studies. Strict compliance with these procedural prerequisites includes prior approval by an independent institutional review board, the collection of informed consent, and thorough detailed recordkeeping associated with product usage and logistics (Department of Defense Directive 6200.2, 2008). Adherence to the myriad of

procedures and documentation steps can be difficult—if not impossible—to execute during military operations.

In 1990, in response to a request from the Department of Defense, the Food and Drug Administration published an interim rule which addressed the Department of Defense's concerns about the use of products with Investigational New Drug status in combat situations (Lemon, Thaul & Fisseha, 2002). The interim rule, as provided, granted authority to the Food and Drug Administration commissioner to waive the informed consent requirement upon submission of a grant of waiver request from the Assistant Secretary of Defense for Health Affairs (Lemon et al., 2002). However, as discussed by Lemon et al. (2002), the application of the interim rule was subjected to the restriction of "use of an investigational drug (including an antibiotic or biological product) in a certain protocol under an investigational new drug application." Furthermore, it was "limited to a particular military operation involving combat or the immediate threat of combat" (Lemon et al., 2002). Thereafter, the interim rule was applied during the Gulf War, thereby, allowing the use of pyridostigmine bromide and a botulinum toxoid vaccine as a protective measure against the potential use of weaponized biological or chemical agents (Rettig, 1999).

When service members returned from the Gulf War deployment and reported medically unexplained symptoms, the safety and efficacy of the vaccine and drug products used during the war and the wisdom of Department of Defense's use of the interim rule was called into question by many (Lemon, et al., 2002). These negative perceptions, which may have been different had there been credible evidence of the actual use of chemical or biological weapons by forces opposing U.S. and allied personnel, sparked changes in the government's policy regarding the Investigational New Drug waiver. Partially because of concerns that grew out of the use of the

interim rule during the Gulf War, the U.S. Congress passed the Strom Thurmond National Defense Authorization Act for Fiscal Year 1999 (Strom Thurmond Act, 1998), whereby, the authority to waive the informed consent requirement was vested solely with the President of the United States. In accordance with the passage of the Strom Thurmond Act, the Food and Drug Administration revoked the 1990 interim rule and established a new interim final rule outlining the limited circumstances in which the President could waive the informed consent requirement. Specifically: "if the President finds obtaining informed consent (1) not feasible; (2) contrary to the best interests of the members; or (3) not in the best interests of national security" (Food and Drug Administration, 1999).

The use of Investigational New Drugs or Investigational Device Exemptions by the military in a combat theater of operations or in another deployed military environment presents challenges to successful implementation. It must be noted that the applicable regulations that governs the use of Investigational New Drugs and Investigational Device Exemptions is to build a body of clinical scientific evidence of safety and efficacy necessary for the Food and Drug Administration to make a determination of the medical product's availability for interstate commerce. Hence, for this purpose, the Food and Drug Administration requires a substantial amount of pre-clinical data and well-controlled human clinical trials in the conduct of Investigational New Drug protocols. Nevertheless, there are situations where the best medical product available to U.S. military medical personnel may not be approved for use in the U.S. and there may not be a market place demand in the U.S. for such a product. Such was the case with tick-borne encephalitis vaccine (Rettig, 1999).

The Department of Defense was subsequently subjected to additional criticism for breaching and failing to strictly adhere to the Food and Drug Administration guidelines for the

many years of administration of the tick-borne encephalitis vaccine product which bore Investigational New Drug status. The tick-borne encephalitis vaccine had been administered to U.S. personnel who inspected military sites in the Soviet Union, where tick-borne encephalitis was endemic.

The tick-borne encephalitis vaccine was developed by scientists from Austria and the United Kingdom and had been widely used in Europe, but it had not been licensed for use in the U.S. In 1993, the Armed Forces Epidemiological Board was asked to conduct an evaluation and make a recommendation regarding the use of the tick-borne encephalitis vaccine (for which the U.S. Army held an Investigational New Drug application) (Rettig, 1999). Upon evaluation, the Armed Forces Epidemiological Board determined and recommended that the vaccine against tick-borne encephalitis be used under Investigational New Drug protocol with informed consent to protect military personnel with significant potential for exposure to tick-borne encephalitis (Rettig, 1999).

In 1996, the Assistant Secretary of Defense for Health Affairs issued the Department of Defense policy regarding the use of a vaccine against tick-borne encephalitis and instructed that the tick-borne encephalitis vaccine should be offered to personnel at very high risk of tick exposure (Rettig, 1999). This limited instruction expressly provided that tick-borne encephalitis vaccine should not be used to routinely immunize all Department of Defense personnel and should be offered to soldiers deployed to areas in Bosnia known to be affected by tick-borne encephalitis. It should be noted that the administration of tick-borne encephalitis vaccine in the Bosnian theater of operations was limited solely to individuals who volunteered to participate in a study of the Investigational New Drug product and, accordingly, provided written informed consent to that effect (Rettig, 1999).

The General Accounting Office conducted an audit of the Department of Defense tick-borne encephalitis vaccine campaign in the Bosnian theaters of operations and the U.S. Army's recordkeeping practices during vaccination implementation (General Accounting Office, 1997). The General Accounting Office reported that nearly one-fourth of the immunizations against tick-borne encephalitis in Bosnia were not supported by proper documentation. Additionally, the Food and Drug Administration found significant deviation from Food and Drug Administration guidelines with regard to the use of a product with Investigational New Drug status in Department of Defense's implementation of the tick-borne encephalitis vaccine in Bosnia (Food and Drug Administration, 1997). Although Department of Defense officials acknowledged faulty recordkeeping, they did nonetheless, maintain that there was full compliance with Investigational New Drug guidelines (Gillert, 1998). Nonetheless, the tick-borne encephalitis vaccine is no longer available to U.S. military personnel under the Food and Drug Administration Investigational New Drug status.

The aforementioned sequence of events highlights some of the difficulties inherent in complying with Food and Drug Administration rules as they relate to the use of an Investigational New Drug product in military personnel engaged in combat or participating in peacekeeping duties under hazardous conditions. Similarly, the aforementioned sequence of event, calls attention to the difficulties that U.S. military commanders face when they must confront and conform to the extant rules and regulatory practices during the process of deploying forces into situations that are likely to expose those forces to infectious disease threats for which licensed vaccines may not be available.

The Department of Defense's Experience with the Emergency Use Authorization

The Department of Defense clearly understands the provisions of the Emergency Use Authorization and was the first Federal agency to use that authority for national security purposes in 2005. This represented the first use of the Emergency Use Authorization authority as an example of an effective national security and military public health response to the necessity for a large-scale use of a medical countermeasure to a biologic agent to protect U.S. military forces (Nightingale, et al., 2007). The policy of the Department of Defense since 1998 was to protect U.S. military forces assigned to certain areas where anthrax was determined to be a military threat. The anthrax vaccine was licensed since 1970 to protect against cutaneous anthrax among wool workers. As a biological warfare agent, the military threat of anthrax is primarily delivered by aerosolized anthrax spores causing inhalation anthrax.

A federal court in 2004 issued an injunction against the Department of Defense Anthrax Vaccination Program on the grounds that the Food and Drug Administration was required to obtain public comments prior to making a determination that the anthrax vaccine license covered use for prevention of inhalation anthrax in addition to cutaneous anthrax (Nightingale, et al., 2007). The decision by the federal court was that the use of the anthrax vaccine by the Department of Defense to prevent against inhalation anthrax was not an approved use since the approved use was to prevent against cutaneous anthrax. The decision from the federal court made the Department of Defense immediately suspend the Anthrax Vaccination Program. In order to continue anthrax vaccinations for selected military forces, the Department sought the first use of the Emergency Use Authorization pursuant to the Act.

The Department made a determination on December 22, 2004 that there was a significant potential for a military emergency involving the threat of anthrax to selected military forces and requested to the Secretary of Health and Human Services that an Emergency Use Authorization

be issued for anthrax vaccine. Subsequent to the request from the Department of Defense, the Secretary of Health and Human Services issued a Declaration of Emergency on January 14, 2005 (Food and Drug Administration, n.d.; Nightingale, et al., 2007). Based on this declaration, the Acting Commissioner of the Food and Drug Administration consulted with the Directors of the National Institutes of Health and the Centers for Disease Control and Prevention and subsequently issued an Emergency Use Authorization for anthrax vaccine on January 27, 2005 (Food and Drug Administration, n.d.; Nightingale, et al., 2007). The Emergency Use Authorization for anthrax vaccine required the Department of Defense to inform service members that they had an option to refuse the vaccine and that no adverse action would be taken against those who declined the vaccine (Food and Drug Administration, n.d.; Nightingale et al., 2007).

The Emergency Use Authorization for anthrax vaccine was initially issued for a period of six months and then subsequently extended for the duration of the Declaration of Emergency that terminated on January 14, 2006 (Food and Drug Administration, n.d.; Nightingale, et al., 2007). During the Declaration of Emergency, the Department of Defense administered over 100,000 anthrax vaccinations (Nightingale et al., 2007). As reported by Nightingale et al. (2007), the Emergency Use Authorization for anthrax vaccine was permitted to expire because the Food and Drug Administration issued a final order concluding that anthrax vaccine is safe and effective for its labeled indication, to protect persons at high risk for anthrax disease (Nightingale, et al., 2007). Since the final order concluded that the anthrax vaccine is safe and effective for its labeled indication, to protect persons at high risk for anthrax disease, the Department of Defense could resume anthrax vaccinations consistent with its licensed indication, and an Emergency Use Authorization was no longer necessary.

There are three important aspects of this Emergency Use Authorization for anthrax vaccine. First, the issuance of the Emergency Use Authorization enabled the Department of Defense to resume the Anthrax Vaccination Program for selected service members assigned to high threat areas for anthrax attack and therefore mitigate a potential breech in national security. Second, the issuance of the Emergency Use Authorization for anthrax vaccine was based upon the statutory provision that the medical product intended for use, (i.e., anthrax vaccine) was the best available medical countermeasure to mitigate the potential national security emergency caused by the heightened threat of anthrax attack. Furthermore, it was determined that it is best product available for treatment or prevention regardless of its approval status by the Food and Drug Administration. Third, the Department of Defense demonstrated that it could successfully implement an Emergency Use Authorization by successfully administering over 100,000 vaccinations to selected service members around the world. The fundamental question is why shouldn't the provisions of an Emergency Use Authorization include other military emergencies beyond chemical, biological, radiological, and nuclear agents?

Ethical Consequences of the Current Regulatory Process

The Department of Defense is obligated to treat service members as autonomous persons entitled to basic rights and protections. Embrey (2003) reports that on May 31, 2002, the Food and Drug Administration amended their new drug and biological product regulations, to address instances where it is infeasible or immoral to attempt to pursue substantial evidence of human clinical efficacy. This amendment permits marketing and use of certain drugs and biologics, for reduction and prevention of serious or life threatening conditions. As Embrey (2003) reported, such permission requires evidence from appropriate animal studies, showing that rigorous research efforts have resulted in use of an optimal animal model to accurately mimic human

disease. Additionally, it must also show that follow up thorough research refinements to the animal use is sufficient to ensure that the animal model meets and illustrates product effectiveness in preventing or substantially reducing damage. Of no less importance, the product must come with rigorous scientific reassurance sufficiently characterized to be predictive of efficacy in humans, and bear pharmacokinetics and pharmacodynamics which allow the determination of an effective dose in humans. Thereafter, upon human subject use, proof of efficacy, when used for the approved purpose, is required, and labeling notice of efficacy must state that this was determined solely through animal use (Embrey, 2003).

The 2004, BioShield Act (42 U.S.C. 243 et seq.) allows the Health and Human Services (HHS) Secretary to authorize emergency use of a drug or medical product without normal Food and Drug Administration approval, upon evidence of product effectiveness, and the absence of an existing approved alternative (Gottron & Fischer, 2004). This is a critical component of Homeland Security strategy which is designed to accelerate and streamline government research on countermeasures, create incentives for private companies participation concerning countermeasures, give government the ability to make products widely and quickly available in public health emergency, all with the intent that we arrive at citizen protection from a chemical, biological, radiological, or nuclear agent attack.

Three ethical principles, beneficence, non-maleficence, and paternalism, discussed by Thomasma (2009), provide an analytical framework useful to apply to situations such as the ethical dimensions of expanding the Emergency Use Authorization beyond chemical, biological, radiological, or nuclear agents to include instruments of war. As discussed by Thomasma (2009), beneficence refers to the act of doing good for the patient and includes acting in the patient's own best interest, without concern for outside interests, while non-maleficence refers to

avoiding “doing harm” to the patient (i.e., primum non nocere). Paternalism refers to the fact that medical professionals make decisions about diagnosis, therapy, and prognosis for the patient on the belief about what is in the best interest of the patient (Butts & Rich, 2008). Since these principles employ differing approaches and interests, they may conflict with each other on a given case or situation.

It is evident that, despite the availability of Food and Drug Administration approved medical products, there are promising medical products that are not Food and Drug Administration approved as well as promising off-label uses of medical products approved by the Food and Drug Administration for other indications. Such unapproved or off-label medical products may be the very best preventive, diagnostic, or therapeutic options available. While a practicing physician can prescribe an approved drug for an off-label use or an unapproved drug on a patient-by-patient basis, such privilege cannot be extended further (Nightingale et al., 2007).

The principles of beneficence, non-maleficence, and paternalism offer solid ethical support of the Emergency Use Authorization that provides timely and practical medical treatment under chemical, biological, radiological, or nuclear emergency conditions based upon the best product available for treatment or prevention despite its Food and Drug Administration status. The provision of utilizing the best product available for chemical, biological, radiological, or nuclear agent treatment or prevention comports to beneficence in that the medical community acts with compassion and takes positive action to help others in need of the best treatment or prevention and thereby avoids “doing harm” to the patient’s condition (i.e., non-maleficence) by using a lesser efficacious treatment or preventive measure. Utilizing the best medical product available under the Emergency Use Authorization also comports to the

principle of paternalism whereby the medical community may act with the best available medical product to intervene based upon the belief that "the doctor knows best."

Ethical deliberation, not rote application of rules, is important while giving serious considerations to and properly harmonizing, the rights of the service member as a volunteer research subject against national security interests. Such is often the case in research and the quest for the advancement of knowledge where service members are utilized as human subjects in research. Thus, concurrent attention is paid to the determination of the appropriate methodology for new product approval, protection of the service member volunteer subject from coercion, while simultaneously utilizing the service member as a national warrior who may at any time be ordered into harm's way. Ethicists must understand, honor, and act in furtherance of these important factors when rendering and implementing decisions. The threat of chemical, biological, radiological, or nuclear agents demands that our nation provides a means to create new treatment modalities, decrease pain and suffering, even death, and remove unnecessary impediments to valuable clinical inquiry; the Emergency Use Authorization has established that pathway. On the other hand, there are compelling reasons to expand the Emergency Use Authorization beyond chemical, biological, radiological, or nuclear threat agents that would further protect the health of service members and U.S. national security interests.

Morbidity and Mortality on the Battlefield

In the last 13 years of war in Iraq and Afghanistan, the principal mechanism of injury in combat has been predominantly penetrative in character occurring in nearly 75% of casualties associated with explosive blast fragmentation and gunshot wounds (Eastridge, Mabry, Seguin, Cantrell, Tops, Uribe, & Holcomb, 2012). As reported by Bumbaširević, Lesic, Mitkovic, &

Bumbaširević (2006) blast trauma is a complex physical force event where pathophysiologically, the blast injuries are characterized as primary (attributed primarily to the direct effect of blast overpressure on the body), secondary (attributed to airborne objects or fragments interacting with the body), tertiary (attributed to bodily displacement), or quaternary (indirectly caused by the explosion). The scope of primary blast injuries includes hemorrhage, fractures, amputations, crush injury, burns, cuts, lacerations, acute occlusion of an artery, air embolism–induced injury, compartment syndrome, and others (Bumbaširević, et al., 2006). Moreover, Bumbaširević et al. (2006) report that secondary blast injuries are most frequently seen as extremity injuries and similar to primary injuries, may involve limb amputation, heightened risk of mortality, and severe contamination. Lastly, tertiary blast injuries of the extremity may result in traumatic amputations, fractures, and severe soft-tissue injuries, whereas quaternary injuries most frequently are associated with burns (Bumbaširević, et al., 2006).

The survivability of those injured on the battlefield is an unprecedented historical level of 90%, compared with 84% in Vietnam and 80% in World War II (Holcomb, Stansbury, Champion, Wade, & Bellamy, 2006). Butler (2010) reports that some of the likely factors influencing this improved survivability include advances in personal protective equipment, a deployed trauma system, and improved training of medics and corpsman based on the concepts of Tactical Combat Casualty Care. Moreover, given the history of modern warfare, the current conflicts in Iraq and Afghanistan are characterized by enemy tactics and procedures that employ small improvised explosive devices.

These enemy tactics and procedures are fundamentally distinct from the small unit fire and maneuver capability well-known in Vietnam or the mass unit heavy armor and artillery, aerial bombs, and maritime battle engagements seen in World War II. As a result, the wounding

patterns among these conflicts differ. Studies of combat casualties over the last 100 years have shown significant mortality on the battlefield prior to the wounded service member could be evacuated to forward surgical care (Bellamy, 1984; Champion, Bellamy, Roberts, & Leppaniemi, 2003). These studies, as summarized, employed convenience sampling techniques, assessed military administrative databases in addition to weapons effectiveness analyses (Bellamy, 1984). Eastridge et al. (2012) reported on 4,596 casualties across the current conflicts in Iraq and Afghanistan and 87% of those casualties died prior to reaching surgical care. The principal cause of injury in these casualties was due to blast generated from explosive devices. Death on the battlefield in the Iraq and Afghanistan conflicts occurred in two temporal periods: 35% of combat casualty mortality occurred instantaneously and 52% acutely in the minutes to hours subsequent to injury (Eastridge et al., 2012). Moreover, Eastridge et al (2012) further reported that prior to arrival to the forward medical treatment facility that 3,040 (75.7%) of the pre-hospital mortality were catastrophic and non-survivable, on the other hand, 976 (24.3%) of mortality were potentially survivable from a strictly medical perspective.

Mortality that was instantaneously catastrophic and non-survivable was characterized by blast induced physical dismemberment, catastrophic brain injury, and destructive cardiovascular injury (Eastridge et al., 2012). On the other hand, acute, but not instantaneous mortality was associated with severe traumatic brain injury, thoracic vascular injury, high spinal cord injury, and destructive abdominal pelvic injury (Eastridge et al., 2012). Destructive abdominal pelvic injury was somewhat unique in the counter-insurgency period of the Iraq and Afghanistan conflicts and was associated with the increased enemy use of ground improvised explosive devices engaging U.S. service member during ground (i.e., foot) operations and producing a distinctive injury signature known as dismounted complex blast injury characterized by multiple

amputations of the lower extremities; massive abdominal, pelvic, and urogenital injury; and exsanguination from truncal or junctional hemorrhage which was non-compressible. Eastridge et al. (2012) report that an expert medical panel reviewing the non-survivable injury data determined that these injuries would not have been survivable with currently available medical treatments in theater and the only means to reduce this type of mortality was through primary injury prevention.

Compared with the mortality that was determined potentially survivable, the majority of mortality in this category was the result of hemorrhage (90.9%) and specifically of this 90.9%, 67.3% of the hemorrhage was truncal, 19.2% was junctional, and was 13.5% extremity Eastridge et al., 2012). In a previous study reported by Eastridge, Hardin, Cantrell, Oetjen-Gerdes, Zubko, Mallak, & Blackbourne (2011), casualties who died of wounds (that is they were evacuated and received treatment but died) that were potentially survivable hemorrhage showed 48% truncal, 31% extremity, and 21% junctional. The difference between the two sets of data reported by Eastridge et al. (2012) and Eastridge et al. (2011) maybe a survival bias in that some casualties with extremity and junctional hemorrhage may have been more likely to have survived long enough to reach the medical treatment facility subsequent to the application of hemorrhage control techniques to include the use of tourniquets, pressure dressings, and hemostatic dressings that have continuously increased in quantity and quality over the last ten years of combat casualty care (Eastridge et al., 2012).

On the other hand, the study period reported by Eastridge et al. (2012) is characterized by the fact that there was no effective treatment to control junctional or truncal non-compressible hemorrhage on the battlefield. This indicates a significant gap in pre-hospital combat casualty care, yet also represents a potential for medical products that are in research and development

and unapproved for use or medical products that maybe be approved outside of the US but not available to U.S. medical Forces to improve combat casualty outcomes.

Such medical products are currently not approved by the Food and Drug Administration and are not available to U.S. medical Forces unless used under an Investigational New Drug or Investigational Device Exemption. The use of Investigational New Drugs or Investigational Device Exemption with informed consent is extremely challenging in a combat theater of operations and would also be extremely difficult, if not impossible to execute, in the immediate medical response to a civilian natural disaster. The basic premise for the conventional pathway of an Investigational New Drug or Investigational Device Exemption is to enable the acquisition in well-controlled clinical and/or laboratory settings of data to eventually support a New Drug Application or comparable for devices to the Food and Drug Administration for clearance into interstate commerce. In this instance sufficient evidence of product efficacy has not been established and therefore the Investigational New Drug or Investigational Device Exemption pathway is appropriate. On the other hand, utilization of the conventional Investigational New Drug or Investigational Device Exemption pathway in a combat environment or natural disaster environment is challenging, if not inappropriate.

Lastly, it is important to show how a medical product when used can affect health outcomes in combat casualty care. The use of tourniquets (a Food and Drug Administration cleared device) has had a significant impact on reducing mortality associated with extremity hemorrhage on the battlefield. Eastridge et al. (2012) reports that casualty deaths from extremity hemorrhage occurred at a rate of 23.3 deaths per year in the pre-tourniquet years of the war; yet, when approved and fielded for that purpose, tourniquets reduced mortality to 3.5 deaths per year.

Therefore, as demonstrated in the discussion above, hemorrhage is a major mechanism of mortality in potentially survivable combat injuries, emphasizing the need for regulatory measures to make the best scientifically supported medical product (whether or not approved or not approved for that intended purpose) available for combat casualty care in the pre-hospital environment. Such a construct can also have direct benefit to mass trauma in civilian applications; therefore, it is important to consider the trauma literature related to civilian emergencies such as natural disasters and acts of terrorism.

Mass Trauma in Civilian Emergencies Associated with Natural Disasters

Earthquake injuries include crush syndrome, lacerations (from debris) and fractures (from blunt force trauma), sepsis, acute renal failure, multiple extremity injuries, psychological stress, dehydration, hypothermia, and waterborne infections from sanitation collapse or airborne infections from inhalation of airborne pathogens released by the quake. Phalkey, Reinhardt, & Marx (2011) conducted a study on the injury epidemiology after the 2001 Gujarat earthquake in India and reported that orthopedic injuries, (particularly fractures of the lower limbs) were predominant and critical injuries such as head, chest, abdominal, and crush syndrome occurred to a lesser extent. Moreover, wound infections were found in almost 20% of the admitted cases and the most frequently performed surgical procedures were open reduction with internal fixation and cleaning and debridement of contaminated wounds (Phalkey, Reinhardt, & Marx, 2011). The injury epidemiology reported by Phalkey, Reinhardt & Marx (2011) is generalizable to other injury epidemiology studies with the exception that they reported a higher incidence of distal orthopedic injuries particularly to the lower extremities. The most critical element of medical care for reducing mortality in earthquakes is immediate prehospital casualty care for individuals with life-threatening injuries that must be attended to within the first six hours

(Fawcett and Oliviera, 2000). In this case, the availability of the best medical product regardless of Food and Drug Administration status is essential.

Pediatric morbidity and mortality have borne grim epidemiology following earthquakes. The emergency pediatric care begins with the inclusion of equipment and medicines essential to the effective treatment of children, and continues with quick, accurate, on scene assessment and categorization into treatment groups (Bartels & VanRooyen, 2012). Also, pediatric treatment demands special attention to pulmonary, cardiovascular, integumentary, musculoskeletal, and nutritional issues. Additionally, in providing care, the emergency medical service must anticipate the necessity for intubation, intravenous or intraosseous access and contemplate age, size and weight in medication calculation and administration, including administration via inhalation or intramuscular routes. Bartels & VanRooyen (2012) report that children are often at higher risk of injury and mortality during earthquakes than their adult counterparts. Hence, as in the case with all-hazards encountered across a broad spectrum of disasters and hostile environments, the availability of the evidence-based medical products to treat morbid conditions is essential regardless of the Food and Drug Administration regulatory status of the product.

Meredith & Bradley (2002) report that physical traumatic injury accounts for the principal cause of death and the major cause of morbidity associated with tropical cyclones. The most frequent trauma associated with tropical cyclones include lacerations, abrasions, contusions, puncture wounds, sprains, and fractures (Shultz, Russell, & Espinel, 2005). Moreover, Noji (1993) reports that the top three types of injuries associated with cyclones are lacerations, blunt trauma, and puncture wounds, and that 80 percent of these injuries occur in the lower extremities.

Mass Trauma in Civilian Emergencies Associated with Terrorist Blast Incidents

Frykberg & Tepas (1988) conducted a review of 14 published studies of terrorist bombing incidents occurring between 1969 and 1983 that accounted for an aggregate of 3357 casualties with associated morbidity and mortality patterns. Of the 3357 casualties, 423 or 12.6% died prior to receiving medical care. Frykberg & Tepas (1988) found that soft tissue and bony extremity injuries were predominant among survivors and that traumatic amputations in this group were associated with 10% mortality in what could be concluded as a potentially survivable injury. Injury to the body wall and body cavity (i.e., abdomen and chest) was associated with the greatest risk of late deaths among those who initially survived the blast (Frykberg & Tepas, 1988).

Civilian morbidity and mortality associated with blast resulting from bombs and exploding devices cause both blunt and penetrating types of trauma injuries. Three principal causes of injuries associated with bombs and exploding devices include the blast effect or shock wave, flash burns created by the thermal energy of the explosion, and penetrating wounds from the ballistic effects of the shrapnel (Frykberg, & Tepas 3rd, 1988, Frykberg, 2002). Explosive events that occur within infrastructures such as buildings tend to cause more severe primary blast injuries when compared to open air outdoor explosions (Frykberg, 2002). Leibovici, Gofrit, Stein, Shapira, Noga, Heruti, & Shemer (1996) report a 7.8% mortality rate among 204 casualties involved in open air bombings in Jerusalem, and a 49% mortality rate among 93 victims of explosions within bus vehicles. It is clear that there are some similarities that exist between the trauma injuries experienced in civilian explosive events and those experienced during combat military operations.

Theoretical Framework

Section 564 of the Food Drug and Cosmetic Act permits the Food and Drug Administration, under the principle of the best available medical product, to intervene with that medical product in a public health emergency caused by chemical, biological, radiological, or nuclear agents. However, this authority does not extend to instruments of war that have claimed many lives in Iraq and Afghanistan. Instead, the authority is expressly available and delimited to intervention to deal with mass casualties that result from chemical, biological, radiological, or nuclear disasters.

Therefore, there is a current exclusion or gap in the Emergency Use Authorization that extends beyond chemical, biological, radiological, or nuclear agents and should include instruments of war or terrorism (such as explosive devices or agents), or hazards which cause or threaten to cause massive physical and/or psychological trauma. Does this gap in the Emergency Use Authorization potentially lead to unfortunate health consequences for U.S. military forces? Moreover, is there an essential need for mitigation of this gap and inclusion of "all hazards" to deal with wartime hazards and public health preparedness?

Methodology

Design, Data Collection and Evaluation

A literature search on PubMed, the Defense Technical Information Center (DTIC), and Google Scholar yielded 26 articles (1982-2014) that examined the effects of blast as an instrument of war on combat casualty care using the keywords: military; civilian; mortality; hemorrhage; pre-hospital; outcomes; war; combat; injury; trauma; died of wounds; survivability; plasma; freeze dried plasma; tranexamic acid; recombinant factor VIIa; blast injury; coagulopathy; and explosion. A comprehensive evaluation of findings in 11 of these articles was then conducted.

An assessment was made of each article that included a medical product in either pre-clinical or clinical trial status, a medical product that the Food and Drug Administration approved for another indication other than a particular trauma indication, or a product approved by a regulatory entity other than the Food and Drug Administration such as a foreign regulatory authority. The principle inclusion criterion was that the article addressed a medical product used in either the Iraq or Afghanistan conflicts during the delivery of combat casualty care. The stemming process yielded 11 articles. The product assessments were based on the scientific evidence available, including data from well-designed pre-clinical studies and clinical trials that would support the product being effective in the control of hemorrhage and especially non-compressible hemorrhage. Where appropriate, relative risk and odds ratios were either calculated or assessed.

Results

Unapproved medical products for use in trauma care, and precisely hemorrhage control, represent the most compelling argument to expand the Emergency Use Authorization authority (Kelly, Ritenour, McLaughlin, Bagg, Apodaca, Mallak, & Holcomb, 2008). The results and discussion sections of this paper will focus on the potential use of freeze dried plasma vice fresh frozen plasma, recombinant factor VIIa (commercially known as Novo-Seven®), and tranexamic acid relative to their efficacy in controlling non-compressible hemorrhage and any logistic burdens.

The principal cause of combatant mortality is hemorrhagic shock. Uncontrolled hemorrhage resulting in approximately 50 percent of combat-related deaths, mostly occur in the field prior to transportation to and arrival at a combat support hospital (Alam, Burris, DaCorta, &

Rhee, 2005). However, the U.S. Army has provided clear and demonstrable evidence that a massive transfusion policy delivers a positive reduction in mortality, in face of massive bleeding, when the red blood cell/clotting factor ratio is close to that of whole blood (Spinella, & Holcomb, 2009). This position is supported by Nascimento, Callum, Rubenfeld, Neto, Lin, & Rizoli, (2010) who report that fresh frozen plasma is Food and Drug Administration approved and indicated for management of massive bleedings. Nascimento, et al., (2009) and Shuja, Shults, Duggan, Tabbara, Butt, Fischer, & Alam, (2008) properly note that the early onset of coagulopathy in trauma, demands an early aggressive infusion of responsive hemostatic resuscitation at a near 1:1 ratio of Food and Drug Administration approved fresh frozen plasma/red blood cells in order to achieve a significant reduction in mortality.

Nascimento et al. (2009) also note that utilization of fresh-frozen plasma or fresh plasma is impacted by the logistical problems of transportation, storage, extended thawing time, the potential waste resultant upon the short after-thawing life, the impracticality of achieving immediate access to available universal AB plasma donors in the battlefield environment, and transfusion-associated complications. These have all impacted or otherwise presented a challenge to the implementation of fresh-frozen plasma or fresh plasma on the battlefield. Plasma is therefore essential for massive transfusions; on the other hand, fresh-frozen plasma use in austere battlefield conditions is often challenging when cold-chain transportation and storage present logistical problems. Thawing of fresh-frozen plasma requires precious time, up to 45 minutes prior to transfusion, and logistical loss of units on the battlefield has been observed. Mabry, Holcomb, Baker, Cloonan, Uhorchak, Perkins, Canfield, & Hagmann, (2000) report that, during the battle for Mogadishu the available fresh frozen plasma was stored in bags that fractured one-third of the time when thawed. Due to these problems, the French army has

utilized freeze dried and secured plasma since 1994 (Daban, Clapson, Ausset, Deshayes, & Sailliol, 2010).

Easy to use, freeze dried and secured plasma is created by lyophilizing the separated fresh blood of ten or more donors, in a manner permitting dilution and neutralization of natural anti-A and anti-B hemagglutinins, making it compatible with any blood type, retaining all clotting factors and proteins, giving a shelf-stable life of two years in ambient temperatures for 2 years, after which the fibrinogen and clotting factor levels are equivalent to fresh frozen plasma (Daban, Deshayes, Clapson, Batjom, Shall, Clavier, & Sailliol, 2009). Furthermore, it is easily rehydrated with 200 ml of water for injections in less than 3 minutes, allowing immediate provision with the first packed red blood cells; therefore this removes the logistical problems, accelerates its availability for any blood type in an emergency, without compromising hemostatic properties (Daban, et al., 2010).

Trauma induced coagulopathy is associated with an extremely high mortality and Shuja, Shults, Duggan, Tabbara, Butt, Fischer, & Alam (2008) have shown that survival can be improved by correction of coagulopathy through early, aggressive infusion of fresh frozen plasma. Yet, fresh frozen plasma is a perishable product, and its use is impractical in challenging environments such as a battlefield. Development of shelf-stable, easy to use, low volume, lyophilized, freeze dried plasma can overcome the logistical limitations. Shuja et al. (2008) reported that in vitro analysis revealed no differences in the coagulation profiles of fresh frozen plasma and freeze dried plasma and that the lyophilization process did not decrease the activity levels of the measured clotting factors. Shuja et al. (2008) concluded that plasma can be lyophilized and freeze-dried to create a logistically superior product without compromising its

hemostatic properties and that this product may be suitable for use in austere environments, such as a battlefield, for the treatment of trauma-associated coagulopathy.

As mentioned previously, freeze-dried plasma is approved for use in countries outside of the U.S. for control of bleeding by both French and German military forces in operations conducted under the North Atlantic Treaty Organization (Daban et al., 2010). Since the carrying and thawing of frozen liquids is impractical on the battlefield and in other austere environments, Germany developed and licensed a freeze-dried version of plasma (LyoPlas N-w), which consists of a powder that can be rapidly reconstituted with water prior to intravenous administration, but is not approved by the Food and Drug Administration (Pennardt, 2010). Significant legal barriers exist that prevent U.S. military medical personnel from using non-Food and Drug Administration approved medications and blood products on U.S. service members.

Even though seriously wounded American casualties are being successfully treated with LyoPlas N-w by German medical facilities in Afghanistan, U.S. Special Operations Forces (SOF) medics are prohibited from using this same product on the battlefield hours earlier as a potentially lifesaving measure (Pennardt, 2010). Recognizing the illogic of this disparity and the great potential FDP holds for trauma resuscitation, the Office of the U.S. Special Operations Command Surgeon is actively pursuing authorization for Special Operations Forces to field LyoPlas N-w (Pennardt, 2010). Germany has to date fielded over 500,000 units of LyoPlas N-w without any unusual or significant adverse effects when compared to fresh frozen plasma. Multiple clinical studies have also demonstrated that LyoPlas N-w is at least as efficacious as fresh frozen plasma (Pennardt, 2010).

Illustrative of off-label use is the use of recombinant factor VIIa (commercially known as Novo-Seven®), approved for treatment of bleeding in hemophilia, and used not for that purpose

but for the purpose of treating severe bleeding in trauma casualties in Iraq. Perkins, Schreiber, Wade, & Holcomb, (2007) conducted a retrospective medical records audit of trauma admissions to combat support hospitals in Iraq between January 2004 and October 2005 where patients requiring a massive transfusion and receiving recombinant factor VIIa were identified. Groups were divided into those who received recombinant factor VIIa early or late and found that early administration of recombinant factor VIIa decreased red blood cell use by 20% in trauma patients requiring massive transfusion (Perkins et al., 2007). Spinella, Perkins, McLaughlin, Niles, Grathwohl, Beekley, & Holcomb, (2008) conducted a retrospective review of a database of combat casualty patients admitted to one combat support hospital in Baghdad, Iraq, between December 2003 and October 2005 and compared patients who received recombinant factor VIIa to those who did not. Spinella et al. (2008) found that the use of recombinant factor VIIa was associated with decreased 24-hour and 30-day mortality in patients requiring massive transfusions with severe traumatic injuries, but not with an increased incidence of severe thrombotic events.

Their results showed that twenty-four-hour mortality was 7 of 49 (14%) in those who received recombinant factor VIIa and 26 of 75 (35%) in those who did not receive received recombinant factor VIIa, ($p<0.01$) (Spinella et al., 2008). Moreover, the 30 day mortality was 15 of 49 (31%) for those receiving received recombinant factor VIIa and 38 of 75 (51%), for those not receiving received recombinant factor VIIa ($p<0.03$) (Spinella et al., 2008). Lastly, Spinella, et al., (2008) reported death from hemorrhage was 8 of 14 (57%) for those receiving recombinant Factor VIIa compared with 29 of 37 (78%) for patients not receiving recombinant Factor VIIa. They further concluded that the ability of recombinant factor VIIa to improve outcomes in patients with traumatic injuries, without increasing adverse effects, likely depends upon it being

administered within two hours to patients with life-threatening traumatic injuries who are in a hypocoaguable state.

While the use of recombinant factor VIIa was not based upon a Department of Defense policy position, it was made upon firm scientific rationale, in reliance upon sound practical medical evidence based on familiarity of in-theatre surgeons, with the current documented positive results demonstrative of early use in the trauma facility being associated with a subsequent reduction in the need for massive transfusions and resulting in more positive outcomes overall (Kenet, Walden, Eldad, & Martinowitz, 1999). This use was accompanied by the establishment of local clinical practice guidelines for damage control resuscitation, and maintenance of records on the product's use and effects. It is important to note that the regulatory framework in these cases of off-label use provide a means for one patient or a case by case matter and are not an avenue for several or many patients as that would require Investigational New Drug or Investigational Device Exemption approval.

Intravenous administration of tranexamic acid was approved by the Food and Drug Administration in 1986 for prevention or reduction of bleeding in patients with hemophilia undergoing dental procedures. The Food and Drug Administration approved use of the oral form of tranexamic acid to control heavy menstrual cyclic bleeding in 2009. With regard to unlabeled use, tranexamic acid is not Food and Drug Administration-approved to stop uncontrolled hemorrhage in severe trauma patients. It has been studied in randomized trials to control bleeding during surgery, and most recently in trauma as discussed below. Eastridge et al. (2012) reports recent emphasis in acute combat casualty care has focused on the use of tranexamic acid in reducing mortality associated with non-compressible hemorrhage. Williams-Johnson, McDonald, Strachan, & Williams (2010) showed that the early administration of tranexamic acid

to trauma patients with, or at risk of, significant hemorrhage reduces the risk of mortality from hemorrhage with no ostensible increase in vascular occlusive events associated with mortality or morbidity. Moreover, Roberts, Shakur, Afolabi, Brohi, Coats, & Dewan (2011) showed that the significance of early intervention with tranexamic acid in bleeding trauma was associated with a significant decrease in mortality and from hemorrhage and that tranexamic acid can be administered safely to a wide spectrum of patients with traumatic bleeding and should not be restricted to the most severely injured.

United Kingdom medical forces at Camp Bastion in southern Afghanistan conducted a study and found that the use of tranexamic acid with blood component-based resuscitation following combat traumatic injury results in improved measures of coagulopathy and survival, a benefit that is most prominent in patients requiring massive transfusion (Morrison, Dubose, Rasmussen, & Midwinter, 2011). Morrison et al. (2011) showed that tranexamic acid was independently associated with survival (odds ratio=7.228; 95% CI, 3.016-17.322) and less coagulopathy (P=.003). Morrison et al. (2011) concluded that treatment with tranexamic acid should be incorporated into clinical practice as part of a resuscitation strategy to treat severe combat injury and hemorrhage.

Therefore, due to the delimited scope of section 564 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360bbb-3), the U.S. finds itself in the singularly untenable position of being barred from the use of freeze dried plasma products, tranexamic acid and recombinant Factor VIIa on U.S. military personnel because these products lack not only the Food and Drug Administration authority to permit their use for combat related hemorrhage and coagulopathy, but also lack an Emergency Use Authorization grant of authority as the best available product to address the emergency.

How Many Lives Could Have Been Saved in Iraq or Afghanistan If We Had Had an Effective Intervention?

With regard to non-compressible hemorrhage on the battlefield the fundamental question is how much mortality in Iraq or Afghanistan could be reduced if a more effective intervention had been available? Kelly, Ritenour, McLaughlin, Bagg, Apodaca, Mallak, & Holcomb (2008) examined 982 post mortem combat deaths from Iraq and Afghanistan to assess changes in injury severity and causes of death in which fatalities were categorized as non-survivable or potentially survivable and subsequent analysis of the potentially survivable category to determine mechanism and cause of death. Kelly et al. (2008) found that the total potentially preventable deaths were 232 (24%) and the potentially preventable deaths from non-compressible hemorrhage were 115 (12%).

The current fatality data for the Department of Defense for the wars in Iraq (Operation Iraqi Freedom (OIF)) and Afghanistan (Operation Enduring Freedom (OEF)) as of December 17, 2004 shows that there were 2,356 fatalities in OEF and 4,425 fatalities in OIF for a total fatality count of 6,781 U.S. deaths (Department of Defense, 2014). Using the 12% of total fatalities that were both potentially preventable and that resulted from non-compressible hemorrhage as determined by Kelly et al. (2008) and applying that percentage to calculate the number of potentially preventable fatalities due to non-compressible hemorrhage shows a total of 814 deaths. The results of Morrison et al. (2011) on a more severely injured cohort suggest that as few as seven patients need to be treated to provide the potential benefit, or the number of patients required to treat with tranexamic acid to achieve a mortality benefit of one patient, was seven. This translates to a potential 116 U.S. lives saved had tranexamic acid been used.

A similar methodology may be applied to the data reported by Spinella et al. (2008) on 24-hour and 30-day mortality, and severe thrombotic events, in patients receiving massive transfusions and who received recombinant factor VIIa to those who did not. Using the 12% of total fatalities that were both potentially preventable and that resulted from non-compressible hemorrhage as determined by Kelly et al. (2008) and applying that percentage to calculate the number of potentially preventable fatalities due to non-compressible hemorrhage shows a total of 814 deaths. Spinella et al. (2008) reported that the 24-hour mortality was 7 of 49 (14%) in those receiving recombinant factor VIIa compared to 26 of 75 (35%) in those not receiving recombinant factor VIIa, ($p= 0.01$) resulting in a 21% difference of potential saved lives had recombinant factor VIIa been available for large-scale use other than on a patient by patient basis. In addition, 30-day mortality was 15 of 49 (31%) in those receiving recombinant factor VIIa compared to 38 of 75 (51%) in those not receiving recombinant factor VIIa, ($p= 0.03$) (Spinella, et al., 2008), resulting in a 20% difference of potential saved lives had recombinant factor VIIa been available for large-scale use other than on a patient by patient basis.

Discussion

This study presents an argument for the expansion of section 564 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360bbb-3) beyond the current threat scenario of chemical, biological, radiological, or nuclear agents to include instruments of war or terrorism (explosive devices or agents), or hazards which cause or threaten to cause massive physical trauma. The study determined that: (1) a gap in the Emergency Use Authorization results in potential risk for increased mortality among U.S. military forces subject to combat trauma associated events such as blast forces beyond chemical, biological, radiological, or nuclear agents; and (2) there is an

essential need for inclusion of a “all hazard” condition which includes “instruments of war” to enhance National Security and also better enable public health preparedness.

The Department of Defense can adequately argue that in satisfying its legal and ethical duty and responsibility to military service members, its broader duty to ensure the greatest degree of safety to the military unit, and accomplishment of the combat mission is upheld. This governs and supersedes the personal preference of a particular soldier, particularly where it is impracticable to obtain informed consent in an imminent or ongoing combat environment. Early and effective treatment is extremely important to save more lives, and benefits most (Manring, Hawk, Calhoun, & Andersen, 2009).

It is particularly troubling that the Department of Defense is denied the opportunity to provide meaningful clinical benefit, not only to health in the military service, but also to the national community, while broad legal immunities shield governmental researchers, and the U.S. government from civil claims. Civil claims such as the Feres doctrine preclude raising tort claims against government, government employees, or third party contractors working in furtherance of governmental research, if the injury is sustained incident to service (Turley, 2003). It also shields the U.S. when the underlying injury relates to a discretionary function of military policy. Moreover, the Supreme Court has interpreted the Feres doctrine broadly, to encompass claims arising from experimental research, including covert experimentation on soldiers and civilians, or intentional disregard of legal requirements and informed consent protocols (Turley, 2003). Why then is the Department of Defense the frustrated national stepchild, who stands ready, but is debarred from meeting its duties to properly serve the medical needs of the service members and nation? Such is precisely the case in a combat environment where instruments of

war, such as improvised explosive devices, have caused significant mortality and morbidity which may have been prevented or mitigated had appropriate authorities been put in place.

The current Ebola outbreak crisis in West Africa presents a somewhat analogous ethical dilemma concerning the use of unapproved medical products for prevention and life saving measures against the Ebola virus. In order to address the ethical considerations for use of unregistered interventions for the Ebola viral disease, the World Health Organization commissioned a consultation group to evaluate the ethical implications of using of unapproved medical products. The World Health Organization referred to such unapproved medical products as unregistered interventions that demonstrate promising results in the laboratory and in animal models yet heretofore had not been evaluated for human safety and efficacy (World Health Organization, 2014).

The World Health Organization consultation group included expertise in bioethics, scientific research methods, Ebola research, Ebola management experience, humanitarian crises experience, and patient safety advocacy and regulation of therapeutics. The consultation group noted that the use of unregistered interventions should be driven and guided by strict adherence to ethical, evidentially sound, scientific and pragmatic criteria and have promising laboratory results especially when such interventions had not yet been evaluated for safety and efficacy in humans (World Health Organization, 2014).

Moreover, the World Health Organization consultation group prescribed exact guidelines and standards of operation when the issue of the potential administration of unregistered interventions arose. Among the essential standards set forth by the World Health Organization consultation group are the requirement that there must be an evaluation of the associated risk and benefit, based upon the best possible available information supportive of the proposed use of the

medical intervention (World Health Organization, 2014). Additionally, the consultation group specified the absolute need for transparency about all aspects of the care of patients receiving unregistered medical interventions. Furthermore, the importance of thorough detailed record keeping toward maximization of detailed information on the effects of such medical interventions was delineated. Likewise, informed consent was another factor deemed essential. This criterion may, conversely, give rise to complications within the extant circumstances of the battle theatre. Other factors that were properly deemed important considerations in the use of unregistered medical interventions, include freedom of choice, confidentiality, respect for the person, preservation of dignity and involvement of the community (World Health Organization, 2014).

Additionally, the World Health Organization consultation group provided that where there has been a determination that unauthorized administration of an unapproved drug is appropriate, the administration must be accompanied by efforts to assimilate data toward a determination of the safety and efficacy of the interventions, or to the counter indication of such use where evidence obtained is to the contrary (World Health Organization, 2014). Moreover, the consultation group advised that, whether interventions are implemented for patient treatment or for preventative purposes, the physician operates under various mandates. Included among the mandates are the duties: to supervise the administration, to fully comply with the moral obligation to timely collect data related to the administration, under the extant circumstances; and to share all scientifically relevant data toward continuous studies, evaluation and guidance toward decisions concerning future interventions in relationship to the safety and efficacy of such interventions (World Health Organization, 2014; Rid & Emanuel, 2014).

The position delineated by the World Health Organization concerning the ethical considerations for use of unregistered interventions to treat or prevent Ebola viral disease, is decidedly analogous to the position set forth herein of the paramount importance to protect the health of U.S. service members with the best scientifically supported medical products. Specifically, that section 564 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360bbb-3) be amended and expanded to pandemic and all-hazards preparedness reauthorization act to strengthening all-hazard preparedness through authorization for medical products for use in emergencies caused by all hazards whether natural disasters, act of nature, instrument of war or terrorism, intentional or accidental, or causes or likely causes of physical or psychic trauma. More particularly, it is the position of this thesis that attention to ethical questions must be analyzed and framed within the exceptional exigencies of the wartime theatre, wherein support for compassionate use of unauthorized interventions are revealed.

Criteria, permitting departure from the well-established regulations and governance of therapies and interventions would include the evaluation of the best possible available information supportive of the proposed use of intervention, and provide the determination that the associated benefit outweighed any potential risk. Subsequent to the determination of benefit to the patient, detailed record keeping would be mandated in order to ensure absolute transparency concerning all aspects of the care of patients who were administered unregistered interventions. Although informed consent would be essential, the determination of satisfaction would be made in light of the extant circumstances of the battle theatre. Of no less importance would be strict adherence to the professional ethical standards of medical research and performance concerning freedom of choice, confidentiality, respect for the person, preservation of dignity and involvement of the community.

Nightingale et al. (2007) suggests that after the events of September 11, 2001, and the anthrax letter attacks a month later, the Department of Health and Human Services started developing plans for large-scale off-label use of Food and Drug Administration approved drugs and for the use of unapproved products during a national emergency. Such planning led to the original Project BioShield Act of 2004 that established the comprehensive Emergency Use Authorization; nonetheless, it has fallen short of protecting the health and welfare of civilians and service members due to its deference without any logical consistency to covering threats only from chemical, biological, radiological and nuclear agents. I therefore argue that a right to protect one's health by making medical treatment decisions has fundamentally been flawed by the deference to only chemical, biological, radiological and nuclear agents.

The issue of deference in this case leads to the question: Why restrict the right to receive the best medical treatment available to this narrow scope of threats? As suggested by Hill (2007), such logic does not mean that individuals will have an unqualified right to obtain any medical treatment they and their physicians deem appropriate, but only that a constitutional right to protect an individual's health must be consistently recognized; that the recognition of this right should not be artificially limited by deference to legislative findings of medical fact; and that this right will have to be considered with the government's role in regulating the practice of medicine to protect the public. The autonomy principle in medical ethics treats the right to choose appropriate medical treatment as an aspect of the rights to bodily integrity and decisional autonomy (Hill, 2007).

Moreover, to recognize that individuals possess a constitutional right to protect their health by making autonomous medical treatment decisions is not, by any means, to decide that the right supersedes government regulatory obligations, rather government is obligated to expand

the scope of protection offered by the Emergency Use Authorization (Hill, 2007). The issue of when governmental actions prevail over the individual right to protect one's health through making autonomous medical treatment choices must be resolved to the individual's benefit. Such benefit also compliments the medical ethical principle of paternalism in that "the doctor knows best" and will act to do what he or she believes to be most beneficial to the health of the patient. In emergency medical situations on the battlefield, the service members want and expect immediate actions to provide them with the best available medical product to save their life.

The following case serves as an exemplar to illustrate the ill-logical scope of coverage of the Emergency Use Authorization. In a hypothetical scenario where a terrorist or state-sponsored nuclear detonation occurs on the battlefield, such an event will result in physical blast wave effects resulting in hemorrhage, fractures, amputations, crush injury, burns, cuts, lacerations, as well as the exposure to various levels of radiation to U.S. service members. Under that condition, those trauma casualties could be treated under an Emergency Use Authorization with products such as freeze-dried plasma, recombinant factor VIIa, and tranexamic acid that would be the best medical products available for the purpose of controlling hemorrhage and resuscitation regardless of Food and Drug Administration approval status. On the other hand, if U.S. service members are subjected to a blast on the battlefield caused by an improvised explosive device, without nuclear materials, the Emergency Use Authorization for freeze dried plasma, recombinant factor VIIa, or tranexamic acid would not apply and U.S. service members would be denied the benefit of those medical products to save their life merely because of the origin of the blast (a nuclear device vice an improvised explosive device) (Nightingale et al., 2007; Food and Drug Administration, 2007; Project BioShield Act, 2004).

The exemplar above can be extended to situations involving civilians in the United States subjected to a blast resulting from a terrorist nuclear device detonation whereby the Emergency Use Authorization would provide the best medical product available regardless of Food and Drug Administration approval for trauma care to save lives. On the other hand, a blast resulting from an improvised explosive device, such as what occurred in the Boston Marathon bombing, would once again show the ill-logical constraint of the narrow and inappropriate coverage of the Emergency Use Authorization. Such an inequity must be remedied by expanding the scope of the Emergency Use Authorization (Nightingale et al., 2007; Food and Drug Administration, 2007; Project BioShield Act, 2004). No apparent rationale supports the existence of a preference to protect the health of individuals from chemical, biological, radiological, and nuclear hazards in contrast to protecting the health of those same individuals against the same blast or mechanical hazards associated with improvised explosive devices, or by natural disasters such as earthquakes, storms, floods and hurricanes.

The Emergency Use Authorization provides a mechanism to deal with the problems of administering Investigation New Drug and off-label product protocols during a public health emergency and is thereby complementary to the Byrd Amendment's provisions for military personnel (Javitt, 2005). The Emergency Use Authorization needs to undergo several improvements. First, as discussed extensively above, it will need to be expanded in terms of scope of coverage to apply to all hazards. Second, the Emergency Use Authorization will be to have clear guidance as to what constitutes an emergency and what criteria should be applied to make the determination that a public health emergency exists. In a real world scenario there may be insufficient time to exercise all of the Emergency Use Authorization provisions to provide clinically effective outcomes relative to that emergency situation. Third, the application to off-

label use in the Emergency Use Authorization potentially creates a greater scientific/technical burden on that product compared to what exists today in the routine off-label use as an accepted part of medical practice. Hence, there should be a mechanism to enable health care providers, manufacturers, and government public health agencies to recommend the use of a product for an unapproved use; still, the standards for doing so should be different for a product that has never been approved for any use compared to a product that has already been approved for a use not intended for the present purpose at hand.

The Emergency Use Authorization as it exists today does nothing to address the hazards responsible over the last 13 years of war in Iraq and Afghanistan for causing nearly 75% of casualties associated with explosive blast fragmentation and gunshot wounds (Eastridge, et al., 2012). Moreover, such a gap in coverage has failed to address a potential benefit that could have mitigated to some extent 6781 deaths that have occurred in Iraq (Operation Iraqi Freedom) and Afghanistan (Operation Enduring Freedom) as of December 17, 2014 (Department of Defense, 2014).

In addition to expanding the scope of coverage of the Emergency Use Authorization to all hazards to include instruments of war, another option is to establish a new category of product approval "For Military Use Only." Such a classification could be applied to products that have sufficient pre-clinical and clinical efficacy data as well as manufacturing data to make a determination that it is clinically prudent to offer it to US service members at high-risk of morbidity or mortality under military operations. A classification of "For Military Use Only" should require surveillance of the product for the purpose of identifying adverse events and provision of appropriate product information on risks and benefits to the recipients of the product. Similar to the Emergency Use Authorization, a special classification "For Military Use

Only" would be situation dependent and regulated by the Food and Drug Administration to permit surveillance of the product for adverse events and appropriate product information is provided to the consumer. Manufacturers of "For Military Use Only" products would have to prepare package labels and inserts to address both consumers and health care providers on intended use, mechanisms of action, contraindications, warnings, adverse events, dosage and administration, and how the product is supplied.

A product classification "For Military Use Only" would carry the same obligations as an Emergency Use Authorization but would not have to be subject to the difficult formal regulatory procedures required by an Investigation New Drug in a military operational environment. The greater good of the military would be served by reducing the nearly 75% of casualties associated with explosive blast fragmentation and gunshot wounds. This is so, even in the face of assertions that creating a separate classification "For Military Use Only" could provide a less worthy medical product, to military forces whose autonomous rights may have been diminished as a result of serving in the military and in military operations. Likewise, such a special category could also be perceived as unauthorized experimentation on military forces without appropriate human subject protections.

The greater good of our military warriors is not well served, neither is their respect for person, self-determination, autonomy, or individual dignity well served without provision to expand the Emergency Use Authorization. Rather, these as well as our duties of beneficence, and justice are violated when potentially lifesaving treatments capable of protecting against foreseeable soldier and national injuries is limited or prohibited in face of our duty to serve our nation. In light of the foregoing discussion, it is morally and ethically proper to waive the requirement for provision of substantial evidence of human clinical efficacy, where a great deal

of animal efficacy and inferable human safety data exists. Furthermore, it is arguably supportable to assert that an ethical mandate exists toward meeting our charge to protect the health of U.S. service members and thereby protect our nation.

Limitations of the Current Study

This study is retrospective and therefore has several limitations. First, most of the mortality data in the studies cited and used in the analysis from the Joint Theater Trauma Registry and the Mortality Trauma Registry have the inherent limitations of large registries such as misclassification bias, inter-observer subjectivity, variance in clinical data interpretation, and input errors of omission as well as input errors of commission (Eastridge, et al., 2011). These errors could have potentially led to invalid frequencies, rates, time estimates and statistical measures. Second, as reported by Eastridge et al. (2011), based upon gross examination, data contained in the registries may include a potential under-measurement of lethal traumatic brain injury due to extreme rotational trauma associated with the magnitude of forces that casualties are subjected to from explosive incidents. As a result, it is possible that some cases classified as "non-survivable" could have been inadvertently misclassified as "potentially survivable" based on gross autopsy findings (Eastridge et al., 2011).

With respect to the retrospective observational study reported by Morrison et al. (2011) comparing tranexamic acid administration with no tranexamic acid, there are some limitations that need to be noted. Since the clinical practice guideline that included tranexamic acid was not implemented until the later part of the study, there is a potential for variability in the indications for use and levels of dose that may be confounding factors in the outcome data. On the other hand, because this study reflects use of tranexamic acid at only one medical treatment facility such variability in use could be minimal. Morrison et al. (2011) reported that the exact cause of

death or time of death could not be captured in those who died. Hence, there is a potential that some patients who died very early in the course of admission could be included in the study cohort and since these patients are less likely to be affected by any therapeutic intervention there is a potential for an immediate mortality bias (Morrison et al., 2011). Conversely, since there was no difference in the mortality rate between cohorts at the 24-hour period, it is probable that patients who died very early were evenly distributed across the groups (Morrison et al., 2011).

With respect to retrospective studies such as these, the interpretation of results may be limited by the lack of randomization and the potential for selection bias. Yet, this limitation is a characteristic in all retrospective studies and in trauma studies such as these there could be a selection bias involving the preference of the physician to use the intervention when they believed the patients had a greater probability of surviving. Lastly, it is important to acknowledge that this study is the first attempt at synthesizing the literature on this topic from the perspective of potential lives lost as a result of a gap in coverage of the Emergency Use Authorization and should be viewed as a relative strength in this important area.

Conclusions

It is necessary to offer a proposed amendment to the Pandemic and All-Hazards Preparedness Reauthorization Act. The proposed amendment will strengthen all-hazard preparedness through authorization for medical products for use in emergencies caused by all hazards whether natural disasters, act of nature, instrument of war or terrorism, intentional or accidental, or causes or likely causes of physical or psychic trauma. The analysis of § 564 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 360bbb-3 elucidates a significant gap in the Food and Drug Administration authorization of the emergency use of medical products to

diagnose, prevent, or treat major health emergencies. Currently, there is a major gap in scope of coverage of the Emergency Use Authorization authority as it only applies to chemical, biological, radiological, or nuclear agents. Such a limitation is similar to the same gap in emergency preparedness authority before the enactment of the Pandemic and All-Hazards Preparedness Act – specifically, that the emergency authority does not deal with all hazards.

Expansion to all hazards would allow the Food and Drug Administration to grant an Emergency Use Authorization for an unapproved medical product (or unapproved use of an approved product) that is the best available medical countermeasure for mass casualty trauma care. Such expansion would cover trauma care whether brought on by natural disaster, large accident, instruments of war or terrorism such as explosive devices, or other hazard causing or threatening large scale physical or psychic trauma, and thereby close this gap and ensure "all hazard" preparedness. These potential all-hazard response improvements have value for domestic, international, and military emergency preparedness. The results of the analysis would expand the Emergency Use Authorization authority, which has been implemented prudently and successfully, to preparedness for all hazards. All other aspects of the Emergency Use Authorization authority would remain unchanged.

Future Directions and Research

Medical treatment facilities on the battlefield store plasma as fresh frozen plasma, and then thaw prior to administration in casualty care. On the other hand, to administer blood products in the pre-hospital environment such as at the point of injury, there needs to be a method and means to deliver the plasma on the battlefield far-forward in a reliable manner. Such a logistical gap can be overcome by the utilization of freeze-dried or lyophilized plasma. As previously mentioned, although available overseas, these products, lack Food and Drug Administration approval presently. Gaining this approval or accelerated fielding through the Food and Drug Administration process must become a top priority among the military science community.

The US Special Operations Command has identified accelerated fielding of a dried plasma product to be a top priority for battlefield trauma care and Special Operations Forces who must often conduct operations in immature or under developed theaters and austere environments (Deal, McDowell, Benson, Iddins, Gluck, Griffay, & Wedmore, 2010). Such military operational contingencies are associated with a risk of delayed or lengthy evacuation and delayed definitive care where care and evacuation may be delayed for several hours or days (Deal et al., 2010). While Special Operations medical personnel may not treat US service members with non-Food and Drug Administration approved products, US military casualties are being treated effectively by coalition medical forces with a German freeze dried plasma product in Iraq and Afghanistan. German medical forces have ministered over 500,000 units of the freeze dried plasma product and no significant or atypical adverse events have been reported (Pennardt, 2010).

Such a gap in U.S. military medical capability demands the requirement for a dried plasma solution for US combat medical personnel. Furthermore, it is essential that such a requirement for a dried plasma solution should not be limited to the Iraq and Afghanistan theaters of operation and should further extend to under developed and immature theaters worldwide that require Special Operation missions.

There are dried plasma research data gaps and needs that must be addressed. At present, there are an inadequate number of studies that have assessed clinical improvements and outcomes following transfusion of prehospital fluids among trauma patients; hence, there is a paucity of data regarding the effectiveness and indications for current blood products (Holcomb, 2010; McSwain, Champion, Fabian, Hoyt, Wade, Eastridge, & Blackbourne, 2011). Mc Swain et al. (2011) report that the majority of data that indicate the benefits of fluid replacement therapy are based on animal models of controlled hemorrhage.

Current research initiatives should include quality assessments to examine and improve stored human blood products, studies to identify new techniques for blood component preservation, product development for fielding blood products within 2 to 5 years, and product testing to determine the feasibility of currently available blood product use in theater of operations. In conclusion, the military is obligated to treat its troops as autonomous persons entitled to basic rights and protections yet the Military Health System must make every effort to care for injured service members in theaters of war with the medical products supported by the best body of science regarding clinical efficacy regardless of that medical product's regulatory status.

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