OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

The Honorable Ike Skelton
Chairman, Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

MAY 12 2009

Dear Mr. Chairman:

This letter provides the final report to Congress on the requests in the Joint Explanatory Statement, accompanying H.R. 2638, the proposed Consolidated Security, Disaster Assistance, and Continuing Appropriations Act, 2009, DoD Appropriations for Fiscal Year 2009, regarding life-saving blood technologies. The Department of Defense has an inherent interest in fielding effective measures to treat combat casualties who have suffered significant blood loss and may still be bleeding upon arrival at the surgical suite.

The enclosed report addresses the concerns of the Joint Explanatory Statement language and provides an assessment of the feasibility and advisability of accelerating research, development, and fielding of blood technologies that will improve the capacity to save lives of members of the Armed Forces receiving combat medical care.

Thank you for your continued support of the Military Health System.

Sincerely,

Ellen P. Embrey
Deputy Assistant Secretary of Defense
(Force Health Protection and Readiness)
Performing the Duties of the
Assistant Secretary of Defense
(Health Affairs)

Enclosure:
As stated

cc:
The Honorable John M. McHugh
Ranking Member

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

The Honorable Carl Levin
Chairman, Committee on Armed Services
United States Senate
Washington, DC 20510

MAY 1 2 2009

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cc:
The Honorable John McCain
Ranking Member

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

The Honorable Ben Nelson
Chairman, Subcommittee on Personnel
Committee on Armed Services
United States Senate
Washington, DC 20510

MAY 1 2 2009

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Enclosure:
As stated

cc:
The Honorable Lindsey O. Graham
Ranking Member

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

The Honorable Susan Davis
Chairwoman, Subcommittee on Military Personnel
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

MAY 12 2009

Dear Madam Chairwoman:

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(Health Affairs)

Enclosure:
As stated

cc:
The Honorable Joe Wilson
Ranking Member

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

The Honorable Daniel K. Inouye
Chairman, Subcommittee on Defense
Committee on Appropriations
United States Senate
Washington, DC 20510

MAY 1 2 2009

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Enclosure:
As stated

cc:
The Honorable Thad Cochran
Vice Chairman

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

The Honorable John P. Murtha
Chairman, Subcommittee on Defense
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515

MAY 1 2 2009

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Performing the Duties of the
Assistant Secretary of Defense
(Health Affairs)

Enclosure:
As stated

cc:
The Honorable C. W. Bill Young
Ranking Member

Report to Congress
Life-Preserving Blood Technologies

In Accordance with Joint Explanatory Statement accompanying H.R. 2638, the proposed Consolidated Security, Disaster Assistance, and Continuing Appropriations Act

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Life-Preserving Blood Technologies

INTRODUCTION

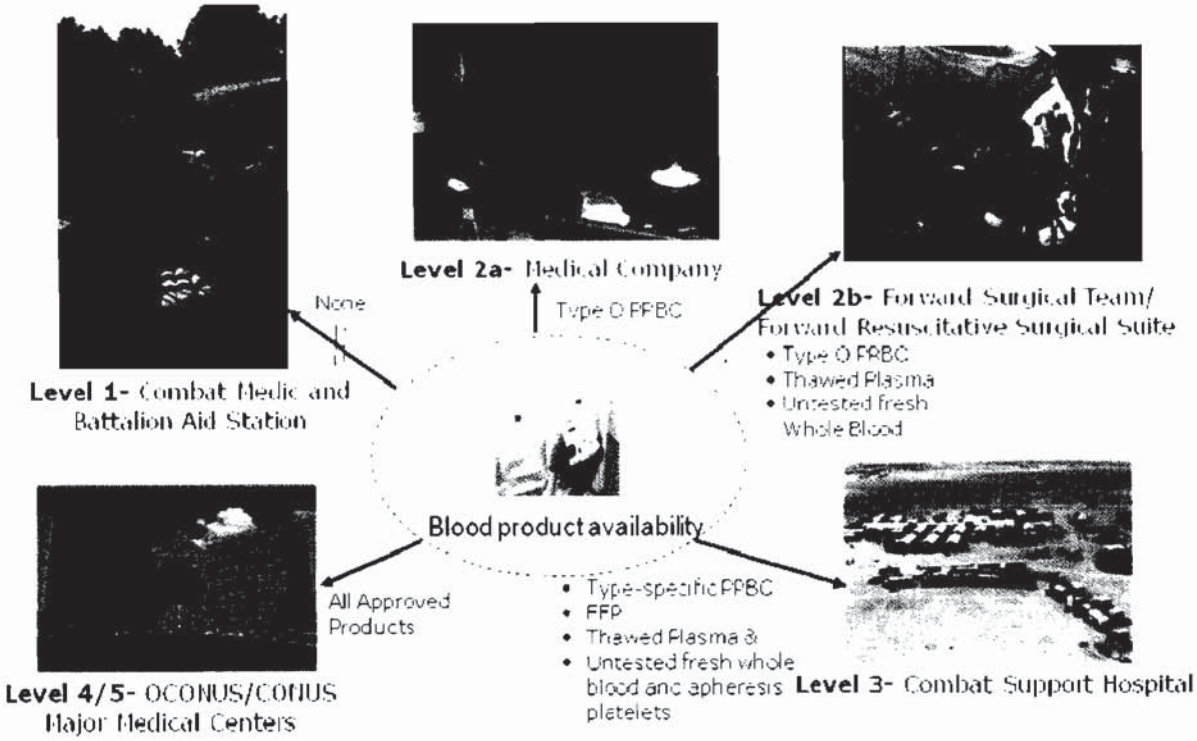
The Department of Defense (DoD) has an inherent interest in fielding effective measures to treat combat casualties who have suffered significant blood loss and may still be bleeding upon arrival at the surgical suite. Treatment of bleeding and blood loss can be divided into three distinct objectives:

- Restoration of circulating blood volume;
- Restoration of oxygen-carrying capacity; and
- Stop bleeding (hemostasis) with restoration of normal blood clotting mechanisms.

In the United States, trauma centers, including military medical treatment facilities (MTFs), the full panoply of usual and, frequently, not so usual and/or experimental measures are readily available for the treating physician for treatment of bleeding, especially so-called "massive transfusion." However, physicians and other providers are frequently limited in treatment options by the realities and exigencies of battlefield logistics and environmental conditions.

Battlefield treatment of hemorrhage begins at the point of wounding (Combat Life-Saver and Combat Medic) and continues to the surgical suite at the Forward Surgical Team (FST, Role 2b) and the Combat Support Hospital (CSH, Role 3). Availability of blood products at each level (Role) of medical care is depicted in the Figure below.

Figure 1. Availability of blood products



Availability of state-of-the-art blood products for management of severe bleeding has always been problematic for forces and medical personnel in the field. DoD has expended great effort over many years to discover and license innovative blood products or substitutes to meet the needs of the warfighter (Table 1 and Table 2).

BLOOD PRODUCTS CAPABILITY NEEDS

Recent capability documents prepared and validated by the Air Force (Initial Capability Document (ICD) for Ground Contingency Medical Support System (GCMSS), October 16, 2003) and the Army (ICD for Theater Combat Casualty Care (TC3), January 9, 2008) describe multiple capability needs and gaps:

- Noninvasive treatment to stop severe bleeding at point of injury, GCMSS, paragraph 4.c(2);
- Blood substitutes/expanders in field environment for rapid resuscitation, GCMSS, paragraph 4.c(2);
- Preparation, storage, and transport equipment for the full range of blood products required for in-theater patient care, GMCSS, paragraph 4.c(2);
- Hemostatic Agents and Equipment [for treatment of Internal bleeding and external bleeding], TC3, Table 4.1, page 7-8;
- Blood Substitutes [to restore tissue oxygenation and circulating blood volume], TC3, Table 4.1, page 7-8; and

- Coagulopathy Prevention and Treatment Agents, TC3, Table 4.1, page 7-8.

The Army is currently developing or collaborating in development of multiple life-preserving blood technologies that address the needs described in validated capability documents and that serve each of the treatment objectives outlined above to improve treatment capability at all levels of care on the battlefield.

SCIENCE AND TECHNOLOGY (S&T, BA 1, 2, and 3) FUNDED RESEARCH

Component Ratios

Studies will be initiated or are underway to elucidate the appropriate ratio of blood components required to ensure the highest likelihood of survival for our combat casualties. Studies are needed to compare fixed ratio treatment outcomes with goal-directed treatments defined as treating to effect determined by serial blood sampling and lab testing, as well as a prospective clinical study to identify the risk/benefit of specific treatment ratios.

Hemostatic Adjuncts

It will be logistically advantageous to have a small volume product that could be administered to a hemorrhaging casualty to stem the flow of blood from non-compressible wounds (e.g., pelvic bleeding). Two products currently under consideration are recombinant Factor VIIa and fibrinogen. Products are currently in animal efficacy testing. Additional adjuncts might include platelet derived hemostatic agents such as dried platelet products.

Rapid Blood Screening Tests

All blood collected for use in the United States is tested for a panel of infectious disease agents. Unfortunately, this requires a sophisticated laboratory system not sustainable in the combat theater. An alternate testing system is required for situations when it is necessary to collect blood or platelets in theater due to logistical supply constraints. A number of rapid infectious disease test kits (used to detect active disease) that are either in development in the United States, or available for sale in foreign markets are being tested for their accuracy and precision as blood screening tests. Current rapid test kits are generally not sensitive enough to meet Food and Drug Administration (FDA) requirements for blood borne pathogen testing of transfusion products. Work is carried out in conjunction with industry, academia, and government agencies to develop sensitive, reliable rapid test systems that can gain FDA approval. We need to accelerate FDA approval if feasible.

Universal Blood Products

Universal blood products could be used in any patient without concern for their blood type. Universal type for cellular based products is O and for plasma is AB, both Rh negative. Both types are rare and always in high demand.

- **Blood Pharming**. This is an active Defense Advanced Research Projects Agency (DARPA) research project seeking to develop a small, automated, cell culture and packaging system capable of producing transfusable amounts of universal donor (Type O negative) Red Blood Cells in combat theater. Successful demonstration of red blood cell (RBCs) production using this technology may lead to similar advances in production of fieldable platelet units. Research concerns that still need to be addressed include the potential for a post-transfusion immune response in recipients after multiple transfusions, or, rarely, during the initial transfusion. Success of the "Creation of Universal Red Cells" (see below) would eliminate the recipient immune response issue. Feasibility is yet undetermined due to immune response potential in multiple transfusions (which occurs in many forward operating DoD patients) and production capability to sustain operations.

- **Creation of Universal Plasma.** There are a number of techniques under development to create universal plasma through removal of the A and B antibodies. One process is in late stage clinical trials in Europe with plans to put it forward for licensure in the U.S. as well. Product will assist with inventory management of plasma due to limited collections of universal AB plasma. We will monitor industry research for incorporation into DoD use. This process is feasible.

- **Creation of Universal Red Cells.** There has been some basic research performed outside DoD seeking techniques to mask the antigens on red blood cells allowing them to behave as universal cells. Product would enhance inventory management of red blood cells, allowing any collection for any patient. However, the technology requires further proof of concept. We need to monitor further developments before investing. Feasibility is yet undetermined.

Dried Platelets

Platelets processed by freeze-drying (lyophilization, fdPLT) or by spray-drying (sdPLT) are in pre-clinical development by two biotechnology firms. Such a product, if successfully developed and licensed, offers the Army and DoD substantial logistical and deployment benefits with potential for far forward use as "infusible hemostatic agents"

with greatly reduced logistical expense. However, there remain substantial issues of clinical safety and efficacy that must be resolved before these products can be licensed for clinical use. A dried platelet product for trauma use could not be licensed and deployed until 2012 or later. Research is needed to further develop this technology. Feasibility has been demonstrated in pre-clinical studies with small and large animal models.

Alternatives to packed Red Blood Cells (pRBCs): Perfluorocarbon-Based Oxygen Carriers (PFBOC)

PFBOCs are a potential substitute for RBCs on the battlefield, especially far forward at Role 1 and Role 2. PFBOC consists of a fluorocarbon based compound in an emulsion or nanoparticle that carries five to ten times the volume of oxygen as hemoglobin. Although temperature stable and generally non-reactive *in vivo*, PFBOC has not been able to maintain oxygen saturation at less than 100 percent ambient oxygen or at normal atmospheric pressure. These technical difficulties are being overcome and at least one product is in Phase II clinical trials. PFBOCs offer potential for deployment to far-forward positions on the battlefield, including the Forward Surgical Team (FST), the Battalion Aid Station, or even the combat medic and can be administered regardless of recipient blood type. We need to reduce the development timeline of this product.

Perfluorocarbon compounds have been shown to improve the delivery of oxygen to tissue resulting from traumatic injury and hyperbaric decompression stress when coupled with normobaric hyperoxia. Additional research in the area of treating traumatic tissue (with an emphasis on brain injury) with perfluorocarbon compounds with normobaric and hyperbaric oxygen is needed.

ADVANCED DEVELOPMENT (BA 4 and 5) PROGRAMS

Plasma

Plasma, the liquid part of circulating blood, contains many proteins, the majority of which are critical to blood clotting (coagulation). Coagulation proteins (factors) may become deficient, diluted, or dysfunctional in the presence of severe hemorrhage for the same reasons suggested below for platelets. Current and potential treatments for coagulation protein deficiency or dysfunction include the following alternative to fresh-frozen plasma (FFP) in development:

- **Freeze-Dried Plasma (FDP)** FDP is a potential substitute for FFP. As a dried powder or cake, FDP offers the potential for reduced waste due to bag breakage and also offers advantages associated with no freezing requirement and reduced product weight. As such FDP may be deployed to more forward positions. FDP is currently licensed in

Germany as a blood banked product by the German Red Cross. FDP is currently being developed by a U.S. manufacturer under contract to the U.S. Army. Licensure in the United States is not expected before 2012 or 2013. Other manufacturers in the United States. and Europe are in varying stages of development of a FDP product. This product is very feasible and would greatly enhance the treatment of combat casualties.

Platelets

Platelets are cell fragments circulating in blood that are vital for effective clotting (coagulation) of blood. Platelets may become deficient, diluted, or dysfunctional in the presence of severe hemorrhage, probably due to a combination of factors, including loss of blood, dilution by resuscitation fluids, reduced body temperature (hypothermia), and consumption in abnormal clotting activity such as disseminated intra-vascular coagulation. Liquid-stored platelets, collected by donation from healthy donors have traditionally been unavailable for use on the battlefield because of a very short shelf-life, 5 to 7 days, after collection. Additionally, platelets collected on the battlefield by apheresis can not be fully tested for infectious agents by FDA approved methods in combat theater. Therefore, a platelet preparation or a platelet substitute with a longer shelf life and/or fieldable pathogen inactivation is sought. An alternative to liquid stored platelets (Cryopreserved platelets) is in development:

- **Cryopreserved Platelets (CPP)**. CPP is being developed by the U.S. Army. CPP offers the possibility of screening and collecting platelets in CONUS that can be frozen and stored up to 2 years before use. CPP has shown effectiveness in baboons and in a human clinical study in 53 patients undergoing cardiopulmonary bypass. CPP is currently fielded by Dutch military forces for battlefield use and has been used in over 200 transfusions without apparent safety issues. However, CPP requires -80°C cold storage, difficult to field with a mobile force because of weight and power characteristics. FDA licensure and fielding of CPP is not likely before 2014 or 2015, but providing this product as a replacement to theater collected platelets, should reduce the risk of transmission of infectious disease.

Red Blood Cells (RBCs)

RBCs are necessary for transport of oxygen to vital tissues including brain, heart and kidneys. Liquid, stored packed RBCs (pRBCs) have limited availability on the battlefield due to refrigeration requirements. They are generally limited to use at the Combat Support Hospital (Role 3). If circumstances permit, universal donor (Type O) RBCs may be deployed to the FST (Role 2b). However, in the past 10 years, concerns have been raised regarding the safety of stored RBCs that have been stored for

longer than 2 or 3 weeks (currently approved for up to 6 weeks storage).

Alternatives to pRBCs in development:

- **Extended Shelf-Life RBC (RBCXL).** RBCXL is a new RBCs collection and storage system that incorporates a new additive solution and integrated in-line leukofiltration (removal of white blood cells). The combination of a new additive solution and leukofiltation may result in "fresher" RBCs at any given time period in storage. Pre-clinical studies of the additive solution in RBCXL suggest a longer possible shelf-life for RBCs, up to 8 or 9 weeks. RBCXL is approximately 2 years from approval by the FDA and is being co-developed by the Army and a U.S. manufacturer. Evaluation of effects of "fresher" RBCs are in early stages but may effect feasibility of a longer storage life product.

- **Hemoglobin-Based Oxygen Carriers (HBOCs).** HBOCs are a potential substitute for RBCs on the battlefield, especially far forward at Role 1 and Role 2. HBOCs consist of purified hemoglobin (bovine or human) that have been processed into larger molecules or polymers still capable of binding oxygen reversibly and thereby transporting oxygen from the lungs to vital tissues. Additionally, HBOCs have greater stability in ambient temperatures, offering potential for deployment to far-forward positions on the battlefield, including the FST, the Battalion Aid Station, or even the combat medic. HBOCs can be administered regardless of recipient blood type. There are several HBOCs in development commercially. At least two are in clinical development. One product has been submitted to the FDA for licensure. HBOC therapy, alone and in combination with other components (multi-functional blood substitute), holds promise for treatment of polytrauma and traumatic brain injury.

Cryogenic Storage of White Blood Cells

Traumatic injury often involves diminished immune function that could improve with the infusion of thawed, cryogenically-stored white blood cells. The U.S. Army Medical Research and Materiel Command's Telemedicine and Advanced Technology Research Center (TATRC) reviewed a proposal in 2008 from a U.S. firm to address this potential concern. The proposal was to prove the concept of a process to collect and cryogenically store autologous white blood cells to hold in readiness for reinfusion into battlefield casualties. TATRC reviewed the proposal and declined this initiative. The proposed white blood cell product has no known animal studies or human clinical trials to demonstrate efficacy in trauma patients. Logistical support and transport of cryogenic

white blood cells is intense and currently not feasible for use in the austere conditions of a theater blood bank setting.

Blood Safety: Pathogen Inactivation/Pathogen Reduction (PI/PR) and Rapid Pathogen Testing

Transfusion transmitted infectious diseases (TTD) have been a principal complication associated with transfusion of blood products. Advances and standards in donor screening, donor interview, and donor deferral have reduced the occurrence of TTD when incorporated into modern blood banking practices in the United States.

The use of "walking donor" whole blood transfusions and platelet collection on the battlefield are currently used in battlefield MTFs, especially in cases of massive transfusion (more than 10 units of blood in 24 hours). However, it has not proved possible to implement standard donor testing and screening when blood products are obtained from the "walking donor" pool. As a consequence, there is significantly greater risk than would occur in the U.S. for infection of recipients of such blood products in battlefield MTFs. The Defense Health Board recommended in June 2008 that "DoD limit the employment of emergency blood transfusion protocols to instances where the available supply of FDA-licensed blood and blood products is exhausted or unavailable. The use of untested fresh whole blood and blood products outside of established, human subjects-protected, trauma research protocols should be discontinued." However, fresh whole blood use is still required in a limited number of cases to save the lives of massive trauma victims.

Recently approved (in Europe) technology for inactivation of virtually all infectious agents, known and unknown, offers promise for solving issues related to unscreened blood products on the battlefield. Two companies currently market pathogen inactivation/pathogen reduction (PI/PR) instruments for treatment of platelets and plasma and one of these companies is seeking licensure in the United States. One of the companies has initiated development of PI/PR for whole blood. Other noncommercial entities also have research efforts targeting PI/PR for whole blood.

The Army Medical Department Center and School has stated that PI/PR of whole blood is one of the highest biomedical materiel priorities for the Army. Given the limited demand for whole blood PI/PR, there is a need to accelerate development of this technology for the battlefield. Pathogen inactivation, while potentially portable, would be restricted to a combat support hospital due to the need to process donor blood post collection. The development of a rapid screening for infectious agents would be an advantage in far forward situations where pathogen inactivation/reduction is not possible.

Licensure of Pathogen Inactivation technology for use in whole blood may be possible but, feasibility remains unclear and only one industry entity is pursuing

inactivation in whole blood. DoD would greatly benefit from pathogen inactivation in whole blood due to the necessity for continued use.

CONCLUSION

Despite major advances in medical care that save more lives on the battlefield than ever, death from hemorrhage remains the greatest cause of preventable death from battlefield wounds and blood and/or blood products are key elements of the solution for this problem. Numerous technologies are in development for use in a wide array of situations, and selected technologies merit increased emphasis to preserve additional lives of wounded Service members.

Table 1. Life-preserving blood products and technologies in early stages of Research & Develop

Product/Technology	Advantages to Warfighter	Research Status	C
1. Ratio of Packed Red Blood Cells (pRBCs): Plasma:Platelets	• Clinical guidelines based on strong scientific data for proper administration of blood products in trauma patients	• None	• Level 1 Scienti Clinical Guide • Prospective ob underway – ad necessary to fu • Fixed guideline to goal-directe to clinical outc • Need accelerat
2. Use of recombinant Factor VIIa and/or fibrinogen in trauma	• Adjunct to blood products to hasten coagulation	• Army Retrospective study; otherwise none	• Results of trial • Fibrinogen unt • Retrospective s underway • Monitoring ind
3. Rapid blood screening tests for infectious agents (pathogens)	• Safer use of blood collected in Theater • Improved survival of battlefield casualties	• Limited	• Advance the de approved rapi detection meth • Protect force h by preventing infections • Need to accele
4. Blood Pharming	• Production of a ready supply of fresh, universal donor packed red blood cells (pRBCs) • Theoretical unlimited blood supply • Bioreactors could be located in or near the theater of operations, reducing shipment time and the potential for storage lesions • No chance for transmission of infectious disease No chance for administration of the wrong blood type, eliminating the time required to type and cross match donor blood	• **Defense Advanced Research Projects Agency**	• Supply may be Red Blood Cel constant immu reduce the prol immune respo multiple transf • Feasibility yet continue curre

Product/Technology	Advantages to Warfighter	Research Status	C
5. Universal Plasma	• Plasma can be administered more rapidly without knowing patient blood group	• Industry	• Industry active technology • Monitor indust
6. Universal Red Blood Cells	• Red cells can be administered without typing since cells converted to Type O universal RBCs	• Industry	• Industry develo not entirely pr • Monitor indust
7. Freeze dried platelets	• See Advanced Development	•	• Monitor indust
8. Perfluorocarbon-based oxygen carrier	• Improved resuscitation fluid for medic use and for medical treatment facilities without capability for stored red blood cells • Longer shelf life than red blood cells • Blood typing not necessary	• Limited Army	• Industry pursu •

Table 2. Life-preserving blood products and technologies in or near Advanced Developme

Product/Technology	Advantages to Warfighter	Research Status	
1. Freeze-dried plasma	• Reduced waste • Simplified logistical chain • Deployable further forward than current equivalent	• Army, Special Operations Command Navy	Additional r • Second c reduce ri • May acce
2. Cryopreserved (frozen) platelets	• Reliable source of FDA licensed platelets	• Army	•
3. Red Blood Cell Extended-Life (RBCXL)	• Improved shelf-life of stored red blood cells (RBCs) • Reduced transportation costs for RBCs to battlefield • Improved battlefield management of blood supplies • Potential improvement in red cell quality	• Planned	• Some co about red stored fo weeks. • Leukofilt blood cel donation storage o
4. Hemoglobin-based oxygen carrier	• Improved resuscitation fluid for medic use and for medical treatment facilities without capability for stored red blood cells • Longer shelf life than red blood cells • Blood typing not necessary	• Navy (ONR) • DoD (DUSD-ALT) • Congressional (USAMRMC) • Pending FDA approval for one product	• FDA app because c concerns. suspende • Other R& to discov oxygen-c fluids.
5. Cryogenis Storage of White Blood cells	• Improved immunologic function in traumatic injuries	• None	• Not reco • Technolo • Logistica feasible

Product/Technology	Advantages to Warfighter	Research Status	Comment
6. Freeze-dried platelets (fdPLT, aka "infusible hemostatic" or PDHA)	• Reduced weight & cube • Deployable forward • Possible supplement to fill gaps when standard platelets not available	Industry Navy Army (USAMRMC and USASOC)	• Promote c existing i • Use as an trauma is • Clinical T pathologi
7. Pathogen Inactivation/Reduction (PI)	• Essential elimination of risk from blood-borne infection (known and unknown) • Theoretical elimination of risks associated with transfusion of residual white blood cells in blood products	• Industry • Plasma and platelet PI; FDA approval pending • Partially Industry: Whole blood PI	• Will assur developm • FDA has prior to a platelet P • Need acce blood PI