Changes on the Horizon
The Alpha-1 Foundation Research Registry
IDF’s Marcia Boyle Honored by White House Champions of Change
Martha and Hans Eibl: Making Their Mark In Immunology
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I am writing this column in Shanghai where PPTA was the co-organizer of a two-day conference to address various issues in Asia. One topic was the hemophilia care in China. A long time ago I learned that you talk about persons with hemophilia (PWH), not patients. And what impressive persons have I seen.

The program started with a PWH from the United States who described his journey with hemophilia. It was one of the most impressive talks I have ever heard. With an enormous openness, he shared the difficult moments growing up, the many hospitalizations, the pain, his wheelchair and so on. He wrote in his diary that he would develop a cure for hemophilia. And guess what? He did it. But not after all the problems and fears associated with being seroconverted for HIV and losing friends. There were many moments that he thought that his end was near. He fortunately received a treatment that was the beginning of a turnaround. But in the meanwhile the joint damage continued and his liver was giving up. He ultimately received a liver transplant and he was cured of his hemophilia. He showed X-rays of his knees pre- and post-surgery and the same of his ankles. He was called a legend by the Chinese PWH who spoke later.

The Chinese PWH was 42-years old and wheelchair-bound since he was 12. He told us a very moving story about what he had to go through and the difficulty to get treatment. It was incredible to witness the strength that he showed when he spoke about all the work that he was doing to help other people. This included the formation of a patient organization. When he broke down and showed his true emotions, it brought tears in the eyes of many in the audience.

Nowadays, thanks to prophylactic care, many PWH’s can lead a normal life and even become athletes performing at the highest levels. However, when one realizes that 75 percent of the available therapies are consumed by 15 percent of the world’s population, then we all know that there is an enormous task waiting.

The consumption of FVIII in China is currently estimated at 0.15 unit per inhabitant, a sharp contrast with many countries. This number means that there is not even enough for on-demand therapy. It was mentioned many times that there is a shortage of FVIII in China.

FVIII is available with the production of plasma derived FVIII in China and the (limited import of rFVIII). There are currently 29 manufacturers in China; seven have a license to produce FVIII but only four are doing it. The production can only be done with plasma collected through plasmapheresis; using recovered plasma is not allowed. All recovered plasma is discarded. As a contrast, in India it is exactly the opposite. Only recovered plasma is available.

Would it not be fantastic if those hurdles can be removed so that children (and adults) in these countries have the same opportunities for a life without pain? Together we must be able to work on a solution.

Jan M. Bult, PPTA President & CEO
Patient registries play an important role in collecting data used by a plethora of individuals to make decisions. First, valuable patient data is collected under a transparent set of guidelines, confidentiality agreements, and safeguards. The data is then used to provide a broad array of entities such as physicians (treaters), researchers, manufacturers, insurers (payers), national patient organizations, and policymakers with information.

We’ve all heard the adage, information is power. Nothing could be truer with regards to patient registries. The interesting question for the patients who use plasma protein therapies is how will that information be used by decision makers and will that information impact their ability to access the therapies?

In today’s complex health care system, information is necessary to make decisions that impact patient access: access to therapies, specialists, and treatment. It is important for the patient voice to be heard by the entity making the decision. Instead of an individual voice, the strength of a registry is reflected in the number of patients participating. The voice of many patients sharing their experiences, outcomes, and health status can strengthen the community by providing data that ideally should be used as a tool by entities to make patient centered decisions. But often times, cost-effectiveness drives decisions.

Several patients in the community of our rare disease space—hemophilia, immune deficiencies, and Alpha-1, for example—participate in patient registries. Registries can be publicly or privately funded and are often internet-based. In the United States, registries are broad and represent the patient group countrywide (U.S. Immunodeficiency Network [USIDNET Registry or the ATHNdataset that works with Hemophilia Treatment Centers]. European patient registries can span the continent (European Society for Immunodeficiencies [ESID] Registry) or be country specific such as for example, the French National Reference Center of Primary Immunodeficiencies (CEREDIH) or the German National Registry for Primary Immunodeficiencies.

This first article in a series will explore the Alpha-1 registry and provide insight into its utility and value in shaping how decisions are made that impact patient’s lives.

**Alpha-1 Antitrypsin Deficiency (Alpha-1)** is a genetic condition that can lead to lung disease in adults and/or liver disease at any age.

In Alpha-1, there is a low level of protein in the blood called alpha-1 antitrypsin, or AAT. The low level of AAT in the blood occurs because the AAT is abnormal and cannot be released from the liver at the normal rate. This leads to a build-up of abnormal AAT in the liver that can cause liver disease and a decrease of AAT in the blood that can lead to lung disease.

The only specific treatment for Alpha-1 lung disease is augmentation therapy: intravenous infusions of AAT, made from pooled donated blood plasma that has been highly purified. The infusions are usually given once a week. Other than liver transplant, there is no specific treatment for Alpha-1 liver disease.

The Alpha-1 Foundation was created in 1995 after the announcement by the National Heart, Lung, and Blood Institute that it would end its intramural research on Alpha-1 when the NHLBI’S major longitudinal study of the natural history of Alpha-1 ended in 1996.

“It was clear that the Alpha-1 community would have to take responsibility into our own hands for research into Alpha-1,” says John Walsh, co-founder and CEO of the Foundation, which has invested more than $54 million for Alpha-1 research and programs at 100 institutions in North America, Europe, the Middle East, and Australia.

A major impediment into research for any rare disease is the difficulty in finding enough patients for studies. So the Foundation established its Research Registry in 1997 as part of a longitudinal study of the natural history of Alpha-1 ended in 1996.

“Through the Registry and the ACT study, we have data on more than 5,500 patients in the U.S. and over 20,000 patients internationally,” says Walsh. “With this data, we can better understand the natural history of Alpha-1 and how it affects patients.”

The Alpha-1 Registry has been used to study the effects of smoking, exercise, and other factors on Alpha-1 patients. The Registry has also been used to study the effects of new therapies on Alpha-1 patients.

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A new program, the ACT study, is providing free and confidential testing to people at risk for Alpha-1. The ACT study has tested more than 24,000 people for Alpha-1.
The Registry has assisted in more than 100 research studies, and the pace is accelerating. “We sent out 18 invitations to Registry participants in 2014, and the rapid pace is continuing this year,” says Dr. Strange.

Since inception, the Registry has depended on data reported by patients through a questionnaire given to all those who register. “But Alpha-1 researchers often need more,” Dr. Strange says. “They may need blood samples, detailed genetic test results, and standardized questionnaires. This is why we are creating the new Alpha-1 Foundation Clinical Resource Center Registry.”

There are more than 80 Alpha-1 Foundation Clinical Resource Centers (CRCs), which are centers that specialize in patient care and education for Alpha-1. Some of these centers specialize in lung disease, others in liver disease.

The goal of the CRC Registry is to have Alphas visit one of the Clinical Resource Centers around the United States, and to enroll in the CRC Registry at the time of their visit. “This rollout will take years, and every CRC may not have the resources to participate at the beginning. But over time, the CRC Registry will create a rich data source to help us find a cure for Alpha-1,” Dr. Strange says.

The Medical University of South Carolina (MUSC) will provide the database to cross-index the information gathered for the CRC Registry. The National Institutes of Health in 2008 launched a program called the Clinical Translational Science Awards to pay for computer programs that make data collection easy. The program being used for the CRC Registry is called Research Electronic Data Capture, or REDCap, which assures confidentiality of personal health information.

After storage, a critical need of a research registry is a convenient way to find and use the stored data. MUSC is one of more than 35 medical research centers in the United States and Europe that use a program called Informatics for Integrating Biology and the Bedside (called i2b2 for short). This computer program allows data that contains no personally identifying information to be kept in a public database where it can be queried by anyone in the community.

The Alpha-1 Research Registry also has a new website: http://alphaoneregistry.org.

Since inception, the Registry has depended on data reported by patients through a questionnaire given to all those who register. “But Alpha-1 researchers often need more,” Dr. Strange says.

The website includes a page with information about all current study invitations being managed by the Registry. The Registry website will ultimately serve as a portal for researchers to access the new CRC Registry.

Mr. Walsh noted that augmentation therapy has been available in the United States since 1988. “We Alphas in the U.S. have four available augmentation products, but in many other countries, no augmentation therapy is available. Access to proper care for Alphas around the world was a major reason for the founding of Alpha-1 Global in 2013,” he said.

Mr. Walsh pointed out that the Alpha-1 Research Registry has been critical to researchers needing patients for research into potential new therapies for Alpha-1.

“To Alphas, the Research Registry represents hope — that we will develop additional therapies and ultimately a cure for Alpha-1,” Mr. Walsh said.

BOB CAMPELL, Communications Director, Alpha-1 Foundation
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It may have started in her kitchen, but the Immune Deficiency Foundation catapulted to the national stage this July when founder Marcia Boyle was honored by the White House Champions of Change for Precision Medicine.
The July 8 event honored nine patients, researchers, innovators, and advocates for their dedicated efforts in advancing the understanding of health and disease by using data to improve patient health. Ms. Boyle and IDF were recognized for IDF ePHR, the organization’s electronic personal health record that empowers members of the primary immunodeficiency (PI) community to better manage their health.

“Even though the award was to me, the award really was for the Immune Deficiency Foundation and what we’re doing with primary immunodeficiency diseases. It gives these disorders a spotlight that you might not ordinarily get,” Ms. Boyle said.

Ms. Boyle, along with her husband, John Boyle, Ph.D., Dr. Jerry Winkelstein, an immunologist, and the Greenhawk family, founded IDF 35 years ago. Marcia and John were inspired to get involved after their son, John, was diagnosed with X-Linked Agammaglobulinemia in 1978. Frustrated by the lack of information on primary immunodeficiency diseases, they set about creating a national patient organization, and Marcia has since dedicated her life to educating and advocating for the PI community. Today, IDF has a staff of 35 and helps thousands of patients and their families each year.

Since 1992, IDF has used technology to help give researchers insight into the patient experience. In 2013, the organization received an award from the Patient-Centered Outcomes Research Institute (PCORI) to create PI CONNECT, IDF’s Patient Powered Research Network to bring together patient data from IDF ePHR with clinical data from the U.S. Immunodeficiency Network (USIDNET) patient-consented registry. IDF just received notification that PI CONNECT has been selected to receive Phase II funding from PCORI for the next three years.

“Patients can see firsthand that if they participate, they can make a difference.” Ms. Boyle said. “Researchers won’t know the true patient experience unless patients share and give them a better idea of what’s really happening.”

These are exciting times for IDF. PI CONNECT has already attracted more than 1,200 registrants looking to make a difference and drive more precise treatment and individualized care.

“We’ve always been on the cutting edge of technology,” explained Ms. Boyle. “We’ve done a very good job with education, our educational materials and sessions,

President Obama Launches Precision Medicine Initiative

Precision medicine takes into account individual differences in people’s genes, environments, and lifestyles, according to the White House.

In January 2015, U.S. President Barack Obama unveiled the Precision Medicine Initiative (PMI) during his annual State of the Union Address. The new research initiative, which launched with a $215 million investment in President Obama’s 2016 budget, hopes to “revolutionize medicine and generate the scientific evidence needed to move the concept of precision medicine into every day clinical practice.”

“I want the country that eliminated polio and mapped the human genome to lead a new era of medicine—one that delivers the right treatment at the right time,” said President Obama.

The new initiative “will pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients,” according to a White House release.

According to the National Institutes of Health, PMI “was prompted by the need to gain insights into diseases that do not have proven means of prevention or effective treatments … While significant advances in precision medicine have been made for select cancers, the practice is not currently in use for most diseases.”

Immune Deficiency Foundation founder Marcia Boyle was named a White House Champions of Change for Precision Medicine for IDF’s commitment to using data to improve patients’ health.

Since receiving the award on July 8, Ms. Boyle said she and IDF staff have been inundated with well wishes from patients and physicians thrilled with the national recognition for the organization.

“These are disorders that are in many ways on the cutting edge of research. Many of the companies have supported our efforts and I hope that they feel proud that they played a role in IDF being recognized at this level. Personally I am proud, but I am really proud of our staff and board who have all worked hard on this.”
“We’ve done a very good job with education; our educational materials and sessions, outreach, public policy, and advocacy help transform lives. But if you really want to have improvement, research and data are essential.”

— Marcia Boyle

Marcia Boyle advocating for severe combined immune deficiency (SCID) newborn screening in Louisiana, at an IDF rally in New Orleans June 2015.

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For her blog entry on the White House Champions of Change website, Ms. Boyle wrote, “Bringing together this information and the patient voice holds great promise to provide researchers further insights about the diagnosis and treatment of PI, ultimately helping to improve quality of life for patients.”

Since receiving the award, Ms. Boyle said the organization has received an outpouring of congratulations from across the IDF community. Not only have the people who live with PI expressed pride, but the physicians are equally thrilled.

“They’re excited that this award brought primary immunodeficiencies to a national stage,” she said. “IDF represents a group of rare diseases, and to be up there with cancer and other better known disorders was quite remarkable. There was quite a bit of pride and excitement to be highlighted.

“But any accomplishment that I may make, there’s an organization and other people behind it as well, and that’s something you don’t lose sight of. This award has brought primary immunodeficiencies to a national stage and we are very grateful.”

JULIE BIRKOFER, Senior Vice President, North America & Global Health Policy

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In 1958, Martha Eibl returned to Vienna to practice internal medicine as a resident and to continue her studies. She received her Specialist degree in Internal Medicine in 1965 and remained until 1970 at the Clinic of Internal Medicine of the University of Vienna. From 1970-97 she worked at the Institute of Immunology of the Vienna University. In 1973, she received the Lecturers Degree and in 1980 became Professor and Head of the Department of Pediatric Immunology and Infection and Immunity.

Professor Martha Eibl is a very impressive person. She spent 20 years as the consultant physician for clinical immunology for all municipal pediatric hospitals in Vienna and is a world renowned immunologist who has taught many specialists the intricacies of immunology. The author of 294 peer-reviewed articles, she was the head of the clinical-immunological research for Immuno AG from 1966-96. Those who are trained by her speak highly about her scientific skills and dedication to patients.

"Ever since I first met Prof. Martha and Dr. Johann Eibl, at the time enjoying the privilege of doing my Ph.D. thesis under her supervision, I cannot imagine better company for being introduced to the love of science; always with a focus on the best interest of patients," said Thomas R. Kreil, Ph.D.,
Key individuals of Immuno

When you talk about the “old days” of Immuno, you have to talk about some key individuals that made the company strong:

**DR. OTTO SCHWARZ**
Responsible for Manufacturing and Operations

**DR. HANS EIBL**
Responsible for R&D

**DR. FRIEDRICH DORNER**
Responsible for Biotechnology and Pathogen Safety

**DR. KNUT HANSEN**
Legal counsel and first Chairman of the European Association for the Plasma Protein Industry. He worked hard to establish the foundation of what has become PPTA.

Associate Professor of Virology, Senior Director, Global Pathogen Safety, Baxalta. “It’s a passion that has stuck with me ever since.”

It was during her medical training in 1951 that Martha Eibl met Johann “Hans” Eibl, a chemist, who was one of the founders of the company that later became Immuno AG, one of the premier biopharmaceutical companies in the world.

Dr. Hans Eibl is someone you cannot miss when you see him: tall, charismatic, with a memory like a computer; he is driven by his desire to make new and improved drugs for the treatment of patients.

During World War II, he studied chemistry at the High School for Chemistry and continued his studies at the University of Vienna and received his PhD in 1952. His professional career started in 1948 working at the Serotherapeutic Institute in Vienna with Professor Eisler-Terramare as his mentor.

One of the problems of these early times was the adverse effects caused by the use of curative horse serum against tetanus and diphtheria. The most frequent adverse effect, serum sickness, occurred in about 15 percent of treated patients while the anaphylactic shock, the most severe side effect, occurred less frequently. By partial enzyme treatment of the horse serum tetanus anti-toxin as well as diphtheria anti-toxin did no longer cause serum sickness but the danger of anaphylactic reactions remained.

During World War II and thereafter, a cold ethanol fractionation process for human plasma was developed by Cohn in the United States and taken up by several pharmaceutical manufacturers in the U.S. and Europe. In Vienna, based on the experience of salt fractionation for manufacturing of anti-diphtheria horse serum and by the most advanced electrophoretic technology, teaming up with Professor Auerswald made it possible to produce human gamma globulin and albumin by salt fractionation.

Wilhelm Auerswald, with commercially interested partners around him, masterminded the setting up of a commercial production of plasma derivatives, the “Österreichisches Institut für Haemodervative.”

After World War II, the Western World was regularly struck by polio epidemics and the solely successful treatment as proven by a large study in the US was the prophylaxis with gamma globulin. This led to an explosive increase of demand.

The virus-neutralizing potency of the gamma globulin, produced by the Österreichisches Institut für Haemoderivate (OEIH), met the requirements of the U.S. regulatory authorities and the OEIH was successful in obtaining the U.S. Establishment License 258 and the Product License for gamma globulin.

In the early 1950’s, the research centered on how to produce blood products and how to characterize these fractions. Inspired by this work, in the late 1950’s, Dr. Auerswald and Dr. Eibl became the leaders of the OEIH, the company that later became Immuno.

Hans and Martha were married in Greenport Long Island, N.Y., in 1958, and by 1965 were a family of six. Their four children all developed different careers in Austria, Germany, and the U.S.

Dr. Hans Eibl was, from the beginning, very interested in the biochemistry of blood products and vaccines and that has never changed. He has worked with a team, including his wife, on research and development, and there are more than 200 patents globally associated with his name.

Good examples are the development of Tetanus Immunglobulin in the 1960’s and factor eight inhibitor bypassing activity (FEIBA) in the 1970’s. By immunizing plasma donors with Tetanus Toxoid, tetanus immune plasma could be obtained for the manufacturing of human tetanus immune globulin. In field trials in Ontario, Canada, the efficacy of as little as 250 tetanus antitoxin units were proven to be sufficient for protection. These results made treatment with horse serum obsolete.

The introduction of concentrated Factor VIII preparations was exciting since it dramatically improved the life expectancy of persons with hemophilia. The downside was that inhibitors also emerged. This led to the effort to find a solution to overcome the hemostatic failures and focus on an “activated prothrombin complex.” Dr. Eibl is very modest when he states that they were lucky. Like many scientific developments, there is a lot of trial and error. The introduction of FEIBA has helped many persons with inhibitors to lead a normal life again.

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There was another important milestone: the introduction of plasmapheresis. Important work was done to develop the first plasmapheresis machine by Grifols in Spain, but the first plasmapheresis center was established in Austria in 1963. The development of plasmapheresis in Austria was parallel to and independent from similar developments in the U.S. This historic fact was recognized with a special symposium in Vienna in October 2013.

Most of the developments Dr. Eibl worked on were achieved with an international orientation. His professional work with his laboratory is still focused on research on blood components and vaccine antigens.

When I asked Dr. Eibl if there is anything he would do differently, his first response was “I am still constantly working on improvements in blood products and vaccine antigens.”

To bring the focus back on patients, the area where Professor Martha Eibl has earned her reputation, I asked her about her present efforts. She answered by emphasizing to be a strong advocate for early diagnosis and treatment.

She stressed the importance of closing the gap between scientific developments and treatment possibilities with an ongoing dialogue “One of the most important things is to think about treatment options and to talk about it,” she said.

Members of advisory committees of international, national and professional healthcare agencies are responsible for recommendations in accordance with good clinical practice. These recommendations are taking the lead in improving the quality of treatment for patients worldwide.

Vienna (and Austria) can be proud to have these two eminent experts as citizens! It is indeed very stimulating to meet both of them and become “infected” with their energy! I am honored to have the privilege of knowing them personally!

JAN M. BULT, PPTA President & CEO

References
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Hemolytic disease of newborns (HDN) is a serious and often fatal disease caused by incompatibility occurring during pregnancy, mainly between the blood group of an Rh- mother and her Rh+ child.  

During pregnancy, an Rh- woman (from <1 percent up to 15 percent of population, depending on ethnicity) who carries an Rh+ baby may be exposed to fetal blood and become sensitized. This typically occurs after delivery or invasive procedures such as amniocentesis or abortion. At subsequent pregnancy, there will be a rapid immune response of the mother, with a large quantity of antibodies directed against the red blood cells of the fetus (fig 1). As a result, 14 percent of affected pregnancies result in stillbirth; 30 percent of survivors have serious disease (hemolysis and severe anemia); and an additional 30 percent have a moderate disease (accumulation of bilirubin into tissues, particularly into brain with lifelong neurological sequelae).  

Preventing Hemolytic Disease of Newborn (HDN) has been one of the most relevant accomplishment in the struggle against neonatal mortality and childhood disability. In the 1960s, hemolytic disease of newborn was responsible for 10 percent of perinatal deaths in the U.S. The development of Anti-D immunoglobulin (Ig) and its administration after delivery decreased the immunization risk of 90 percent, thus preventing the onset of HDN in subsequent pregnancies. No doubt, it can be affirmed that introduction of Anti-D Ig prophylaxis in the 1970s has been one of major milestones in women’s and children’s health medicine.

A second accomplishment was the introduction of Anti-D Ig antenatal prophylaxis, based on the finding that a few pregnant women were still immunized in spite of post-partum prophylaxis. It was discovered that immunization can occur even in absence of clinically evident events, such as delivery, trauma, or invasive procedures. Exposure to fetal blood normally occurs during the third trimester (occasionally earlier), and is responsible for
Fig. 1 Pathogenesis of Rh Hemolytic disease of newborn

Fig. 2: Decline in death rate for all causes of HDN in U.S, 1968-75 (modified from 6)
<table>
<thead>
<tr>
<th>EVENT</th>
<th>IMMUNIZATION RATE (PERCENT)</th>
<th>STRATEGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery</td>
<td>17%</td>
<td>Post-partum prophylaxis</td>
</tr>
<tr>
<td>Abortion</td>
<td>4-5%</td>
<td>Targeted prophylaxis (within 72 hours)</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>5-7%</td>
<td>Targeted prophylaxis (within 72 hours)</td>
</tr>
<tr>
<td>3rd trimester “occult” fetomaternal hemorrhages</td>
<td>1-2%</td>
<td>Routine Antenatal prophylaxis (28-30 weeks)</td>
</tr>
</tbody>
</table>

Table 1: Strategies to prevent mother's immunization and hemolytic disease.

**KEY WORDS**

**RH OR D ANTIGEN**
Designate same red blood cell group. Women who carry the “D” antigen are designed as positive (Rh+), women who don’t are negative (Rh-).

**HDN**
Hemolytic disease of newborn. Mother’s immunization results in destruction of fetus' red blood cells (hemolysis), accumulation of metabolites of red blood cell in tissues, such as skin (jaundice) or brain (kernicterus).

**ANTI-D IG**
Anti-D Immunoglobulin is human antibody solution, directed against D/Rh antigen. These are obtained from Rh- donors sensitized by Rh+ erythrocyte booster. Dosage is in mcg or IU; depending from the standard adopted in Country. Full dose is typically 200 to 300 mcg (1000-1500 IU). Micro doses (50 mcg /500 IU) are available in some Countries, used for small hemorrhage as in first trimester events.
It was discovered that immunization can occur even in absence of clinically evident events, such as delivery or trauma or invasive procedures. Exposure to fetal blood normally occurs during the third trimester, and is responsible for 10 percent of total immunizations.

10 percent of total immunizations. Anti-D Ig prophylaxis during pregnancy was assessed by randomized clinical trials,\(^7\)-\(^9\) which clearly demonstrate that this strategy is more effective than the sole postpartum prophylaxis. Risk of immunization was reduced from 2 percent to 0.1 percent (table 1) probably by covering “occult” feto-maternal hemorrhages.

Today, several countries recommend routine antenatal prophylaxis (1 full dose of Ig Anti-D at 28-30 weeks to all pregnant Rh- women) in addition to post-partum prophylaxis (only Rh- women delivering a Rh+ child).\(^10\)-\(^15\) The question of cost effectiveness has been raised but the favorable economics of this approach has been demonstrated by different authors.\(^16\), \(^17\)

Anti-D Igs obtained by cold alcohol-fractionation of plasma can claim a long standing record of viral safety,\(^18\) additionally improved by the introduction of specific viral inactivation methods such as nanofiltration, heat or solvent detergent treatments. The industrial process of Anti-D Igs relies on specific pools of sensitized blood donors, who have saved millions of lives with their dedication. Its complexity is a permanent challenge for the plasma derived industry and it works as an example of commitment which entails ethics, even more than industry profit. Despite all this progress, the eradication of HDN is still far from being accomplished.

Today in emerging and low-income countries, there is still limited access to prophylaxis, sometimes complicated by difficulties in point-of-care Rh blood-type testing. It is estimated that the lack of adoption of Anti-D Ig prophylaxis is responsible for more than 100,000 avoidable neonatal deaths per year and a larger burden of infant disability.\(^19\) In order to eradicate this preventable disorder, a global initiative has been started, also with unrestricted grant from the industry such as Kedrion Biopharma and Eldon Biologics. This initiative is called CURhE (from the acronym Consortium for Universal Rh disease Eradication) and has been prompted by three neonatologists who have devoted most of their professional careers to the struggle against hemolytic diseases and infant brain injury. These are: Giuseppe Buonocore Full Professor at Molecular and Developmental Medicine Dept. Siena University and member of Council of UENPS (Union of European Neonatal & Perinatal Societies); Vinod K. Bhutani Professor of Pediatrics and Neonatology at Stanford University School of Medicine and author of several original studies on this topic; and Alvin Zipursky, Professor Emeritus, Hospital for Sick Children, Centre for Global Child Health in Toronto who pioneered Anti-D prophylaxis.

CURhE goals will be achieved by improving patients’ access, educating health professionals, patients, and maternal child healthcare providers, enhancing the capacity for timely diagnosis and therapeutic networking mostly in emerging countries. “There is a huge gap that we need to fill and resolve; over the last almost 45 years we’ve done a phenomenal job in North America and Europe. But this
knowledge was not transferred and what we have to do is to implement this knowledge into practice in places which are most at risk for Rh disease hemolysis says Prof. Bhutani when launching CURhE initiative.

However we cannot forget that also in developed countries Anti-D prophylaxis practice has not been completely implemented. Today in European countries, we have not yet reached the eradication goal, mainly due to the incomplete adoption of antenatal prophylaxis. This issue is neglected and in some way overlooked; sporadic data reported from national registries should be a wake-up call for healthcare professionals and their stakeholders. Reaching the zero disease rate should be a common objective of industry and health decision makers, particularly in case of an avoidable disease such HDN.

Anti-D Ig, with many other plasma derived therapies, is a life-saving drug which has marked the history of a therapeutic area. After 50 years, its role still deserves development in order to save more lives, both in emerging and established countries. Disease awareness, plasma availability, and access to therapy are the keys to accomplish this goal. Industry, healthcare professionals, and stakeholders should work together for improving global access to this pivotal prophylactic tool.

GIOACCHINO DE GIORGI, Global Marketing Manager, Anti-D Franchise, Kedrion Biopharma

References
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The Continuous Path of Changes
IN HEALTHCARE: EU MEMBER STATES

BY SEBASTIAN ROHDE

How the Lisbon Treaty, the coming of power of the European Parliament changed healthcare policy at the EU

THE EU SERVICES DIRECTIVE
It was supposed to be groundbreaking legislation. The EU Services Directive in 2006 was meant to liberalize all services (energy, finance, construction, healthcare...) —a so-called horizontal Directive. For some EU Member States, it was taking things too far. What followed was a mechanism that Member States regularly used to halt legislation that was not in their favor: the veto. For instance, vetoing legislation allowed Member States to avoid harsher rules on CO2 emissions of cars or healthcare services to ensure limited national spending on healthcare would not be threatened. In some cases, such EU Council veto power was sufficient to stop a legislative process that was being prepared for years.

LISBON TREATY
The Lisbon Treaty that came into force December 1, 2009, has fundamentally changed decision making at the EU. During prior decades, the decision making at the level of the European Council was based on consensus —decision by unanimity or it was rejected, even by a single Member State’s veto. This meant that for hard decisions, Member States could apply a veto at last minute and a cumbersome topic was off the table.

The new majority principle, however, still allows vetoing. But it would require, for most cases of legislation, the votes of Member States making up a total of 35 percent
Silently over the years, the EU healthcare agenda and health policy at the Member State level agenda are becoming more and more focused on budget considerations.

of EU’s population. For instance, a rather EU-skeptic United Kingdom could no longer veto decisions without the support of a number of other EU Member States. What is also the case, however, is that at least one of the large Member States: Germany, UK, France, or Italy—will likely be needed to win those majorities or block them.

For decision makers and advocacy groups representing interests, this results in two major changes: decisions do not have to be based on the most common (or weakest) denominator and everyone needs to look for majorities. This is unusual for the Council, but not for the EU as such. The European Parliament has always been a place where decisions needed to be approved by clear majorities and that is what the Parliament is used to and what the Council still may need to learn.

For advocacy work, this particularly means one thing: a one-sided focus on the European Parliament and the hope for consensus at Council may no longer do the job. Interest representation can only be credibly and successfully done by those who can operate both at the EU and Member State level at the same time.

Regarding the EU Services Directive, the veto led to the exclusion of healthcare services from the scope of the horizontal Directive. As national governments considered the inclusion of healthcare services into the scope of the Services Directive—a violation of their national competencies—they had vetoed the Directive and insisted, among other items, on an exclusion of healthcare. However, for this they needed the approval of the European Parliament. The Parliament, having come of age, would only agree to such a measure if it would include a “deal.” This foresaw that Parliament would approve the exclusion of healthcare when, in return, a separate legislation of healthcare services would be initiated in the following years. This was the official birth of the “Cross-Border Healthcare Directive.”

EU HEALTHCARE POLICY PRIORITIES SHIFT
Silently over the years, the EU healthcare agenda and health policy at the Member State level agenda are becoming more and more focused on budget considerations. EU institutions have ignored, for many years, the cost containment developments in the Member States. However, it allowed unrestricted discussions on new health approaches and concepts, which, at the end of the day, have resulted in real Member States priorities.

For example, the Member States wanted the EU to regulate quality and safety standards for medicinal products since 1965. What were first technical Directives, have increasingly become legislation with political content. Similarly, the EU has introduced rare diseases on the political agenda in Europe, by adopting the Orphan Medicinal Products legislation.
The Paediatric Medicines Regulation is another excellent example of where health competencies have started to become blurry. Whereas the proposal for the Regulation mainly foresaw a designation of such products at the European Medicines Agency, the finally adopted legislation opened a question of access. Indeed, the original proposal did not exclude the plasma protein therapies which had already proven to be successfully used for children. An amendment by the European Parliament changed the scope of the Regulation in the favor of patient continuous access to treatment. Therefore, the regulation clearly and directly influences direct access to medication in Member States.

A major milestone in EU healthcare legislation was the introduction of the ‘Public Health Article’ in the Amsterdam Treaty of 1998. This article requested the EU to introduce measures for the protection of public health and specifically requested legislation in the area of blood (Blood Directive), tissues and cells (Tissues and Cells Directive and subsequently the “Advanced Medicinal Products Regulation”) and Organs (The Organs Directive). One objective was that some challenges can be better faced together, particularly in the area of communicable diseases.

For the plasma manufacturers the Blood Directive created a legal framework at the EU level. Before this legislation, the plasma-derived therapies were governed by the EU Pharmaceuticals Directive, whereas the collection of blood and its components including plasma was governed by Member States. The role of the EU Parliament in leaving some competencies to Member States was pivotal in the voting phase.

For the EU, the Blood Directive was a groundbreaking legislation as it was the first legislation based on the then new “health article.” What followed were important dossiers that were based on the framework of this Directive such as Tissues and Cells Directive and the Organs Directive. But these Directives introduced minimum standards of safety and, although broadening the field of competence, they remained extensions of the now existing approach.

**CROSS-BORDER HEALTHCARE DIRECTIVE AND TRENDS IN EU HEALTHCARE POLICY**

The real groundbreaking change in healthcare policy is now in front of us. Many healthcare advocates in Brussels still need to consider its significance, which has an impact now and will continue to have an impact for years to come. It is, however, interesting to look at the context of this new development and how it came about. It all started actually with real EU citizens’ calling for their rights. Since the late 1990s, the European Court of Justice became increasingly busy dealing with cases of EU citizens taking their Member States to court on the basis of non-granted compensations and reimbursements of treatments the citizens would seek outside their Member State of residence. The European Commission and the Council did not take into account this increasing topic, whereas, typically, the European Parliament identified a real need to politically address this topic, rather than having the Court decide on such rules on a case-by-case basis. In addition, all European Court of Justice rulings in this matter had been ruled in favor of citizens, claiming that the free movement of
persons and services cannot be compromised by national healthcare competences.

It was a former UK Minister of Health and then Member of the European Parliament, John Bowis, who initiated a report on the mobility of patients on the basis of the preceding court cases in Luxembourg. The report called for clarity for cross-border care, the first EU document took this initiative, adopted on June 9, 2005. This report, the rapporteur’s and Parliament’s political will, persistence, as well as the Parliament’s request to come up with a separate health services legislation as a result of the changed scope of the EU Services Directive led to this Cross-Border Healthcare Directive.

The groundbreaking aspects are two-fold: the title of the Directive and then its content.

Although often cited as the “Cross-Border Healthcare Directive,” the title is only complete when adding the ‘patients’ rights to cross-border care’. This aspect alone highlights the innovation: an EU Directive addressing patients’ rights and therefore access to healthcare across the EU and by crossing borders. There are limits of this, of course, but the Directive also clearly outlines the options for such cross-border care. This is groundbreaking in itself, but it was to be expected when the legislation was initiated.

The second groundbreaking element of the Directive, however, was its, to a great extent, unexpected content. The Directive, intending to govern patient rights in cross-border care, went far beyond this initial scope. Decision makers included items such as e-health, health technology assessment and interestingly repeated the definition of a rare disease based on the prevalence figure already defined by the Orphan Medicines Regulation of 2000. None of these items have a direct impact on cross-border care, but decision makers believed it would be the occasion to regulate several EU healthcare policy items, which so far did not have a legal base for further action.

The repetition of the rare disease definition will have great impact on patient access. The Orphan Drugs Regulation, while not based on the public health article, but being an ‘internal market’ legislation, some Member States still had their own prevalence-based definition. This must now be changed and it will also constitute that a rare disease prevalence must be based on a European prevalence, not a national one. This has direct impact on a plasma disorder, as alpha-1 antitrypsin deficiency (at times also called the Viking disease) has a greater prevalence in the Nordic countries – and it was, in fact, Sweden and Denmark still working on the basis of their national prevalence figures.

Other items of the Cross-Border Healthcare Directive will have an even broader effect on the healthcare systems. The granting of a legal base for Health Technology Assessment (HTA) at European level will have a major impact on healthcare, and its access in Europe. Although that this does not show fully yet, some indicators are there. It starts with the definition of health technology. The definition in the Directive states that this means not only the product (medicinal product or medical device) but also the surgical procedures, measures of prevention, diagnosis or treatment used in healthcare. In parallel to this development, EUnetHTA, the EU Network for HTA, was founded on the base of specific
It is an irony of history that all of this has been started by a veto of Member States to change the scope of the EU Services Directive, to exclude healthcare from such EU action. The result has taken more time, but actually turned into the opposite.

The current Presidency of the European Union, led by Luxembourg, remains in the current trend and has also included under its “Health Chapter,” topics that fully relate to all that has been described above: the evaluation of success of the Cross-Border Directive, the promotion of acceptance of innovative payer models, the empowering of patients when it comes to the sharing of data and, unsurprisingly, HTA. EU Presidencies change every six months and they had the bad habit of changing their priorities also in such short time. HTA, however, is there to stay. The next Dutch Presidency has already announced that its “Health Chapter” in itself will be a holistic Presidency priority.

It is an irony of history that all of this has been started by a veto of Member States to change the scope of the EU Services Directive, to exclude healthcare from such EU action. The result has taken more time, but actually turned into the opposite. ●

SEBASTIAN ROHDE, CEO Rohde Public Policy

References

PPTA Publishes Qualitative Analyses of IVIG-Associated Hemolysis Case Series

BY MARY CLARE KIMBER

Plasma donors provide the starting material used to manufacture lifesaving therapies. Through a manufacturing process known as fractionation, proteins are separated from the plasma to create a number of plasma protein therapies. These therapies are unique, biologic medicines that are either infused or injected to treat a variety of rare, life-threatening, chronic, and genetic diseases, including immunodeficiencies, bleeding disorders, pulmonary disorders, neurological disorders, shock and trauma, liver cirrhosis, and infectious diseases, such as tetanus, hepatitis, and rabies.

Immunoglobulins (IGs), proteins used to neutralize foreign objects, such as bacteria and viruses, are lifesaving plasma protein therapies for patients with primary and secondary immunodeficiencies and autoimmune disorders. Primary immunodeficiency (PID) is a life-threatening genetic defect that compromises the immune system. Secondary immunodeficiency is caused by outside factors, such as viruses, chemotherapy, other immunodeficiencies, and autoimmune disorders. IGs also treat chronic inflammatory demyelinating polyneuropathy, a rare disorder of the peripheral nerves, and idiopathic thrombocytopenic purpura, a bleeding disorder in which the immune system destroys platelets, which are necessary for normal blood clotting. IGs provide an improved quality of life, increased life expectancy, and infection prevention for patients with these rare disorders.

IGs have a long history of safety but, as with all medical therapies, there are rare side effects. IGs are made from many donors and are a mix of antibodies, including antibodies of the red blood cell ABO system. Some of these antibodies, in certain conditions, may lyse the patient’s different ABO-type red blood cells. Hemolysis has been long recognized as a rare but important side effect of IG therapy. All IG products contain a warning about risk of hemolysis. Delayed hemolytic anemia can develop, and acute hemolysis, consistent with intravascular hemolysis, has been reported. In addition, cases of hemolysis-related renal failure have been reported following infusion of intravenous IG (IVIG). Isolated cases of hemolysis have been observed following administration of subcutaneous IG (SCIG).

In January 2014, PPTA, along with the U.S. Food and Drug Administration (FDA) and the National Heart, Lung and Blood Institute, jointly hosted a workshop entitled, “Strategies to Address Hemolytic Complications of Immune Globulin Infusions.” The workshop examined strategies to reduce the occurrence and severity of hemolysis, including: patient risk factors, the potential of in vitro testing, and the link between hemolytic events and new indications for IG products.

All of the strategies covered in the workshop are spotlighted in a special supplement to the July issue of Transfusion. The supplement consists of 19 referred papers and focuses on the frequency and pathogenesis of and strategies to mitigate IVIG-mediated hemolysis. George Schreiber, Sc.D., Director, PPTA Epidemiology, and Harvey Klein, M.D., Chief, Department of Transfusion Medicine, Clinical Center, NIH, served as guest editors.

Of note are PPTA and member companies’ contributions to the workshop and supplement. In 2013, PPTA and four member companies (Baxter*, Biotest AG, CSL Behring, and Kedrion) agreed to pool and analyze data from the companies’ individual postmarketing surveillance systems pertaining to IVIG and hemolysis. The PPTA case series represents one of the largest analyses of IVIG-associated hemolysis cases to date and affords the opportunity to examine patient outcomes and risk factors that could provide additional insight into strategies to mitigate the workshop examined strategies to reduce the occurrence and severity of hemolysis, including: patient risk factors, the potential of in vitro testing, and the link between hemolytic events and new indications for IG products.
the risk of hemolysis. Roger Berg, M.D., Baxter Innovations GmbH, presented preliminary PPTA analyses of data from 263 hemolysis case reports at the workshop. A paper with additional PPTA analyses has been published in the supplement.

The following PPTA member companies also contributed individually with presentations at the workshop and papers in the supplement:

- **Baxter**: Anti-A and anti-B titers in donor plasma, plasma pools, and immunoglobulin final products (John McVey, Don Baker, Rajesh Parti, Roger Berg, Maria Gudino, and Wolfgang Teschner)
- **CSL Behring**: Donor screening reduces the isoagglutinin titer in immunoglobulin products (Brigitte Siani, Katharina Willimann, Sandra Wymann, Adriano Marques Antunes, and Eleonora Widmer); Effects of the manufacturing process on the anti-A isoagglutinin titers in intravenous immunoglobulin products (Val Romberg, Liane Hoefferer, and Ibrahim El Menyawi); Isoagglutinin reduction by a dedicated immunoaffinity chromatography step in the manufacturing process of human immunoglobulin products (Liane Hoefferer, Isabelle Glauser, Annette Gaida, Katharina Willimann, Adriano Marques Antunes, Brigitte Siani, Sandra Wymann, Eleonora Widmer, Ibrahim El Menyawi, Reinhard Bolli, Martin Spycher, and Martin Imboden)
- **Kedrion**: Anti-A and anti-B hemagglutinin depletion during Cohn purification process of 5% immunoglobulin (Alfonso Salvatore, Semih Esin, Giovanna Batoni, Ester Ascione, Claudio Farina, and Claudia Nardini)

PPTA’s contributions were only one part of the FDA workshop and Transfusion supplement exploring strategies to address hemolytic complications of IG infusions. PPTA also is collaborating with FDA to develop consensus labeling pertaining to hemolysis for all normal IG products. Along with clinicians, regulators, and hematology researchers, PPTA member companies are a key part of the on-going effort to address this important issue for IG patients.

Transfusion is free to AABB members. Nonmembers may subscribe through Wiley-Blackwell or by calling +1.800.835.6770.

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**PPTA Hosts 2015 Plasma Protein Forum**

**BY JULIE BIRKOFER**

The 2015 Plasma Protein Forum kicked off June 16 with a keynote address from Rep. Doris Matsui (D-CA), a longtime champion of rare diseases and access to care issues.

Rep. Matsui, who received the 2015 PPTA Leadership Award, shared her enthusiasm for the 21st Century Cures Act, which she thinks will be “a great turning point” in leading to more innovation and advances in medical technology. The bill, which passed unanimously out of the Energy and Commerce Committee, will next head to the House of Representatives. It is expected to provide funding to telehealth services to expand practices into underserved communities and help ensure that federal policies are consistent with needs for rare disease patients.

More than 300 people attended the June 16-17 event in Washington, D.C., which covered diverse issues such as industry challenges, patient voices, plasma donation benefits, self-sufficiency, and regulatory. The conference was well attended by patient group representatives, industry, regulators and academics and provided substantive and thoughtful discussions while highlighting key challenges facing patient access to plasma protein therapies.

Alabama Senate Majority Leader Greg Reed (R-5) received a special recognition for his commitment to getting his state to lower the minimum plasma donation age. Earlier this year, Alabama Gov. Robert Bentley signed Senate Bill 13, which lowers the minimum age to donate plasma in that state from 19 to 18. “It was a privilege and an honor for me to help you in our state,” Sen. Reed told Forum attendees in thanking PPTA for the honor. He also promised to talk to other politicians in other states on the importance of allowing individuals 18 and older to donate. Nebraska is now the only state that doesn’t allow plasma donation at 18.

PPTA President and CEO, Jan M. Bult, moderated the Access to Care Panel: Vision for the Future in which the CEOs of the National Hemophilia Foundation (NHF), Immune Deficiency Foundation (IDF), Hemophilia Federation of America (HFA), and Alpha-1 Foundation all took part. The importance of access to treatments globally was discussed

*Now known as Baxalta Inc.*
Herbert Dichtelmüller Honored With Otto Schwarz Award

Since 2012, the Otto Schwarz Award has recognized leadership in the plasma protein therapeutics industry and related scientific fields. This year’s recipient, Herbert Dichtelmüller, Ph.D., was recognized posthumously for his contributions to pathogen safety and his significant contributions to improving the safety profile of plasma protein therapies.

Dr. Dichtelmüller, who worked for Biotest AG, died in February 2015. His son, Cornelius Dichtelmüller, accepted the award at this year’s Forum, saying, “I would like to thank all of you for supporting my father’s work. He would have been very proud today.”

The Otto Schwarz Award was created in honor of Dr. Schwarz, one of the founders of the International Plasma Products Industry Association (IPPIA), the association representing the manufacturers of plasma protein therapies, and the forerunner of PPTA. As one of the first Chairs of IPPIA, he recognized the importance of developing an industry view and was the first to recognize the importance of qualified donors and how to best apply nucleic acid amplification test (NAT) technology. PPTA is pleased to recognize his legacy through the Dr. Otto Schwarz Award.

NEWS FROM AROUND THE GLOBE

as were the challenges of obtaining patient access to plasma protein therapies around the world. All patient groups expressed their focus on access, advocacy, education, awareness and research. Some groups expressed the importance of finding a cure for their respective diseases and increasing support for patient registries.

“We try to build relationships and teach patients to be good stewards of their own care,” said Val Bias, NHF president and CEO.

Marcia Boyle, IDF president and founder, echoed that, saying: “We give patients a voice and teach them to advocate for themselves.”

HFA Executive Director Kimberly Haugstad agreed. “There can’t be enough overlap when it comes to advocacy,” she said.

Of his organization, Alpha-1, John Walsh, CEO and president, praised all of the patient groups for working together: “We are committed to working with other plasma-user organizations.”

During the Changing the Global Perspective on Compensation: Focus on Patient Need panel, Dennis Young, vice president, Global Plasma Sourcing, Baxalta, praised industry for the advances it’s made, saying, “The changing of perception happens one mind at a time.” In that same panel, Cristiana Spontoni, an expert in EU biotechnology, pharmaceuticals, and medical devices, explained that in regards to compensation “we must be sensitive to cultural issues because in the end we want safe plasma for the world.”

The International Perspectives: Access to Care Panel covered issues that included: increasing primary immunodeficiency (PID) diagnoses in Germany, the importance of newborn screening; political issues surrounding the blood banks in the Netherlands and the high price that hospitals pay for blood; the vast challenges facing India as it tries to increase not only the plasma supply but the quality of it as well. The difficulty in getting patients diagnosed was also highlighted; and a journey through some PID case studies from Japan and the effect of treatments.
During his panel, Shinji Wada, PPTA Source Board of Directors Chairman and president/CEO of Grifols Plasma Operations, shared his enthusiasm for the industry’s response to the global challenges it faces. Calling the challenges “opportunities,” Mr. Wada cited the FDA’s draft guidance on MSM, nomogram, Ontario legislation, and Rome Declaration among a spate of global issues the industry has faced in the last year. “We are making progress,” he said. “Serious, serious progress.”

Whitney Goulstone, director, communications, Canadian Immunodeficiencies Patient Organization (CIPO), presented “Protecting Patient Access in Ontario: A Patient’s Voice.” A PID patient herself, Ms. Goulstone took the audience through CIPO’s advocacy efforts opposing legislation banning compensated plasma donation in Ontario. Although the legislation passed in 2014, she said that the patients and advocates in Canada will continue to fight on behalf of access and highlight support for compensated plasma collection.

Two donors took time to speak to the audience about their dedicated donation routines and the pride they take in saving lives. A 20-year-old college student who has donated more than 80 times at the BioLife Plasma Center in Harrisonburg, Va., told the crowd, “It is great to learn about the people who are in need of my plasma and that some of the people are close to home.” Another donor, a 43-year-old military officer who has been deployed several times, said he donates twice weekly whenever possible at the Biomat USA Frederick center, a Grifols facility in Frederick, Md. He shared how he has seen firsthand the necessity of plasma during war. “Without plasma and without the life-saving benefits, they would not have made it off the battlefield,” he said.

Dr. Mark Becker, Director, Grifols Plasma Medical Department

PPTA Hosts Regulatory Workshop

More than 100 people attended the June 15 PPTA Regulatory Workshop, “Evaluation of the Safety of Source Plasma Collection.” The workshop was held in conjunction with the Plasma Protein Forum and included an overview of all the industry initiatives related to donor safety including the physiology of plasmapheresis, FDA’s nomogram, blood donor safety data, and the overall safety of plasma collection. Building on successful 2013 and 2014 workshops, the PPTA Medical Policy Committee developed the event with the support of the PPTA Regulatory Policy & Compliance Steering Committee. Participants included PPTA members Linda Roochvarg (Octapharma Plasma); Mark A. Becker (Grifols Plasma Medical Department); Jim Lenart (BioLife Plasma Services/Baxalta); Janet C. Hershman (BioLife Plasma Services/Baxalta); Toby L. Simon (CSL Plasma); and Shinji Wada (Biomat USA, Inc./Grifols). Peter Tomasulo (Consultant to PPTA) and Benjamin D. Levine (UT Southwestern) also participated. The following PPTA representatives participated: Joshua Penrod, Vice President, Source & International Affairs; Mary Gustafson, Vice President, Medical & Regulatory Policy; and George Schreiber, Director, Epidemiology.

During his presentation, “A Scandal in Geneva: National Self-Sufficiency & The WHO,” Dr. James Stacey Taylor urged stakeholders in every facet of industry to demand better evidence when policymakers declare self-sufficiency as the best way for countries to take care of their citizens in regards to blood and blood products.

“Of a country which pursues national self-sufficiency in blood or plasma or any other medical product that it can import cheaper, it’s wasting its health care resources on an ideological, ideologically-motivated policy,” said Dr. Taylor. “In human terms, this means that it is not helping its patients in the way that it should. It’s spending money badly.”

The Forum opened with a moment of silence for Dr. Víctor Grífols Lucas, a founder of Grifols and innovator known for his work on plasmapheresis. He passed away on June 1, 2015, and was remembered for his valuable contributions to the industry.

JULIE BIRKOFER, Senior Vice President, North America & Global Health Policy
Alabama Senate Majority Leader Reed Champions Plasma Donation Legislation

BY BILL SPEIR

“I have the perfect sponsor in mind. If he is willing to carry our bill, we’ll be in good shape.” Curt Lee, PPTA’s Alabama Lobbyist, mentioned this to me over the phone back in December of 2013. Truer words have never been spoken. The sponsor Curt Lee had in mind was Senate Majority Leader Greg Reed. Because Sen. Reed agreed to champion our bill, 18-year-olds can now donate plasma in Alabama. This is a victory for everyone who relies on plasma donations for their life-saving plasma protein therapies.

There are 511 International Quality Plasma Program (IQPP) certified centers in the United States, including 15 in Alabama. As of July 1, 2015, Alabama plasma donation centers may accept donations from 18-year-olds just like the rest of the country. It wasn’t always that way.

Prior to the passage of Sen. Reed’s Senate Bill 13, Alabama law indirectly prohibited 18-year-olds from donating plasma since Alabama law establishes 19 as the age of majority. Two exceptions to the law allow 16-year-olds to donate with parental consent, and 17-year-olds to donate blood without parental consent, as long as they are not compensated for the donation. This meant plasma donation centers, which compensate donors for their time, were not allowed to accept 18-year-olds as plasma donors.

Anyone who knows anything about legislation knows that passing legislation is difficult. It takes a committed sponsor and a good idea. Even then, success is not guaranteed. Sen. Reed first sponsored legislation to lower the age to donate plasma during the 2014 Legislative Session. The bill had a great start; rocketing through the Senate with his leadership. The Legislative Session began on January 14, 2014. A week later, the Alabama Senate Committee on Health, chaired by Sen. Reed, passed Senate Bill 204 by a vote of 8-0. The bill passed the Senate on February 6, 2014.

Unfortunately, the bill did not do as well in the House of Representatives. The bill made it through the committee process and was listed on the special order calendar the last week of session. There it died when the Alabama Legislature concluded the 2014 Legislative Session on April 3, 2014.

Maj. Leader Reed stayed committed to the legislation that would help so many people. He stated, “The law in Alabama doesn’t make sense when you consider an individual can enlist in the military and fight for their country at 18, but they can’t donate plasma. We should do everything we can to allow people to donate plasma. Plasma is necessary for the manufacturing of life-saving plasma-derived therapies that treat patients with rare and chronic conditions. Allowing 18-year-old Alabamians to donate their plasma represents an important step in helping ensure patients continue to have access to these important plasma protein therapies.”

Maj. Leader Reed sponsored the legislation again during the 2015 Alabama Legislative Session which began on March 3, 2015. Nine days later the Senate passed his bill. Senate Bill 13 was received in the Alabama House of Representatives on the same day, March 12, 2015. By April 14, 2015, the bill had passed. The law became effective on July, 1, 2015. Curt Lee was right: Sen. Reed was the perfect sponsor.

BILL SPEIR, PPTA Senior Director, State Affairs

Prior to the passage of Sen. Reed’s Senate Bill 13, Alabama law indirectly prohibited 18-year-olds from donating plasma since Alabama law establishes 19 as the age of majority.
Dominika Misztela
MANAGER, REGULATORY POLICY EUROPE

Q How long have you been with PPTA?
I started in June 2015.

Q What do you focus on in your role as Manager for Regulatory Policy in Europe?
My role is to manage the regulatory policy activities related to the plasma protein sector, primarily in Europe. This includes monitoring, identifying and evaluating issues of regulatory nature, and developing strategies to address these together with our industry members. I work with PPTA committees to develop consensus points on regulatory policies, guidelines and issues, and also with European and national regulators and stakeholders, such as the European Commission (EC), European Medicines Agency (EMA), European Directorate for the Quality of Medicines (EDQM), EU members’ states National Competent Authorities, and the WHO Expert Committee on Biological Standardization, towards a constructive dialogue and to foster a beneficial regulatory environment. For example, I develop position papers, guidelines, standards based on industry consensus, prepare workshops and meetings of regulatory nature, and liaise with government officials, clinicians, expert academics and patient organizations in matters of regulatory strategy and public policy.

Q Tell us about your background.
I am a typical ‘European’: I was born in Poland and brought up in Austria and lived and worked in the UK for 12 years, moving to Belgium in 2011. I am fluent in four languages, and learning a fifth one, French, by default through my 2 year old daughter who is attending French-speaking daycare. I have a Joint Honours BSc. in Biochemistry and Immunology from King's College London, UK, and a Ph.D. in Molecular Immunology from the University of Oxford, UK. After completing my Ph.D. in 2007 and a stint as a researcher at GlaxoSmithKline Pharmaceuticals working on atherosclerosis and metabolic syndrome X, I went into managing cancer clinical trials for a CRO. In 2008, I joined the International Cancer Clinical Trials Unit (ICCU) at Imperial College London, UK, and worked on breast cancer studies, including coordinating associated translational projects and Quality of Life research. In 2009, I was presented with the opportunity to lead a high-profile maternal and child health research program portfolio at the National Perinatal Epidemiology Unit (NPEU) at the University of Oxford.

Prior to coming to PPTA, I worked at the European Organization for the Research and Treatment of Cancer (EORTC) in Brussels as the Associate Head of the Regulatory Affairs Unit. I was responsible for the regulatory oversight of the organization’s entire trials portfolio, and managed, amongst others contact and communication with global regulatory agencies, pharmaceutical and academic partners, implementation of regulatory strategies and a team of six regulatory affairs specialists. My specialty area was multi-country multi-center submissions using the Voluntary Harmonization Procedure (VHP). I worked closely with the Heads of Medicines Agencies (HMA) Clinical Trials Facilitation Group (CTFG) to pilot the VHP process for companies in Europe. On behalf of the
EORTC, I took part in the revision of the EU Clinical Trials Directive, which became the EU Clinical Trials Regulation in May 2014, as well as in testing of the pilot versions of EMA’s public results database, which will host publicly available clinical trial results from April 2016 onwards.

**How did you get involved in this industry?**

I always enjoyed being a specialist, so my background in life sciences and my experience in regulatory affairs and clinical trials on a European level fitted very well with the role of the Manager for Regulatory Policy in Europe. Coming to PPTA allowed me to expand my knowledge of a very specific and increasingly important therapeutic field and the very unique Plasma industry. In addition, PPTA works all across the world, which inspired and interested me, as I previously just mainly worked on European projects. I also wanted to work in an environment which allowed for very close interaction with industry and regulators – and this is definitely the case at PPTA.

**What’s your favorite city in the world?**

I enjoy travelling in Europe and other countries throughout the world. One of my favorite cities is Berlin. I think in large part this is because I watched the Berlin Wall fall on TV when I was quite young. It was one of the very first times I was allowed to stay up late and watch TV. It made a huge impression on me and since then I have a particular relationship with Berlin. Apart from its role during the Cold War and the fall of the Iron Curtain, I am taken by its originality, the differences between the districts and between the east and west parts (still), and of course the striking architecture. It is also very spacious, so one rarely feels confined unlike in many other European capital cities. Also, it is incredibly cosmopolitan, has many superb cafes, bars and restaurants, without being too snobbish. One can eat really well for less than 5 euros! Just ask our VP!
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ATLANTA
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Norcross, Georgia 30093

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## Upcoming Events

### October

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>11–17</td>
<td>International Plasma Awareness Week</td>
<td>Budapest, Hungary</td>
</tr>
<tr>
<td>15–16</td>
<td>10th Annual Meeting of the International Conference on Rare Diseases &amp; Orphan Drugs</td>
<td>Mexico City, Mexico</td>
</tr>
<tr>
<td>18–21</td>
<td>Combined Annual Scientific Meeting of the Haematology Society of Australia and New Zealand &amp; New Zealand Society of Blood Transfusion/Australasian Society of Thrombosis and Haemostasis</td>
<td>Adelaide, Australia</td>
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<tr>
<td></td>
<td>World Federation of Hemophilia Global Forum on Research and Treatment Products for Bleeding Disorders</td>
<td>Buenos Aires, Argentina</td>
</tr>
<tr>
<td>22–23</td>
<td>Annual Meeting of the American Association of Blood Banks</td>
<td>Anaheim, California, United States</td>
</tr>
<tr>
<td>25</td>
<td>PPTA Business Forum (Members Only)</td>
<td>Anaheim, California, United States</td>
</tr>
</tbody>
</table>

### November

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Location</th>
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</thead>
<tbody>
<tr>
<td>2–6</td>
<td>Haemophilia Academy 2015</td>
<td>Edinburgh, Scotland</td>
</tr>
<tr>
<td>5–6</td>
<td>International Primary Immunodeficiencies Congress 2015</td>
<td>Budapest, Hungary</td>
</tr>
<tr>
<td>11–13</td>
<td>6th Annual World Orphan Drug Congress</td>
<td>Geneva, Switzerland</td>
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### December

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Location</th>
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<tbody>
<tr>
<td>14–16</td>
<td>26th Regional Congress of the International Society of Blood Transfusion</td>
<td>Bali, Indonesia</td>
</tr>
<tr>
<td>18–21</td>
<td>4th Meeting of the Latin American Society for Immunodeficiencies</td>
<td>Buenos Aires, Argentina</td>
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</tbody>
</table>

### 2016

### February

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–5</td>
<td>9th Annual Congress of the European Association for Haemophilia and Allied Disorders</td>
<td>Malmö, Sweden</td>
</tr>
<tr>
<td>29</td>
<td>Rare disease day</td>
<td></td>
</tr>
</tbody>
</table>

### March

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Location</th>
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</thead>
<tbody>
<tr>
<td>22–23</td>
<td>International Plasma Protein Congress</td>
<td>Barcelona, Spain</td>
</tr>
</tbody>
</table>

### July

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Location</th>
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</thead>
<tbody>
<tr>
<td>24–28</td>
<td>World Federation of Hemophilia 2016 World Congress</td>
<td>Orlando, Florida, United States</td>
</tr>
</tbody>
</table>
### Glossary of Terms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>AAT</td>
<td>Alpha-1 Antitrypsin</td>
</tr>
<tr>
<td>ACT</td>
<td>Alpha-1 Coded Testing</td>
</tr>
<tr>
<td>BPWP</td>
<td>Blood Products Working Party</td>
</tr>
<tr>
<td>CEREDIH</td>
<td>French National Reference Center of Primary Immunodeficiencies</td>
</tr>
<tr>
<td>CIPO</td>
<td>Canadian Immunodeficiencies Patient Organization</td>
</tr>
<tr>
<td>CRC</td>
<td>Clinical Resource Center</td>
</tr>
<tr>
<td>CTFG</td>
<td>Clinical Trials Facilitation Group</td>
</tr>
<tr>
<td>CURhE</td>
<td>Consortium for Universal RH Disease Eradication</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organization for the Research and Treatment of Cancer</td>
</tr>
<tr>
<td>ESID</td>
<td>European Society for Immunodeficiencies</td>
</tr>
<tr>
<td>EUenetHTA</td>
<td>European Network for Health Technology Assessment</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>FEIBA</td>
<td>Factor Eight Inhibitor Bypassing Activity</td>
</tr>
<tr>
<td>HDN</td>
<td>Hemolytic Disease of Newborns</td>
</tr>
<tr>
<td>HFA</td>
<td>Hemophilia Federation of America</td>
</tr>
<tr>
<td>HMA</td>
<td>Heads of Medicines Agencies</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>I2B2</td>
<td>Informatics for Integrating Biology and the Bedside</td>
</tr>
<tr>
<td>ICCU</td>
<td>International Cancer Clinical Trials Unit</td>
</tr>
<tr>
<td>IDF</td>
<td>Immune Deficiency Foundation</td>
</tr>
<tr>
<td>IG</td>
<td>Immunoglobulin</td>
</tr>
<tr>
<td>IPPIA</td>
<td>International Plasma Products Industry Association</td>
</tr>
<tr>
<td>IQPP</td>
<td>International Quality Plasma Program</td>
</tr>
<tr>
<td>IVIG</td>
<td>Intravenous Immunoglobulin</td>
</tr>
<tr>
<td>MUSC</td>
<td>Medical University of South Carolina</td>
</tr>
<tr>
<td>NAT</td>
<td>Nucleic Acid Amplification Test</td>
</tr>
<tr>
<td>NHLBI</td>
<td>National Heart, Lung, and Blood Institute</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>NPEU</td>
<td>National Perinatal Epidemiology Unit</td>
</tr>
<tr>
<td>OEIH</td>
<td>Oesterreichisches Institut Fuer Haemoderivate</td>
</tr>
<tr>
<td>PCORI</td>
<td>Patient-Centered Outcomes Research Institute</td>
</tr>
<tr>
<td>PI</td>
<td>Primary Immunodeficiency</td>
</tr>
<tr>
<td>PMI</td>
<td>Precision Medicine Initiative</td>
</tr>
<tr>
<td>PWH</td>
<td>Persons with Hemophilia</td>
</tr>
<tr>
<td>PUP</td>
<td>Previously Untreated Population</td>
</tr>
<tr>
<td>REDCaP</td>
<td>Research Electronic Data Capture</td>
</tr>
<tr>
<td>SCIG</td>
<td>Subcutaneous Immunoglobulin</td>
</tr>
<tr>
<td>UENPS</td>
<td>Union of European Neonatal and Perinatal Societies</td>
</tr>
<tr>
<td>USIDNET</td>
<td>U.S. Immunodeficiency Network</td>
</tr>
<tr>
<td>VHP</td>
<td>Voluntary Harmonization Procedure</td>
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</tbody>
</table>
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