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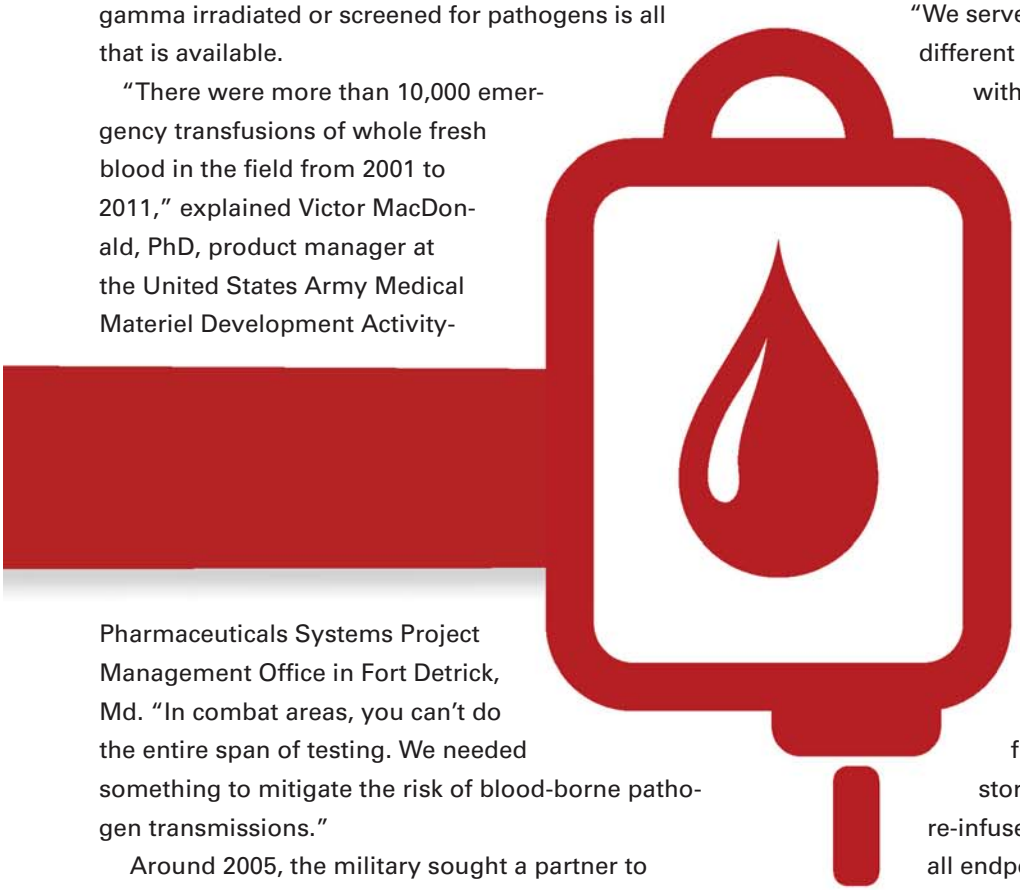
Pathogen Reduction Technologies

FOR WHOLE BLOOD

Where once whole blood transfusions were common, the standard practice has transitioned to separating whole blood into red blood cells, or RBCs, plasma and platelets for efficient processing and storage. However, in settings such as combat situations, fresh whole blood that has not been gamma irradiated or screened for pathogens is all that is available.

"There were more than 10,000 emergency transfusions of whole fresh blood in the field from 2001 to 2011," explained Victor MacDonald, PhD, product manager at the United States Army Medical Materiel Development Activity-Pharmaceuticals Systems Project Management Office in Fort Detrick, Md. "In combat areas, you can't do the entire span of testing. We needed something to mitigate the risk of blood-borne pathogen transmissions."



Around 2005, the military sought a partner to develop a transportable pathogen treatment system for whole blood. "The army was aware of the work we were doing around our platelet and plasma pathogen reduction system, which is licensed in Europe and for which we are doing clinical studies in several countries, including planned studies in the U.S.," said Raymond Goodrich, PhD, vice president of scientific and medical affairs at Terumo BCT in Lakewood, Colo. "Initially, we said no, but it got us thinking. After some studies we did in collaboration with colleagues at Ohio State University, we went back to the army and said yes."

With funding from the Department of Defense, Terumo BCT organized research efforts to develop the Mirasol Pathogen Reduction Technology System at a dozen institutions, including several universities, the American Red Cross, the Centers for Disease Control and Prevention and the Walter Reed Army Institute of Research.

"We served as the hub of the wheel of many different collaborators," said Goodrich. "And with the support of the grant from DOD, we were able to advance the project over many years through in vitro, animal and preclinical testing and human trials in the U.S. We are now ready to start our third U.S. trial."

Clinical Research Moves Forward

The second human trial finished collecting data in the spring of 2014 and will be published early this year. The study included 24 healthy volunteers and evaluated the 24-hour post-transfusion recovery rate of RBCs derived from Mirasol-treated whole blood, stored for 21 days, radiolabeled and then re-infused. "I'm happy to report we did meet all endpoint criteria," stated Goodrich. Key criteria set by the Food and Drug Administration include greater than 75 percent survival of 70 percent of RBCs and less than 1 percent hemolysis at 24 hours after the transfusion. Study investigators also submitted to FDA in vitro testing data that support the efficacy of the product in pathogen reduction, or PR, while maintaining suitable cell quality characteristics, said Goodrich.

The third trial will look at the ability of RBCs derived from Mirasol-treated whole blood to support patients who need repeated transfusions as a regular part of their care — such as individuals with thalassemia — and

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compare it with that of the untreated red blood cell products used today. The double-blinded study will be a crossover design — half the patients will receive treated product for six months and the standard product for six months, and the other half the reverse. The target enrollment is about 100 patients, who will be randomly assigned to the two groups. "We just need to get approval for the final protocol, and we're on track to submit it for review in the next few weeks," said Goodrich.

Terumo BCT plans to file for premarket approval of the Mirasol system for RBCs. This will allow the company to submit data to FDA as it conducts its phase III trial. "You submit all of your manufacturing data, all of your toxicology data and all of your in vitro testing data while you are doing the pivotal trial," explains Goodrich. "FDA reviews these modules and gives comments back. They're looking at all aspects of how the product is made, what your quality system looks like. When you finish the clinical trial, you submit the clinical module, and then FDA gives you a final decision on the final package." Premarket approval would allow Terumo BCT to put its product on the market for use with whole blood in the U.S. The decision from FDA could be made in early 2018.

"The short-term goal is to get the Mirasol system approved for emergency whole blood transfusions," said Andrew Atkinson, product manager at the U.S. Army Medical Materiel Development Activity-Pharmaceuticals Systems Project Management Office. "The long-term goal would be to get it approved for various components, so we can actually use it not just in the theater, but in our blood banking facilities here in the U.S."

Researchers are exploring use of PR technologies for whole blood in developing nations where the conditions may be challenging and blood testing capabilities limited. In collaboration with the government of Ghana and medical researchers in Ghana and the United Kingdom, Terumo BCT is doing a clinical study evaluating the use of Mirasol-treated whole blood for the prevention of transfusion-transmitted malaria. "We recently completed patient enrollment in that study and expect to have the data in the early part of 2015," said Goodrich.

Another company, Cerus Corporation, envisions a whole blood process for use in developing countries. "We have a humanitarian project with the Swiss Red Cross and the University Hospitals of Geneva to develop technology for whole blood. We wouldn't commercialize it in the U.S. because we use blood components here, and the same thing is true in Europe," said Laurence Corash, MD, senior vice president and chief medical/scientific officer of Cerus Corporation, Concord, Calif. The goal of the project is to help improve global health by alleviating shortages of safe blood in African countries where the rates of transfusion-transmitted diseases are high and whole blood transfusions remain common.

The company also recently completed a phase III acute anemia trial of its Intercept Blood System for RBCs in cardiovascular surgery patients in Europe. The study met its primary endpoint and will be used to file for CE mark approval — required to sell the system in the European Union — next year. The company plans to discuss a proposed phase III clinical trial protocol for the red blood cell system with FDA in the second half of 2015. In December 2014, FDA approved Intercept for use with plasma and single donor apheresis platelets.[1,2]

Screening Strategies for PR Technologies

The key issues for PR technologies are the same as they are for much of health care today: what is the balance between risk and benefit? Specifically for PR technologies, how many infectious agents can be inactivated, and can they be totally inactivated or partially inactivated? If they are partially inactivated, what percentage is acceptable?

"In a thalassemia patient, you want the red cells to survive as long as possible. If they can survive as long as the traditional ones, the clinician may accept a 5 to 10 percent, but not a 20 percent, loss of red blood cells over those cells lost after transfusion of conventional stored RBC products," said Jose Cancelas, MD, PhD, deputy director of the Hoxworth Blood Center in Cincinnati, Ohio. "That is the reason why the results from in vivo recovery studies are so important and determinant for the implementation of PR technologies."

The center has been conducting PR technology studies since the early 2000s using both Intercept and Mirasol technologies.

Some question the need for PR technologies when currently available tests for infectious diseases are efficient and accurate. "Our current assays do a very good job – nucleic acid tests are very good. Where I've seen PR technologies have the best effect has been in eliminating bacterial contamination in platelets. Much of it, as it is with everything, is going to come down to costs and trade-offs in the system," said F. Blaine Hollinger, MD, professor of medicine, molecular virology and epidemiology at Baylor College of Medicine and director of the Eugene B. Casey Hepatitis Research Center in Houston.

Several transfusion medicine experts interviewed for this article agree that while PR technologies may add cost, they could remove the need for – and cost of – bacterial cultures and testing for cytomegalovirus and enveloped viruses, which can be readily activated and eliminated by ultraviolet light. It may also eliminate the need for gamma irradiation, which is performed to lower the risk of transfusion-associated graft-versus-host disease.

Screens for HIV and hepatitis C virus are not likely to be totally eliminated by using PR technologies, according to Harvey Alter, MD, distinguished investigator, chief of clinical studies and associate director for research in the Department of Transfusion Medicine at the National Institutes of Health in Bethesda, Md. "Current testing has been so effective, and the disease consequences so devastating, we will want to take a 'belt and suspenders' approach," said Alter.

While the elimination of several tests and processes may balance out the cost of the PR systems, several experts pointed to a benefit that is harder to quantify: safer blood. PR technologies could reduce the need to screen out donors because of certain risk factors. "For example, donors who travel to certain areas where

Blood Center Adoption

Now that there are FDA-approved PR technologies for platelets and plasma (see table at right), how readily will they be adopted? Much of PR involves the same techniques as conventional blood component collection and processing. It can be performed by laboratory technicians and does not require a licensed laboratory technologist.

In terms of operations, the Intercept and Mirasol PR systems are designed to be set up quickly and simple to run. During operational testing at Camp Bullis in San Antonio, the U.S. Army set up the Mirasol system in mobile army hospital tents like those used in Afgahanastan and Iraq and provided three days of training to its personnel. "We were able to demonstrate that we could do all of the things that would be required to transport the sytem; set it up; complete the training; and have people use it effectively in settings very similar to what they would have in the field," said Goodrich.

Corash reports that technicians who have been working with Intercept in Europe get satisfaction from the hands-on process. "In the past biologicals, like clotting concentrates, have been treated with pathogen inactivation technology, but always in a manufacturing setting. This is the first time it's being done in blood centers. What we've seen in Europe is that the people in the blood centers really become engaged in creating with their own hands what they perceive to be a better blood component," he said.

malaria is endemic may not have malaria, but we screen them out because of the concern that they might," said Goodrich. "There's no methodology now other than to ask them whether they have been to an area where malaria might be present."

The most dramatic effect of implementing PR technologies may be preventing the time lag that now exists between the detection of a new pathogen and the availability of an FDA-approved assay to test for it in blood products.

"With West Nile virus, we did pretty well once it was recognized, but it was still about a year or more to develop a test," said Alter. "Pathogen reduction would avoid this lag phase and make us pre-emptive rather than reactive. If the next lethal AIDS-like agent comes along and it's an enveloped virus or a virus that is susceptible to pathogen reduction, then we will have prevented the tragedy."

REFERENCES:

1. FDA approves first pathogen reduction system to treat plasma. FDA News Release; December 16, 2014. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427111.htm. Accessed December 17, 2014.
2. FDA approves pathogen reduction system to treat platelets. FDA News Release; December 19, 2014. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427500.htm. Accessed December 20, 2014.

PR Technology Development and Approval

Component	Company	Technique	Status
Plasma	Cerus Corporation	Amotosalen + ultraviolet light	- CE marked 2006 - FDA approved 2014
	Terumo BCT	Riboflavin + ultraviolet light	- CE marked 2008
Platelets	Cerus Corporation	Amotosalen + ultraviolet light	- CE marked 2002 - FDA approved 2014
	Terumo BCT	Riboflavin + ultraviolet light	- CE marked 2007
Red blood cells	Cerus Corporation	S303	- European phase III clinical trial completed - U.S. phase III clinical trial planned
	Terumo BCT	Riboflavin + ultraviolet light	- U.S. phase II clinical trial completed; phase III clinical trial planned

CE = Conformité Européenne

Modified from: Pathogen Inactivation: The Penultimate Paradigm Shift. AuBuchon JP and Prowse CV, ed. Bethesda, Md: AABB Press; 2010.