

Comprehensive US government program for dried plasma development

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Transfusion of plasma early after severe injury has been associated with improved survival. There are significant logistic factors that limit the ability to deliver plasma where needed in austere environments, such as the battlefield or during a significant civilian emergency. While some countries have access to more logistically supportable dried plasma, there is no such product approved for use in the United States. There is a clear need for a Food and Drug Administration (FDA)-approved dried plasma for military and emergency-preparedness uses, as well as for civilian use in remote or austere settings. The Department of Defense (DoD) and Biomedical Advanced Research and Development Authority are sponsoring development of three dried plasma products, incorporating different technologic approaches and business models. At the same time, the DoD is sponsoring prospective, randomized clinical studies on the prehospital use of plasma. These efforts are part of a coordinated program to provide a dried plasma for military and civilian applications and to produce additional information on plasma use so that, by the time we have an FDA-approved dried plasma, we will better understand how to use it.

IMPORTANCE OF PLASMA IN COMBAT TRAUMA

In 2007, military researchers reported that survival was improved when the ratio of blood products transfused to severely wounded combat casualties approached 1:1 (plasma:red blood cells), compared to 1:2.5 or 1:8.¹ Based on this report and other available information, the US Department of Defense (DoD) implemented a policy to use a 1:1 ratio in massive transfusion for combat casualties and by 2009, data on blood product use confirmed that the policy had been widely adopted in the combat theater.² A number of civilian centers also adopted higher ratios for massive transfusion protocols. The majority of retrospective reports related to transfusion

ABBREVIATIONS: BARDA = Biomedical Advanced Research and Development Authority; DoD = Department of Defense; FLYP = French lyophilized plasma.

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ratios examined the ratio at 24 hours after admission. Subsequent reports suggested that it was not just the overall ratio that was important, but the early ratio, and that the survival benefit was achieved in the first 6 hours after injury.³⁻⁵ Although retrospective and observational data were promising, the lack of prospective data on transfusion ratios raised the question of whether the observed effects were the result of survival bias, rather than a true effect of the transfusion ratio.⁶ The issue of the potential need for early transfusion of plasma is of particular importance to the military, especially when one considers that movement of casualties to traditional hospital facilities may be significantly delayed due to distance, terrain, mission, or other factors.

LOGISTIC CHALLENGES

Hemorrhage is the leading cause of potentially preventable deaths on the battlefield.⁷ Casualties with hemorrhagic shock often receive blood transfusions at forward positioned hospitals and surgical teams. The magnitude of this requirement is evidenced by the fact that more than 335,000 units of blood products had been transfused in Iraq and Afghanistan as of February 2015 (US Armed Services Blood Program Office). Of these, nearly 110,000 units were fresh-frozen plasma (FFP). Delivering blood products where needed on the battlefield presents a significant logistic challenge for the military. FFP for military use is collected at US blood centers and shipped thousands of miles to the military point of use. This requires cold chain management over vast distances.² The problem of bag breakage and loss of FFP during shipment has been significant, at times up to 40%. Before use, FFP must be thawed, a process that takes approximately 30 minutes. Once thawed, it must be refrigerated and used within 5 days. This presents challenges in inventory management and surge capacity when casualties requiring massive transfusion may arrive with little notice. Generally, FFP is only available where adequate freezers, refrigerators, thawing equipment, and electrical supply can be positioned and maintained. This limits availability in austere combat areas, at sea, and during aeromedical evacuation. While it has been possible to move blood products closer to the patient during evacuation,⁸ the options are extremely limited where FFP is concerned, and battlefield plasma use remains limited by logistic constraints.

Similar logistic challenges may be expected in civilian mass casualty events, where infrastructure may be compromised and local supplies overwhelmed. The Biomedical Advanced Research and Development Authority (BARDA), a part of the US Department of Health and Human Services, has estimated that casualties following a 10-kiloton nuclear event in a major city could require hundreds of

thousands of units of plasma (BARDA estimate, 2015). Additionally, there are remote civilian hospitals and medical facilities around the world that are challenged by long pre-hospital transport times or limited by lack of laboratory facilities. Therefore, a cold chain-independent dried plasma could provide benefit far beyond military applications.

THE NEED FOR DRIED PLASMA

There is a clear need for a Food and Drug Administration (FDA)-approved dried plasma. The US DoD and BARDA are working together in development of dried plasma products. These programs are designed to develop an FDA-approved dried plasma that can be used wherever medically needed on the battlefield or in austere civilian settings, instead of only where freezers and thawing equipment are available. A dried plasma product, with less cold chain dependence and more rapid reconstitution, would reduce logistic constraints, improve inventory management and surge capability, and make it possible to distribute plasma much more widely in these scenarios. Additionally, the US DoD is sponsoring prospective randomized clinical studies to provide data on the safety and potential beneficial effects of very early transfusion of plasma after severe injury. The remainder of this article will discuss the approach and progress in this comprehensive program.

HISTORICAL PRODUCTS

Large-scale use of dried plasma began in WWII, when millions of units were distributed to Allied Forces worldwide. Both the British and the Americans produced pooled, lyophilized plasma to support the effort.^{9,10} However, by the end of the war, it was apparent that hepatitis transmission was a problem.¹¹ The use of dried plasma continued through the first part of the Korean War, but in 1953, Army policy recommended that plasma be used only in emergencies and when no plasma expander was available, and albumin largely took the place of plasma in US war resuscitation.¹² By 1968, dried pooled plasma was essentially abandoned in the United States.¹³ The French Military Blood Institute produced dried plasma from 1949 to 1984 and provided nearly 40,000 units to French military forces during the Indochina War.¹⁴ In 1985, production was discontinued due to risk of HIV infection.

MODERN PRODUCTS

In 1994, the French resumed dried plasma production to support military operations, incorporating a robust hemovigilance program. This French product began as a universal, minipooled (<11 donors) product, using carefully screened and monitored donors. After additional improvements over the years, the current product

TABLE 1. Characteristics of FFP and current dried plasma products

Criteria	FFP	Existing dried plasma products ^{14,15,17}
Efficacy	All coagulation factors within normal range. Unit to unit variability based on variability among normal donors.	Factor activity within normal range for nearly all factors. There are decrements in levels of selected factors as a result of drying and pathogen reduction procedures (varies among products). Pooled products (FLYP, Bioplasma FDP), have reduced unit to unit variability compared to FFP.
Blood type	ABO	ABO (LyoPlas N-w) or Universal (FLYP and Bioplasma FDP)
Preparation/reconstitution time	30–40 min	<10 min
Preparation/reconstitution requirements	Water bath or other FDA-approved thawing device	None
Storage temperature	≤ -18°C	Refrigerated or up to room temperature (25°C)
Shelf-life	12 months	15–24 months
Product packaging	Bag (200 to 250 mL)	Bottle (50 or 200 mL)

excludes plasma from women positive for anti-human leukocyte antigen (HLA) antibodies and also incorporates pathogen reduction using an amotosalen and ultraviolet light process (Cerus Corporation, Concord, CA), a process that has been available in Europe and has recently been approved for plasma in the US. French lyophilized plasma (FLYP) has been used in military operations around the world and has also been authorized for civilian use in austere settings.¹⁴ In the early 1990s, a solvent/detergent (S/D) pathogen reduced pooled lyophilized plasma was developed by the German Red Cross. More than 300,000 units of the German S/D lyophilized plasma were used through 2006. Since 2007, the German Red Cross has produced LyoPlas N-w, which is a single-donor, quarantined lyophilized plasma.¹⁵ This product has also been used extensively and has an excellent safety record. The National Bioproducts Institute (Pinetown, South Africa) produces a pooled, S/D-treated, ABO-universal lyophilized plasma, Bioplasma FDP, which has been in use in South Africa since 1996, with a strong record of safety.¹⁶ Each of these products is currently available within each respective country and limited others. However, none is approved for use in the United States. Some key characteristics of currently available dried plasmas are shown in Table 1.

As an interim solution, US Forces are now able to use FLYP, under an agreement between the US and French Governments and an expanded access investigational new drug application. To provide a long-term solution, the US DoD is sponsoring two dried plasma development programs, using different technologic approaches to improve the likelihood that at least one will make it to market. The BARDA is sponsoring a third program, employing yet another technologic approach. The DoD and BARDA programs are conducted in close cooperation and make up

an integrated, three-product approach for the US Government. One DoD program is aimed at developing a lyophilized, single-donor, tested plasma product manufactured from individual FFP units. The second DoD program is designed to develop a pooled, S/D-treated, spray-dried plasma product. The BARDA is developing a single-donor spray-dried plasma. While these programs were initiated to meet single service or agency requirements, it is recognized that each product has potential to meet the needs of the other agency and that a unified, coordinated approach is optimal.

The programs incorporate innovative approaches to areas such as manufacturing, packaging, and location of production. Successful production of an FDA-approved dried plasma will necessarily require a balance of safety, efficacy, ease of use, minimal logistics, and business case. Each of the pathogen reduction and drying technologies have an impact on the profiles of coagulation factors and hemostatic balance,^{15,18,19} and these must be carefully managed in manufacturing development. It is clear that safe and effective products can be produced using the various methods.^{14,15,20}

The DoD programs are targeted at meeting a set of performance variables designed to make distribution, storage and use of plasma in austere environments much more feasible. Target product characteristics are shown in Table 2. An additional common requirement is to avoid glass bottles and to produce packaging that can better withstand field conditions. These are desirable characteristics, which may evolve over time. However, FDA approval is an absolute requirement. It is expected that unit cost will be competitive with FFP, with a premium commensurate with the beneficial logistic and other aspects of the product. The goal is to develop a product that is commercially viable and not dependent on the US Government purchases.

TABLE 2. Dried plasma target characteristics

Criteria	Developmental threshold	Developmental objective
FDA clearance	FDA clearance	FDA clearance
Efficacy	80% of normalized plasma activity	90% of normalized plasma activity
Blood group	ABO	Universal
Final transfusable volume	200 to 250 mL	200 to 250 mL
Reconstitution time	<6 min	<6 min
Storage temperature	2-8°C	20–24°C
Operational temperature	0-40°C	0–40°C
Shelf-life	1 year	3 years
Reconstituted shelf-life	24 hr	120 hr
Product packaging	≤48 cubic inches with ruggedized container	≤48 cubic inches with ruggedized container

LYOPHILIZED PLASMA DEVELOPMENT

In 2008, the US Army Medical Research and Materiel Command (Fort Detrick, MD) initiated a dried plasma development program to meet combat requirements for the care of wounded soldiers, with the understanding that a dried plasma was needed by all the military services. The development program was designed to produce a FDA-approved, single-donor, tested, lyophilized plasma. From 2008 to 2013, the Army’s corporate partner was HemCon Medical Technologies, Inc. (Portland, OR).

The development approach was to use licensed FFP, with all associated safety measures, including donor screening, testing, quarantine period, and retesting, to produce single-donor lyophilized plasma. It was recognized that pooling would provide more consistent factor levels. However, it was decided to pursue a single-donor approach for safety and traceability purposes. The German Red Cross had recently switched from producing a pooled S/D-lyophilized plasma in favor of a single-donor, lyophilized plasma product, which has since demonstrated a strong safety record with more than 230,000 units used as of 2013 and no reports of poor efficacy.¹⁵

Although lyophilization has been extensively used for producing dried plasma in the past, the development program has been challenging. Lyophilization results in a reduction in activities of some coagulation factors. In general the changes are small. However, an isolated factor reduction of up to 25% has been reported.¹⁵ All previous and current lyophilized plasma products have been produced in a glass bottle. The current program specifically requires that glass not be used.

Licensed FFP from nonremunerated volunteer donors is aseptically placed into single-unit lyophilization containers and frozen under vacuum for 4 to 6 days in a commercial-scale lyophilizer. A unique container was developed that serves both as a lyophilization container and as a ruggedized administration container suitable for the field (Fig. 1). The program made significant progress in optimizing conditions, developing a process that resulted in factor levels within the normal range, with a loss of less than 15% activity for all measured factors, compared to FFP.²¹ The reconstitution time for the dried

plasma is approximately 2 minutes. In 2011, the product was successful in a Phase I clinical trial.²² The partnership with HemCon ended in 2013, for business reasons.

The Army reinitiated the program in 2014, with a new corporate partner, Vascular Solutions (Maple Grove, MN). It is expected that this program will produce an FDA-approved product by 2020 or 2021.

S/D-SPRAYED DRIED PLASMA DEVELOPMENT

This program began as a Navy and Marine Corps program and the approach taken to provide a plasma product had to carefully consider the expeditionary nature of naval forces. In 2008, the Office of Naval Research initiated a program to develop a group AB (universal), pooled-donor, S/D-treated, spray-dried plasma product that can be safely administered to all casualties regardless of blood type. The Office of Naval Research corporate partner is Entegriion Inc. (Research Triangle Park, NC), along with its European biopharmaceutical partner, Kedrion S.p.A (Barga, Lucca, Italy). Kedrion is the second largest manufacturer of plasma-derived products in Europe.

Plasma for the Office of Naval Research product is “source plasma” (from paid donors), collected at Kedrion’s existing US collection centers. All centers in the United States are FDA licensed and utilize a stable donor pool for whom annual physical examinations are provided free of charge. Both serologic and nucleic acid testing are performed. To remain qualified to donate, donors are tested at least twice per year or at each donation, whichever is more frequent. After plasma donation (plasmapheresis) the plasma is tested for HIV, HAV, HBV, HCV, and B19 parvovirus. Internal controls are in place to allow a full “lookback” capability to identify infected donors, if that should ever occur.

Risk of infection is further reduced by S/D treatment, using a process licensed from Octapharma (Lachen, Switzerland), that is effective against lipid-enveloped viruses and other pathogens,²⁰ many of which represent emerging or reemerging infections (examples include yellow fever viruses, arboviruses, measles, Middle East respiratory



Fig. 1. Unique ruggedized lyophilization, storage, and administration container.



Fig. 2. Packaging concept for the spray-dried, S/D-treated, pooled plasma product. The rehydration fluid is citrate-phosphate buffer, which allows maintenance of levels of coagulation factors to 7 days at 4°C after reconstitution.

syndrome coronavirus, Japanese encephalitis, and tick-borne encephalitis).²³ Pooling provides the ability to assay each lot of plasma (typically 1000-1500 units) so the specific levels of factors are known. The plasma is more of a pharmaceutical in this regard and there should be consistency between “doses,” in contrast to individual plasma units, which can vary up to fourfold based on thrombin generation potential.²⁴ The S/D process also removes immunogenic lipids, and a filtration step removes cellular debris and proinflammatory microparticles.

Since the 1990s, advances in testing and pathogen reduction have made it possible to effectively manage disease risk in pooled plasma. A number of pathogen reduction technologies are available and have potential for use in a dried plasma product in the United States. As men-

tioned, both amotosalen and S/D treatments have been used successfully in pooled, dried plasma products outside the United States. For this DoD program, S/D treatment was selected, based on its long history and safety record.

Pooled, S/D-treated plasma has been marketed in Europe since 1992 (Octaplas, Octapharma), and multiple millions of doses of Octaplas and the similar Plasmasafe (Kedrion S.p.A) have been administered. European hemovigilance data suggest that these products are very safe with a very low incidence of adverse events (incidence of TRALI is essentially zero).²⁵ Since the DoD plasma is manufactured by Kedrion, it is designed to meet or exceed European Union criteria for pH, osmolality, electrolytes, phosphate, coagulation factor levels, hemagglutinins anti-A and anti-B, protein S, α 2-plasmin inhibitor, and others.

The truly innovative step in the development of this dried plasma product was the application of a spray-drying technique, where a stream of plasma is exposed to high-temperature nitrogen gas (131°F) for 15 milliseconds, which removes the water with minimal alteration of plasma protein levels (similar to that obtained by freeze-drying and within EU and FDA limits). This approach has been developed by Entegrion for plasma and can dry a unit (250 mL) of plasma in approximately 10 minutes. This reduction in processing time translates into cost savings. Nova Laboratories (Leicester, UK), who has been performing aseptic spray-drying since 2008, will perform the spray-drying and packaging for the DoD pooled, S/D-treated plasma product. The product will be distributed with an intravenous administration set (Fig. 2).

Producing an S/D-treated spray-dried plasma presents some technical challenges. Both spray-drying¹⁹ and S/D treatment¹⁸ reduce levels of a number of coagulation proteins and may impact hemostatic balance. Therefore, it will be important to carefully optimize the processing conditions. A previously marketed plasma product, Plas+SD manufactured by Vitex (Melville, NY) was required by the FDA to carry a “black box” label warning, due to serious adverse events that may have been associated with low protein S concentrations in the product.²⁶ Although still technically approved in the United States, this product is no longer available. Current S/D treatment protocols avoid this issue by employing a different S/D process. Octaplas LG (Octapharma) received FDA clearance to market in the United States in 2013. Spray-drying, although used in the food production industry, has not previously been employed in blood products manufacturing in the United States. However, the FDA recently approved (May 2015) the fibrin sealant Raplixa (ProFibrin BV), which contains spray-dried thrombin and spray-dried fibrinogen, which are blended and filled aseptically at

TABLE 3. Prehospital plasma clinical studies treatments

Parameter	COMBAT	PAMPer	PUPTH
Blood group	AB	AB or A	A
How carried	Carried frozen and thawed in ambulance in <5 minutes using custom thawing device	Carried as thawed plasma in the air or ground ambulance	Carried as thawed plasma by EMS supervisor
Administration	Administered at scene or en route by paramedic	Administered at scene or en route by paramedic	Administered at scene or en route by emergency medical service supervisor

Nova Laboratories. The DoD S/D-treated spray-dried plasma product is currently in an FDA Phase I clinical trial and is part of a Joint Service Medical Advanced Development Program being led by the Navy Advanced Development Office, with oversight and primary funding from the Defense Health Agency.

SINGLE-DONOR SPRAY-DRIED PLASMA DEVELOPMENT

The BARDA is sponsoring the development of a single-donor, spray-dried plasma that is designed to be produced at local blood banks. The government’s corporate partner, Velico Medical (Boston, MA), is developing a plasma spray-drying device that will enable blood banks to produce licensed spray-dried plasma units locally within approximately 30 minutes.¹⁹ The company’s business model is one that is different from either of the current DoD partners and one that has not been tried in any other known large-scale dried plasma program, which have previously focused on centralized dried plasma production approaches. The product will use a unit of FFP to produce a unit of spray-dried plasma. The device that is currently in development will produce 1 unit at a time. It is expected that labeling and recordkeeping will be similar to FFP and compatible with existing blood bank systems. From the perspective of meeting US Government emergency-preparedness or military requirements, this approach would mean that the government would not be dependent on a single source for dried plasma and that military or other government blood centers could participate in production as a matter of routine. As an example, for military use, DoD blood banks in the United States could produce the dried plasma and ship it to field units utilizing existing logistic processes. For a civilian emergency, the product may be stockpiled and/or provided by surge production by regional blood centers. A technical challenge inherent with spray-drying is the potential impact of the process on coagulation proteins.¹⁹ Therefore, process optimization will be very important. The program is currently in the preclinical stage, and there are active discussions with FDA to explore potential development pathways.

PREHOSPITAL USE OF PLASMA FOR TRAUMATIC HEMORRHAGE

To determine the potential beneficial or negative effects of the use of plasma in the prehospital setting under varying modern trauma care conditions, the US DoD is sponsoring three prospective, randomized clinical studies that are expected to enroll a total of approximately 950 patients. Although the studies are independent, an overarching harmonization protocol has been developed to maximize potential for combined analyses, while still retaining the unique features of each study. The harmonized protocol was developed with informal consultation from the US FDA Center for Biologics Evaluation and Research. The studies are being conducted in close coordination with the National Heart, Lung, and Blood Institute of the National Institutes of Health.

The studies will enroll acutely injured trauma patients with penetrating or blunt trauma and hemorrhagic shock from acute blood loss (systolic blood pressure ≤ 70 mmHg or 71-90 mmHg and heart rate ≥ 108 beats/min), who are transported by ground or air ambulance. The Control of Major Bleeding after Trauma (COMBAT) study is a single-center study conducted at Denver Health Medical Center (Denver, CO).²⁷ The Prehospital Air Medical Plasma (PAM-Per) study is a six-site study being led out of the University of Pittsburgh (Pittsburgh, PA).²⁸ The Pre-Hospital Use of Plasma for Traumatic Hemorrhage (PUPTH) study is a single-center study located at the Virginia Commonwealth University Medical School (Richmond, VA). Each study required exception from informed consent in accordance with the US Code of Federal Regulations and an approved investigational new drug application. Specifics for each study are shown in Table 3.

The hypothesis driving the primary outcome measure is that prehospital administration of 2 units of plasma will reduce mortality at 30 days, compared to prehospital crystalloid fluids. Secondary outcomes will assess the effects of 2 units of prehospital plasma on: mortality at ED arrival and at 24 hours, transfusion requirements, coagulation variables, clot viscoelastic properties, hemodynamic variables, cellular hematologic variables, metabolic status, and disseminated intravascular coagulation score.²⁹

It is expected that these clinical studies will be completed by 2018 and that they will provide valuable information on whether and how to use plasma for trauma in the out of hospital environment. This information will inform future decisions on how best to use dried plasma products when they become available.

CONCLUSION

There is a great need for an FDA-approved dried plasma for military and emergency-preparedness uses, as well as for civilian use in remote or austere settings. The DoD and BARDA are sponsoring development of three dried plasma products, incorporating different technologic approaches and business models. At the same time, DoD is sponsoring prospective, randomized clinical studies on the prehospital use of plasma. These efforts are part of a coordinated program to provide a dried plasma for military and civilian applications and to produce additional information on plasma use so that, by the time we have an FDA-approved dried plasma, we will better understand how to use it.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

REFERENCES

- Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*. 2007;63:805–13.
- Spinella PC, Dunne J, Beilman GJ, et al. Constant challenges and evolution of US military transfusion medicine and blood operations in combat. *Transfusion* 2012;52:1146–53.
- Maegelé M, Lefering R, Yucel N, et al. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. *Injury* 2007;38:298–304.
- Zink KA, Sambasivan CN, Holcomb JB, et al. A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. *Am J Surg* 2009;197:565–70.
- Holcomb JB, del Junco DJ, Fox EF, et al. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMTTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg* 2013; 148:127–36.
- Brown JB, Cohen MJ, Minei JP, et al. Debunking the survival bias myth: characterization of mortality during the initial 24 hours for patients requiring massive transfusion. *J Trauma Acute Care Surg* 2012;73:358–64.
- Eastridge BJ, Mabry RL, Seguin P, et al. Death on the battlefield (2001–2011): implications for the future of combat casualty care. *J Trauma Acute Care Surg* 2012;73:S431–7.
- Malsby RF III, Quesada J, Powell-Dunford N, et al. Prehospital blood product transfusion by U.S. army MEDEVAC during combat operations in Afghanistan: a process improvement initiative. *Mil Med* 2013;178:785–91.
- Schmidt PJ. The plasma wars: a history. *Transfusion* 2012;52: 2S–4S.
- Harding AJ. A brief history of blood transfusion. *Biomed Scientist* 2005;49:1147–57.
- Rappaport EM. Hepatitis following blood or plasma transfusions. *JAMA* 1945;128:932–9.
- Kendrick DB. Blood program in World War II. Washington (DC): Office of the Surgeon General, Department of the Army; 1964.
- Statement on normal (whole pooled) human plasma prepared by Committee on Plasma and Plasma Substitutes of the Division of Medical Sciences, National Research Council. *Transfusion* 1968;8:57–9.
- Sailliol A, Martinaud C, Cap AP, et al. The evolving role of lyophilized plasma in remote damage control resuscitation in the French Armed Forces Health Service. *Transfusion* 2013;53(Suppl1):65S–71S.
- Bux J, Dickhorner D, Scheel E. Quality of freeze-dried (lyophilized) quarantined single-donor plasma. *Transfusion* 2013;53:3203–9.
- Solheim BG, Chetty R, Flesland O. Indications for use and cost-effectiveness of pathogen-reduced ABO-universal plasma. *Curr Opin Hematol* 2008;15:612–7.
- Bioplasma FDP product information [Internet]. Pinetown (South Africa): National Bioproducts Institute; c2015 [cited 2015 Jul 16]. Available at: <http://www.nbi-sa.co.za/index.php/products/30-products/90-pharmaceuticals>
- Rock G. A comparison of methods of pathogen inactivation of FFP. *Vox Sang* 2011;100:169–78.
- Booth GS, Lozier JN, Nghiem K, et al. SPRAY: single donor plasma product for room temperature storage. *Transfusion* 2012;52:828–33.
- Hellstern P, Solheim BG. The use of solvent/detergent treatment in pathogen reduction of plasma. *Transfus Med Hemother* 2011;38:65–70.
- Cancelas J, Rugg N, Pratt PG, et al. A safety clinical trial of dose-escalation of autologous lyophilized plasma versus fresh frozen plasma in normal healthy subjects. *Transfusion* 2011;51(Suppl):S85–040A.
- Winata E, Culbertson KE, Egan A, et al. Production of single donor lyophilized plasma for phase I clinical trials. *Transfusion* 2011;51(Suppl):SP21.
- Stramer SL. Current perspectives in transfusion-transmitted infectious diseases: emerging and re-emerging infections. *ISBT Sci Ser* 2014;9:30–36.
- Brummel-Ziedins K, Vossen CY, Rosendaal FR, et al. The plasma hemostatic proteome: thrombin generation in healthy individuals. *J Thromb Haemost* 2005;3:1472–81.
- van Eerd MC, Mario Ouwens JN, de Peuter MA. Cost-effectiveness study comparing pharmaceutically licensed plasma for transfusion (OctaplasLG[®]) versus fresh frozen plasma

- (FFP) in critically ill patients in the UK. *Transfus Apher Sci* 2010;43:251–259.
26. Salge-Bartels U, Breitner-Ruddock S, Hunfeld A, et al. Are quality differences responsible for different adverse reactions reported for SD-plasma from USA and Europe? *Transfus Med* 2006;16:266–75.
27. Moore EE, Chin TL, Chapman MC, et al. Plasma first in the field for postinjury hemorrhagic shock. *Shock* 2014;41:35–38.
28. Brown JB, Guyette FX, Neal MD, et al. Taking the blood bank to the field: the design and rationale of the Prehospital Air Medical Plasma (PAMPer) trial. *Prehosp Emerg Care* 2015;19:343–50.
29. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. *Br J Haematol* 2009;145:24–33. ■