Closing the Gap: A Combined Lyophilized Product Strategy for Forward Resuscitation

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Executive Summary

Current U.S. military medical doctrine demonstrates significant capability gaps in executing large-scale resuscitation protocols at forward-deployed positions, particularly at echelons below Role II medical facilities. Analysis of contemporary peer-conflict data, observations from large-scale combat operations (LSCO)–focused training, and emerging clinical evidence suggests that lyophilized blood products may provide a viable bridge therapy to traditional whole blood–based resuscitation in logistically constrained environments.

This paper examines the operational and clinical feasibility of implementing lyophilized plasma and platelet protocols for military trauma care. It proposes a combined lyophilized product approach to mitigate current forward resuscitation shortfalls when whole blood is unavailable or insufficient, and offers recommendations for doctrine, training, and materiel development to enhance resuscitation capability in contested, resource-limited settings.

Introduction

The past two decades of military operations have afforded the U.S. Army the strategic advantage of air superiority, rapid medical evacuation, and access to robust blood supplies. This operational environment enabled the development and refinement of the "golden hour" concept, the critical first 60 minutes after injury when prompt medical intervention significantly increases survival rates. Under these favorable conditions, casualty mortality rates declined substantially through rapid evacuation to fully equipped surgical facilities.

However, the operational landscape is shifting. Peer and near-peer conflicts, characterized by contested skies, advanced air defense systems, and widespread use of unmanned aircraft systems, present a fundamentally different challenge. Lessons from the war in Ukraine, combined with U.S. Army strategic guidance, indicate that leaders can no longer assume rapid medical evacuation in large-scale combat operations. Medical personnel at forward echelons must be prepared to provide extended, field-based resuscitation without reliance on centralized blood supplies or rapid transport to definitive care.

This paper addresses that reality by examining lyophilized blood products, freeze-dried plasma, and platelets as operational solutions to forward resuscitation in resource-constrained environments.

Background and Current Operational Context

Capability Gaps at Echelons Below Role II

Military units participating in Joint Multinational Readiness Center (JMRC) and other LSCO–focused training consistently demonstrate a lack of preparedness for mass-casualty resuscitation at echelons below Role II. Combat medics and battalion aid station teams train to prioritize stabilization and rapid evacuation. However, modern conflicts like the war in Ukraine reveal vulnerabilities when enemy threats degrade, delay, or deny evacuation routes.

In a future LSCO environment, which will likely involve contested evacuation corridors that extend times to reach surgical care, and a high volume of casualties, rapid evacuation and centralized blood product support alone are insufficient. Therefore, forward medical elements must have the capability to initiate resuscitation at or near the point of injury using products that are logistically sustainable in austere and dynamic environments.

The Challenge of Whole Blood Logistics

Fresh whole blood remains the clinical gold standard for hemorrhagic shock resuscitation. However, whole blood delivery at the point of injury presents substantial logistical and operational challenges.

Cold chain requirements present the first constraint. Whole blood and component therapy require temperature-controlled storage and transport. This presents a logistical burden that may be untenable in distributed, highly mobile combat operations. Maintaining refrigeration across dispersed forward positions requires dedicated assets and reliable power generation, both of which are vulnerable to disruption.

Supply-demand mismatch compounds this challenge. Current U.S. military medical systems cannot deliver whole blood at the scale and tempo required for LSCO that may produce hundreds of daily casualties. Theater blood banks have finite inventory and cannot surge production in response to continuous mass casualty events and suffer from logistical handicaps. Without local donor capacity or prepositioned reserves, units will quickly exceed available supply.

This reliance on existing infrastructure creates vulnerabilities. Forward whole blood programs depend on reliable evacuation and predictable resupply from theater blood banks, all of which are vulnerable to disruption in contested environments. When enemy air defense systems threaten evacuation routes or precision fires damage supply infrastructure, centralized blood management becomes unsustainable.

The U.S. Army has not standardized blood resuscitation practices to the same level as other operations, hindering interoperability with its allies. NATO and the EU do not have a standardized policy for blood resuscitation, and default to member state laws to oversee each nation’s blood use programs. DoD Instruction 6480.04 Armed Services Blood Program (ASBP) provides exemptions to use non-Food and Drug Administration (FDA) approved blood and blood sourced from coalition forces, but it is restrictive in obtaining blood from local populations. Medical operations in a joint environment compound logistical constraints due to these differences.

Operating over extended distances, in dispersed formations, and under persistent threat from long-range fires and unmanned aircraft systems magnifies operational constraints. In these environments, threats can prevent the protection of medical supply convoys or compromise refrigeration infrastructure. Consequently, forward medical elements lose access to whole blood precisely when they need it most.

Walking Blood Bank Constraints

Walking Blood Bank (WBB) protocols utilizing low titer group O donors from within the unit mitigate some supply challenges but carry significant operational limitations that restrict their utility in LSCO.

Time requirements represent the first constraint. Data collected at JMRC through autologous transfusions shows an average time of execution of WBB protocols requires approximately 40 minutes from donor identification through initial product administration, with longer timelines when personnel lack experience with the procedure. Already a time intensive procedure, in a dynamic casualty environment where multiple wounded arrive in rapid succession, this 40-minute window may not be realistic. A combat medic and combat-life saver team managing multiple casualties simultaneously cannot concurrently activate donor screening, perform collection, and manage ongoing resuscitation for each patient.

Donor pool limitations further restrict availability. Low titer group O donors may be scarce within tactical formations. Many group O individuals have antigen titers that exceed acceptable limits. Beyond availability, the FDA and ASBP mandate 56-day deferral intervals between donations from individual donors. After the first operational surge, a unit of 150 Soldiers with only 30 suitable low titer O donors has severely constrained current donation capacity.

The operational environment compounds these challenges. Ukrainian forces conducting defensive operations have had success with walking blood bank protocols. They leverage integrated civilian donor populations from the territories they defend, an option unavailable to U.S. units conducting offensive operations in hostile territory where civilian donation is not attainable or approved and military personnel are the sole potential donor pool. The geographic dispersal inherent in offensive operations, with smaller unit elements scattered across terrain, makes concentrating suitable donors for rapid collection impractical compared to operations seen in the Global War on Terror.

Mission load represents perhaps the most critical constraint. Combat medics require additional trained combat lifesavers to assist in trauma management. Activating WBB protocols requires personnel to step out of their primary roles to identify donors, obtain medical history, screen for risk factors, perform blood collection, and coordinate product delivery. These tasks compete directly with other critical responsibilities i.e. command and control, security, and maneuver execution during periods of high operational stress when every Soldier has primary mission tasks. The cognitive burden of implementing WBB under fire, while simultaneously managing other tactical imperatives, is substantial.

These factors collectively challenge the ability of point of injury and pre–Role II elements to deliver timely, balanced resuscitation at scale using WBB protocols alone.

Casualty Volume and Supply Considerations

Preliminary analysis of historical casualty data and operational models suggests that approximately 15–20 percent of wounded personnel require resuscitation interventions. In LSCO scenarios with projected daily casualty rates in the hundreds, even this modest proportion rapidly exhausts traditional cold-chain capacity and walking blood bank throughput. Without alternative

or adjunctive resuscitation strategies, current blood product supply chains are unlikely to sustain operations, resulting in preventable mortality from hemorrhagic shock.

Clinical Evidence for Lyophilized Blood Products

Lyophilized Plasma

Medics can store lyophilized (freeze-dried) plasma at ambient temperature and rapidly reconstitute the processed blood product with sterile water at the point of care. Recent clinical trials and international operational experience support its use as an effective alternative to fresh frozen plasma when conventional products are unavailable or impractical.

Key Clinical Trials

The **Prehospital Air Medical Plasma (PAMPer) trial**, published in 2018, examined plasma administration during aeromedical transport for patients with hemorrhagic shock.[1] The trial demonstrated a clinically meaningful reduction in 30-day mortality, with particular benefit observed when transport times exceeded 20 minutes. While the PAMPer trial utilized liquid plasma rather than lyophilized formulations, its findings underscore the critical importance of early plasma administration in improving survival. The operational implication is clear: when plasma reaches casualties within the early resuscitation window, mortality improves substantially.

The **French Lyophilized Plasma (FLyP) trial** extended these findings by examining lyophilized plasma specifically.[2] The trial demonstrated that lyophilized plasma achieved superior fibrinogen concentrations at 45 minutes post-administration when compared to fresh frozen plasma. More importantly, this superior fibrinogen concentration resulted in more rapid correction of coagulopathy and reduced requirements for additional fibrinogen concentrate. These findings directly support the hemostatic effectiveness of lyophilized plasma formulations in practical trauma resuscitation settings. The data suggests that the freeze-drying process does not compromise the functional capacity of plasma to restore hemostatic potential, making lyophilized plasma a viable alternative when conventional products are unavailable.

Clinical Applications

Current literature and international experience support lyophilized plasma as a clinically acceptable alternative to fresh frozen plasma in remote, rural, prehospital, and austere environments characterized by extended transport times or limited access to conventional blood

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[1] Sperry, J. L., Guyette, F. X., Brown, J. B., et al. (2018). Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. *The New England Journal of Medicine*, 379(4), 315–326. https://doi.org/10.1056/NEJMoa1802345

[2] Garrigue D, Godier A, Glacet A, Labreuche J, Kipnis E, Paris C, Duhamel A, Resch E, Bauters A, Machuron F, Renom P, Goldstein P, Tavernier B, Sailliol A, Susen S. French lyophilized plasma versus fresh frozen plasma for the initial management of trauma-induced coagulopathy: a randomized open-label trial. J Thromb Haemost. 2018 Mar;16(3):481-489. doi: 10.1111/jth.13929. Epub 2018 Jan 22. PMID: 29274254.

products.[3] The medics ability to store the product at ambient temperature and rapidly reconstitute makes it well-suited to forward military deployment.

Lyophilized Platelets

Critical Timing of Platelet Administration

Clinical data shows that administering platelets early in hemostatic resuscitation provides the greatest survival benefit. Observational trauma studies indicate significant survival curve divergence within approximately 15 minutes of platelet administration in severely injured patients despite control and experimental groups receiving equivalent packed red blood cell units. The median time to death in patients who do not receive platelet transfusion is approximately 0.6 hours (36 minutes), underscoring the urgency of early platelet delivery.[4]

This timing requirement creates an operational challenge: conventional platelet delivery typically occurs at Role II or higher echelons, either through isolated product or as whole blood. In LSCO, with contested evacuation, achieving this therapeutic window may not be feasible. Lyophilized platelets promise a solution to the constraints of current platelet storage and administration and offer a rapidly reconstituted product useable within minutes of injury.

Research Status and Gaps

Most existing clinical studies evaluating platelet efficacy in trauma have assessed platelets as part of combination component therapy of packed red blood cells, plasma, and platelets together.[5] A knowledge gap, particularly relevant in resource-constrained scenarios, exists because of limited data on administering platelets and plasma without a red blood cell transfusion.

Preclinical studies of lyophilized platelet products demonstrate hemostatic performance comparable to fresh platelets in animal trauma models, including enhanced aggregation capability, reduced coagulation times, and effective clot formation despite shorter in vivo circulation times.[6] While clinical data remain preliminary, these findings support further investigation. Phase 1 clinical safety trials showed no discernible risks from administration in humans, while phase 2 efficacy trials are ongoing.[7]

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[3] Agency for Clinical Innovation. (2023). *Freeze-dried plasma administration in trauma: Evidence review*. New South Wales Health. https://aci.health.nsw.gov.au/__data/assets/pdf_file/0007/836521/ACI-Freeze-dried-plasma-administration-in-trauma-evidence-report.pdf

[4] Cardenas JC, Zhang X, Fox EE, et al. Platelet transfusions improve hemostasis and survival in a substudy of the prospective, randomized PROPPR trial. *Blood Adv*. 2018;2(14):1696-1704. doi:10.1182/bloodadvances.2018017699.

[5] Ibid.

[6] Bode, A. P., & Fischer, T. H. (2007). Lyophilized Platelets: Fifty Years in the Making. *Artificial Cells, Blood Substitutes, and Biotechnology*, *35*(1), 125–133. https://doi.org/10.1080/10731190600974962

[7] Cellphire Therapeutics, Inc. (2019). *A phase I, multi-center, open-label, dose escalation study of Thrombosomes® in bleeding thrombocytopenic patients in three cohorts.* ClinicalTrials.gov. Retrieved January 13, 2026, from https://clinicaltrials.gov/ct2/show/NCT03394755

The Combined Lyophilized Product Approach

Rationale

Until advanced synthetic oxygen-carrying products achieve clinical validation and operational fielding at scale, red blood cell replacement in large-scale combat operations will remain limited to fresh whole blood and conventional packed red blood cell components. This confirms whole blood as the resuscitation gold standard, but it also highlights the critical need for alternative treatments when whole blood is unavailable, delayed, or in short supply.

A combined protocol using both lyophilized plasma and lyophilized platelets offers theoretical advantages over plasma monotherapy by:

- addressing both the humoral (coagulation factor) and cellular (platelet) components of trauma-induced coagulopathy
- enabling formation of stable platelet-fibrin clots earlier in resuscitation
- potentially reducing total red blood cell requirements once whole blood becomes available by reducing blood loss
- providing operational flexibility in logistically austere environments

Hemostatic Mechanisms

Freeze-Dried Plasma restores hemostatic capacity through multiple complementary mechanisms. It provides comprehensive coagulation factor replacement, delivering factors II, V, VII, VIII, IX, X, XI, XII, and XIII—the complete spectrum of vitamin K-dependent and contact factors necessary for clot formation. Beyond factor replacement, lyophilized plasma supplies fibrinogen, which serves as the essential substrate for fibrin clot formation. The product also maintains physiologic anticoagulant balance by providing antithrombin and protein C, preventing overcorrection toward a prothrombotic state. Finally, freeze-dried plasma supports endogenous thrombin generation and restoration of hemostatic potential, reestablishing the body's intrinsic capacity to form and maintain clots.

Lyophilized Platelets address the cellular component of hemostasis that plasma alone cannot provide. They deliver immediate functional platelets capable of participating in primary hemostasis at the site of vascular injury. Unlike stored liquid platelets that gradually lose hemostatic function, lyophilized platelets demonstrate enhanced aggregation and adhesion capability at vascular injury sites in preclinical studies. By providing a procoagulant surface and accelerating clot propagation, they enable formation of platelet-fibrin clots more rapidly than plasma alone. Additionally, platelet products theoretically augment coagulation cascade initiation through complement activation and surface-mediated hemostatic mechanisms.

Together, these mechanisms offer a biologically plausible pathway to improved early hemostatic control when whole blood is unavailable or delayed. Plasma addresses the coagulation factor deficit, while platelets address the primary hemostatic deficit that develops in severe trauma. The combination is more than additive because functional platelets require plasma factors to aggregate effectively, and plasma factors require a platelet surface on which to generate thrombin. By restoring both components simultaneously at the point of injury, combined

lyophilized product therapy addresses the complete hemostatic derangement characteristic of severe hemorrhagic shock.

Implementation Considerations

Operational Employment Concepts

Proposed forward deployment concepts include:

- **Prolonged field care:** Inclusion of lyophilized product modules in standardized Medical Equipment Sets (MES) to support prolonged care operations at casualty collection points in contested evacuation scenarios.
- **Role I:** lyophilized plasma and platelets inherent to the Role I to provide organic stabilization resuscitation capabilities not available outside of WBB capabilities due to cold-storage limitations in the current Role I configurations.
- **Role II augmentation:** Integrate lyophilized products to buffer against supply chain disruptions and for use when whole blood is not feasible or medics must triage supplies based on patient injuries.

Managing the Deadly Diamond

For successful resuscitation, providers must comprehensively address the "deadly diamond" of trauma. This includes treating hypothermia with environmental interventions that go beyond blood product therapy. It also means recognizing that tissue hypoperfusion causes metabolic acidosis, which signals inadequate oxygen delivery. Any lyophilized product protocol must account for all four points of the diamond—metabolic acidosis, coagulopathy, hypothermia, and hypocalcemia—to achieve successful outcomes.

Metabolic acidosis. Tissue hypoperfusion causes metabolic acidosis through lactic acid build up secondary to anaerobic cell metabolism. Plasma-based resuscitation supports correction of lactic acidosis through improved perfusion by restoring coagulation capacity and enabling faster hemostasis. When clotting occurs more rapidly, bleeding slows and cardiac preload improves, allowing the cardiovascular system to maintain perfusion pressure. As perfusion restores, tissues clear accumulated lactate through aerobic metabolism.

Coagulopathy. The primary target of lyophilized product therapy is coagulopathy. Combined lyophilized plasma and platelet administration directly restore coagulation factor and cellular hemostatic capacity. Complementing this restoration, administer tranexamic acid to inhibit fibrinolysis, and prevent clot breakdown. The combination of restoring clotting components and preserving clot integrity addresses trauma-induced coagulopathy through multiple mechanisms.

Hypocalcemia. Approximately 50 percent of patients in shock develop hypocalcemia because the coagulation cascade consumes calcium and massive resuscitation dilutes it. Medics should supplement calcium by administering either calcium chloride or calcium gluconate when following lyophilized products protocols. Restoring ionized calcium capacity is essential for effective thrombin generation and coagulation factor function.

Hypothermia. Since hypothermia is a distinct physiologic problem, medics must use appropriate interventions to treat it, as blood product therapy alone is insufficient to address all facets of the lethal diamond. Fluid warming, active, and passive rewarming measures remain essential components of resuscitation. Medics and medical teams must integrate blood products, pharmaceutical interventions, and environmental temperature management to successfully address all components of the lethal diamond.

Integration with Permissive Hypotension

Resuscitation using lyophilized products should follow damage control resuscitation principles, including permissive hypotension to avoid dislodging early clots and preserve volume capacity for whole blood administration when available. This approach also reduces risk of transfusion-related complications including transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO).

Recommendations

Immediate Actions (0–12 Months)

Doctrine and Training Development

The Joint Trauma System should prioritize development or updating of clinical practice guidelines specifically addressing lyophilized plasma administration. These guidelines must address clear indications for use, appropriate dosing protocols, sequencing of product administration in relation to other resuscitation interventions, and integration with existing whole blood protocols. Training developers should work with Joint Trauma System to incorporate lyophilized product preparation, administration, and complication management into point of injury, Role I and Role II trauma training curricula. To guarantee effective performance in combat, units must integrate competency-based training into their standard operating procedures and rehearse it regularly during collective training events. This training must include rapid reconstitution drills performed under realistic operational conditions, such as limited visibility, communication challenges, and high casualty loads, to ensure personnel can execute these procedures effectively. Lyophilized platelets, once approved for use following clinical trials, should be implemented immediately.

Supply Chain Assessment

Medical planners must evaluate current lyophilized product availability through established defense medical supply chains and identify gaps in inventory and distribution capacity. Initial focus should be on establishing preliminary theater distribution frameworks that position lyophilized products at forward echelons without requiring cold-chain logistics. Personnel should identify compatible lyophilized product sources, with preference for products meeting NATO standards and consistent with protocols used by allied partners. Early exploration of multinational interoperability with allied partners already employing lyophilized plasma, particularly European NATO allies with operational experience in Ukraine-support missions, will accelerate understanding of practical employment and identify proven procurement channels.

Long-Term Strategic Development (1–3 Years)

Clinical Research Initiative

The Department of Defense Medical Research and Development Program should fund prospective clinical studies evaluating combined lyophilized plasma and platelet therapy in trauma patients, with specific emphasis on scenarios involving limited red blood cell availability. These studies should examine the independent effects of early combined lyophilized product therapy outside traditional trauma center settings, prioritizing endpoints including 24-hour and 30-day mortality, total transfusion requirements, and complication rates. Study design should include prehospital and austere care scenarios relevant to military operations, not solely traditional civilian trauma center patient populations. Research outcomes will establish the clinical evidence base necessary to support broader military adoption and doctrine development.

Materiel Integration

Joint procurement planners must develop acquisition pathways that establish sustainable supply chains for lyophilized products across multiple theaters of operation. Planners should conduct analysis to determine prepositioned stock requirements at various echelons, ensuring forward medical elements have ready access without requiring contingency requisitions during operations. Medical supply personnel should begin integration of lyophilized products into joint blood program management frameworks, establishing compatibility with existing inventory management systems, expiration tracking protocols, and reconstitution procedures. The U.S. Army Medical Research and Development Command (USAMRDC) should prioritize securing FDA approval (outside of Emergency Use Authorizations) and promoting domestic manufacturing and procurement initiatives.

Operational Testing

Military operations researchers should incorporate lyophilized product employment concepts into Combat Training Center rotations and analytical models, identifying second and third-order effects on medical supply requirements, personnel workload, and casualty disposition. Army Medical Center of Excellence subject matter experts should develop table-top exercises and field training events that test lyophilized product protocols under realistic operational conditions, including degraded communications, power-limited environments, and mass casualty scenarios. Iterative evaluation of these exercises will refine employment concepts, identify training gaps, and validate doctrine before operational implementation.

Conclusion

The anticipated operational environment of future large-scale combat operations, characterized by contested evacuation corridors extended times to surgical care, and sustained high casualty volumes demands contingency resuscitation strategies less dependent on traditional cold-chain logistics and centralized support.

While fresh whole blood remains the optimal resuscitation medium for hemorrhagic shock, it is unlikely to be available in sufficient quantity, at the required echelon, and within the necessary timeframe for all casualties in high-intensity conflict. Lyophilized plasma and platelet products

offer a clinically plausible and operationally attractive means to extend hemostatic resuscitation capability into resource-constrained environments.

A combined lyophilized product protocol, integrated into resuscitation frameworks and supported by doctrine development and targeted training, represents a viable pathway to closing current capability gaps in forward trauma resuscitation. Proactive adoption and rigorous evaluation of these modalities will be essential to sustaining combat power and reducing preventable death from hemorrhage in future large-scale combat operations.