

THE SOURCE

THE MAGAZINE OF THE PLASMA PROTEIN THERAPEUTICS INDUSTRY

Special Issue

DECADES OF SAFETY

**Healthy Donors:
The Cornerstone
of Plasma Protein
Therapies**

**The Evolution of
Safety in Source
Plasma Collection**

**Decades of
Safety Measures:
Plasma Protein
Therapies**



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SPECIAL ISSUE

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These companies have earned
QSEAL certification.
The PPTA QSEAL program
is a promise to stakeholders
worldwide, that the
highest levels of care
were invested into
the production of
these unique
life-saving therapies.
BAXTER BIOSCIENCE
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IN MY VIEW

SAFETY REMAINS INDUSTRY'S FIRST PRIORITY

IN THIS SPECIAL EDITION of *The Source* magazine we pay attention to many innovations in safety. We are proud of working for an industry that is producing therapies that have such a profound impact on the lives of many patients. We remember the tragedy of the 1980s when many hemophilia patients were infected with HIV and we do not want to see that happen ever again. Nobody wants that.

The situation today is much different. We have not seen viral transmissions for a very long time and can therefore now talk about decades of safety. The World Federation of Hemophilia at its 3rd Global Forum in Budapest, Hungary in September 2003 concluded that the debate needed to shift from "Supply and Safety" to "Supply and Affordability." This is important because in today's world about 30 percent of people with hemophilia have no access to any form of treatment. This did not mean that safety was no longer important, but it meant that within the hemophilia community there was recognition of the enormous progress that had been made in producing lifesaving plasma protein therapies.

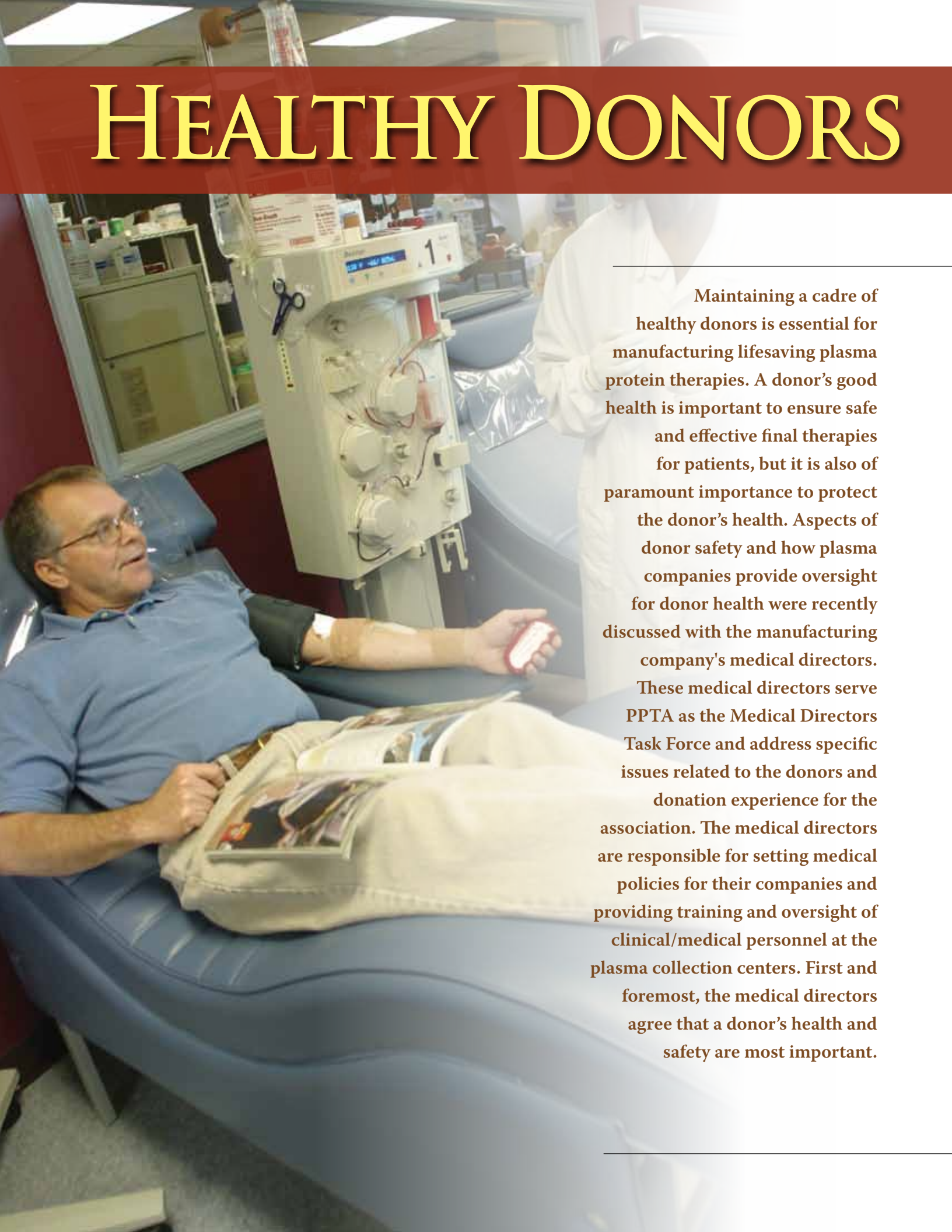
Talking with users of these therapies is always stimulating. You hear the stories of joint problems in the hemophilia community from the older users, whereas those who have benefitted from early treatment are almost leading a normal life. In many cases, the infusions are the only time

when people are reminded of their disorder.

The same is true for patients with immune deficiencies. Hearing the stories of returning to a normal life after regular treatments with immune globulins is encouraging and sometimes heartbreaking. And what about the patients with alpha-1 antitrypsin deficiency? The moment they are diagnosed and treated with the augmentation therapy, further lung damage can be stopped. There are so many more groups of people suffering from Guillain Barré Syndrome, chronic inflammatory demyelinating polyneuropathy and many more people benefit from therapies. Many people who get the concentrated immune globulins (hyperimmunes) to treat special infections like cytomegalovirus (CMV), hepatitis B, tetanus, rabies and others. Some pregnant women receive anti-D therapy to protect their newborn babies against antibodies attacking the child because of a Rhesus factor incompatibility. The good results of these treatments are impressive.

All of these therapies are safe as a result of the hard work of many that are involved in the collection of plasma and the manufacturing of these lifesaving therapies. Though we agree that the main focus today is on availability of therapies throughout the world, we must not forget that safety remains the first priority. I am proud that in our magazine we can present so many different accomplishments that contribute to this. ☞

HEALTHY DONORS

A photograph of a man in a blue polo shirt and glasses lying in a blue reclining chair at a plasma collection center. He has a blood pressure cuff on his left arm and is holding a small red and white device. A plasma separation machine is positioned next to him. In the background, a person in a white lab coat is partially visible. The setting appears to be a clinical or medical facility with shelves of supplies in the background.

Maintaining a cadre of healthy donors is essential for manufacturing lifesaving plasma protein therapies. A donor's good health is important to ensure safe and effective final therapies for patients, but it is also of paramount importance to protect the donor's health. Aspects of donor safety and how plasma companies provide oversight for donor health were recently discussed with the manufacturing company's medical directors. These medical directors serve PPTA as the Medical Directors Task Force and address specific issues related to the donors and donation experience for the association. The medical directors are responsible for setting medical policies for their companies and providing training and oversight of clinical/medical personnel at the plasma collection centers. First and foremost, the medical directors agree that a donor's health and safety are most important.

THE CORNERSTONE OF PLASMA THERAPIES

BY MARY GUSTAFSON AND JOSHUA PENROD

Donor health is a primary consideration in the donor selection process. Prospective donors are screened using a health history questionnaire and a physical examination designed to ensure that the donor is healthy, both for the plasma donated and for the donation procedure. During this process, donors are provided information about plasma donation including: general health parameters; tests that are performed both to ensure the safety of the plasma collected and that the donor is healthy to donate; and any risks associated with donating plasma (informed consent). The one-to-one opportunity for the prospective donor to be interviewed and examined by the center's clinical/medical personnel is considered most important in determining the donor's fitness for donation. This time also is used to help educate the donor about the center's deferral policies as they relate to health. For example, the donor is informed that the trained center staff will monitor the donor's plasma protein levels to ensure that the donor replaces proteins lost in the plasma donation. If the plasma protein drops below a certain level, the donor will be deferred from donating until an acceptable plasma protein level returns.

In addition to monitoring protein levels, the center personnel provide guidance on the importance of maintaining a healthy diet with adequate protein and fluids. This helps minimize the

possibility of the donor's level dropping below the acceptable level and encourages donors to make healthy food choices. Donors are asked about medical treatments and medications, as this information may point to an underlying condition that would indicate a potential difficulty with the donation. While the donor answers a donor history questionnaire at each donation, it is in the context of the physical examination (performed initially before a donor starts a donation program and at least annually thereafter) that valuable information is obtained about the donor's health that helps the center determine

It is important to note that donor education is of paramount importance. However, center staff are careful not to cross the line between education and diagnosis.

whether the donor is healthy enough to donate and provides the center the opportunity to educate the donor about how to maintain a healthy lifestyle.

One of PPTA's voluntary standards is the Donor Education Standard. This standard requires that plasma collection centers provide information to the donor regarding risk behaviors (protecting the safety of the plasma) and also encourages that information be provided on steps to be taken by the donor to have a healthy lifestyle (helping to protect the donor.) This information may include pointers on nutrition, hydration, and smoking cessation.

It is important to note that donor education is of paramount importance. However, center staff are careful not to cross the line between education and diagnosis. Whenever a question arises as a result of the physical examination, test results or medical history, the donor is referred to his personal physician. In fact, it is common practice to include the donor's physician in deciding whether the donor can start or continue a plasmapheresis program whenever there is a question of whether or not the donor is healthy to donate. If a prospective donor does not have a personal physician, he is referred to local clinics.

Concern about the safety of the donor continues to the plasmapheresis procedure itself. Donors are constantly observed and monitored while donating. Plasma donation is a very safe process, in large part because of the care exerted by the staff and the elaborate safety and quality measures that have been developed through regulation, voluntary industry standards and best industry practices.

Donors are the cornerstone of our industry. Without donors committed to participate, there would be no plasma protein therapies for the patients whose lives depend on them. Keeping donors healthy through education and monitoring is an important function of the medical staff of the collection centers. Healthy donors are in everyone's best interests, and nothing is taken more seriously by plasma collection facilities than the safety and welfare of plasma donors. ☞

MARY GUSTAFSON is PPTA's vice president, Global Regulatory Policy and JOSHUA PENROD is PPTA's vice president, Source.

PPTA's Medical Directors Task Force contributed to this article. The Task Force consists of Doctors MARIA GUDINO (Baxter BioLife), MARILYN ROSA-BRAY (Biomat USA), SHAILESH CHAVAN (Biotest), TOBY SIMON (CSL Plasma), TIMOTHY REESE (PlasmaCare), DENNIS THOMAS (Octapharma), WOODY JACKSON (Talecris Plasma Resources).

LEADING IN RESEARCH: LEADING IN SAVING LIVES

PPTA's Pathogen Safety Steering Committee (PSSC)

BY ILKA VON HOEGEN, PH.D.

THE PATHOGEN SAFETY STEERING COMMITTEE (PSSC) is one of the earliest and most experienced committees, with a predominant presence within the PPTA organization. Many of its members have contributed to the committee's success since the early days of the Association's existence. The highly experienced, well-seasoned PSSC members take special pride in the proactive approach they take at increasing the margin of safety of the therapies they manufacture, most importantly, the development and introduction of voluntary standards for nucleic acid testing (NAT) testing for HIV, hepatitis B (HBV) and hepatitis C (HCV), which preceded the implementation of the first mandatory NAT testing for HCV in the European Union in 1999. Furthermore, PPTA member companies introduced a 60-day inventory hold for plasma donations to minimize the risk of "window period" donations entering a plasma manufacturing pool. It also allows for the discarding plasma prior to manufacturing, if post-donation information becomes available that would disqualify the donation.

The overall goal of the PSSC is to provide data for patients, healthcare providers, and regulatory authorities to demonstrate that plasma-derived medicinal products are manufactured with the greatest safety margin.

One of the most significant programs that the PSSC led was the development and adoption of a voluntary standard for Parvovirus B19 in 2000. This effort is an example of where the plasma industry, through the coordination of the PSSC, took the lead in advance of international regulatory authorities. When the standard was developed, the PSSC concluded, based on scientific data that a cut-off level for Parvovirus B19 DNA of 10^5 IU/ml in the plasma production pool was the right cut-off to ensure safe therapies without unnecessary loss of plasma. The standard was established because PPTA member companies demonstrated that robust virus removal steps in their manufacturing processes had the capability to remove a virus load to a much greater magnitude than the 10^5 IU/ml level with minimal plasma waste. Since its introduction, PPTA member companies have generated an abundance of data demonstrating the value of this

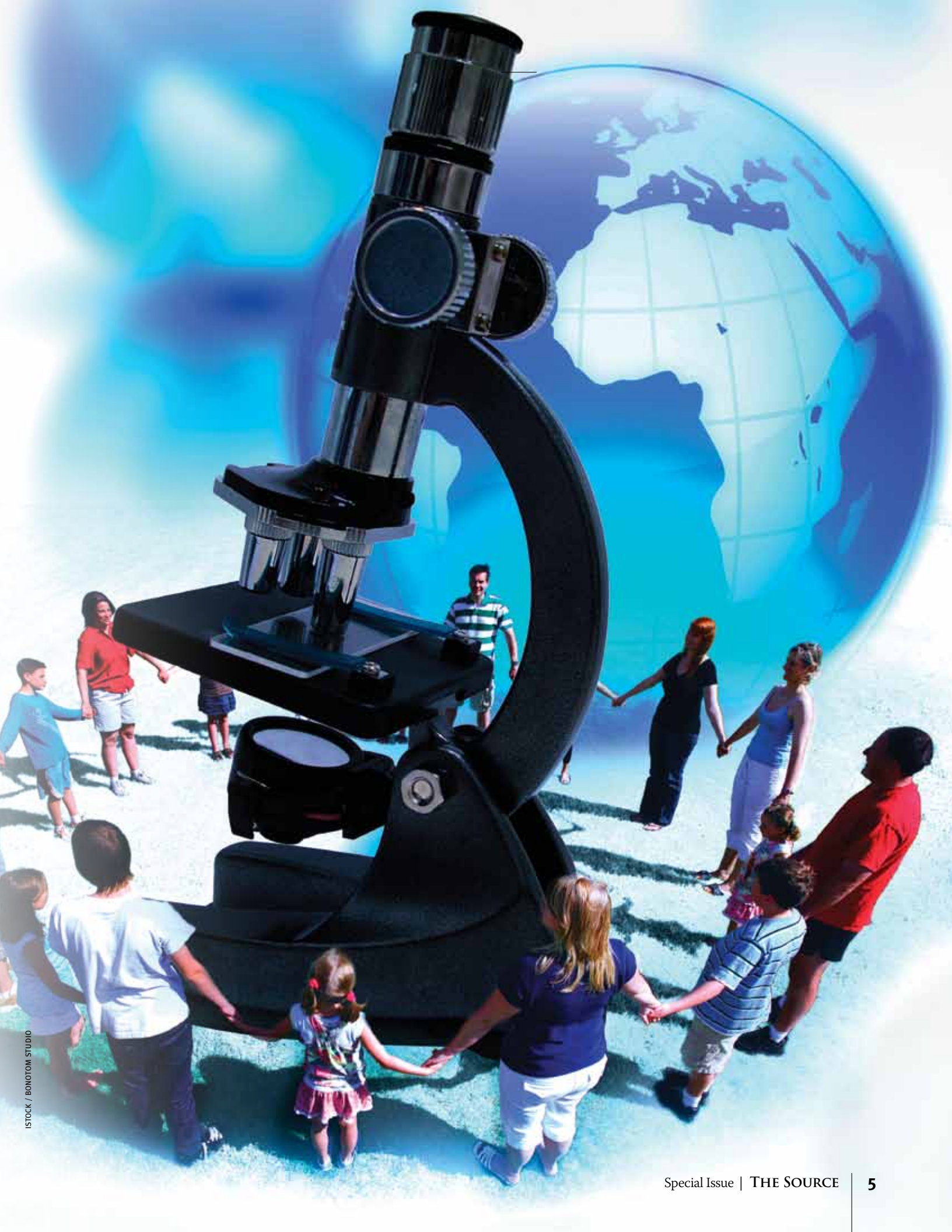
voluntary standard. In the past years, regulatory authorities followed the PPTA initiative and requested an even stricter cut-off limit of 10^4 IU/ml.¹

PSSC Works Collaboratively With Regulatory Authorities

When in 2003 West Nile Virus (WNV) started to spread across the U.S. raising concern about the safety of plasma protein therapies, PPTA responded immediately to this challenge by compiling existing data and also proactively generating new data demonstrating that plasma protein therapies are safe with respect to WNV. The newly generated data for WNV inactivation confirmed the predictions of the model virus concept. In addition, the PSSC worked with the U.S. Food and Drug Administration (FDA) to ensure clear communication on this issue. As a consequence, U.S. regulatory authorities implemented specific safety measures for labile blood products, but refrained from introducing comparable measures for plasma protein therapies in acknowledgement of the scientific evidence PSSC provided.

When it first appeared, variant Creutzfeldt Jakob





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Lothar Biesert



Thomas R. Kreil



Herbert Dichtelmüller

Disease (vCJD) had not been transmitted through transfusions. Nevertheless, PSSC members collaboratively generated data on the clearance of prion proteins by the manufacturing process and facility cleaning procedures either through individual companies or as a collaborative PPTA effort². When it appeared that vCJD may be transmitted by blood transfusion, concerns were raised that it could be also transmitted by plasma protein therapies. With the recent discovery of a hemophilia patient in the United Kingdom whose autopsy demonstrated presence of abnormal prion proteins in the spleen, the concern for transmission of vCJD was heightened, particularly for the hemophilia community. To address this concern, PSSC presented data at a FDA Transmissible Spongiform Encephalopathic (TSE) advisory committee in June 2009 that reiterated the efforts PPTA member companies are taking to reduce the risk of the vCJD threat to our patients. These efforts included additional controls on the plasma donor population, increased diligence on the sourcing of the production of raw materials to reduce the opportunity for the introduction of prions in the production systems and, finally, the PSSC provided its most up-to-date scientific evidence demon-

strating effective removal of prions in the production processes.

Over the past 15 years, PSSC and the industry have provided leadership to the regulatory landscape by introducing voluntary standards as a collaborative initiative, as well as proactively working with regulatory authorities and patient organizations to ensure the safety of the products. The revised European Medicines Agency (EMA) Guideline on Plasma-derived medicinal products 269/95, which is currently under discussion, reflects the joint effort of regulatory authorities and industry to develop robust regulatory guidance.

In conclusion, a number of pathogen associated challenges have been encountered, such as WNV, severe acute respiratory syndrome (SARS) or vCJD. Thanks to the excellent work of the PSSC in collaboration with regulatory agencies and other stakeholders, none of these challenges has substantiated itself to put patients at risk.

The Role of PSSC

PSSC plays several roles within the PPTA including 1) providing the experts who generate scientific data for regulatory policy mak-



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Albrecht Groener



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Rodrigo Gajardo




Juan I. Jorguera



Douglas Lee

ing, 2) representing PPTA within the scientific community, 3) participating in communications to stakeholders regarding the safety of plasma protein therapies and 4) responding to immediate challenges imposed by existing or newly emerging pathogens. Particularly with respect to the latter, the focus of the PSSC over the years has changed from reactive initiatives driven by immediate public concerns towards that of a more strategic organization focused on the overall public health of our patient and donor communities. This change in direction is illustrated in efforts of the committee by providing data either in the form of peer reviewed publications^{3, 4}, or by presentations at scientific congresses.

Today, PSSC's mandate is to provide state-of-the-art scientific evidence to reassure the patient and donor community and provide a basis for regulatory agencies to develop sound and reasonable policies. Even without immediate threats through known and emerging pathogens, PPTA's member companies remain committed to research and development. 

ILKA VON HOEGEN, PH.D., is PPTA Europe's Senior Director of Quality and Safety

¹Guidance for Industry Nucleic Acid Testing (NAT) to Reduce the Possible Risk of Human Parvovirus B19 Transmission by Plasma-Derived Products - <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

²Zerlauth, G NAT testing for source plasma. Presented to the 18. Meeting of the Advisory Committee for Blood Safety and Availability, (ACBSA), "Prioritizing Decisions in Transfusion Medicine: Transfusion Transmissible Diseases"; US Department of Health and Human Services, Washington DC, USA, January 23-24, 2003
Transcript: <http://www.hhs.gov/ophs/bloodsafety/pastmeetings/transcripts/20030123.html>

³Dichtelmüller et al. 2009 Robustness of Solvent / Detergent Treatment of Plasma Derivatives: A Data Collection from PPTA Member Companies. *Transfusion*: in press

⁴Collaborative Study of PPTA Member Companies on Virus Removal by the Steps of the Cold Ethanol Fractionation Process, manuscript in preparation

THANKS!

TO PLASMA DONORS
FOR HELPING HER GET
HER LIFE BACK

Without her immune globulin therapy, Judy Kozulak of Hockessin, Delaware, “would be barely functioning.” Diagnosed in August 2007 with common variable immunodeficiency (CVID) at the age of 51, there was finally an answer to why this once vital mother of two was unable to shake a string of serious illnesses that caused her health to spiral downhill and threatened her ability to work and raise her family.

Chasing and Conquering Illness

As a child, Judy suffered from asthma and allergies, which extended into adulthood and were treated with inhaled steroids. In her 40s, she started getting more and more sinus infections that were increasingly difficult to treat. In 2004, her IgG (immunoglobulin G) levels were tested and were within the acceptable range. However, by February 2005, Judy became extremely sick with the flu, which was the beginning of a year-and-a-half long battle with debilitating illnesses that eventually led to two sinus surgeries, a battle with the antibiotic-resistant staph infection MRSA, the need for a percutaneous intravenous central catheter (PICC) line for intravenous antibiotics and a stint on short-term disability from her job as an information technology (IT) project technician. Finally the infections started to clear up in September 2006, but she continued to “feel really lousy.” It was at that point that Judy sought a second opinion for the sinus infections that had been plaguing her. She consulted a new Ear, Nose and Throat specialist at Johns Hopkins University Hospital in Baltimore, Maryland and, after a full work up of her blood revealed that her IgG levels were low and that she exhibited a poor immune response to vaccines, she was officially diagnosed with CVID.

Now Judy infuses 23 cubic centimeters (CCs) of immunoglobulin (Ig) twice a week on Sundays and Wednesdays at home, having been trained by a nurse practitioner at her immunologist’s practice. Once she started taking the therapy, “It was incredible.”

“I’m not who I was, before I got sick,” says Judy, describing her former ability to bounce back easily from “weekend warrior” activities like painting and assembling complicated closet organizers. “But, I’m able to hold a job and I’m able to be a mother to my daughter and a contributing member of society.”

“Thanks” Plasma Donors

Judy also is quick to thank plasma donors who make it possible for her to lead a healthier, productive life. “With this donation, this gift from people giving plasma – they are doing for me what I can’t do on my own,” she says. “This is a huge gift whether [plasma donors] realize it or not.” Judy says there is no way to describe how she felt before she started her Ig therapy, explaining how she would fall asleep during rock concerts she attended with her teenage daughter. “I was barely

functioning as a parent and now I’m a mom again. I owe my life to the donors.”

Judy’s daughter Cara remembers that when her mother was sick, she had so much more responsibility than her teenage friends had to face. The honor student describes being overwhelmed by helping her mother manage the household. Judy adds that during the most severe time of her illnesses, she was “present but not accounted for” and is proud of Cara for, “doing the right thing.”



From Nursing to IT and Back

Having earned a Bachelor of Science degree in nursing and being licensed as a registered nurse, Judy worked in a critical care setting for many years, before taking

a 10-year break from work to concentrate on raising her children – now ages 23 and 18. Rather than going back into nursing when she reentered the workforce, Judy pursued her interest and aptitude for computers and technology, working for the local school district. Knowing the school district's budget was strained, Judy spent the spring of 2007 completing her nurse refresher course work, only to be laid off from her IT position just days after receiving her active Delaware nursing license in the mail. The timing was particularly fortunate, minimizing the amount of time Judy had to COBRA her state benefits to ensure that she was able to begin her twice weekly Ig treatments. COBRA is health insurance for those who lose coverage due to loss of employment. Judy describes her COBRA benefits as, "the most important monthly payment I made."

Today, she works as a nurse auditor at Thomas Jefferson University Hospital and has an even keener knowledge of the cost of healthcare in this country. Judy feels that she is "very, very lucky" to have good insurance coverage through the hospital.

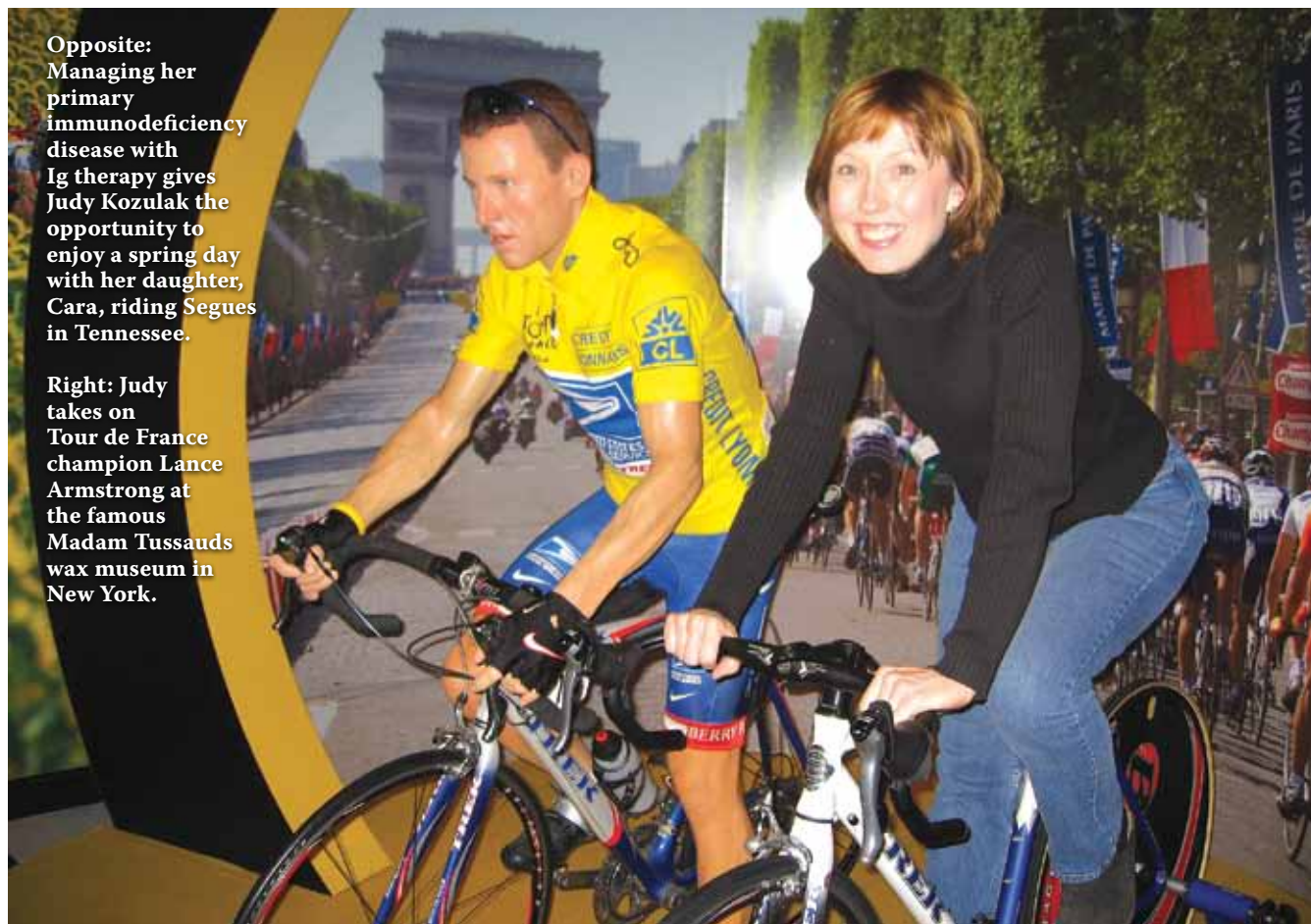
Giving Back

More recently, as a volunteer for the Immune Deficiency Foundation (IDF), Judy has organized an IDF support group for individuals and family members who live with primary immunodeficiency diseases (PIDD). The group draws attendees

from four states and had 17 individuals at the last meeting—the group's second—which featured Dr. Stephen McGeady, an associate professor with Thomas Jefferson University who also treats pediatric patients with immunodeficiencies at A. I. duPont Children's Hospital in Delaware. The first meeting helped attendees navigate the complicated maze of private and public insurance coverage for their chronic disease—a growing challenge for the community.

Judy describes health insurance coverage as the biggest and most stressful issue facing families coping with PIDD. "The product is available, but it has to do with reimbursement issues and getting insurance to pay." Many individuals with chronic illnesses like primary immunodeficiency diseases risk hitting the maximum lifetime benefit of their health insurance. "The problem is that you are backed into a wall and need the medicine to survive or to have any quality of life, and there are no easy solutions out there right now if you don't get insurance with a high lifetime cap or meet criteria for public assistance," she says. The situation scares Judy because she will need the therapy forever. "I'm very, very lucky insurance has stood by me – so many people don't have that." ☞

KYM H. KILBOURNE is PPTA's Assistant Director, North America Communications



Opposite:
Managing her
primary
immunodeficiency
disease with
Ig therapy gives
Judy Kozulak the
opportunity to
enjoy a spring day
with her daughter,
Cara, riding Segues
in Tennessee.

Right: Judy
takes on
Tour de France
champion Lance
Armstrong at
the famous
Madam Tussauds
wax museum in
New York.

THE EVOLUTION OF SAFETY IN SOURCE PLASMA COLLECTION

BY JOSHUA PENROD AND MARY GUSTAFSON

HUMAN PLASMA, INCLUDING SOURCE PLASMA, is the genesis for most plasma protein therapies. The millions of liters collected in the U.S. and Europe yearly sustain the lives of thousands of people worldwide. Fractionators process source plasma collected from more than 1,000,000 donors into numerous therapies, including immune globulins (IG), clotting factor concentrates, including Factor VIII and Factor IX, albumin, and other critical proteins. For the lives saved by these therapies, we should be grateful for our dedicated plasma donors. And for these reasons and the importance of the plasma itself, keeping donation a safe and enjoyable experience is of central importance.

Plasma donation today is safe for the donor and performed in an atmosphere that provides a donor-friendly experience. From collection centers that radiate a welcome, efficient, and friendly operating environment to highly monitored procedures designed to ensure that the plasma donation process is as safe as possible, donors have rightly come to expect a high degree of customer service from donation centers. Indeed, the plasma donation experience is predicated on the evolution of safety of the donation process itself, which helps foster a donor's commitment to a lifetime of donation.

This article will examine and summarize several areas (donor screening, automated plasmapheresis, and industry standards) in which donor safety has advanced. Advancement in these areas, coupled with comprehensive industry quality systems, and regulatory oversight in both the U.S. and Europe, represent the safeguards in plasma collection today.

Donor Screening

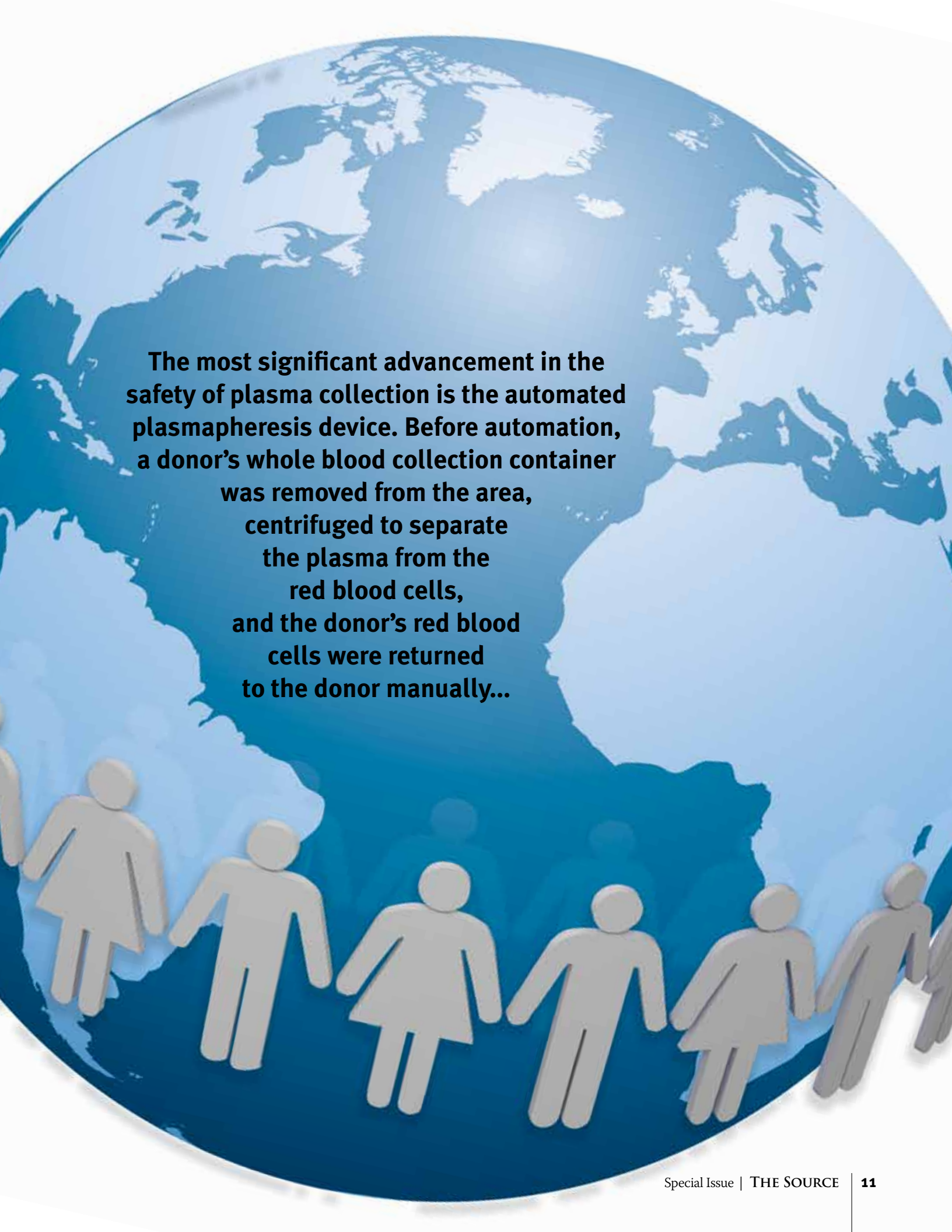
Prospective donors are greeted at the plasma center with a request for personal identifying information. This private information, including government-issued identification cards, permanent address and a photograph, may seem "too much information" for some. However, this information is necessary to ensure that the donor can be positively linked to his donated plasma. This link is necessary so that important information about the donor's health can be transmitted to him if necessary.

The prospective donor's information is checked with the National Donor Deferral Registry to determine whether the individual was deferred in the past because of positive test results. If that is the case, the person will not be accepted.

The donor next is asked to provide information to questions from a health history assessment tool. The questions cover the



ONURDONGEL / ISTOCK. BONOTOM STUDIO



The most significant advancement in the safety of plasma collection is the automated plasmapheresis device. Before automation, a donor's whole blood collection container was removed from the area, centrifuged to separate the plasma from the red blood cells, and the donor's red blood cells were returned to the donor manually...



donor's general health, medical history, medication history, and lifestyle. The questions are understandably intrusive. But honest and accurate responses to these questions are necessary to make sure that the donation process does no harm to the donor as well as to ensure that the donor does not harbor infectious agents that may be transmissible through plasma. The questionnaire, as well as other screening interactions, are conducted privately to ensure confidentiality.

At the donor's first donation and annually, the center's medical personnel perform a limited physical examination. The center physical is not intended to replace routine medical care nor is it intended to diagnose any condition. However, through examination of the donor's systems, i.e., head and neck, chest, extremities, abdomen, and reflexes, conditions that would prevent the donor's safe donation may be detected. The donor is also asked to provide his "informed consent" for donation after the donation process, testing, and risks of the donation process are explained to him .

At every donation, the donor's vital signs, i.e., blood pressure, pulse, temperature, are obtained, and the donor is weighed. The donor must have normal vital signs in order to donate. The donor's weight is used to calculate the amount of plasma that may be collected safely from the donor. The donor's finger is pricked to obtain a small amount of blood to determine the donor's red blood cell volume (hematocrit) and total protein. While there is minimal red blood cell loss in the plasmapheresis process, monitoring the hematocrit initially and over time is a measure of the donor's general health. Protein monitoring is important to ensure that plasma proteins, harvested during the donation process, are replaced

In all, the donation process is a complex but efficient process that enables donors to be screened and examined to donate and to exit the facility in an orderly, easy-to-follow manner.



as occurs in donors who maintain a healthy diet and lifestyle.

Following the successful completion of the screening process, the donor moves to the donation area, which may contain anywhere from a handful of donation beds to dozens. After the center staff situates the donor on a donation bed, the staff member will perform another check to ensure that the donor has been screened and that the donation station is properly prepared. The automated plasmapheresis device is then prepared for use, the phlebotomy is performed, and the plasmapheresis process is underway.

Automated Plasmapheresis

The most significant advancement in the safety of plasma collection is the automated plasmapheresis device. Before automation, a donor's whole blood collection container was removed from the area, centrifuged to separate the plasma from the red blood cells, and the donor's red blood cells were returned to the donor manually; this increased the risk of unmatched red cells being improperly returned. With the automated plasmapheresis process introduced in the 1980s, this type of incident can not occur as the donor's blood never leaves the circuit between the donor and the automated device. At any one time, only a small amount of blood (extracorporeal volume) is held outside of the donor's body and in the machine. Tubing and other plastic goods used in the plasmapheresis process are disposable and used once only. The system itself is monitored by a computer and carefully calibrated to ensure proper functioning and a smooth donation process. The devices have alerts and alarms that signal any interruption or aberration from the normal process. The automatic device incorporates safety in two critical areas: first, components exposed to bodily fluids are not reused and second, it eliminates the risk of human error in returning red blood cells to donors.

After the donor has completed his donation, the "disconnect" occurs. At this point, the trained staff will observe the donor, checking for signs of physical distress. All plasma donation centers have well-trained staff and are equipped to handle any emergencies, though adverse events are rare. Nevertheless, a watchful eye remains upon him for several minutes, after which the donor is allowed to leave.

Industry Standards

As a part of the International Quality Plasma Program (IQPP), certified centers are required to adhere to standards that help to further enhance the donation experience. These eight Standards comprise the IQPP, which has been built around areas identified by the industry as opportunities for improvement, not currently addressed by regulation.

- Use of the National Donor Deferral Registry
- Qualified Donor Standard
- Donor Education Standard
- Professional Plasma Collection Facility Standard
- Community-Based Donor Standard
- Quality Assurance Standard
- Viral Marker Standard
- Personnel Education and Training Standard

Three particular standards enhance the donor's experience and aid in further enhancing the safety of plasma collection. The Professional Plasma Collection Facility Standard sets guidelines for operational flow through the center, in addition to appearance and general upkeep. The Personnel Education and Training Standard helps to solidify center staff professionalism through training, education, and quality requirements. The Donor Education Standard helps educate donors about high-risk behaviors, and also encourages donor wellness through emphasizing the importance of a balanced diet and smoking cessation.

Summary and Conclusions

In all, the donation process is a complex but efficient process that enables donors to be screened and examined to donate and to exit the facility in an orderly, easy-to-follow manner. The automated plasmapheresis process is an extraordinarily safe and effective method of obtaining plasma from a donor and stands as the central pillar of safety in plasma donation. The well-trained plasma center staff, in conjunction with regulatory requirements, best industry practices, and industry standards, creates an environment in which plasma collection is not just performed, but perfected. ☞

JOSHUA PENROD is PPTA's Vice President, Source and MARY GUSTAFSON is PPTA's Vice President, Global Regulatory Policy

DECADES OF SAFE

BY PROF. ALBERT FARRUGIA, MARY GUSTAFSON AND ILKA VON HOEGEN, PH.D.

THE PLASMA PROTEIN THERAPEUTICS ASSOCIATION (PPTA) represents the plasma protein therapeutics industry, which manufactures plasma protein therapies by purifying them from human plasma and genetically engineered cell lines. These therapies are used to treat a number of diseases in which the naturally occurring plasma proteins are deficient or present in amounts lower than required by the body. These disorders include deficiencies of the blood clotting mechanism, leading to bleeding disorders such as hemophilia, or the lack of ability to synthesize antibodies, leading to chronic infections. In addition, healthy individuals such as travelers and pregnant women are protected from certain illnesses with the antibodies produced by the plasma protein therapy industry.

This article will explore the “Decades of Safety Measures” that the plasma protein therapeutics industry has put in place over the years to demonstrate its commitment to continuing safety. This industry is very different from traditional pharmaceuticals. Manufacturing plasma protein therapies that are infused or injected by patients results in the formulation of a unique class of biologics that are dissimilar from chemical compounds. PPTA member companies exemplify vigilance and innovation through the various safety measures that have been implemented over the decades. From, vein to vein—from the plasma donor to the patient—today’s plasma protein therapies represent a compilation of state-of-the-art collection, viral inactivation and manufacturing protocols that have been fine tuned over the decades.

Plasma Therapies Start with Healthy Donors

Blood component therapies and plasma protein therapies start with the same source material—blood and plasma donations from people who are willing to give of themselves to help others. It is important to make sure that donors of both blood and plasma are healthy to donate and that their donations do not harm the eventual recipients of therapies produced from their donations. To help ensure this goal, donors are selected by subjecting them to a series of steps to make certain that they are eligible to donate. Donors must meet certain criteria that include age, minimum weight and normal vital signs; the use of a health history questionnaire that screens for certain health conditions, diseases or behaviors that might indicate infections that would be transmissible to the recipients of therapies manufactured from their donated blood or plasma; and freedom from diseases transmissible by blood as determined by specific testing, eg., tests for hepatitis B and C and human immunodeficiency virus (HIV). For a potential donor of source plasma, used exclusively for the manufacture of plasma protein therapies, the donor is more closely monitored because the donation frequency and volumes collected exceed those for routine blood donation. Donors of source plasma have an initial and annual physical examination and are monitored for protein levels. In addition, PPTA maintains a voluntary standards program for collectors of source plasma, the International Quality Plasma Program (IQPP), which includes additional criteria and safeguards to ensure the health of donors and the safety of plasma protein therapies produced from source plasma. These standards include having donors be part of the community in which they donate, the qualification and testing of donors, and

standards that cover the suitability of the collection facility in which they donate. All of these measures help insure that plasma used in the manufacture of plasma protein therapies is of the highest quality.

In addition to ensuring the quality of donations, plasma for use in the manufacture of plasma protein therapies undergoes manufacturing processes beyond the selection of the donor and testing (the first and second legs of the tripod, see page 16). The manufacture of plasma protein therapies includes steps that further ensure the safety and purity of plasma protein therapies. Some of these steps are integral to the process of separating and purifying the proteins; some are added specifically to eliminate pathogens that inadvertently may be in the plasma. These processes are effective for known and unknown pathogens.

Plasma Protein Therapies Treat Rare, Chronic, Genetic Diseases

The patients treated with these therapies manufactured from human plasma are generally severely ill or at considerable risk of life-threatening illness. These conditions are rare, and some of them are poorly understood, making these patients vulnerable, and the therapies life-saving.

As these therapies are necessarily derived from biological sources, including human plasma and animal cell-lines, the therapeutic plasma protein products are at risk of

TY MEASURES

contamination by pathogens from the biological source material. These pathogens include viruses, bacteria and prions (abnormal proteins which can self-replicate and cause lethal diseases of the brain). Such contamination still constitutes a rare but observable risk for patients receiving blood transfusions. In addition, biologically-derived therapies such as blood are vulnerable to contamination by emerging pathogens which are still unknown but which can, nevertheless, cause disease. For example, over the past ten years, a virus, previously unknown in the United States but prevalent in Africa and the Middle East, entered the United States and ultimately, contaminated the whole blood supply. This virus, called West Nile Virus (WNV), caused illness, including some fatalities, in people given blood transfusions. On the other side of the Atlantic, some recipients of blood in the United Kingdom were infected with prions transmitting variant Creutzfeldt Jakob Disease (vCJD). In both these instances, the blood-borne infections were previously unknown, and infections were transmitted through blood transfusions before measures to minimize their risk were understood, developed and applied.

Why have the recipients of these therapies, when manufactured in the high-quality facilities of the PPTA member companies, not been infected with a single external pathogen for the past fifteen years? This has not been a fortuitous situation, but has been



the result of the commitment, investments and dedication shown by the industry as it has hastened to apply safety measures as risks have become known, and to apply prudent, precautionary and preemptive measures to minimize the effect of unknown and emerging risks. These measures, which have been introduced ahead of and in excess of measures legally required by government agencies, are linked together through the so-called "Safety Tripod" underpinning the safety of products. The combined effect of selecting safe raw material for manufacture, testing this material to exclude contamination and treating this material during manufacture to eliminate pathogens, results in the production of safe, high-quality and efficacious plasma protein therapies.

Measures Taken to Exclude High-Risk Donors

Through the decades as the epidemiology of infectious pathogens became known, the industry introduced measures to exclude the entry of high-risk donors into the plasma pool used to manufacture plasma protein therapies. For example, in 1982-83 PPTA companies introduced selection measures to exclude donors at high risk of HIV-AIDS before these were mandated by authorities or implemented by the whole blood sector. Once the risk factors associated with other diseases were known, appropriate selection procedures were also introduced. The first plasma borne pathogen which could be tested, hepatitis B virus (HBV), was tested with methods of increasing sensitivity by the industry in the 1970's, which also introduced testing for HIV and Hepatitis C virus as soon as these were available and ahead of government regulations. The testing for evidence of infections was strengthened with the introduction of nucleic acid testing (NAT) for the actual pathogens in the late 1990's, again ahead of regulators and leading to considerably enhanced safety of the manufacturing pool. The possibility that other viruses, such as human parvovirus B19, may cause illness in the recipients of plasma protein therapies, led the industry to introduce this test in 2000, again in the absence of government regulation and similar measures in the whole blood sector.

These measures depend on knowledge of the epidemiology of pathogens and the availability of tests to screen them out. The minimization of risk from unknown and emerging agents, where scientific knowledge has not yet come to the stage of understanding how pathogens are transmitted and tested, depends on the processes which the industry has developed to eliminate pathogens through manufacturing steps which are designed for this purpose. These measures started to become available in the early 1980's and over the succeeding decade, they were rapidly adopted by the industry so that, by the early 1990's, the risk of plasma protein therapies from the known blood borne pathogens was immeasurably low. The processes introduced are very robust so that the emergence of WNV did not affect plasma protein therapies. While no biologically-derived product can be declared

risk free, the characteristics of pathogen elimination procedures gives us great confidence that future threats can also be avoided.

The products of the plasma protein therapeutics industry have a safety profile which exceeds that of most of the therapies of the other biological sectors and of the products of big pharma. This enviable position is the result of a commitment to product improvements and a state of constant vigilance to ensure currency in safety, quality and efficacy.

The PPTA Pathogen Safety Steering Committee (PSSC)

In 1994 the Virus Safety Working Group (VSWG (Later Pathogen Safety Steering Committee or PSSC) was established as the industry's scientific expert committee to address virus safety issues of plasma protein therapies on a global basis. The members of this PPTA expert group on pathogen safety are all well seasoned scientists striving to remain accepted members within the scientific community, while at the same time ensuring that within their commercial environment pathogen safety of plasma protein therapies is always addressed according to state-of-the-art developments in technology.

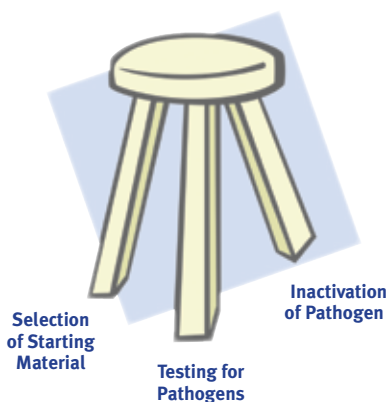
Over the years since its foundation the PSSC has established itself as the globally accepted industry expert group on issues related to the safety of plasma protein therapies. PSSC is responsible for the identification and prioritization of key safety issues. The experts monitor, assess and comment on newly emerging pathogens and are responsible for advancing the scientific credibility of the industry. The most important task for PSSC is the liaison with authorities on scientific issues including the initiation and supervision of task forces dedicated to specific targets, such as WNV for example.

PSSC is recognized by the U.S. Food and Drug Administration (FDA) as a valuable contributor to the discussions within the Blood Products Advisory Committee (BPAC), the Transmissible Spongiform Encephalopathy (TSE) Advisory Committee (TSEAC) and other FDA expert groups. Within the European Union regulatory framework PSSC is the scientific expert group in discussions with the European Medicines Agency's (EMA) Biotechnology Working Party and their TSE expert group. Within the World Health Organization (WHO) PSSC contributed to their TSE and NAT standard committees.

PSSC has had many achievements and successes over the years of which the introduction of industry wide standards for HIV, Hepatitis B virus (HBV), Hepatitis C virus (HCV) and Parvovirus B19 have to be regarded as the most significant initiatives to raise the credibility of the industry and assuring patients, physicians and regulators about the margin of safety of these often life-saving medicines.

The Parvovirus B19 standard can serve as an example of how a proactive industry initiative can assure stakeholders and at the same time hold up unnecessary regulatory constraints. The Parvovirus B19 standard

Safety Depends on Three Measures



was introduced in 2000 in reaction to concern about its impact to the patient community, particularly to pregnant women. The standard set a cut-off limit for Parvovirus B19 in the plasma pool of 10^5 IU/ml and has proven its value since its introduction, by simultaneously avoiding unnecessary loss of the precious starting material, human plasma. It is very unfortunate that despite the abundance of available experience over the years U.S. regulators have recently decided to require a cut-off limit of 10^4 IU/ml. European regulators have refrained from considering a similar approach in the context of the revision of the Note for Guidance on plasma-derived medicinal products (CPMP/BWP/269/95).

Sanitization Agents are Introduced

At the height of the discussion pertaining to the possible transmission of the vCJD agent by plasma protein therapies, the TSE Task force mostly composed of PSSC members undertook a comprehensive investigation of the inactivation of a model TSE agent using Sodium Hydroxide NaOH, the most commonly used sanitization agent. The study, which was published in a peer reviewed journal after its finalization, investigated the influence of concentration, temperature and time on the effectiveness of TSE inactivation by NaOH. This unique database of inactivation data was also intended to serve as a basis for additional company specific studies of combined cleaning and sanitization. The results were presented to U.S. and European regulators as well as at a number of international scientific events. Most importantly the study was helpful to prevent regulators to request segregation of production lines for European and U.S. plasma by demonstrating the effectiveness of cleaning and sanitization procedures. According to Dr. Harvey Alter, an infectious disease specialist at the National Institutes of Health in Bethesda, Md., solvent-detergent treatment of commercial plasma and its derivatives has established the principle that pathogen reduction of even a single blood component is enormously valuable and has simultaneously established the principle of preemptive pathogen reduction.¹ "Universal solvent-detergent treatment has rendered the formula that the formerly, most risky of blood transfusion products, plasma and plasma derivatives, will now be the safest," says Dr. Alter. "As blood transfusionists scramble to find a way to stop West Nile virus from whole blood and platelets, how reassured the plasma industry must have been to know they already had this agent preemptively covered. Those same measures would protect against Dengue in plasma or any lipid-encapsulated agent that threatens the blood supply."

In the past years a number of emerging infectious diseases have challenged manufacturers of plasma protein therapies. In case of an Influenza A virus or H5N1 (bird flu) pandemic it can

**Over the years
PSSC has
demonstrated
to regulators
and stakeholders
that the industry
has responded
vigorously and
vigilantly
to mitigate
virus transmission.**

be expected that 10 to 30 percent of donors would be lost temporarily, which would mean a significant, although, temporary reduction in supply of these life-saving medicinal products. In view of this threat, which has fortunately not yet manifested itself, PPTA launched a Pandemic preparedness website (www.ppta.pandemic.info.us) to inform all involved parties about the newest developments regarding H5N1 virus.

PPTA Sponsors Round Tables

In order to establish a globally operating system to monitor and react to emerging infectious diseases, PPTA sponsored two Round Tables in 2004 and 2005 with partici-

pation from WHO, FDA, EMEA, patient groups and industry. The discussions at the Round Tables were considered as a helpful tool to shape the understanding of a more precautionary, but reasonable approach to deal with emerging pathogens, for example Severe Acute Respiratory System (SARS).

Another initiative that demonstrated the benefit of a scientific approach beyond its purely scientific recognition is the industry-wide data collection of robustness studies with solvent detergent treatment. This data collection was initiated at a PDA Viral and TSE Safety conference in 2005, where regulators indicated their willingness to reduce the requirements for robustness studies with solvent detergent treatment if a comprehensive data base was available to them. The data base was greatly appreciated by regulators, although an additional caveat was added in that the data should be published in a peer-reviewed journal. The robustness of the data collection should be seen as the first step in an ongoing process, where industry-wide data bases could help to provide regulatory relief.

Over the years PSSC has demonstrated to regulators and stakeholders that the industry has responded vigorously and vigilantly to mitigate virus transmissions through plasma protein therapies. Regulators, scientists, consumer organizations, researchers and treaters have also made significant contributions over the decades towards improved safety. PSSC has established a proactive approach to respond to the challenges of pathogens following the precautionary principle, which is transparently discussed and developed with all involved parties. While in the beginning, PSSC actions were driven by immediate needs for action, PSSC today has increasingly taken the role of a group developing the scientific credibility with stakeholders and assuring the general public about the high margin of safety of the therapies PPTA members manufacture. ☞

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¹Taken from a presentation entitled, "A Reductionist's View of Pathogen Reduction," from the transcript of the 33rd meeting of the U.S. Department of Health and Human Services' Advisory Committee on Blood Safety and Availability, January 9, 2008.

ANN ROGERS

Executive Director, Delaware Valley Chapter (Pennsylvania) of the National Hemophilia Foundation

“THERE’S NEVER BEEN A BETTER TIME TO HAVE HEMOPHILIA IN THE U.S.,” says Ann Rogers.

With a personal and painful association with hemophilia, Rogers also is quick to stress that it is a very serious and complex blood disorder that is expensive to treat. As a mother who lost a son with hemophilia to HIV and who watches another manage a severe form of von Willebrand disease, she chooses to look at how far the community has come in the last two decades and to continually focus on the future.



Ann Rogers has been involved with the Delaware Valley Chapter of the National Hemophilia Foundation for 33 years.

What has been your history with hemophilia?

Since the beginning of factor concentrates in the early 1970s, we’ve seen an evolution in safety and efficacy of plasma protein therapies, which are life-sustaining, that is, we need them to control bleeding and we cannot live without them. We have watched the evolution of safe and effective therapies over 30 years of development and innovation from manufacturers around the world.

The HIV epidemic in the hemophilia community was a terrible time. We lost children, husbands and brothers due to contaminated factor concentrates. However, like many tragic events in history, there was a positive outcome from that tragic event—the development of safe, effective therapies. That positive outcome doesn’t balance our personal loss, but I do believe that

dark time in our history fueled the innovation more quickly. We will never forget what happened to us.

Today, we benefit as a national community of patients affected by bleeding disorders from that innovation. We now have therapies with smaller volumes that are safe and effective.

Today, children with bleeding disorders are healthy and many lead active, normal lifestyles and that is a major shift from previous generations. While the therapies are not a cure, they are like a cure, because for many patients with bleeding disorders they do a great job of controlling bleeding or preventing it altogether. Good medical management and the evolution of plasma protein therapies have changed the lives of people with hemophilia and von Willebrand disease in a dramatically positive way.

Independence Hall, shown in the background, is a U.S. national landmark located in Philadelphia, Pennsylvania.

The Delaware Valley is a term used to refer to the metropolitan area centered on the city of Philadelphia, Pennsylvania.

What do you see as the biggest concern of the hemophilia community today?

Today, our community still has big issues, but the issues are centered on how to maintain access to these life-sustaining therapies. The critical question is: How do we maintain access to care and medicine? My firm belief is that we achieve this through legislation at the state level by establishing hemophilia standards of care. We must legislate what we really need as patients with bleeding disorders. In Pennsylvania we are doing that with the introduction of HB 620 and SB 668, The Hemophilia Standards of Care Act. This proposed legislation, when passed by the General Assembly, will ensure that patients with hemophilia and von Willebrand Disease maintain:

- Access to all U.S. Food and Drug Administration (FDA)-approved plasma protein therapies for the treatment of hemophilia and related bleeding disorders.
- Access to the seven hemophilia programs in Pennsylvania.
- Access to the coagulation laboratories associated with the hemophilia programs in Pennsylvania. Outside laboratories contracted with insurance companies in Pennsylvania cannot perform specialized coagulation studies accurately or in a timely fashion. We need to have our laboratory studies done at the treatment centers.
- Access to options in pharmacy and home supportive services, including "full service pharmacies," 340B and mail order pharmacies. Patients' pharmacy needs can change over time. For example: An adult patient may be able to use a mail order pharmacy for his hemophilia needs, which reduces the cost for the insurance company. However, if that patient has shoulder surgery and can't self-infuse, he may need supportive care at home, including a homecare nurse, as ordered by his hemophilia

physician. We must make sure that insurers have different pharmacy options available as the needs of patients change. We have hundreds of examples of bleeding disorders patients in Pennsylvania who can't access the services they need at any given time.

In Pennsylvania, we don't believe that insurers are deliberately trying to hurt us. We believe they are trying to apply a disease management model that has worked well with other chronic conditions, such as asthma and diabetes, to patients with hemophilia. Disease management models have been very effective with some disease states, in reducing costs to insurers, while preserving the integrity of medical care. But it doesn't work well for patients with hemophilia. In fact, placing restrictions on the type of medicine (plasma protein therapy) a person can have, applying "fail first" requirements or preferred formularies, as well as restricting the amount of factor concentrates a patient can have on hand at home, has placed many people with hemophilia at risk.

How long have you been involved with the Delaware Valley Chapter?

My oldest son was born in 1976 with hemophilia and within a year we got involved in the Delaware Valley Chapter. My husband and I both have served on the board. In 1992 my son died of AIDS-related complications. I then took on the role as the Chapter Executive Director. Additionally, I have served in various leadership positions with the National Hemophilia Foundation (NHF), including being president of the Chapter Staff Organization of the NHF for six years. I have two other sons; the youngest has severe type three von Willebrand disease. ☾

KYM KILBOURNE is PPTA's Assistant Director,
North America Communications

"Today, our community still has big issues, but the issues are centered on how to maintain access to these life-sustaining therapies."



Far left:
A chapter family
after successfully
catching a fish.

**Left: Children with
bleeding disorders
are healthy and
many lead active,
normal lifestyles.
Seen here are
children from the
Delaware Valley
Chapter community
enjoying canoeing
on the river.**



DONOR EPIDEMIOLOGY

Top of Mind for Plasma Protein Therapeutics Industry

BY JOSHUA PENROD

DONOR EPIDEMIOLOGY STANDS AS AN IMPORTANT MATTER for the plasma collection and fractionation industry. It has been brought back to the forefront by the institution of the European Medicines Agency (EMA) Epidemiology Guideline EMEA/CPMP/BWP/125/04 and ongoing industry efforts to address this complex, nuanced and global issue. In recent months, the PPTA Epidemiology Task Force (EPITF) has discussed and analyzed several different approaches, which can provide a solution and a system that can accommodate the many diverse issues in donor epidemiology and the policies regarding it. In addition, the 2008 Business Forum in Montreal featured a panel discussion of epidemiology by industry experts, which served as a vehicle for the membership's better understanding of current undertakings. This article will summarize the current work of the EPITF, the Business Forum discussion and briefly outline some general next steps to be taken.

EPITF Activities

The PPTA Viral Marker Standard (VMS) has been in place since 1999. This Standard, an integral component of the International Quality Plasma Program (IQPP), uses plasma center collections and average industry rates for HIV, hepatitis C, and hepatitis B to create limits within the IQPP certification program for centers to use as a guide for determining epidemiology within the center. One of the more important features of the VMS is its use of donations as a denominator for the calculated rates, along with the distinction of applicant and qualified donations. The limits themselves are controlled by the industry average and are adjustable for population trends.

The VMS, therefore, is a form of statistical and quality control over some of the steps in the complicated plasma manufacturing process. It has been used with great success for nearly a decade and has helped the industry to ensure collection from a low-risk donor population. It has also helped instill stakeholder confidence in the industry's processes and high-quality products.

In contrast, the EMA Epidemiology Guideline uses a different system for calculation of viral marker rates. Its measures of prevalence and incidence are based on the number of donors, rather than donations as under the PPTA VMS system. Similarly, instead of applicant and qualified categories, the Guideline uses First-Time and Repeat donors. With these definitions, a Repeat donor is a donor that has previously donated at any time, in contrast to the qualified category in the IQPP, which has a six-month period in which a donor remains qualified.

In 2006 PPTA created a new template and system for data collection by the member companies beginning in 2007. The new web-based system allowed for simultaneous collection of data based both on the IQPP and EMA definitions and comparisons of rates. At this point, with only a single year's worth of data to review, no trending or tracking has been undertaken, although with the completion of the 2008 data set, more insight will be attained.

With all of the data category requirements, the EMA Guideline requires that the holder of a plasma master file (PMF) be able to report on and interpret a number of different elements—for both source and recovered plasma. First, the PMF holder is responsible for observing and analyzing individual plasma center epidemiology; second, the PMF holder is expected to facilitate tracking and trending of these data. Lastly, the PMF holder is to establish a range of limits for acceptability of epidemiological data. This final point has been the area of the most recent discussions for the industry.

The establishment of an industry-wide system for use in reporting and interpreting epidemiology data has therefore occupied the interest of many of the industry's leading experts. The discussions and consensus-building approach has been complex, and its importance is magnified due to the many different technical challenges, regulatory scrutiny, and policy implications. The two main lines of thinking include the residual risk (as used currently in the VMS) and end-product (currently

in development, and which captures the complete manufacturing and testing paradigm used by the industry) approaches. The EPITF and others are currently examining and these approaches in an effort to create an updated system that addresses all of the industry's and regulatory authorities' concerns.

Business Forum

Because of the member companies' interests in the epidemiology issues, and the ongoing dialogues with regulatory authorities and within the industry, the PPTA Source Business Forum held a panel discussion focusing on epidemiology. Specifically, the panel addressed the EMA Guideline, the EPITF's efforts, and the Guideline's impact in the EU and the U.S. The four distinguished panelists noted some of the more pressing concerns entwined in the debate:

- The importance of having global epidemiological limits established to ensure collection from low-risk donor populations to avoid different interpretations by national regulatory authorities on the meaning and impact of epidemiology.
- The inclusion of a holistic approach and a context that recognizes safety and quality of plasma and finished product at each and every step in the chain.
- To ensure that any industry-wide system will be consistent with the policy concerns and requirements of various regulatory authorities.

Outcomes and Next Steps

The EPITF will be preparing an industry position for consideration. The EPITF outcomes will be the basis for the future decision-making and industry policies, such as the VMS, and the industry position for purposes of interacting with regulatory authorities. Several of the most important industry touchstones for incorporation in the future direction of the management of the epidemiology issue, both from a regulatory and industry operations perspective are:

- Industry's vigilance and quality and safety of plasma and finished products.
- The need for healthy, committed donors.
- The ability for the industry to maintain a global, holistic system that incorporates the industry's best thinking and best efforts.
- The proper approach and methods taken in—and feasibility of—constructing a singular industry solution.
- The importance for the industry in having an approach that equitably treats all starting materials.

The EPITF has not yet reached a conclusion for its recommendation. A preliminary meeting with regulatory authorities is currently being planned to exchange ideas and current thinking regarding the industry position and regulatory input. Over the next several months, the EPITF and other related industry working groups will move toward a consensus establishing the industry's position with regard to the complex epidemiology issue. ☞

JOSHUA PENROD is PPTA's Vice President, Source.

PPTA STAKEHOLDER REPORT

November 2007

PLASMA COLLECTION PRACTICES, concerns regarding centers located along the U.S.-Mexican border and questions surrounding plasma donated by Mexican nationals in those centers were the principal subjects of a Stakeholder Meeting held on November 14, 2007 in Washington, D.C. PPTA was encouraged by the excellent attendance, which included patient group representatives from the hemophilia, alpha-1, primary immune deficiency, and Guillian-Barré Syndrome communities, as well as a representative from the U.S. Food and Drug Administration (FDA) and leadership staff from PPTA member companies that manufacture therapies for U.S. distribution.

After a brief welcome and discussion of the genesis of this meeting, patient group representatives addressed participants with their chief concerns and questions for discussion during the meeting, paving the way for an open dialogue on these serious and sensitive issues. Key topics and questions raised during this dialogue included the need to clarify the definition of U.S. plasma; patient access to therapies, primarily intravenous immunoglobulin (IVIG); safety of plasma-derived therapies; viral marker rates for border centers; the potential for donor exploitation; donor incentives; patient and public perception; and the opportunity for greater communication and awareness surrounding source plasma collection practices and plasma protein therapy fractionation.

PPTA staff presented information to educate stakeholders about the process of source plasma collection in the U.S., the International Quality Plasma Program (IQPP) standards, the viral marker standard, the safety of plasma protein therapies and observations and data regarding border collection center practices, donors and plasma that addressed these stakeholder concerns by fully exploring the processes and standards, and answering any question.

Emphasizing the industry's concerns for safe, high-quality plasma



protein therapies, PPTA staff presented information on each facet of plasma collection in the U.S., from donor eligibility requirements, to medical screening, the health history questionnaire, risk-behavior education and specifics of IQPP, which certifies plasma collection centers that meet voluntary standards that exceed those required by government regulators. Key components of IQPP include the layered approach to selecting donors, who need to successfully complete the following before becoming classified as a "qualified donor:"

- Only people lawfully permitted to be in the U.S. can give plasma in a FDA-licensed plasma collection center, and all individuals are asked to produce valid, government-issued photo identification.
- In addition to verifying their identity, donors must provide proof of a local residential address in a defined area near the plasma collection center. Plasma collection center staff verify the information against a list of known, transient addresses such as temporary housing and hotels prior to permitting the donation.
- All new donors are checked against the National donor Deferral Registry (NDDR) database, which contains information about persons permanently deferred from donating plasma due to positive test results for HIV, Hepatitis B and Hepatitis C. Use of the NDDR prevents donors who have been deferred at any IQPP-certified plasma collection center from donating at any other IQPP-certified donor center. The NDDR is a first-of-its-kind program in the source plasma collection industry.



- Only individuals who have completed two, separately administered medical screenings, passed a physical exam and have been tested and found negative twice for HIV, Hepatitis B and Hepatitis C can donate plasma for therapeutic use. If a donor has lapsed in giving plasma for more than six months, the entire medical screening, physical examination and testing process is repeated before those plasma units are used to produce plasma protein therapies. No plasma from one-time donors is used to manufacture life-saving therapies.
- In addition to ID verification, medical screening and plasma testing, it is important that plasma is collected from a low-risk population. IQPP-certified plasma collection centers engage in educational programs and follow-up assessments with all new donors regarding high-risk activities to identify potential behavioral risks that could increase the donor's likelihood of contracting an infectious disease. Those potential donors who confirm to being involved in defined high-risk behavior activities are deferred from donating.

A veteran, independent IQPP auditor provided context and insight on both the corporate and plasma collection center audits that are performed to evaluate centers from IQPP certification. A frank discussion of the meticulous nature of the audits, the audit process and procedure, and what some of the audit finding might be was conducted.


Further it was shared that in addition to IQPP audits, the U.S. FDA, European Agency for the Evaluation of medicinal Products

(EMA), country-specific and corporate audits all contributed to a heightened level of quality and safety at U.S. plasma collection centers, including those near the border.

Dr. George Schreiber, a biostatistician from Westat, Inc., presented detailed statistical information regarding viral marker rates and alert limits for HIV and Hepatitis B and Hepatitis C with respect to the window-period, and factors that contribute to residual risk for plasma protein therapies. He stressed that the layers of safety built into the plasma collection, pooling and fractionation steps lead to high-quality plasma-derived therapies. His data revealed industry progress in reducing residual risk for pathogen transmission over the years and provided data comparisons to demonstrate quality and safety improvements.

PPTA staff continued by discussing in detail the fractionation process and methods and effectiveness of pathogen reduction and elimination. Emerging infectious agents were discussed, as well as the roles of public health organizations such as the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) in surveillance and epidemiology, and PPTA's Pathogen Safety Steering Committee in remaining vigilant to challenge pathogen clearance procedures when new entities are identified.

Arguably the most anticipated report of the day focused specifically on plasma collection center practices in the Texas border centers and the comparison of viral marker rates of donors in those centers versus the U.S. as a whole. The epidemiological data confirmed that the plasma collected in the Texas border centers is high in quality and that more than 90 percent of donors in those centers regularly give plasma. Conditions for earning a visa into the U.S. were discussed, including the U.S. requirement for visa holders to be employed, and the costs associated with obtaining that visa, which provides limited access into the country. Further, the existence of a family atmosphere at the Texas border centers where donors expressed that they feel that they are helping others, while being fairly compensated, was reported.

The meeting concluded with Stakeholders expressing their appreciation for being able to meet to discuss these important issues. It was requested that industry and PPTA continue to expand upon and enhance the current communications with patient groups in order to build education and awareness surrounding access to plasma protein therapies and to help them better understand the process of plasma donation and fractionation. 

THE FACTS ABOUT...

SOURCE PLASMA DONORS

THE QUALITY AND SAFETY OF PLASMA-DERIVED and recombinant analog therapies (collectively referred to as plasma protein therapies) is the highest priority for manufacturers worldwide that produce these life-saving medical treatments. While the U.S. and European government authorities license and regulate all plasma collection and manufacturing operations, the industry has gone beyond those requirements by proactively developing rigorous, voluntary standards for certification that help ensure that plasma protein therapies are of the highest quality. These robust programs are in their second decade, showcasing the industry's commitment to continuous improvement and to helping ensure the availability of effective and high-quality plasma protein therapies.

One vital component of ensuring that plasma-derived therapies are of the highest attainable quality is to place strict eligibility requirements on donors giving plasma in the 400+ government licensed and International Quality Plasma Program (IQPP)-certified plasma collection centers located in the United States, Europe and Canada. Those layered requirements follow:

- Only people lawfully permitted to be in the country can give plasma in a government licensed plasma collection center, and all individuals are asked to provide a valid, government-issued photo identification.



Source Plasma Donor Eligibility

- 18 years-old *
- Weigh at least 110 pounds (50kg)
- In good health
- Meet proper identification and residency requirements
- Live within a defined recruitment area of the collection center

*This may vary by state or country

- In addition to verifying their identity, donors must provide proof of a local residential address in a defined donor recruitment area near the plasma collection center. Plasma collection center staff verify the information against a list of known, transient addresses such as temporary housing and hotels prior to permitting the donation.
- All new donors in the U.S. are checked against the National Donor Deferral Registry (NDDR) database, a leading-edge program containing information about persons permanently deferred from donating plasma due to positive test results for HIV, hepatitis B (HBV) and hepatitis C (HCV). The NDDR prohibits deferred donors from giving plasma at any IQPP-certified plasma collection center. The NDDR is a first-of-its-kind program in the source plasma collection industry.



- Potential donors must pass two separate medical screenings and testing for HIV, HBV and HCV on two different occasions. Only after those satisfactory screenings and negative test results does that person become a Qualified Donor.

If a donor does not return within six months, that person loses his/her Qualified Donor status and must qualify again.

Therefore, plasma from a one-time-only donor (even when all test results are nonreactive) cannot be used for further manufacture. The standard results in committed donors and eliminates the risk that so-called “test-seekers” are accepted.

- In addition to identification verification, medical screening and plasma testing, it is important that plasma is collected from a low-risk population. New donors are required to engage in an educational program and follow-up assessment regarding HIV/AIDS and activities that place them at risk for HIV/AIDS. The educational program also encourages donors to lead a healthy lifestyle. Those potential donors, who acknowledge being involved in defined high-risk behaviors, are deferred from donating.

The plasma protein therapeutics industry is proud of its leadership in establishing plasma collection standards, which further ensure that only plasma from healthy, committed individuals is used to manufacture the replacement therapies that enable patients worldwide to lead healthier, productive and fulfilling lives.



International Quality Plasma Program

The Worldwide Standard for Plasma

	SOURCE PLASMA DONATION		WHOLE BLOOD DONATION	
	U.S.	EUROPE	U.S.	EUROPE
REGULATED FREQUENCY	Up to twice a week with two days in between	Up to twice a week, but limited to 33 times per year	Once every 56 days	Up to 6 times a year for men and 4 times a year for women, minimum of 2 months in between
NUMBER OF FACILITIES*	400+	27	2,000	No data available
USES	Produce life-saving therapies	Produce life-saving therapies	Primarily for transfusion medicine in local hospitals	Primarily for transfusion medicine in local hospitals
TIME TO DONATE	1.5 to 3 hours	1.5 to 3 hours	Less than 1 hour	Less than 1 hour
UNITS DONATED**	18.8 million	1.4 million	14 million	18.8 million

*Source plasma centers that are government licensed and IQPP-certified. Blood center number from FDA registered blood establishments (June 24, 2008 FR notice) and does not include mobile collection units.

**Figure refers to number of source plasma donations made in government licensed and IQPP-certified centers in 2008. U.S. blood donation figure cited from FDA and the American Red Cross websites. European blood donation figure cited from the Council of Europe (2003).

SOURCE PLASMA DONORS

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PPTA Japan
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Tokyo 150-6018 Japan
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THE FACTS ABOUT...

QSEAL INDUSTRY STANDARDS

A COMPREHENSIVE, RIGOROUS INITIATIVE

to strengthen the continued safety and quality of life-saving, plasma-derived and recombinant analog therapies (collectively referred to as plasma protein therapies) worldwide, the Quality Standards of Excellence, Assurance and Leadership (QSEAL) certification represents steadfast industry commitment to producing safe plasma-derived therapies worldwide.

Safety is the number one priority of the plasma protein therapeutics industry. People around the world depend on therapies derived from human plasma proteins to treat conditions such as hemophilia, primary immunodeficiencies, alpha-1 antitrypsin deficiency, and other life-threatening diseases or serious medical conditions, including burns and shock.

The Plasma Protein Therapeutics Association (PPTA), on behalf of the manufacturers of these life-sustaining therapies, supports efforts by regulatory agencies to establish requirements to ensure the safety of these products. Nevertheless, PPTA has adopted voluntary standards that go beyond established government regulatory requirements and further define the regulations as they apply to the production of plasma protein therapies.

The QSEAL certification is based on an independent, third-party evaluation and recognizes strict adherence to a set of voluntary standards, which underscore the industry's quality and safety commitment to patients who rely on essential plasma protein therapies.

In order for a manufacturer of plasma therapies to become QSEAL certified, each one of its facilities must pass inspection by an independent auditor for adherence to the QSEAL Standards. To maintain QSEAL certification, audits are required every two years.

QSEAL-certified Companies

- Baxter BioScience
- Biotest AG
- CSL Behring
- Grifols, S.A.
- Kedrion
- Talecris Biotherapeutics



The primary focus of the QSEAL audit is to assess adherence to the following standards:

QUALIFIED DONOR

Potential donors must pass two separate medical screenings and be tested for HIV, hepatitis B and hepatitis C on two different occasions. Only after those satisfactory screenings and negative test results does that person become a Qualified Donor. If a donor does not return within six months, that person loses his/her Qualified Donor status and must qualify again.

This standard means that plasma from a one-time-only donor (even when all test results are nonreactive) cannot be used for further manufacturing. The standard results in committed donors and eliminates the risk that so-called "test-seekers" are accepted.

VIRAL MARKER

It is important that donations are collected from a low-risk donor population. Although every donation is tested for transmissible disease, the Viral Marker Standard represents an industry continuous quality improvement measure by assuring that donor centers are attracting healthy donors.

Under this standard, each donor center must report the number of positive test results it receives each month. These data are then compared against a national standard to assure the safety of the donor population. If a donor center exceeds the national standard, corrective action must be taken or it will risk losing its QSEAL status.

INVENTORY HOLD

The inventory hold standard requires that each plasma donation be held in inventory for a minimum of 60 days prior to being used in the production of plasma protein therapies. This robust standard allows for the identification, retrieval, and destruction of any plasma donation as a result of post-donation information. In light of the comprehensive screening criteria for plasma donors, there could be many reasons for retrieving and destroying a plasma donation. For example, a donor may have received a tattoo or piercing that would have disqualified him/her at the time of the original donation, or perhaps the donor failed to report foreign travel to certain parts of the world that would have disqualified him/her. Regardless of the reason, the Inventory Hold Standard offers a strong, important measure of quality control to the production of plasma protein therapies.

NUCLEIC ACID AMPLIFICATION TECHNOLOGY (NAT) SCREENING

Nucleic Acid Amplification Technology (NAT) screening uses state-of-the-art technology to allow for the earliest possible detection of transmissible disease. NAT screening compliments regulatory requirements for serology testing (an antibody test),

which occurs most often at the donation level. NAT testing, which can detect disease, is done at the donation or pool level and is an additional safety measure for final therapies.

INTERMEDIATES STANDARD

The intermediates standard is another layer of QSEAL that further assures the consistency, quality and traceability of intermediate products being incorporated into final therapies by manufacturers. An intermediate is a plasma-derived starting material that must undergo further manufacturing steps, before it becomes a final therapeutic product. The exchange of intermediates allows producers to focus on the production of their specific products, while not wasting precious material that can benefit other patients. As an additional quality control measure, a “chain of custody” must exist between the supplier and the purchaser of any intermediate subject to QSEAL.

PARVOVIRUS B19 TESTING

All plasma that is used for therapeutic purposes also is tested for Parvovirus B19, a common infection that is often asymptomatic. The goal of the NAT in-process testing component of the QSEAL standard is to further reduce the risk of Parvovirus B19 transmission through plasma-derived therapies, without affecting current protective antibody titers (a measurement of how much an antibody is produced in the body) that patients need. The standard, which addresses this common virus, represents an exceptional level of safety and quality.

All companies that participate in the QSEAL certification process demonstrate their commitment to produce safe therapies.

Information as of July 2009

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Tokyo 150-6018 Japan
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THE FACTS ABOUT...

BECOMING A PLASMA DONOR

IF YOU ARE INTERESTED in becoming a plasma donor, first visit www.donatingplasma.org to find the location of a plasma center closest to you by conducting a zip code search. You then can contact the center to learn of any specific requirements for donating your plasma and to request an appointment as a first-time donor.

It takes commitment to become a plasma donor; commitment to the rigorous donation screening process of medical testing and health history questions. It takes dedication to lead a healthy lifestyle, so that you remain in good health and can continue to donate. Because of the highly specialized and sensitive therapies made from donated human plasma, and the sophisticated amount of testing involved with each donation, plasma from one-time-only donors is not used to produce medical therapies. This means that plasma donors must return to the center to donate at least twice in order for their plasma to be used to help those in need.

Become a part of a lifesaving journey that plasma takes from a dedicated donor to the thousands of patients with rare diseases that depend on plasma protein therapies to lead healthy, productive and fulfilling lives.

Source Plasma Donor Eligibility

- ♦ 18 years-old *
- ♦ Weigh at least 110 pounds (50kg)
- ♦ In good health
- ♦ Meet proper identification and residency requirements
- ♦ Live within a defined recruitment area of the collection center

*This may vary by state or country



Donations Needed for One Patient for One Year*

Primary immunodeficiency disease	130
Alpha-1 antitrypsin deficiency	943
Hemophilia A	1,237

*Based on 150 lb. adult treated for one year



STEPS FOR DONATING PLASMA

1. Check in at reception

When a donor enters the plasma donation center, he or she must meet the basic requirements for donating found on the center or company website and present a valid form of identification (such as a government-issued driver's license) and proof of a social security number.

2. Health screening and physical exam

Qualified medical staff at the center will verify eligibility as a plasma donor, which includes performing a physical examination for new donors. Vital signs will be checked and a "fingerstick" check will be performed to measure the level of red blood cells and plasma proteins in the blood. Center staff will also review the donor's medical history.

3. Plasmapheresis procedure

Once the donor successfully completes the health and suitability screening, the donor is ready to be escorted to a comfortable plasma donation bed, where a trained staff person will complete the venipuncture or "blood draw"

and will connect the donor with the plasmapheresis device, a specialized piece of medical equipment used to collect plasma. The automated medical device removes whole blood, separates the plasma from the other blood components and then returns those components to the donor. During the procedure, a sterile, single-use kit is used, and the donor's blood never leaves the device.

4. Thanks for time and commitment

Once a donor has completed plasmapheresis, he or she is able to rest and recover in a dedicated area of the center. The donor may receive compensation for the time and commitment involved with voluntarily donating plasma.

5. Plan the next visit

Before a donor leaves the center, he or she is encourage to plan the next visit to donate plasma. The center may accept appointments, or the donor may choose to walk in to donate.

Information as of July 2009

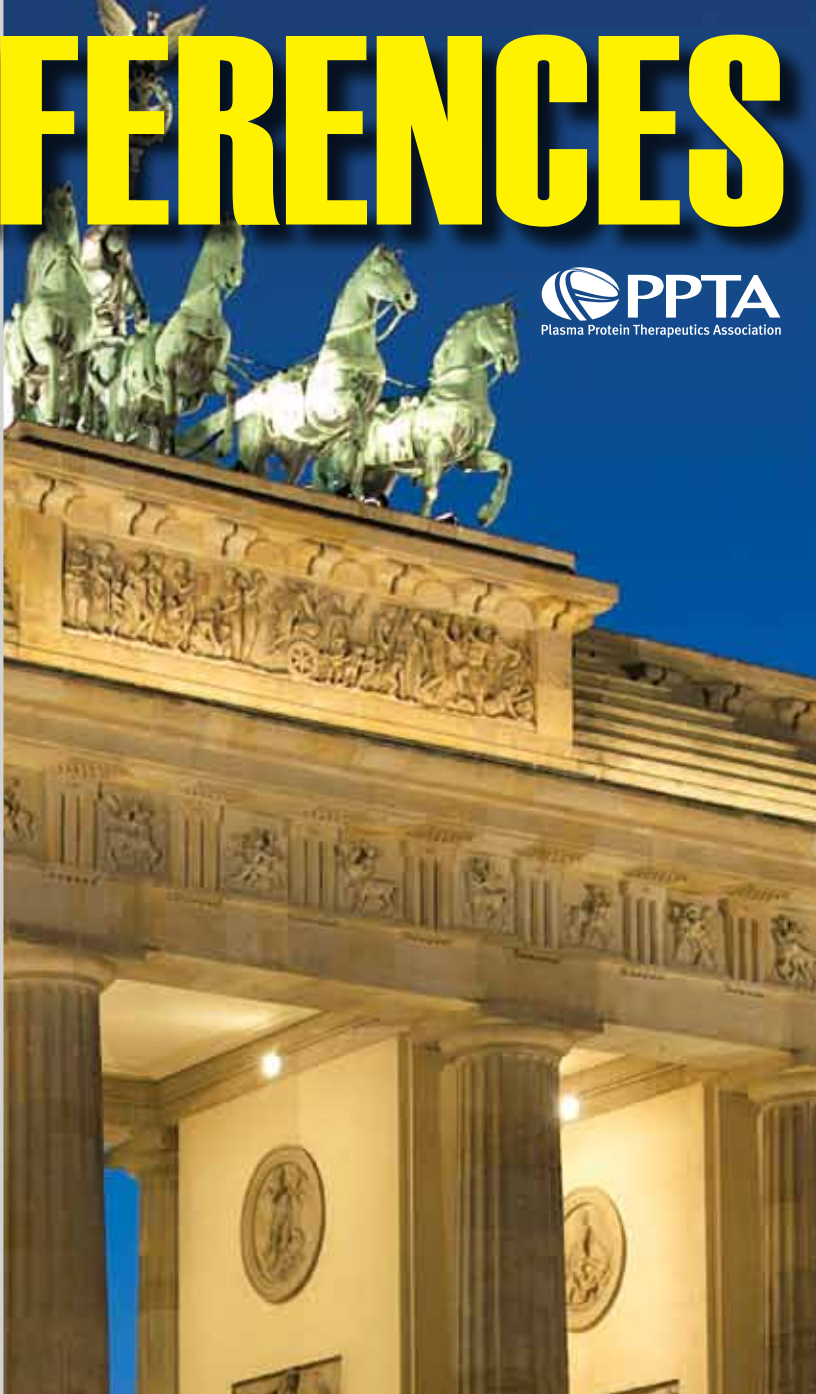
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PPTA CONFERENCES



PLASMA PROTEIN
FORUM



PLASMA PROTEIN FORUM

Held Annually in June

www.plasmaproteinforum.com



**INTERNATIONAL
PLASMA PROTEIN
CONGRESS**

Held Annually in March

www.IPPC2010.com

PPTA welcomes attendees from government agencies, patient groups, physicians, consumers and policymakers to attend its world renowned annual conferences on a wide array of topics pertaining to plasma protein therapeutics.