The Journey of Freeze Dried Plasma Within the Army Blood Program

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Abstract

• In addition to meeting hospital blood requirements on a daily basis, the Army Blood Program is charged with the responsibility of supporting the warfighter.
• Research and development efforts are vital to the future success in providing this support and a Freeze Dried Plasma product is required for Damage Control Resuscitation (DCR).
• While the theater blood management of FDA licensed products has been successful, frozen plasma products are only available at Role II/III Medical Treatment Facilities due to logistical constraints.
• Freeze Dried Plasma provides tremendous advantage in providing battlefield damage control resuscitation beginning at the point of injury.
• Once reconstituted, this product combats the coagulopathy of trauma and restores circulatory volume.
• This product will be used to treat life threatening, severe hemorrhage arising from injuries sustained during contingency operations in remote, austere environments where access to standard blood products and immediate damage control surgery is not readily available.
Objectives

• Learning Objective #1:
  • Discuss the Freeze Dried Plasma development effort within the Army Blood Program.

• Learning Objective #2:
  • Discuss recruitment efforts and challenges associated with the collection of apheresis plasma for the manufacturing of Freeze Dried Plasma in France.

• Learning Objective #3:
  • Discuss the way ahead and timeline for product availability on the battlefield (and potentially at home).

Disclaimer

• The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense
Objective 1

Discuss the Freeze Dried Plasma development effort within the Army Blood Program.

Historical Background

- Clinical use of plasma for shock and hemorrhage was a development of World War II.
- Military use of blood plasma as a substitute for whole blood in combat casualties was proposed in 1918:
  - eliminating the risk of whole blood transfusions given at casualty clearing stations.
  - Citrated plasma would be easy to store and administer.
- The first use of plasma as a hemostatic agent and in the treatment of hemolytic shock was in 1935.
- The following year, it was proposed that both plasma and serum be used in the treatment of surgical, obstetric, or traumatic shock whenever transfusion was indicated.
Plasma Defined

Plasma is the supernatant fluid that separates from the cellular elements when an anticoagulant is added to blood. Serum is the liquid portion that separates during the process of clotting. Plasma contains fibrinogen. Serum does not. The distinction in nomenclature should be carefully observed, for the plasma and serum albumin programs in World War II were separate projects, though the serum program was a development of the plasma program.

Selection of Plasma for the Armed Forces

- By the time World War II broke out, it was clear that either serum or plasma would be the most desirable agent for the management of shock in battlefield casualties and in forward hospitals.
  - Liquid Plasma – stored for months
  - Frozen Plasma – kept for indefinite periods
  - Dried form of Plasma – could be produced

- Advantages of Plasma:
  - Contains fibrinogen
  - Yield was 15-20% greater/unit of blood than serum
Freeze Dried Plasma Development Effort Within the Army Blood Program

Selection of Plasma for the Armed Forces

- Recommendation: Frozen or Dried Plasma
- Armed Forces had to accept the recommendation:
  - Required quantities of Whole Blood and logistical considerations.
  - Preservative solutions for Whole Blood in early stages of development.
  - Plasma could be administered without typing or cross-matching.
  - Low number of reactions.
  - Dried plasma presented logistical and storage advantages.
  - Immediate need = dried plasma could be easily, safely, and quickly produced commercially in large quantities.

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Freeze Dried Plasma Development Effort Within the Army Blood Program

General Considerations

- The procurement of plasma on the major scale required by the Armed Forces in World War II was a cooperative effort:
  - The general public/volunteer donors
  - The Army Medical School
  - The Army and the Navy
  - The American Red Cross
  - The National Research Council
  - The Army Medical Procurement Agency
  - Commercial biologic firms
  - Equipment manufacturing firms

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US Discontinues Production of FDP

- US Military used dried plasma throughout WWII.
- At close of the war, there was an increased focus on hepatitis risk from dried plasma:
  - Pooled product, increased donor exposure.
- Civilian institutions did not use excess dried plasma from US military.
- Production and use ceased within a few years after WWII.

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Freeze Dried Plasma Development Effort Within the Army Blood Program

The French Military Blood Institute (Centre de Transfusion Sanguine des Armées [CTSA])

- Created after World War II by Jean Juliard, a military physician.
- Production was based on successful use of FDP (produced by the US) during WWII.
- The CTSA became the first European center of FDP production in 1950.
- During the Indochina war, almost 40,000 units were delivered to support French military operations.
- In 1985, production was suspended to prevent the spread of HIV infection from the pooled plasma used in FDP.
- Production restarted in 1991 at the time of the Gulf War and continues to the present.

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French Lyophilized Plasma (FLYP)

- **FLYP**
  - Manufactured from pooled fresh frozen plasma (FFP) obtained from less than 11 donors by apheresis.
  - Leukoreduced since 2003.
  - As of 2010, plasma from women with a history of pregnancy has been tested for antihuman leukocyte antigen (HLA) antibodies and excluded if positive.
  - Has been secured with the amotosalen and ultraviolet light process (Cerus Intercept technology, Cerus Corporation, Concord, CA) to inactivate RNA/DNA pathogens.
  - In 2011, FLYP was authorized by the French Agency for Sanitary Safety of Health products (AFSSAPS) for civilian use in austere settings, or when thawed plasma is unavailable in emergency situations.
  - No adverse events, including transfusion-related acute lung injury, have been reported since 1994, when the French hemovigilance program began.

Current plasma product (frozen) distributed to deployed MTFs

- Current standard is to provide frozen plasma to Role II/III MTFs.
- Frozen plasma requires freezer and plasma thawer.
- Shipment of product requires dry ice.
- Once thawed, product has a 5 day shelf life.
- Frozen plasma manufactured at CONUS BDCs and shipped overseas.
- Military attempts to maximize use of thawed 5-day plasma for use on MEDEVAC aircraft.
Armed Services Blood Program

Supporting Base
- Joint BDC (ASBPO)
- Army BDC
- Air Force BDC
- Navy BDC
- Civilian BDC

Theater of Operations
- Combatant Command (JBO)
- Joint Task Force (JBO)
- BPD
- First Responders (unit level)
- Allied / Coalition Hospitals
- Forward Resuscitative Surgery
- Theater Hospitals
- En-route Care
- US Navy Ships

Blood Flow
- BTC / EBTS
- BSD
- First Responders (unit level)
- FSSG / FRSS

Reports
- COORDINATION
- PREPOSITIONED FROZEN BLOOD

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CONUS Blood Donor Centers

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**US FDP Development Efforts**

- US Military has a need for FDP on the battlefield.
- Development efforts underway between DoD and private industry.
- Critical to identify DoD requirements for a dried plasma product.
- Product may be carried into a variety of theaters/operational areas.
- Attributes must be selected which provide for safety while at the same time brings the product closest to point of injury.
- The most critical requirement is FDA approval.
Freeze Dried Plasma

- **Product Description:** Single-donor, pathogen tested, freeze-dried FFP, packaged in ruggedized plastic binary container with reconstitution fluid

- **Indication for Use:** Patients with massive transfusion who have clinically significant coagulation deficiencies

- **Prevalence and Risk to Warfighters:** Up to 50% of battlefield mortality is attributable to hemorrhage; Up to 1/3 of hemorrhage mortality (~450 deaths in OIF) may be prevented with improved battlefield management of hemorrhage

Freeze Dried Plasma Development Effort Within the Army Blood Program

- **Freeze Dried Plasma Benefits:**
  - FDP will reduce waste by eliminating breakage and outdating after thawing.
  - FDP will reduce the logistical burden associated with storage requirements because it does not require freezing.
  - FDP will also permit positioning of plasma forward of ROC-3 for earlier use by physicians/combat medics managing severe hemorrhage.
USASOC

- USASOC 2011 granted authority under FDA IND #14872 in November to procure FLYP.
- Although there are efforts both within and outside the military to develop an FDA approved FDP product, Army Special Operations has immediate need.
- Procure 200 units of FLYP per year.
- USASOC could use larger amount; SOCOM also expressed interest.
- French limited in production by French Donor availability.

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Discuss recruitment efforts and challenges associated with the collection of apheresis plasma for the manufacturing of freeze dried plasma in France.

OBJECTIVE 2

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Objective 2

- CTSA could increase production of FDP if a larger source of plasma available.
- Army Blood Program could fill the plasma need by providing donor retested apheresis FFP.
- CTSA uses Pathogen Inactivation Technology from Cerus Corporation on all French donor plasma.
- CTSA is able to use donor retested plasma / approved for use by their regulatory agency.
- Army Blood Program plasma will be donor retested plasma:
  - Military donor centers not currently utilizing pathogen inactivation technology.
  - Donor must be tested a second time no sooner than 60 days of original donation.
- Plasma collected at Army Blood Donor Centers and shipped to CTSA/France.

Efforts/challenges with the collection of apheresis plasma for the manufacturing of FDP in France

CONUS BDCs

- ASB/2 + 2 Satellite
- USA-6 + 1 Satellite
- USN-4 + 1 Satellite
- USAF - 3

FDP Collection Site
Efforts/challenges with the collection of apheresis plasma for the manufacturing of FDP in France

**OCONUS BDCs**

- ASBBC - 2
- USA - 1
- USN - 1

**FDP Collection Site**

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**Blood Donor Centers Involved**

- Army Blood Program – Blood Donor Centers involved
  - Womack AMC/Fort Bragg Blood Donor Center, Ft Bragg, NC
  - Landstuhl RMC/Armed Services Blood Bank Center, Germany
  - Eisenhower AMC/Kendrick Memorial Blood Center, Ft Gordon, GA
  - Madigan AMC/Armed Services Blood Bank Center-Pacific Northwest, Ft Lewis
  - Robertson Blood Center (RBC), Ft Hood, TX
  - William Beaumont AMC/Blood Donor Center, Ft Bliss, TX
  - Brooke AMC/Akeroyd Blood Donor Center, Ft Sam Houston, TX
  - Ft Leonard Wood Hospital/RBC Satellite, Ft Leonard Wood, MO
  - Tripler AMC/Blood Donor Center, Honolulu, HI
  - Ft Benning BDC, Ft Benning, GA

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Required Equipment

- Required Equipment:
  - Trima Accel Automated Blood Collection System (Must be configured for high volume plasma collection).
  - Trima Accel Automated Blood Collection System Tubing Set - Kit# 80700.
  - Apheresis Fresh Frozen Plasma (AFFP) Plastic Storage container.
  - TempTale4 Probeless Dry Ice Monitors.
  - Collins Box – shipping containers.

Required Validations

- Required Validations:
  - Collection of Multiplasma Units from single donors, which consisted of the following:
    - Collection process
    - Manufacturing
    - Labeling
    - Shipping
  - Plasma Shipping Containers.
  - TempTale4 Probeless Dry Ice Monitors.
Donor Criteria

- Donor selection/criteria -
  - In addition to standard donor eligibility criteria, the following apply:
    - Gender – male
    - Weight – 175lbs
    - ABO – not Group O
  - In addition to standard Infectious Disease Testing requirements, the following apply:
    - PT/PTT, INR, Fibrinogen (≥ 220) and Factor VIII (>75)
    - Anti-A and Anti-B Titer (< 64)
- Infectious Disease Testing:
  - Initial donation – Negative
  - 2nd donation/60 days – Negative

Inventory Management

- Inventory Management -
  - Initial and 60 day donation Infectious disease Testing NEGATIVE AND
  - Additional Testing within acceptable limits THEN
  - 1st donation = acceptable for IND/Shipement to France

NOTE: Units remain in a quarantine status until shipment.
**Shipping Requirements**

- **Units must have at least four months before expiration.**
- The following are included in the shipment –
  - Acceptable Infectious Disease Testing Results (spreadsheet/hard copy).
  - Consumables used.
  - Trima Collection Worksheet.
- **Packing the shipment** –
  - Pre-cooled Collins Box.
  - 18 plasma units (clear plastic) or 14 plasma units (cardboard box).
  - Add TempTale4 close to units.
  - Add 8 more pounds of dry ice and shipping bubble wrap to fill.
  - Add required documentation (taped to inside lid of the Collins Box).

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**Multi Plasma Program**

**Eligibility Requirements**

- A, B & AB
- **TYPE DONORS**
- By APRT Only – 910-396-9025
- Gender: Male Only
- Weight: 175 lbs. or more
- Donation Cycle – 2 donations every 60 days
- Donor must be able to meet all donation appointments
- Call today to be pre-screened over the phone.

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**RECEIVE A COA WORTH 5 PROMOTION POINTS FOR YOUR DONATION**

- Call the Fort Bragg Blood Donor Center:
  - 910-396-9925
- Visit http://www.blood.dmd.mil
- Receive a COA worth 5 promotion points for your donation.

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**ASBP**

- American Society for Blood Programmers
- militaryblood.dod.mil
Recruitment Efforts and Challenges

- Recruitment efforts and challenges:
  - Difficult finding dedicated donors willing to return over an extended timeframe.
  - Weight requirements limit potential donors.
  - Gender requirements limit potential donors.
  - Blood type restrictions limit potential donors.
  - Conflicts with Apheresis Platelet Program.

The Challenge of Collecting Apheresis Plasma

- Challenges associated with the collection of Apheresis Plasma (for shipment to France):
  - Donors failing Fibrinogen and Factor VIII level requirement greater than expected.
  - Challenges with acquiring and distributing shipping containers.
  - Initial challenges with local on-site testing capabilities.
  - Supply storage space limitations at some sites:
    - Apheresis kits.
    - Shipping containers.
The Challenge of Collecting Apheresis Plasma

- Storage equipment limitations (60-day storage requirement).
- Addition of a FDP Lot Release process:
  - Some sites have 3 process timelines: whole blood, apheresis, and FDP.
- Excellent organizational skills required for tracking donors, phlebotomy schedules, and documentation of lab results:
  - Additional staffing may be needed; dedicated team would be optimal.

FDP Expanded Access IND

- Partnership with French Military Blood Bank (CTSA)
- Meet short term operational need for US Military Forces.
- Buys time for US Manufacturing capability.
Efforts/challenges with the collection of apheresis plasma for the manufacturing of FDP in France

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Discuss the way ahead and timeline for product availability on the battlefield (and potentially at home).

OBJECTIVE 3
Tasks Completed to Support Expansion

- Goal is to expand number of FDP units to meet all of USASOC needs if not more customers throughout SOCOM.
- CTSA completed on-site supplier qualification audit of Ft. Bragg BDC Feb 2014.
- "Bioequivalence" test completed comparing US and French donor plasma.
- Army Blood Program issued standardized SOPs and quotas to designated donor centers.

Way ahead and timeline for product availability on the battlefield (and at home)

FFP Test Shipments

- Week of 27 Dec 2013, two test shipments from Fort Bragg sent to CTSA:
  - Identify customs issues / resolve packing concerns.
  - One shipment sent from Ft. Bragg BDC directly to CTSA.
  - Second shipment sent from Ft. Bragg hospital to CTSA.
  - Both arrived within acceptable temperature range.
  - Customs questions/concerns resolved.
  - Temp data logger settings established.
  - Result: Direct shipments can be successfully completed.
  - Donor retested plasma will be sent directly from ABP donor centers to CTSA.

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Audit Ft. Bragg BDC

- Director CTSA completed a supplier qualification of Ft. Bragg BDC in February 2014.
- Two day on-site assessment completed.
- Processes and procedures reviewed.
- Donation event was audited during the visit.
- All Army BDCs in program will follow same processes and procedures for plasma collection.
- Determined that Army BDCs meet or exceed CTSA standards for collection, processing and shipping of blood products.

US Donor Plasma Studies

- “Bioequivalence” study to determine if different donor population results in different FDP properties.
- 75 units of donor retested FFP sent in 3 lots to CTSA from Ft. Bragg BDC.
- 15 unit pools produced and units tested by both CTSA and Institute of Surgical Research (ISR).
- FFP shipped to CTSA met their quality standards for processing.
- Post-lyophilization sample analyses of factor activities and protein content met or exceeded the published parameters for French sourced plasma.
- Both facilities determined results were acceptable.
- MRMC is confident that donor retested plasma from US can replace French donor plasma (which has been treated w/ Intercept system).
Way ahead and timeline for product availability on the battlefield (and at home)

### US Donor Plasma Studies

<table>
<thead>
<tr>
<th>Instrument</th>
<th>STA-R</th>
<th>ST4</th>
<th>ELISA</th>
<th>i-STAT</th>
<th>Chronolog</th>
<th>TEG</th>
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<td>pH, Lactate, PCO₂, TCO₂, HCO₃, BE, sO₂</td>
<td>vWF:RCoF</td>
<td>Kaolin-Activation</td>
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Way ahead and timeline for product availability on the battlefield (and at home)

### FDA IND Expansion Review

- MRMC to package documents for FDA submission to expand IND #14872.
- Staffing actions and coordination will be ongoing between FDA and MRMC to answer any FDA concerns/questions.
- If approved, MRMC will coordinate with USASOC/USSOCOM for appropriate regulatory oversight.
- While packet submission and review is pending with FDA, Army to proceed with drawing donor retested Apheresis FFP.

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Apheresis FFP Quotas

- ABP has issued standardized SOPs and assigned freezing quotas to 5 Blood Donor Centers.
- Currently approximately 700 units of Apheresis FFP available in inventory.
- This product is being produced in addition to supplying routine blood product requirements.
- Goal to maintain inventory level and keep donors engaged and enrolled in the program.
- When FDA approval is received, anticipated the assigned quotas will supply enough A FFP for increased FDP production.
- Unknown exactly how much FDP per year may eventually be required, but not anticipated to be beyond 2000 units.

Way Ahead

- USASOC/SOCOM to establish receiving points for additional FDP units.
- All requirements of IND will have to be followed as program is expanded.
- This will increase regulatory oversight management.
- Possibility that product may be stored and issued from Army Blood Banks/Transfusion Services located on same base as USASOC/SOCOM units.
- Teams would draw plasma from the blood bank just prior to deployment.
- As DoD plans for lighter, more expeditionary capabilities in austere settings, the need for dried plasma will only increase.
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