

A woman with dark hair is lying in a hospital bed, smiling. She is wearing a light blue hospital gown. A red tube is connected to her arm, secured with white tape. The background is a bright, clinical setting with other patients and medical equipment visible but out of focus.

Saving Lives Through **PLASMA** DONATION

The road to producing lifesaving plasma therapies is long and complicated, made possible only with the millions of donations collected each year.

By Ronale Tucker Rhodes, MS

NEARLY 30 MILLION PEOPLE in the U.S. have been diagnosed with a rare disease,¹ a great number of whom have genetic, chronic conditions caused by an inability to produce plasma proteins in sufficient quantities or of sufficient quality. These individuals depend upon access to plasma protein therapies, including coagulation factors used to treat bleeding disorders and immune globulins to treat primary immune deficiencies, neurological disorders and autoimmune diseases. Generally, these therapies are infused or injected throughout life to replace missing or deficient proteins that allow individuals to lead healthy and more productive lives. But sustaining the need for these therapies requires millions of liters of plasma each year that must be donated and then manufactured into lifesaving medicines.

How Plasma Is Donated

Plasma is the pale yellow portion of blood that functions as an aid in the circulation of red and white blood cells and platelets.² In the U.S., there were more than 32 million donations of plasma collected in 2014, according to the Plasma Protein Therapeutics Association, which is more than triple the increase of 12 million donations over the previous decade.³ Most of the world's plasma is collected in about 400 plasma donation centers scattered throughout the U.S., with some of it exported to other countries.⁴

In U.S. plasma donation centers (owned exclusively by plasma therapy manufacturers), donors receive a small financial compensation (between \$15 and \$40)⁴ for their time to donate plasma and to incentivize them to return. To donate, individuals must meet certain requirements. They must be 18 years or older (19 years in Nebraska or 18 years with an authorized consent form), weigh at least 110 pounds and be in general good health. When arriving at a donation center, they are required to produce either a Social Security number or an INS number, as well as a valid picture ID (driver's license or student or military ID) with their current address.⁵ And, they are checked against the National Donor Deferral Registry (NDDR) before being allowed to donate.⁶

Donors must also proceed through a process that ensures they are healthy enough to safely donate their plasma. Before the first donation and once a year thereafter, donors must receive a physical evaluation during which their pulse, blood pressure and temperature are taken. They are also given a hematocrit test via a small finger prick to confirm a healthy level of red blood cells, and they must give a urine sample.

Questions are asked of them to ascertain if they have participated in any high-risk behaviors or have any medical conditions that may disqualify them from donating.⁶ For instance, those who have recently had tattoos or body piercing, who have lived for a prolonged period in Europe, and have cancer and/or other medical conditions are ineligible to donate.⁵ And, in some instances, donors may be asked for medical records from their personal physician.⁶

New donors are required to donate two times. The second donation provides two sets of test results and health screenings to assure the safety and reliability of the plasma supply. If new donors donate only one time, their plasma donation is discarded. Plasma can be donated two times within a seven-day period with at least 24 hours between donations because the body replenishes the donated plasma within 24 to 48 hours.⁵

A NEWLY DEVELOPED PATENTED TECHNIQUE IS EXPECTED TO GREATLY IMPROVE UPON THE PLASMA EXTRACTION RATE.

Once all the requirements are met, donors are ready to begin plasmapheresis, a process that separates each donor's plasma from the red cells, collects the plasma and returns the red cells to the donor. Once the donation is made, the plasma is placed on a 60-day hold while it undergoes further testing for viral agents. If it is found to be unsafe, it is discarded. Any donors whose plasma tests positive for hepatitis B, hepatitis C or HIV will be automatically entered into the NDDR and will be permanently barred from donating blood or plasma in the U.S.⁶

How Therapies Are Made

Once the plasma is released from inventory (the 60-day hold), it is ready for fractionation. The Cohn cold fractionation process has been the most common protocol for plasma protein extraction since its inception in the 1940s. During the fractionation process, plasma is pooled from multiple donations, purified and processed in a specific order to extract specific plasma proteins that have a proven health benefit. The steps and regulations required to



collect donated plasma and complete the manufacturing process that ultimately results in the final therapies take between seven and nine months. Between weeks 0 and 4, the plasma is collected. Then, between weeks 4 and 12, it is batched and transported to the fractionation plant, where it is stored from weeks 12 through 16. During this period, a combination of time, temperature, pH and alcohol concentration allows the extraction of the specific therapeutic proteins. At that point, the plasma is inspected and released for production. Production occurs between weeks 20 and 24. Then, between weeks 24 and 28, internal testing of the therapeutic proteins takes place, and the therapies are then released by the U.S. Food and Drug Administration (FDA) and shipped between weeks 28 and 32 to the wholesalers and end users.⁷

The Cohn cold fractionation process is long and arduous with a moderately successful extraction rate of 7 percent from blood (with plasma concentration of 1.8 grams to 3.5 grams per liter). But, a newly developed patented technique is expected to greatly improve upon the plasma extraction rate. The Optimized Plasma Process from PlasmaTech Biopharmaceuticals increases the plasma extraction yield tenfold, recovering almost 70 percent of plasma.⁸ As of this writing, it is unknown when this new

plasma fractionation process will be available for use.

Even before the development of this new technique, manufacturers have continued to expand their fractionation capacity. For instance, CSL Behring will spend \$450 million over the next few years to expand its production facilities in the U.S. and Australia, with a \$240 million investment into its Kankakee, Ill., facility, which produces albumin and immune globulin, and a \$210 million investment into its Broadmeadows plant in Melbourne, Australia. Grifols has also expanded its three manufacturing sites in Clayton, N.C., Los Angeles and Barcelona, Spain, the company's global headquarters. The expansions include a new, 185,000-square-foot fractionation facility in Clayton and a new facility in Los Angeles dedicated to the production of immune globulin therapies. These new facilities have increased the company's capacity to fractionate plasma from 8 million liters per year to 12 million liters in 2015. And, according to a statement by Baxter Healthcare, the company is "in the process of building a new state-of-the-art fractionation and production facility in the U.S., with commercial production scheduled to begin in 2018. In addition, [the company has] established an agreement with Dutch company Sanguin to provide additional fractionation

capacity to supplement Baxter's capacity."⁴

Manufacturers are also continuing to expand their network of plasma collection centers. In 2014, CSL Behring opened 18 centers in the U.S. Also in 2014, Grifols hosted a ribbon-cutting ceremony for its fifth Talecris Plasma Resources Center in El Paso, Texas. Grifols now has a network of 150 plasma donation centers across the U.S. Baxter Healthcare's BioLife Plasma Services also continues to expand its plasma collection centers throughout the U.S. with 13 centers having opened or scheduled to open within the next year.⁴

Ensuring the Safety of Plasma

The U.S. plasma fractionation industry is regulated by FDA. Since the 1980s, FDA and international agencies have developed a comprehensive set of measures to ensure the viral safety of plasma products, including multiple levels of regulatory oversight to ensure overlapping safeguards against the risks of transmitting bloodborne infectious agents.⁷

And, during the past few decades, manufacturers have introduced new technologies to further improve the safety of plasma protein therapies. Indeed, donor screening and testing are only the first steps in the complex manufacturing process for plasma products. Each individual plasma product is subjected to multiple purification viral inactivation and removal processes. The type of viral inactivation and removal methods used depend on the plasma product, but common viral inactivation methods include:

- Solvent detergent treatment that consists of adding a soap-like chemical to the plasma that breaks down and destroys the fatty coating surrounding lipid-enveloped viruses. By destroying this fatty coating, the viruses are also destroyed.
- Heat treatment that involves heating each product vial to 80 degrees Centigrade for 72 hours. The temperature is carefully controlled to maintain it at a level that is effective against pathogens but not damaging to the therapeutic proteins.
- Nanofiltration that allows the wanted therapeutic proteins to pass through a specially designed membrane with a reduced pore size, while other particles or pathogens are trapped and discarded.

These procedures have proven to be effective at eliminating a wide array of potential contaminants such as bacteria and viruses, including hepatitis, HIV and many others. It should be noted that there have been no cases of HIV or hepatitis transmission via plasma medicines since the implementation of these validated viral inactivation methods in the early 1990s.

In addition to FDA standards and improved manufacturing processes, many manufacturers adhere to the International Quality Plasma Program (IQPP), a voluntary industry certification

program for plasma collection centers to exceed government standards for safety. IQPP guidelines include the exclusive use of repeat donors, 60-day inventory holds and nucleic acid testing for each donation — procedures that have been incorporated industry-wide in an effort to maximize plasma product supply chain safety.⁹

EACH INDIVIDUAL PLASMA PRODUCT IS SUBJECTED TO MULTIPLE PURIFICATION VIRAL INACTIVATION AND REMOVAL PROCESSES.

A Promising Outlook

The outlook for plasma therapies looks very promising thanks to an increasing number of plasma donors each year, which is welcome news as the number of diseases treated with them grows and off-label (non-FDA-approved) prescribing increases. With more plasma, manufacturers are expanding their fractionation production facilities and new technologies are being developed to meet therapeutic demand. What's more: The plasma supply is safer now than ever with extensive safety measures that eliminate infectious donations and various steps that eliminate and inactivate contaminated viruses, which has all but eliminated the risk of disease transmission by plasma products. ■

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References

1. A Look at Some Key Statistics on Rare Diseases in the U.S. The Associated Press, March 25, 2015. Accessed at www.apnewsarchive.com/2015/A-look-at-some-key-statistics-on-rare-diseases-in-the-US/id-01097580a9848feb68fb9e940bfe4.
2. Plasma Donors Save Lives. Baxter, September 2012. Accessed at www.baxter.com/news-media/newsroom/featured-stories/features_plasma_donation.page.
3. Plasma Protein Therapeutics Association. United States Total Collections 2003-2014. Accessed at www.pptglobal.org/images/Data/Plasma_Collection/US-Total-Collections_2003-2014.pdf.
4. Rhodes, RT. Immune Globulin: Controlling Supply and Demand. *BioSupply Trends Quarterly*, January 2015. Accessed at www.bstquarterly.com/assets/downloads/BSTQ/Articles/BSTQ_2015-01_AR_Immune-Globulin-Controlling-Supply-and-Demand.pdf.
5. Biotest Plasma Center. Plasma Donation Eligibility. Accessed at biotestplasma.com/donation-process/donation-eligibility.
6. McFalls, K. Donating Plasma: The Gift of Life. *IG Living*, August-September 2010. Accessed at www.igliving.com/magazine/articles/IGL_2011-08_AR_Donating-Plasma-The-Gift-of-Life.pdf.
7. Rhodes, RT, and McFalls, K. The Drivers Behind Plasma Protein Therapies. *BioSupply Trends Quarterly*, January 2010. Accessed at www.bstquarterly.com/assets/downloads/BSTQ/Articles/BSTQ_2010-01_AR_Plasma-Therapies-IG-In-The-Driver-Seat.pdf.
8. Dutt, S. Novel Plasma Protein Extraction Technology to Improve Access to Plasma for COPD and Other Disease Treatments. *Lung Disease News*, April 20, 2015. Accessed at lungdiseaseneews.com/2015/04/20/novel-plasma-protein-extraction-technology-to-improve-access-to-plasma-for-copd-other-disease-treatments.
9. Mitschang, T. Good Blood. *BioSupply Trends Quarterly*, April 2011. Accessed at www.bstquarterly.com/assets/downloads/BSTQ/Articles/BSTQ_2011-04_AR_Good-Blood.pdf.