THE SUMMER 2012

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**CE-IVD. The duplex test for B19V and HAV has been filed with the FDA under a Master File. It is available to US laboratories that meet specific FDA requirements.



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THE SOURCE is published four times a year by PPTA, 147 Old Solomons Island Road, Suite 100 Annapolis, MD 21401 Phone:+1.202.789.3100 email: thesource@pptaglobal.org

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In the interest of encouraging broad and open discussion of issues relating to plasma protein therapies, collection and fractionation, THE SOURCE magazine may contain statements of opinion on such issues. These statements are those of the author and do not necessarily reflect the opinion of PPTA or its members.

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Life needs answers

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IN MY VIEW

Reflections on Our History

A Focused Evolution: Safety to Affordability Economic issues force shift in priorities

Patient Access: An Enduring Commitment Sustained collaboration yields appreciation



Source Plasma Collection's Intricate History A look back at the core of this industry



Policymakers Recognize PPTA's Leadership

History of Plasma Protein Therapies Developments in Therapies Prove Significant

Milestones in Pathogen Safety Marked Progress Yields Confidence.

An Industry View: Regulatory Perspectives FDA and EMA leaders provide viewpoint.



Advocating for Free Trade Facilitating a global environment for plasma protein therapies.

The Roots of the Plasma Protein Association and Its Pioneers Early visionaries establish Association.

Looking Back at 30 Years Cathy Izzi Reflects on Long Tenure

Facing Future Challenges Global Board Chair Speaks to Future

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IN MY VIEW

by Jan M. Bult, President and CEO

THIS EDITION OF THE SOURCE MAGAZINE is devoted to the celebration of the PPTA 20th Anniversary; however, our roots go deeper when we consider the start of ABRA in the early seventies. It fascinates me that so many of the companies that are manufacturing plasma protein therapies today, were started by pioneer families who had the foresight to engage in the development of therapies that would save so many lives. The names I am thinking of are Eibl, Grifols, Marcucci, Schwarz and Schleussner. They all founded companies multiple decades ago and created a legacy to be proud of.

But it was not only the manufacturers that played a crucial role. We should not forget the many donors that come in on a regular basis to donate their blood and/or plasma voluntarily to help their fellow citizens who need the lifesaving proteins. The collection of plasma as we all know can be done in two different ways. No matter what the methodology is, it requires commitment, dedication and the expertise of many who are working in the many collection centers in the world, day in and day out!

There has to be a first in every category. In our case it was "Buddy" Moss who brought all the plasma collectors together in the early 70's. I personally never met with Buddy, but did meet his sons, Larry and Stephen, both still very active with the Interstate Blood Bank. Listening to Larry is very entertaining, to say the least!

Today we are living in a world where the challenges are completely different than what they were several decades ago. There has been a shift from safety and quality to supply and affordability. But don't get me wrong! The industry will not be complacent when it comes to safety. We all understand the most important pillar when it comes to our therapies. But we do realize that providing therapies to relatively small patient populations comes with the unique challenges. The amount of time it takes to help people understand the complexity of the various steps involved in the manufacture of these important therapies is enormous but needs to be done, over and over again.

We are very fortunate that we have so many very qualified staff working with us together with the experts from our member companies to do this important work. We are ready to continue our journey to a better world for the patients who depend on the plasma protein therapies. 🦚



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A FOCUSED EVOLUTION: SAFETY TO **AFFORDABILITY**

BY CHARLES WALLER



TWENTY YEARS AGO, the strong focus of all plasma protein stakeholders was on safety. In the context of the time this was understandable. Although regulations in the United States had been in place for some time, in Europe the evolution from blood collection resulted in the sector not being regulated at the European level until the first legislation in 1989¹.

Patients are broadening the definition of safety to include access, availability and affordability; indeed they have gone further and agree that a lack of treatment is the major "safety" challenge facing them today.

As a result of this law, plasma derivatives became part of the laws and regulations for pharmaceuticals. This also coincided with the development and implementation of PPTA's voluntary International Quality Plasma Program (IQPP) and other standards which are written about elsewhere in this publication. As a result of plasma derivatives

being controlled and regulated as pharmaceuticals, quality, safety and efficacy became the foundation that guided the manufacture and distribution of plasma proteins. Tried and tested, in broad terms this regulatory framework has served the multiple interests of all stakeholders very well. Sadly, newspapers remind us that there is a delicate balance to be struck between meeting the escalating expectations of patients and their

doctors who want access to the latest, state of the art medicines; and, at the same time making sure that only drugs that comply with the regulations are available to prescribe. The media is quick to describe the rare cases where the balance has gone the wrong way and to over hype or mislead readers on the promise of new "wonder" drugs. They seldom find space for the significant majority of instances where the "system" gets it right.

In 2012, plasma protein therapies have achieved a very high level of safety, and the pathogen safety record of the last 20 years is commendable; but, constant vigilance is required as the thrombo-embolic experience reminded us in 2011². There must never be any space for complacency when safety and regulatory requirements are being considered, but as patients and doctors are increasingly pointing out; with plasma protein therapies (PPTs) the three requirements should probably be extended a little.

Patients³ are broadening the definition of safety to include access, availability and affordability; indeed they have gone further and agree that a lack of treatment is the major "safety" challenge facing them today.

Payers⁴, increasingly being asked to do more with less, share the patients' concerns about affordability. Pressures on government budgets and healthcare programs in particular have accelerated pressures on manufacturers and these pressures are here to stay. This is forcing all stakeholders to be more knowledgeable about

¹European Directive 89/381 http://eur-lex.europa.eu/LexUriServ/LexUriServdo?uri=CELEX:31989L0381:en:NOT ² http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/09/WC500097037.pdf ³ Johan Prevot, IPOPI Global Leaders Meeting, Nov. 2011: http://www.ipopi.org/uploads/Johan%20Prevot.pdf ⁴ Includes, Insurers, state funding programs, and patients themselves

The Unique Nature of Plasma Protein Therapies



reimbursement practices, and about the "pinch points" imposed by payers to control their spending.

In this publication, we regularly report on the new ways that payers are using. Usually this is based on experiences from spending on other pharmaceuticals and then applied, often inappropriately, to plasma proteins with only modest recognition of the significant differences between plasma protein deficiencies and other treatments.

Rare, inherited and chronic conditions treated with biological, human plasma, which replaces proteins that are lacking in patients, such as most plasma protein deficiencies, actually imposes very difficult challenges for payers. These challenges are the starting point for affordability issues. Taking them one by one it is not surprising that there are challenges: So affordability and the related availability are here to stay as a challenge for all PPT stakeholders. PPTA will continue to fight for the recognition of the various unique aspects of plasma protein therapies 🦚

CHARLES WALLER, Vice President, Europe



PPTA RECOGNIZES THE IMPORTANCE

of working with Stakeholders and is keenly aware of the value of those relationships. Since the early 1990's, PPTA has convened in various forms meetings that included consumer organization representatives, industry experts and on occasion representatives from government entities. The benefits of identifying a unifying theme such as patient access to plasma protein therapies, seeking alignment on advocacy issues and executing on those objectives have been integral to our shared legislative and regulatory successes. The biggest benefactors of these shared relationships are the patients who infuse or inject life sustaining plasma protein therapies and who rely on their access to treatment.

For over two decades, PPTA has been focused on establishing rapport with patient organizations; better understanding the concerns of the patient community; learning about their legislative priorities; discussing ways in which we can advocate together on strategic issues of patient access; and sharing information about important safety developments within the industry as well the industry standards programs.

The following insights from key opinion leaders within the global community of plasma protein users are significant because they offer a glimpse into where we have been and some perspective on where we hope to go. We hope you enjoy reading them.

Julie Birkofer, Senior Vice President, North America



To Our Dear Friends at PPTA;

A few years after we started the Jeffrey Modell Foundation, in the early 1990's, we were invited to participate at a PPTA Board Meeting. We were so appreciative and in awe to be included among such an elite group of people, but frankly, we were a bit intimidated by the very important and esteemed group of senior executives. We tried our best to be polite, respectful and very deferential

However, in a short time, there was a remarkable transformation! We soon came to realize that the company executives representing corporate members of PPTA were really extraordinary individuals. They were compassionate, generous and genuinely interested in the well-being of the patients.

Without exception, for every one of these individuals, The Patients Came First! It was not so much the corporation name or the leadership of PPTA. It was caring individuals who really wanted to help. People like Jan Bult, Julie Birkofer, Charles Waller, Peter Turner, Larry Guiheen, Larry Stern, Rudi Waeger, Paul Perreault, Chris Healy, Victor Grifols, Wolfgang Marguerre, and that is just naming a few. We have made many great friends throughout the years that we have participated at PPTA. New friendships strengthened out of mutual respect and commitment to a single mission... The Best Interests of Patients.

Soon we were given the opportunity to appear before the United States Congress, the European Parliament, and meet with government officials from Argentina, Brazil, Chile, China, Japan, Tunisia and many others. The strength of the PPTA member companies, together, with the support and encouragement of these treasured. friendships, created the impetus that gave us the courage to speak up for patients all over the world. The message of earliest possible diagnosis and access to safe, life-saving and life-enhancing therapies was clearly heard everywhere! Again ... The Best Interests of Patients.

Patient groups working in close collaboration and in harmony with PPTA now represent a formidable voice. Government officials and agencies, payers and even the media are now taking notice of our unified mission. Thank you PPTA for "20 years" of unwavering commitment to bringing a better quality of life for all whom you serve. You have given patients a brighter, safer and more secure future.

You have our warmest and sincerest gratitude on behalf of patients throughout the world.



CONGRATULATIONS TO PPTA IN CELEBRATING 20 YEARS OF SERVICE.

As the authority on source plasma collection, PPTA has striven both on the European front and American shores to develop standards of quality and safety. PPTA has been



a changing force through the decade of despondancy experienced by plasma users to embracing and leading excellence in collection practices. Their partnerships with patients, industry, donors, customers and the federal government prove their vigilence to quality, safety and excellence.

DANA A. KUHN, PH.D. President Patient Service Inc., Bleeding Disorders Advocate



DURING THE PAST 20 YEARS,

patients with a primary immunodeficiency: as well as, those who use other plasma derived medical products, have had the knowledge that the products were increasingly safer and more effective, due to the hard work, perseverance and diligence of the plasma protein therapeutics industry.

PPTA has been the driving force behind setting the quality standards for this particular pharmaceutical industry and the improvements in the fractionating processes.

IPOPI wishes to congratulate PPTA on their 20th Anniversary and on all these achievements so that our patients can have a better quality of life due to the excellent products that are now available.

During the last decade the working relationship between PPTA and IPOPI has become a closer one. Collaboration is taking place on many fronts, such as shared communications on regulatory affairs and policies, political forums, global awareness campaigns, ESID registry and communication on pharmacovigilance. IPOPI highly values the collaboration with its stakeholders such as PPTA. We remain convinced that it is by working together that we can ensure patients affected by a rare plasma related disorder can access life saving treatments and have a better life and future.

Jan Bult has been at the helm of PPTA for many years and is continuing to strive for the supply of these precious medical products, which comes under so much pressure from outside influences, such as the current economic restraints. As a patient and president of IPOPI, I know that there are no alternatives to immunoglobulin replacement therapy and applaud you and your organisation for trying to ensure the future health of our patients.

Many happy returns on your 20th Anniversary.



We hear from patients after they have their first Ig therapy and we know the difference it makes in their lives. Comments like the following

"Before I was diagnosed, I was always sick with pneumonias, sinus infections and other upper respiratory infections, such as bronchilis. I lived coughing and always sick. Once I started receiving IVIG infusions, I got my life back; I have a wonderful family and a full-time job. I now live an active, normal, and productive life. Gamma globulin helps keep me healthier and alive; IVIG is my life line!"

This is my second year receiving immunoglobulin therapy. This treatment has changed my life. Three years ago, I was so sick that my husband and I were considering hiring a full-time caregiver to help look after me and to take care of our 8 year old son. It was difficult to make it through the day without taking extended naps. I was exhausted all the time. Today, I am living a pretty normal life. My outlook has improved dramatically. I wake up each day and look forward to what life will bring."

It is clear that the purpose of the PPTA has touched individuals to the very core of their daily existence!

Through the ongoing efforts and vigilance of PPTA, its member companies, the FDA and the patient communities patients no longer have to worry about the safety of their life-saving therapies. It was not always this way, as we know from the tragic transmissions of HIV and Hepatitis

Looking forward, while safety will always be a top concern, we must also focus on the availability of these unique therapies and continue to work together to ensure that patients have access. No one who needs these life-saving treatments should have to go without.

mpanies affects so many? I hope that all of the individuals associated with PPTA feel proud of what you do every day on behalf of patients with rare, chronic conditions whose lives depend on your plasma-based and recombinant biological therapies Congratulations, and keep up the vigilance!





Congratulations to PPTA on 20 Years of Saving and Improving Lives!

On behalf of the Immune Deficiency Foundation, the national patient organization dedicated to individuals with primary immunodeficiency diseases, I am honored to recognize and congratulate the Plasma Protein Therapeutics Association and the member companies on your 20th anniversary. The importance of PPTA and the PPTA Source division in the lives of patients cannot be over emphasized. Your liventy year commitment to fostering the collection of high-quality plasma, and establishing the highest levels of safety and quality in manufacturing has resulted in vasily improved plasma based products that literally save lives every day.

The majority of individuals with primary immunodeficiency diseases have defects in their immune system's ability to make antibodies to light infections. Immunoglobulin replacement therapy (Ig), produced by the PPTA member companies, is a lifesaving, plasma based literapy used by these patients to replace the antibodies their bodies cannot make, and protects them from life-threatening infections. Like many other patients who require eplacement with plasma-based therapies, Ig therapy is used life-long, and there is no other treatment available

Speaking personally, my son, who has a primary immunodeficiency, is alive and healthy because he has had access to safe, high-quality Ig therapy. He leads a normal and active life, and a few years ago, he and his wife made my husband and me grandparents. Isn't it amazing how the critical work of PPTA and its member

Marcin X. Byl

Immune Deficiency Foundation

40 W CHESAPEAKE AVE . STE 301 . TOWSON, MD 21304 . 800.296.4433 . 41 www.primerysmmune.org kittigp



The IPOPI team



PPTA HAS PLAYED A CRITICAL LEADERSHIP ROLE in establishing safety standards for plasma-derived products that exceed federal standards for its member organizations. This work has led to a safer and more secure supply of products that patient has come to trust and depend on for life saving therapies. PPTA's collaboration with patient groups dependent on plasma therapies has fostered the relationships and coordination to ensure access to therapies and care in a changing health care environment. Furthermore, PPTA's compassion in acknowledging the impact of the era of HIV on patients and their families has been an essential step in building ongoing trust and continued collaboration. The PPTA Board of Directors has worked to achieve a high standard for producing life-saving therapies and their leadership has benefitted both individuals with chronic conditions, as well as the American population as a whole.

VAL D. BIAS, CEO National Hemophilia Foundation





PPTA's continued monitoring of federal and state legislative issues has been extremely educational and keeps us at the ready.

In my short time as Executive Director with the Foundation, one thing that stands out above all else is our community's passion.

Each person I have met cares deeply and genuinely for patients, family members, caregivers, and the cause. I am honored to be involved with such a committed community. With over 29 years of experience working with non-profits, I have a deep appreciation for dedicated and hard-working volunteers and staff. I know that there is no greater reward than the opportunity to work with passionate volunteers in an outstanding organization. I also know we will never be able to do it alone. We depend a great deal on the generosity of individual and corporate donors that provide the funds necessary to advance our critically important efforts in expanding our research, plus our grassroots educational and advocacy initiatives. Our foundation cannot extend our reach to the broader audiences if not for the help, support and guidance we receive from the other patient organizations, especially those in the APLUS consortium. We cannot thank them enough.

That brings me to the Plasma Protein Therapeutics Association (PPTA) and the remarkable impact it has had on our small but resilient group of volunteers. Executives and staff of the PPTA have constantly and without hesitation answered our every call for help and guidance. By sponsoring the key stakeholder meetings at least twice a year, we reap enormous benefits as components of the Affordable Care Act are unfolding. Key issues have been identified by the group and plans for action were implemented to serve the best interest of the various patient populations. Managing this risk collectively under the guiding light of PPTA staff was critical in broadcasting our concerns and getting good, solid results. PPTA's continued monitoring of federal and state legislative issues has been extremely educational and keeps us at the ready. The PPTA /GBS-CIDP webinar was a huge success as we begin to formulate plans for a second one this year. Then we have the yearly Congressional fly-in to Washington that gets bigger and better each year. We take full advantage of the many contacts we make telling our story, while expanding the awareness of Congress.

I know that our founder Estelle Benson shares our respect and admiration for the PPTA and their many years of unconditional support. On behalf of Estelle, the Medical Advisory Board, the Board of Directors, and thousands of volunteers worldwide, we congratulate the PPTA on providing 20 years of highly professional and unparalleled service.

Ken Singleton **Executive Director**



104 172 Donnet Avenue Nammeth, PA 19072

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2937 SW 27th Avenue Suite 302 Miami, Florida 33133 Toll Free: 0898 825-7421 Tel: (305) 567-9888 Fax (305) 567-1317 www.alpha-1foundatio

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anniversary!

What began as an information exchange around areas of concern to the patient community - such as availability, donor recruitment and deferral, and blood safety - has become a true partnership in health policy.

Thank you to the PPTA staff and leadership for your professionalism and dedication to improving patient access to plasma-based therapies. Our heartfelt best wishes on your landmark anniversary. We look forward to a future of continued collaboration.

Best regards,

John Walsh, President & CEO, Co-founder

Director Envertore Manima V. Fernandico Miami, FL President and CEO John W. Walsit⁴

Co-Ftander Clinical Director Robert A. Sandhaun, M.D., Ph.D.

Scientific Director Adam Wanner, M.D.

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WE OFFER CONGRATULATIONS AND OUR HEARTFELT GRATITUDE for the exemplary leadership and vision provided by PPTA over these many years. The WFH has been proud to work alongside PPTA to improve treatment for individuals living with bleeding disorders all around the world. We share a common bond and vision that all patients regardless of where they might live deserve access to safe effective treatment. Through your development of voluntary standards you have not only improved safety but also restored confidence in plasma derived therapies. Your sensitivity to patient concerns and openness in collaboration are hallmarks of PPTA's leadership. Best wishes for many successful years ahead.

MARK W. SKINNER, President World Federation Hemophilia

Congratulations to the Plasma Protein Therapeutics Association on your 20th

We share a common bond and vision that all patients regardless of where they might live deserve access to *safe effective* treatment.





PLUS Statement - PPTA 20th Anniversary

PLUS wishes to congratulate the Plasma Protein Therapeutics Association (PPTA) on the occasion of its 20th anniversary.

In Europe, PLUS and PPTA have collaborated over the years on several projects all geared towards one common objective - to enhance access to treatment and diagnosis for patients living with a rare plasma related disorder.

The support of PPTA to European patient organisations over the years through stakeholder collaborative projects such as the Plasma Protein Users Group and the International Plasma Protein Congress has been pivotal in strengthening the dialogue between European patient organisations and their stakeholders.

These initiatives have been pivotal in promoting a transparent dialogue and information exchange with PLUS member patient organisations on key issues such as quality and safety of plasma derived medicinal products, access to treatment, regulatory and health policy developments.

PLUS greatly values its collaboration and applauds PPTA's commitment to patient access to care and its continuous efforts to improve the quality and safety of plasma derived medicinal products.

We look forward to continuing our dialogue in the forthcoming years and wish PPTA much success in the next 20 years!

Very best wishes to all, Brian O'Mahony, Johan Prevot. Larry Warren.

> Please reply in Johan Bross on PLUS, Finida, Main Road, PUT SLE Downderry, Unlad Kingdon MASI DENSI SO SIL MEMORINA



These initiatives have

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safety of plasma derived

medicinal products, access

to treatment, regulatory and

health policy developments.

Brian O'Mahony

Johan Prevot



Larry Warren







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SOURCE PLASMA COLLECTION'S INTRICATE HISTORY

by Joe Rosen and Joshua Penrod



the donation

experience for

donor and the

center staff.

both the plasma

IN ANY CONSIDERATION OF THE PLASMA PROTEIN THERAPEUTICS INDUSTRY.

one must examine its foundation: the donor and source plasma. Plasma collection has been the core throughout the decades of manufacture of plasma therapies. The long history of plasma collection has seen many social and cultural changes in the U.S. and Europe alike, and the unique nature of it and plasma-derived therapies show that it will witness more changes in the future. Plasma is as irreplaceable as can be imagined.

Origins of the Plasma Collection Industry

The collection of commercial plasma by plasmapheresis

began in the 1960's with the opening of plasma centers by fractionators. Soon thereafter independent companies also opened plasma centers to supply additional quantities of plasma for fractionation. The collection industry operated under the "short supply "provision The adoption of of the Food and Drug Administration (FDA) regulations and therefore were not inspected by the FDA. the automated The fractionators themselves had this crucial role. By plasmapheresis the mid-1970's FDA published specific regulations regarding the requirements for donor suitability, collecprocess tion and testing for plasma collected by plasmapheresis, markedly known as source plasma and assumed responsibility for improved inspecting and licensing centers.

The U.S. plasma collection industry was comprised of independent collectors of plasma both for manufacturing as well as for diagnostic use, and fractionatorowned plasma centers. In an effort to have the industry represented in proposed new FDA regulations and to eventually establish their own industry standards, the independent collectors and fractionators formed their own industry trade association called the America Blood Resources Association (ABRA) in the early 1970's.

With significant discussion beginning to occupy the regulatory sphere, the industry developed several guiding principles which would constitute much of the advocacy for plasma collection for decades into the future. Included in these are the beneficial nature of compensated donation, science-based regulatory policy, standards development, and ethical business practices. Because of the nature of the attention focusing on aspects of donor compensation, the industry grew to understand the need for advocacy on a larger scale.

ABRA was instrumental in helping the collection

industry interact with the FDA through the ABRA Regulatory Affairs Committee and helped collectors in training center managers through the Center Manager Workshops. Over the next decade, the plasma collection industry grew with the addition of new plasma centers and increased plasma center collections. The most significant change in the industry was the introduction of a system of automated plasma collection introduced by Fenwal and Haemonetics. This added safety feature was appreciated by both donors and collectors; and because, it took less time to donate, it attracted more donors and collections increased. The adoption of the automated plasmapheresis process markedly improved the donation experience for both the plasma donor and the center staff. Such devices are now universally used by PPTA member companies and, to many, represent the sights and sounds of plasma collection today.

In the early 1980s the industry was challenged with the emergence of AIDS and its potential risks in collections. Through ABRA, the industry adopted the most stringent donor suitability requirements, donor education programs, employee safety programs, and new testing requirements. These preceded the measures mandated by regulatory authorities, as well as, those implemented by the not-for-profit blood sector. The plasma collection industry forged and has maintained a path, for several decades, of process improvements that protect the patient, the donor and help the safety and quality of source plasma.

Plasma Collection in the 1990s

In the 1990s, approaches to donation became more technologically oriented. Companies steadily searched for ways to improve the plasma donation process for both donors and operational efficiency. Coupled with this were continuing improvements in infectious disease testing,

including the beginning of nucleic acid amplification tests (NAT). These factors, along with the installation of voluntary industry standards and changes in the regulatory sphere provided the industry with the confidence to pursue expansion plans. Fractionators invested in additional capacity the collection industry invested in new and larger collection centers to meet the increased demand.

At the same time, there were numerous changes in the work of the Association. The first institution of what was to become the IQPP began. The Qualified Donor Standard and the design and construction of the first version of the National Donor Deferral Registry (NDDR), and the establishment of the IQPP brought unheralded goodwill and the marked the beginning of trust from the patient and regulatory communities. As the IQPP evolved to include standards encompassing acceptable viral marker rates, quality assurance, donor education, and others, this trust continued to grow. Administered by the industry through the Association and utilizing independent auditors, IQPP

became the touchstone for the credibility and profile of the plasma collection industry.



Changes in regulatory systems also occurred in the 1990s, typified by the institution of greater uniformity of interpretation and greater focus on quality principles and oversight. As the regulatory landscape changed, this manifested in the industry through a series of steady technological improvements in the practices of plasma collection. As mentioned, the usage of technology increased as the variety of applications for technology increased.

Plasma Collection in Europe

While plasma collection in the U.S. accounts for the majority of source plasma collections both currently and historically, countries in Europe have also been important contributors to the global picture of plasma collection. Austria and Germany have the longest histories in the industry, while the Czech Republic has, in recent years, also been instituting a source plasma collection sector.

Historically seen, Austria can be thought as the "European pioneer" in the field of plasmapheresis and of plasma fractionation. The first plasma center opened in Austria in the 1960s and, in 1975, the Plasmapheresis Act was published. The eighteen plasma centers in currently in Austria have long records of production of high-quality source plasma. Germany, on the other hand, is unique within Europe for collecting remarkable quantities of plasma for the European and the international market. The Czech Republic possesses a long history of the highest level of transfusion expertise and state hospitals implemented plasmapheresis many years ago. European patients in need of plasma derivatives can be glad that currently several very modern and efficient plasma centers make a substantial contribution to the ever growing demand for high quality plasma.

European plasma plays an important role in the global context. European collectors have a long experience in producing plasma of highest quality and can be proud of their safety record for donors. To help ensure that the plasma collected (and the therapies produced from it) meets the highest quality and safety standards, European collectors adhere

The fact that centers located in Europe have managed for many decades to collect millions of units of safe, high quality plasma is a success story that would not have been possible without the continuous *effort of highly* motivated medical professionals and even more of tens of thousands of very committed faithful donors.

not only to national and European regulations, but also to a set of voluntary industry standards, e.g. IQPP.

The fact that centers located in Europe have managed for many decades to collect millions of units of safe, high quality plasma is a success story that would not have been possible without the continuous effort of highly motivated medical professionals and even more of tens of thousands of very committed faithful donors. These facts stand for themselves and show the importance of European plasma collected in Austria, Germany, and the Czech Republic.

Recent History

The opening decade of the 2000s has been a story of increasing strength for the plasma collection industry and PPTA Source. With the optimization of IQPP, the standards became updated and grew more relevant, including the most recent efforts to design them for applicability in many different jurisdictions. It also featured the development of another new standard, which helps to prevent over-donation and operations improvements in the landmark NDDR system.

The globalized nature and interrelatedness of all participants in the plasma industry, indeed, every industry, that burgeoned through 2000 to the present made it mandatory to create a viable web presence and be prepared for a 24/7 global news cycle. The industry began a new effort to improve the profile of plasma collection and educate the public, stakeholders, and policymakers about plasma and the collection industry. These efforts manifested themselves through a number of means, including:

- Websites devoted solely to plasma collection (www.donatingplasma.org, www.dieplasmaspende. de and www.dieplasmaspede.at)
- Facebook ad campaigns in several countries
- New brochures and literature describing the
- industry, the IQPP program, and plasma donation. • Videos and CD-ROMs available to PPTA members for
- usage in educating communities about plasma donation. Today, the scrutiny applied to the industry is higher

than ever. While needing to be mindful of this, it also represents an opportunity to explain all of the good that the industry does, and all of the lives saved through plasma collection.

In addition to the work performed in the Association setting, the industry's improvements during this same time frame have continued. Notable is that the incorporation and role of technology has become

so widespread that, in the most modern sense, it is inseparable from plasma collection itself. What began in earnest in the 1990s has become ubiquitous now, with many centers having fully integrated advanced technological systems, including biometrics and donor management software, which created track-and-trace system for all donors and donations, and further improvements in the testing paradigm.

Considering the important dependency of fractionators on plasma collections the time had arrived for ABRA to merge with PPTA and become one trade association representing both collectors and fractionators. The Source division of PPTA emerged and the plasma industry was united and fully integrated with worldwide fractionators and independent collectors in the U.S. and Europe.

This has been both a solution to address needs for greater efficiency for plasma collection, and as a driver for improvement. Efficient and effective plasma collection, by moving donors through the process quickly, has become a cornerstone of customer service. This improved efficiency has been accompanied by improvements in systems which also benefit safety and quality for both the donor and the collected plasma.

Conclusions

The long history of plasma collection is one of steady evolution leading to progress. Throughout all of its history, the industry has worked toward steady improvement in all areas of operations, ranging from donor screening techniques through to testing technology. Monumental and obvious advances such as automated plasmapheresis and NAT testing are noticeable by all, while more subtle improvements have also had a positive impact.

Source plasma has linked donors and patients together for decades. Over the past six years, there have been nearly 100 million plasma collections in the United States and Europe, which, after having been made into finished therapies, have saved thousands of lives around the world. (The authors would like to offer grateful acknowledgement for the assistance of Rudolf Meixner of Europlasma for perspectives on European plasma collection and other topics in this article.

JOE ROSEN, Director, New Business Development, Baxter BioLife, Source Board of Directors

JOSHUA PENROD, Vice President Source

STATE OF MARYLAND OFFICE OF THE GOVE



A MESSAGE FROM GOVERNOR MARTIN O'MALLEY

Dear Friends

Welcome to celebration of the 20th Anniversary of the Plasma Protein Therapeutic Association.

PPTA has been a leader in pushing for greater patient access to plasma protein therapy. You have been a vocal advocate for advancement in this field and have worked diligently to collect plasma from donors, create safe standards in the industry, and increase communication and knowledge around the field of plasma protein therapy.

If there is a common thread running through our efforts together, it is the thread of human dignity; of work, a home and the dignity of every individual. Thank you for protecting the lives of our most valuable resource - our people

Congratulations on your anniversary, and best wishes for many more years to come.













MARTIN O'MALLEY

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POLICYMAKERS RECOGNIZE **PPTA'S** LEADERSHIP

Greetings-Plasma Protein Therapeutics Association 20th Anniversary

June 20, 2012



As Mayor of the District of Columbia, I am pleased to extend greetings to the Plasma Protein Therapeutics Association (PPTA) on the occasion of your 20th Anniversary.

This event provides an opportunity for industry leaders and organizations to discuss the importance of maintaining access to lifesaving plasma protein therapies for the patients who need them. I thank the Plasma Protein Therapeutics Association for your dedication to promote the availability of and access to safe and effective plasma protein therapeutics. As you gather for this special occasion, I invite all of you to enjoy the monuments, museums, restaurants, and diverse neighborhoods that help enhance this city - our nation's capital. Experiencing these landmarks should serve to strengthen the memories of the celebration.

On behalf of all the residents of the District of Columbia, you have my best wishes for an enjoyable and memorable event.

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Vincent C. Oray Mayor, District of Columbia

HISTORY OF PLASMA PROTEIN THERAPIES: The Era of Fulfillment (1992–2012)

by Albert Farrugia, Ph.D.



AS PPTA CELEBRATES ITS TWENTIETH ANNIVERSARY, it is appropriate to reflect on the developments involving plasma protein therapies over this period. I have chosen to call these past twenty years *"The Era of Fulfillment"*. The evolution and impact of plasma protein therapies has had lasting and significant impact. The promise of earlier years, which showed that plasma protein therapies could be beneficial in a number of conditions, was confirmed and expanded by the developments of this period and in particular by the application of clinical research and evidence-based medicine to these therapies. A survey of the various therapies confirms this.

Albumin

The plasma industry came into being during World War II, following Professor Edwin Cohn's pioneering work on behalf of the US military *(see Farrugia, Source Winter 2008).* This first usage of albumin in the treatment of battlefield injuries established the protein as the ideal therapy for acute blood loss and shock. Over the succeeding decades, albumin usage for this indication was essentially, unquestioned. It was not until the modern era of evidence-based medicine that albumin, like all other medical interventions, came under scrutiny. Coupled with increasing pressures to reduce costs, advocates of evidence-based medicine insisted that albumin also needed to "prove" its safety and efficacy through the application of randomized clinical trials. Indeed, in a meta-analysis¹ claiming to summarize such trials, the prestigious Cochrane Collaboration claimed in 1998 that albumin was unsafe. This led to a lot of doubts on the future of the product.

Since then, we have seen these doubts dispelled, and albumin's role as the colloid treatment of choice confirmed. The original Cochrane analysis was quickly contested by other meta-analyses disproving it. But the key finding confirming the safety of albumin was



WWII soldiers in battle.

Albumin used to treat battlefield injured.

a large randomized clinical trial carried out in Australasia—the so-called SAFE trial study—which showed that albumin given to patients in intensive care was truly safe. Furthermore, this study indicated that albumin may be particularly beneficial in patients with sepsis, and the same Australian investigators subsequently performed a meta-analysis showing that albumin decreased mortality in patients in intensive care. Together with the demonstration that other, synthetic, colloids are associated with harmful effects such as bleeding and kidney failure, this has continued to confirm albumin's therapeutic status. And over the past ten years, new indications, such as liver disease, have been found which benefit many patients treated with this unique product.

Serum albumin

molecular structure

Immunoglobulin

For many years, this important plasma protein could not be administered efficiently to patients needing it. This was because features of Cohn's original fractionation scheme led to changes in the protein which resulted in severe reactions in patients. Over recent years, investment in new technologies by the industry has resulted in preparations of immunoglobulin which clinicians can administer in large doses intravascularly and, more recently, subcutaneously. As a result, the life of patients deficient in immunoglobulin and suffering from immune deficiency has been revolutionized. The avoidance of infections which would otherwise damage the lungs, gut and other organs in these patients has resulted in remarkable increases in life expectancy and quality of life. In addition, a number of other serious diseases, mostly involving the nervous system, which ensues from the formation of pathologic antibodies against the body's own systems, have been shown to be treatable with immunoglobulin. Clinical studies have established these indications and have benefited patients suffering from a range of rare disorders for which other treatment options are limited. And the possibility of other indications is being investigated with more clinical trials. There is every reason to hope that immunoglobulin treatments will continue to expand and bring hope to patients.

¹ A Meta-Analysis is a statistical combination of clinical trials performed for the same clinical outcome and having sufficient similarities so that their treatment effects can be pooled into one outcome.

Coagulation factors

Over these past twenty years, the life expectancy of people with hemophilia has increased by twenty years, to approach that of normal individuals. This fulfillment of the promise of coagulation factor therapy has resulted from several factors. These past two decades have seen the establishment of safety measures which have eliminated the risks of previous generations of products In addition, technological innovation has increased greatly the supply of products. This has made possible greatly advanced treatment, particularly in the form of prophylaxis, which practically eliminate bleeding and ensures a high quality of life in patients. We are now in the era of the first generation of aged people who have hemophilia, which presents therapeutic challenges. Whereas the provision of one to two units of Factor VIII per head of population was the standard of care twenty years ago, today, five units and more are expected by treaters and patients alike, and this amount is exceeded in several countries.

Conclusions

The past twenty years have seen the fulfillment of the promise of plasma protein therapies as safe and effective treatments. We now face the challenges of the future. In various countries, continuing financial pressures from the ongoing economic climate threaten the gains. In addition, the majority of people needing plasma protein therapies lack access to these products. We must hope that the past provides a mirror for the future and that the progress achieved since the establishment of PPTA continues. That the potential for plasma protein therapies is still to be fully realized. We have many other products which we can see can help people. All that is needed is goodwill, and commitment, which PPTA will demonstrate, over the next twenty years and beyond. (S)

Albert Farrugia, Ph.D., Vice President Global Access

INDUSTRY REMAINS VIGILANT IN PATHOGEN SAFETY

BY DOUGLAS C. LEE, PH.D AND NATHAN J. ROTH, PH.D.

WE BOTH JOINED the plasma biotherapeutics industry in 1995, but at two different companies. At that time, the industry was still struggling with the aftermath of the tragedies of virus transmission that occurred in the 1980s and early 1990s.

Over the course of our careers, the situation has continually changed for the better and we are proud to be part of an industry that is committed to providing safe and efficacious therapies. The plasma protein therapies of today, manufactured from human plasma, have an excellent margin of safety with respect to bloodborne pathogens. These products are used to treat patients throughout the world in a variety of therapeutic areas including blood coagulation, pulmonology, neurology, immunology, and intensive care.

From a pathogen safety perspective, we have seen the industry evolve from a reactive to a proactive entity. In the past, a "reactive" industry would "bolt-on" a process step or steps to mitigate

the potential transmission of viruses or other pathogens from the final product. These bolt-ons included heat treatment, such as pasteurization of liquid products or dry heat treatment of lyophilized products, to inactivate viruses which may be present in the starting material. The incidents of virus transmission led to the adoption of a new paradigm -- active surveillance and dedicated mitigation strategies to help assure the pathogen safety of plasma protein therapies. Today's more proactive industry integrates pathogen reduction steps directly into new commercial processes during the conceptual phase, processes designed to reduce potential pathogen load by inactivation as well as physical removal.

In 1995, the plasma industry was emerging from the HIV and

HCV issues that it had experienced. In addition to classic bloodborne virus concerns, the prion mediated diseases (e.g. Mad Cow disease) were emerging as a new concern of unknown relevance and magnitude. As a consequence, the industry was reacting to negative perceptions from patients, regulators, and other stakeholders as well as internal pressures to rapidly improve safety beyond the state-of-the-art at the time

In recognition of these challenges, the industry evolved and is thriving today due in large measure to the mindset of the new leadership who demand premium pathogen safety profiles for all therapies. The industry today does not view pathogen safety simply as an add-on or an isolated obligation relegated to the Pathogen Safety or Quality departments. Instead pathogen safety is embraced as part of an overarching paradigm of safety, encompassing all manufacturing stages from early development to final product. Pathogen safety is now prioritized across the industry and is vital to our collective success moving forward.

With regard to technology, the industry has unprecedented options and opportunities to maintain and continuously improve the safety margins for their plasma-derived products. Therapies today are made from human plasma that has been tested using stateof-the-art nucleic acid amplification technologies, that can detect viral infections prior to the donor experiencing clinical symptoms. Source plasma quality practices, such as the Qualified Donor Standard, the Viral

Marker Standard, and minimum 60-day inventory hold times, were devised and self-imposed by industry member companies as additional safety measures to allow identification and destruction of plasma units that are unsuitable for processing. Today's manufacturing processes incorporate integrated pathogen reduction technologies, such as caprylate, solvent/ detergent, and nanofiltration, which are exclusively dedicated to the inactivation or removal of pathogens. In addition, the manufacturing processes have inherent capabilities that are well characterized with respect to the inactivation or removal of pathogens. Finally, PPTA member companies work collaboratively beyond their own "corporate boundaries," working with patient groups, healthcare providers, and international regulatory agencies to ensure that knowledge regarding pathogen safety and new emerging threats are available to all and the quality, safety, and supply of therapies is maintained.

The future of pathogen safety in the plasma industry will capitalize on the momentum of the efforts that have taken us to where we are today. Today's practices will constantly be refined and new technologies will continue to evolve just as they have since we joined the industry. (Image of the since we joined the industry is a since we joined the industry is a since we joined the since we joined the industry is a since we

Pathogen safety is *embraced as part* of an overarching paradigm of safety, encompassing all manufacturing stages from early development to final product.

DOUGLAS C. LEE, PH.D., Vice President, Research and Development, Grifols, Inc. NATHAN J. ROTH, PH.D., Director of Pathogen Safety, Grifols, Inc.

AN INDUSTRY VIEW: REGULATORY PERSPECTIVES

SOURCE PLASMA AND PLASMA PROTEIN THERAPIES ARE HIGHLY REGULATED. We have asked respected regulators from the United States and Europe to provide their perspectives on how the industry and regulation have evolved over the past twenty years and what they see as priorities for the future.

JAY EPSTEIN, M.D.

Director of the Office of Blood Research and Review, Food and Drug Administration

Tell us about your background. I joined the FDA, Office of Biologics (now called the Center for Biologics Evaluation and Research, or CBER) in 1981 as a Medical Officer after completing clinical training in Internal Medicine and Infectious Diseases at The George Washington University Hospital in Washington, D.C. Initially, I was hired in the Division of Virology to engage in vaccine research and related product review. However, after the discovery of the AIDS virus in 1984, I was asked to develop the FDA's regulatory program for AIDS testing of the blood supply due to my laboratory and regulatory experience in viral immunochemistry.

Later, in 1986, I moved to the Division of Blood and Blood Products to establish a retrovirus laboratory. I have stayed in the blood program

since that time, gradually assuming broader responsibilities as Director of a Division of Transfusion Safety (now the Division of Emerging and Transfusion Transmitted Diseases).In my current capacity, I oversee a group of about 200 full time employees and sixty or so contract hires who are involved in regulatory activities related to blood products and to retroviral

diagnostic testing. The program includes mission-related bench research. My regulatory responsibility includes standard setting for blood and plasma collection, as well as the manufacture of blood components, plasma derivatives, certain biotechnology products (e.g. recombinant plasma proteins), and related drugs and medical devices (e.g. anticoagulants, apheresis machines, donor screening tests, blood bank software, etc.) My work also involves substantial interactions with regulators and scientists in other countries, as well as with international public health organizations such as the World Health Organization (WHO) and the Council of Europe.

How would you describe the plasma protein therapies industry today as compared to 20 years ago?

Twenty years ago, and I believe roughly for the decade from 1992 to 2002, the plasma protein therapies industry was in a state of crisis at multiple levels. The impact of AIDS was still felt strongly, both in the need for introduction of validated manufacturing steps to improve viral safety and in the imperative to modernize GMP controls. Also, there was shift of concern from clotting factor safety to safety of immune globulins. Transmission of HCV by certain immune globulins, a bacterial contamination event involving albumin, and market disruptions affecting access to immune globulins were significant public health concerns. Potential threats from CJD and vCJD, the Cochrane meta-analysis questioning safety of albumin, concerns about the safety of large volume plasma donations, and controversy about introduction of tests and viral validations for hepatitis A, human parvovirus B19, and West Nile virus were additional challenges. Many changes were made in the industry to address these issues. As a result, I believe the more recent decade has been characterized less by product safety concerns, though these continue to arise, and more by organizational issues, particularly the increasing consolidation of manufacturing. There has also been a steady expansion in the manufacture of recombinant plasma proteins which has benefitted many patients with various heritable disorders, but also has shifted the way that plasma is utilized to make different products.

What do you view as the contribution of PPTA as the industry's trade and standards-setting organization? PPTA provides its members with a common forum both for developing standards and for interfacing with the FDA. Clearly, PPTA has limitations as it must represent only collective views of its members and must stand clear of competitiveness issues. Nevertheless, PPTA has succeeded in bringing forward voluntary standards such as the IQPP and QSEAL programs. As an advocacy group, PPTA has played a role in bringing its perspective to public discussions of scientific issues bearing on regulation, such as at FDA workshops and advisory committee meetings. PPTA has provided timely and accurate information about product distribution to the public and the FDA that has helped to identify and manage shortage situations. PPTA's support of the Patient Notification System has provided a public service in keeping healthcare providers and patients informed about product recalls and withdrawals. At various times, PPTA has coordinated efforts of its members to provide valuable scientific input for evidence based decision making by FDA, for example in the area of TSE clearance in plasma fractionation. I assume that the participating manufacturers see value in these same activities, but that is for them to judge.

Looking forward, what would you consider priorities related to plasma products to which PPTA could contribute in the coming decade?

Technology change is a constant driver and I would

Regulatory Sessions are heavily attended at IPPC and the Plasma Protein Forum.

expect PPTA to prioritize its efforts to help the industry keep pace with new methods of manufacturing and quality control. Newer analytical methods for protein characterization and standards to address novel recombinant products come to mind. More conventionally, I think there are unmet needs in addressing current practices that affect donor health, product safety and product availability. For instance, I would like to see a reinvigorated effort to better characterize the safety of long term donation of Source Plasma. On the product side, the issues of thrombogenicity and hemolysis associated with certain immune globulin products stand out as current and evolving concerns. PPTA might consider establishing a central funding source for supporting research in areas that would benefit industry as a whole, but that are not necessarily of high priority for the NIH or academia e.g. determinants of Source Plasma quality. At the same time, centralized funding could be targeted to recruitment of young scientists into the field of plasma proteins. With respect to product availability, strategies are needed to assure stable supplies of specific immune globulins such as antivenins and to expand the availability of plasma derived recombinant products for rare diseases and disorders. Other important issues are global adequacy in recombinant clotting factors, and improving adverse event reporting so that timely action can be implemented to address safety signals. (

As an advocacy group, PPTA has played a role in bringing its perspective to public discussions of scientific issues bearing on regulation

GLENDA SILVESTER, PH.D. Principal Scientist, Quality of Medicines Sector, European Medicines Agency (EMA), Human Medicines Development and **Evaluation Unit**

Tell us about your background

I have senior scientific lead for blood products and I am the Scientific Secretary to the Blood Products Working Party (BPWP), which provides recommendations to the Committee for Medicinal Products for Human Use (CHMP) on efficacy and safety aspects of blood products. I joined EMA in 1997 after many years in the UK Medicines Control Agency with responsibilities including the evaluation of the quality of plasma-derived medicinal products and biotech products. I am a pharmacist by training and have worked in the pharmaceutical industry.

How would you describe the plasma protein therapies industry today as compared to 20 years ago?

Plasma-derived medicinal products had only recently been brought within European legislation in 1989 and a review of authorized products on the European markets was needed. Although the available plasma-derived medicinal products had provided major improvements in health and life expectancy for individuals with conditions such as immunodeficiencies and hemophilia, there had been the tragedy of HIV and hepatitis C transmission, particularly coagulation factors in the 1980's. When I became involved, manufacturers had already reacted to the tragic events with the introduction of specific virus inactivation/removal steps into manufacturing processes, particularly for coagulation factors.

Despite these efforts, we still saw occasional batch-related transmissions of viruses in the early 1990s for example hepatitis C and A viruses. This highlighted the importance of the robustness of the virus inactivation/removal procedures that were in place and the need for a continuous dialogue with leading virologists and

industry which lead to major revisions of European guidance for plasma-derived medicinal products. This intensive work has stood the test of time with the principles still reflected today in the latest revision of the guideline on plasma-derived medicinal products and also the guidance CPMP/BWP/268/95 on virus validation studies published in 1996, which remains unchanged.

The focus on quality and safety of plasma-derived medicinal products also triggered the development of the first specific guidance on the control of starting materials for the production of blood derivatives in1994, for which I was rapporteur and the PMF certification procedure was legally established in 2003. In 2002, the Blood Directive (2002/98/EC) established a common legislative basis for collection and testing of blood components both for transfusion and plasma intended for fractionation.

In 1996, there were the first reports of cases of a new variant of Creutzfeldt-Jakob disease (CJD) in the UK. In January 1998, we convened a workshop of international experts in the Transmissible Spongiform Encephalopathy (TSE) field and in February 1998 published the first position statement on vCJD and plasma-derived products. We had to follow a precautionary approach because we were facing a new disease with incomplete information on the risk that it might pose. We have kept this topic under review up to the present day with support from the leading experts in the field. Industry contributed with results of its investigational studies carried out into the capacity of its manufacturing processes to remove Transmissible Spongiform Encephalopathy (TSE) agents.

The CJD approach of engaging experts from the European regulatory network, supplementing this with additional independent expertise, where needed, is also working very well in other areas. Public consultation with all relevant stakeholders ensures that regulators are well-informed to assure a robust approach to developing and maintaining European guidance.

One of the first areas for European guidance was the drafting of core summaries of product characteristics (SmPCs) for classes of blood products, which were licensed nationally. They were developed as a tool to facilitate the review of marketed products in the early 1990s. Today these updated core SmPCs remain useful to facilitate the drawing up of product information for new products.

In the early 1990s, we also saw the establishment of a clinical group for blood products, the BPWP. This group completed its work in 1997. In 1998, it was decided to reconvene a group specifically devoted to efficacy and safety of blood products, the BPWP.

The first Chairperson, Dr Manfred Haase, was keen to have involvement of patients and physicians organizations. I think he was quite ahead of his time. This interaction is well-illustrated by the 2006 EMA expert meeting on FVIII products and inhibitor developments where participants included hemophilia specialists and representatives from the European Haemophilia Consortium (EHC)and World Federation of Hemophilia(WFH)

This initiative on an important safety issue was jointly under-

taken with the Pharmacovigilance Working Party. The BPWP continues to work closely with both PhVWP (for safety) and BWP (for quality). A current example of this is in the area of immunoglobulins, where thromboembolic events associated with two products has been linked to the presence of procoagulant impurities. This issue has also involved close liaison with the European Directorate for the Quality of Medicines & HealthCare (EDQM), the Official Medicines Control Laboratories and the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), because most of these products are still nationally licensed. It is also an important topic for the Blood Cluster between EMA and FDA. This Cluster was established in 2010 under the auspices of the EMA/EC - FDA confidentiality arrangements which allow sharing of confidential information between the Agencies.

Looking more generally at the European legislative framework, there are two significant milestones relevant to plasma-derived medicinal products.

The first is the orphan medicines legislation in 2000 which provides incentives to support the development of products for rare diseases. There are currently 14 orphan designated plasma-derived products.

The second is the 2006 Pediatric Regulation. Since plasma-derived products are used in children, BPWP has worked closely with Pediatric Committee (PDCO), particularly in connection with the latest revision of the clinical guidance for the investigation of new FVIII and FIX products.

How does the regulation of plasma protein therapies today compare with 20 years ago?

The European regulatory framework is well-established through legislation, including mandatory quality requirements through the European Pharmacopoeia (Eur Ph.), supplemented with guidance. In relation to plasma protein therapies, EMA has an important role in developing and maintaining European guidance. We also have a training role and our program also attracts interest from regulators outside the European Union (EU).

Whereas 20 years ago we were only just starting on European harmonization, we are now interacting much more on an international level. US inspections of blood establishments place immense demands on a limited resource of inspectors and in this respect the more general initiatives between EMA and FDA on cooperation in the inspection field is of particular interest.

What was the most important development during this period with respect to the quality and safety of PPTs?

While plasma-derived products are still mainly national authorized, it is mandatory for recombinant blood products to apply for authorization through the centralized procedure. The centralized route is only mandatory for plasma-derived medicinal products that are orphan designated. Other plasma-derived medicinal products have the option of applying centrally under certain conditions such as a new active substance, a medicinal product which constitutes a significant therapeutic, scientific or technical innovation, or where granting an authorization through the centralized procedure is in the interest of patients at community level. In addition EMA activities related to plasmaderived products include Plasma Master File (PMF) certification, scientific advice/protocol assistance, pediatric investigation plans, and orphan medicine designations. We also have responsibility for giving scientific opinions on blood derivatives used in medical devices.

In my perspective, the most important development has been in relation to quality and safety with respect to transmissible agents.

Currently authorized plasma-derived medicinal products have an excellent safety record with respect to the major blood borne viruses.

There is always a potential risk of transmission of infectious agents given the human source of starting material. Therefore, we have to remain vigilant and I would finish with a quote from the 1996 version of the guideline on plasma-derived medicinal products that still remains in the latest revision that came into effect in February this year: "Manufacturers should apply their best efforts to develop methods to inactivate/remove viruses and this should be a continuing process. Previous experience clearly shows that starting material may contain unknown viruses and those new viruses may appear. This emphasises the need to design processes to inactivate/remove as wide a range of viruses as possible. Even this may not preclude new or unknown infectious agents breaking through a process." (📚

The views expressed are those of the interviewed and may not necessarily reflect the views and policies of the EMA.

PPTA has succeeded in bringing forward voluntary standards such as the IQPP and **QSEAL** programs. As an advocacy group, PPTA has played a role in bringing its perspective to public discussions of scientific issues bearing on regulation.

ADVOCATING FOR FREE TRADE

BY JOSHUA PENROD

ONE OF THE STRATEGIC OBJECTIVES OF PPTA and its member companies is securing and facilitating a global environment for the usage of plasma protein therapies. Through the elimination of unnecessary trade barriers, PPTA members can bring the benefits of plasma protein therapies to critically ill patients around the world. Sometimes, however, ideological and political barriers can create hardship when none need exist. Detailed in this article are three specific regions where industry has made efforts at improving the free movement of plasma protein therapies to help patients reliant upon them. PPTA has been active over the past 20 years in Europe, Japan, and China, each of which have had separate and unique challenges to our industry and patients.

Europe

European countries have debated free-trade, compensated plasma, and self-sufficiency for many years. While the European Directive 2002/98 (formerly 89/381) calls for regional self-sufficiency and a marked preference for voluntary, non-remunerated donation, this has taken shape in recent times as a euphemism for national selfsufficiency. Resolution of free-trade and market-access issues are pursued through organs of the European Commission (EC), which determines which path to take in order to resolve a problem.

Two legal actions in Europe shaped much of the dialogue at the outset in the 1990s. In the 1994-1995 timeframe, PPTA informed the EC of problematic aspects of Belgian policies relating to the operation of the plasma protein sector and its misuse to support domestic plasma production favorably over non-domestic producers. The EC agreed to investigate further. As can be imagined, such a situation can be lengthy in resolution.

During the discussions involving the Belgian situation, in 1996, Denmark initiated a different type of policy which favored the domestic Staten Serum Institute. At its heart, the policies effectively created a monopoly requiring hospitals and health care providers to use only products from the Staten Serum Institute. Through its advocacy efforts, PPTA was successful in effecting a legal change. As a result, the Danish market was largely opened in 1998, and continues to be such today.

Several years after the resolution of the Denmark issue, Belgium's policies changed as well, abandoning most of the positions inconsistent with EU law. Belgium, while having a small patient population, has historically had good clinical use of plasma products and effective treatment of patients; as a result, this was an important step in free trade in Europe.

Today, the landscape holds somewhat of a different shape. Overall, market access is better in Europe than it historically has been. While there are still areas of unevenness and lingering difficulty, these past efforts to support fair market access have met with success.

Japan

The Japanese system is both well-known and difficult to fully understand. PPTA has been involved in complex discussions with Japanese policymakers since the 1990s, which often include dialogues on compensated donation, adequate diagnosis and treatment, and reimbursement systems which recognize the unique nature of plasma-derived therapeutics. These factors can be understood as two policy impediments to establishing a truly free-trade relationship with Japan, one in the form of kenketsu labeling, while the other spells out inadequate diagnosis of patient groups in need.

The labeling requirement in Japan differs substantively from normal country-of-origin labeling recognized under international trade law regimes. The distinction between kenketsu and hi-kenketsu, which are terms carried on the label of the finished product, is highly context-dependent. On the surface, the distinction could be read as being similar to the labels required under FDA regulations; in practice, however, the cultural context favors domestically-produced products for prescription by health care professionals. While occupying a gray area, it can be interpreted as being inconsistent with obligations under international trade treaties. Appropriate diagnosis is the other major strategic challenge in Japan. The current demographics in Japan show that less than 2000 patients are currently diagnosed with conditions favoring the usage of immune globulin. By comparison, countries with comparable populations contain around ten times this number. This indicates that a medical and diagnostic infrastructure should be developed to recognize these conditions, such that the critically ill can receive treatment.

Both of these factors are more than just about access to Japanese markets; there is an ethical imperative for effective treatment of ill people. The U.S. Department of Commerce has assisted the industry by leading negotiations with their counterparts from Japan, ensuring that the lines of dialogue remain open for the industry. Recently, some new events in Japan have indicated a greater interest in diagnosis and treatment, especially when shown comparative data showing immune globulin usage patterns in other countries of equivalent size and economic development.

China

One of the best known areas of industry engagement in the sector of free trade has been China. The Chinese Ministry of Health and Ministry of Foreign Economic Cooperation & Trade and Customs General Administration enforce the well-known Article 49, which precludes importation of Factor VIII and other plasma-derived medicinal products, ostensibly to prevent the introduction of HIV into China. PPTA has been active in demonstrating the safety and effectiveness of PPTA member products produced in the U.S. and Europe in an effort to secure access for patients in China in dire need of plasma protein therapies.

While the advocacy has taken place at a number of different levels over the past decade, especially notable are three workshops which have included strong messages of safety and effectiveness of PPTA member company therapies, the extraordinary measures taken to ensure safety, and the inimitable level of attention to detail given to quality. In 2007, the industry held a workshop in Beijing, describing the nature of plasma collection in the West, and many of the critical processes of finished product manufacture. In 2009, another workshop was held which focused on all aspects of quality and safety, from donor selection through testing technologies to the industry standards program. Follow-up workshops were held in 2010 and 2011, which focused on clinical usage of albumin, an exception to Article 49.

These workshops have amounted to an effort to support the profile of PPTA member companies; the most important of the virtues of PPTA members is the commitment to quality and safety of the products. These measures can truly show the unparalleled levels of safety that are not achieved by companies who do not have the experience, know-how, industry standards, or the commitment that PPTA members possess.

All of these have combined to help the industry achieve unparalleled levels of quality; when now considering the combined challenges facing China, such as hepatitis and HIV within its borders, the inadequacy of the Chinese domestic industry to accommodate the current needs of patients, and difficulties with appropriate donor assessment and recruitment, it becomes harder to understand the rationale for Article 49. In the final assessment, all should recognize an ethical mandate for appropriate treatment of patients in need.

Conclusions

Every country has its own culture and challenges, and each have their own histories with domestic industry, policies of self-sufficiency, patient diagnosis, and healthcare infrastructure. The landscape for the plasma industry has been a complex one to navigate all of these differences and divergent concerns. One thing, however, that all have in common is the need for adequate treatment of patients.

Certainly, other trade barriers exist beyond the ones enumerated here; policies exist all over the world that creates needless obstacles for the usage of plasma protein therapies. The plasma industry is not, however, the only industry forced to navigate needlessly difficult systems. All should remain optimistic that, in the fullness of time, systems predicated upon political advantage will give way to policies that encourage access to critically needed therapies for profoundly ill people. (S

JOSHUA PENROD, Vice President, Source

PERSONAL REFLECTIONS: THE ROOTS OF THE PLASMA **PROTEIN THERAPEUTIC ASSOCIATION AND ITS PIONEERS**

BY JAN M. BULT

Early years of Turmoil

Today, we work in a completely different environment than when the Association was formed in 1992. The tragedy of viral infection in the hemophilia community was just behind us. The pain and suffering in this vulnerable community was enormous. Political barriers to trade were raised, especially in Europe where Directives from the EU were made that could potentially eliminate the private sector. (see Free Trade, p. 22) We have witnessed a change in focus from safety then to access and affordability now. In this article I would like to try to explain how we got there.

Call for Action

In the early 1990s, our manufacturing sector was not really represented. In the U.S., we had ABRA, a strongly established association that focused on the many aspects of private sector plasma collection. The Executive Director, Robert (Bob) W. Reilly had enormous experience in plasma collection and broadened the scope to include the manufacturing side. Fractionators' interests in the U.S. were represented by an ABRA committee; but in Europe there was not a representative body. An ad-hoc Working Group within the European Federation of Pharmaceutical Industry Associations (EFPIA), discussed issues pertaining to the plasma protein industry twice a year in a half- day meeting. Needless to say, this was not the most efficient way to represent the industry with its special features and needs.

Three leaders in the industry, Otto Schwarz (Immuno), Ralph Galustian (Bayer) and Guelfo Marcucci (Gruppo Marcucci) decided in 1992 that it was time to establish a fractionators' organization the International Plasma Product Industry Association (IPPIA) that

would focus on the special needs of this industry. Bob Reilly was asked to go to Europe and start focusing on the new European Directives that were being developed. These Directives focused on how to achieve self-sufficiency in Europe. That was the beginning of our activities in Europe. Bob Reilly worked diligently with Knut Hansen (Immuno) to get the industry organized. Knut was a lawyer and had done a lot of good work for the HIV infected hemophilia patients.

Bob and Knut developed an initiative to see whether the ad-hoc Working Group within EFPIA could be restructured. The new entity was called the European Plasma Product Manufacturers (EPPM). This lasted less than a year. Because the EFPIA leadership did not change how they dealt with the plasma protein industry, it was decided to form our own organization on December 7. This became the European Association of the Plasma Product Industry (EAPPI) in January 1994.

Progress in the beginning years was difficult. Not only was the political climate unfriendly for our sector; but, the regulatory

Guelfo Marcucci

Otto Schwarz

agenda was another source of pressure. The European Medicines Evaluation Agency (EMEA) was in its infancy. At that time, there were no meetings between the Association and regulators. The Agendas of the Committee for Proprietary Medicinal Products (CPMP) meetings were not public and industry input was absent The industry had no choice other than to deal with decisions of the CPMP meetings. I participated in a meeting with senior officials of the European Commission to express our concern about

Otto Schwarz was one of the first Chairmen of IPPIA and realized these "secret" CPMP meetings. What a difference today. how important it was to develop an industry view and not just a company view. He brought competitors to the table and was able to identify Leadership common issues. He was succeeded by Ralph Galustian (Bayer). Ralph It is not difficult to understand the difficult environment that was instrumental in creating the necessary funding to get things done. we were operating in. There were issues with trust, confidence, The next Chair was John Sedor (Armour/Centeon). John felt it was credibility, barriers to trade and more. Several crises needed to be absolutely crucial for the Association to develop a Long Term Strategic managed. The Association staff was asked to help guide the in-Plan focusing on the real critical issues. That plan was finalized early dustry out of chronic crisis mode. Skipping ahead 15 years to the 1998. The next Chair was Jan Turek (Bayer). Jan introduced the Manpresent, I think we can say that we did a good job in that respect. agement by Objectives (MBO) and ensured that all objectives were What was needed was leadership to bring the entire in-SMART: (specific, measurable, achievable, realistic, timely).

dustry to the next level. Dr. Schwarz was heading Immuno; he We are still working today with this approach. His successor was Thomas Glanzmann (Baxter). We had just emerged from a difficult shortage period and quality was on the forefront of everybody's mind. He helped the industry to raise the bar and during his tenure, the QSEAL standard program was introduced. Thomas Glanzmann, who was half Swiss, passed the helm to a 100% Swiss citizen, Ruedi Waeger (Centeon/ Aventis Behring). He focused These formed the cornerstone of two successful standard prostrongly on organizational efficiency and wanted to ensure that the PPTA as an organization was ready to deal with the difficult issues of the future. Once the organization was in good shape, the new Chair was Peter Turner (CSL Behring). He immediately focused All manufacturers had to be convinced of the necessity of on patient access to care. Peter did that in the typical friendly, nononsense Australian manner. He was succeeded by Larry Guiheen (Baxter) who continued to focus on patient access to care, emphasizing the importance of appropriate reimbursement.

understood early on that it was important to address all factors that contribute to the safety of therapies. Three important areas were identified: • Collection Centers • Donations Inventory Hold grams. ABRA had already its Quality Plasma Program (QPP) and later, we developed the Quality Standard of Excellence, Assurance and Leadership (QSEAL). having a set of standards which would address critical issues in the defined areas. In the fall of 1996, meetings were held with the leadership of the companies to explain to the importance

of developing meaningful standards. The Association staff was represented by Bob Reilly (IPPIA), Jim Reilly (ABRA) and me (EAPPI). Clearly, these meetings were tough and difficult.

It was a clear sign of leadership that the companies voluntarily implemented several costly standards that exceeded the regulatory requirements. The return on investment was enormous, namely: the re-establishment of credibility and trust. Big kudos for the leadership of Otto Schwarz, Ed Matveld (Alpha Therapeutics), John

Ralph Galustian

Bacich (Baxter) and John Sedor (Armour); it is thanks to the leadership of these gentlemen that we are in a much better place today.

Critical steps to further improve image and credibility

This industry has been very fortunate to have industry leaders who were ready to go the extra mile. The whole paradigm shift from safety to access and affordability did not happen by chance.

In January of this year, Paul Perreault (CSL Behring), became Chair. (see Vision for the Future p. 28)

PPTA has come a long way. I am very privileged to have worked with so many outstanding leaders, competent staff and countless expert volunteers from the member companies. I can truly say that I enjoy my work and hope to be able to witness firsthand the many good things that this industry can continue to do. (🗫

JAN M. BULT, President and CEO

LOOKING BACK AT 30 YEARS

BY CATHY IZZI

LITTLE DID I KNOW BACK IN 1982, that I would remain in the plasma protein therapies industry for 30 years. As I write this retrospective, I realize that there are many members who are still here, even longer than I, and who will certainly have a different and more exciting story to tell. They are the ones who have done the real work and have adapted and persevered. And so I dedicate this retrospective to them—you know who you are. You have always been a champion and challenger of the Association and have recognized our value.

managed by an association management company, Robert W. Reilly Inc. (RWR, Inc.), and operated out of a small downtown office in Annapolis, Maryland. "Coming aboard" is the appropriate term, with Annapolis being the "sailing capital of the world" and Bob Reilly, a true Annapolitan and sailor himself. In addition to ABRA, RWR, Inc. also provided limited services to two other organizations: National Association of Optometrists and Ophthalmologists, and a local group—the Eastport Business Association. At that time, full time staff consisted of Bob Reilly, James

When I came aboard, the

Association, then ABRA, was

Reilly, and me. It was really lovely to work in downtown Annapolis, with the harbor and the Naval Academy only a 1/2 block away. My first project was to assist with the Plasma Forum, taking pictures and holding up question cards. My earliest and foremost recollection was Bob Reilly coming back from a Public Health Service meeting about the AIDS epidemic. From there, the Association led the efforts to reduce the risk to the plasma supply by developing recommendations for donor deferral and infection control within centers and laboratories. I was always impressed by the fact that a Board of Directors, composed of fierce competitors, were able to agree on such measures, which ultimately led to the development of industry quality standards for the betterment of industry.

Working with a limited budget, the office moved from down-

town Annapolis to the basement of the senior Reilly's home. It really didn't matter with only three of us and the location was great: a wooded setting with a small park at the end of the street – a haven when the amount of work became overwhelming. From that office, we continued to organize meetings, forums, workshops; produce newsletters and journals; and, of course, manage issues with FDA, OSHA, CDC and other agencies. We were always relieved after every budget meeting that the Board voted to keep us on!

In a short period of time, we clearly had a need for additional staff and relocated to a two-story townhouse setting. Our staff increased to include administrative support and a meetings manager. At that time, my role had changed to Publications & Special Projects Manager. The Association's focus was on the Quality Plasma Program (QPP) standards development, expansion into the European arena, monitoring development and approval of viral marker tests, improvements to the Center Managers Workshop, just to name a few.

In the early to mid 1990s, exponential expansion occurred for the Association with establishment of the IPPIA and the EAPPI and offices in Washington, D.C., London, U.K., and ultimately Brussels, Belgium, as well as relocation of the Annapolis office to the West Annapolis area. Industry supported staff expansion to include government relations, regulatory affairs, standards, public affairs in Europe, communications, administrative, finance & operations, information technology, at last! It was an exciting and challenging time - the Association was serving many needs for collectors and manufacturers and was developing better relationships with regulators and consumer organizations within the U.S. and Europe and reaching out to Japan.

As we moved into the late 1990s, Bob Reilly retired; RWR, Inc. became Program Management Group; Jim Reilly became President of ABRA; Jan M. Bult headed up IPPIA as its Executive Director, with Charles Waller as Executive Director of EAPPI. Program Management Group operated as a partnership, continuing to lead the Associations - identifying challenges and opportunities within its mission.

By 2002, the three Associations became known as PPTA, Plasma Protein Therapeutics Association - representing "One Voice" for the industry. We had another office move to our current location, closure of the D.C. office, and reorganization of staff, reflecting the industry's economic situation. However, the programs, projects and supporting efforts continued to expand, becoming more complex, more challenging. By this time, I'd probably worn 20 different hats: secretary, meetings, publications, marketing, industry training program development, database management, standards inspection scheduling, photographer. My role then changed to a more internal role within operations to include personnel, benefits, staff training, document management, office management and member services.

In my thirty years in service to the Association, I have seen many people come and go. Some have added incredible value to the role of the Association. I have to give credence to Bob Reilly for his early vision of the industry association, adaptability to its needs, and setting the environment for effectively representing industry. His successors and colleagues have benefited from the relationships established since the early 1970s and beyond, and the Association's successes are built upon that foundation. I am grateful to the current leadership for recognizing my talents and acknowledging the value I bring to the Association, and to be

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a part of the important role of industry in saving and improving lives.

I do not like to look often into the past; this retrospect was a challenge in itself. Lessons learned from my experiences are with me today -and what I do today is what's

Cathy and the Reillys (1982)

important. Although my colleagues call me "the veteran," I am still learning something every day and know that it's not about me or what I've done. It's the collective effort of staff and members, working as a team, respecting each other's experience and expertise that brings value and satisfaction for our efforts. I hope my colleagues find some satisfaction in the important role they play in support of the Association. Overall, I have always believed that Association staff has tried to affect the best outcome for a better today for our members and, ultimately, for the benefit of those who rely on the unique therapies our members produce. (\$

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FACING FUTURE CHALLENGES WITH CONTINUED VIGOR

BY PAUL PERREAULT

IT HAS BEEN MY PRIVILEGE to Chair the PPTA Global Board of Directors since January. I am proud to be part of an industry that is committed to the shared value that it's all about the patients we serve. As we look ahead to the second half of 2012 and beyond, we will no doubt encounter many new challenges as an industry. But where there is challenge, there is opportunity.

While it is true that economies and governments around the world continue to struggle, it is to PPTA's credit that our mission to promote the availability of and access to safe and effective plasma-derived therapies has remained constant. So, too, has our strategy for improving patient access to diagnosis and care, which remains focused on advocacy, improved knowledge, and appropriate reimbursement.

Challenges in the global marketplace have helped shape many of our strategic priorities. Free trade, which is essential to the well-being of our patients and our industry, is one example. We continue to work to eliminate "non tariff barriers" and other discriminatory practices that are an impediment to trading plasma protein products globally.

There is *areater focus* on diagnosis and awareness of rare and serious medical conditions than at any other time, which is positive.

We are also committed to obtaining regulatory and quality policies that enable us to ensure the availability of safe and high-quality plasma for fractionation. PPTA is actively engaged in this area, working to obtain global regulatory and quality policies that reflect the special nature of the plasma protein industry, and that promote a more harmonized regulatory approach.

Last year, the passage of the Cross-Border Health Directive in Europe was a significant victory for patients. We will continue to be vigilant in safeguarding patient interests. As an example, we cannot overemphasize the importance of patient, physician and industry involvement in Health Technology Assessment (HTA), as it is called in Europe, or Comparative Effectiveness Research (CER), as it is called in the United States. Our focus is on ensuring a robust and transparent framework in which these approaches serve as tools to encourage development of new and innovative technologies, and not serve as barriers to care.

In yet another key area of public policy, PPTA continues to support efforts to gain national adoption

of the European Recommendations for Primary Immunodeficiency (PID) across Europe. A German thought leader group has already adopted and promulgated those recommendations in that country. In the United States, we are partnering with legislative leaders to change a provision that imposes new costs on therapies that

treat orphan conditions. These are all positive initiatives that bode well for the industry and the patients we serve.

An overarching goal is to have decision makers understand the special nature of rare diseases in policies, from product regulatory approvals to payment decisions, since most of our therapies treat rare conditions. That is happening in a number of ways, but more remains to be done. For instance, there is greater focus on diagnosis and awareness of rare and serious medical conditions than at any other time, which is positive.

At the same time, rare disease patients can have trouble obtaining access to therapies due to payment decisions. When it comes to a patient's health and quality of life, coverage decisions should not be based just on cost of therapies, but need to be in the context of total patient outcomes. The true value of what we do is not measured in liters or sales, but in the lives of all those whom our products help. (

PAUL PERREAULT, President, CSL Behring, Chairman, PPTA Global Board of Directors

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GLOSSARY OF TERMS

American Blood Resources Association ABRA BPWP Blood Products Working Party CER Comparative Effectiveness Research CBER Center for Biologics Evaluation and Research European Association of the Plasma Product EMEA Industry Association European Commission EC EFPIA European Federation of Pharmaceutical Industry Associations EMA European Medicines Agency EMEA European Medicines Evaluation Agency EPPM European Plasma Product Manufacturers

FDA	Food and Drug Administration
НТА	Health Technology Assessment
IPPIA	International Plasma Product Industry Association
IQPP	International Quality Plasma Program
NDDR	National Donor Deferral Registry
NAT	Nucleic Acid Amplification
РРТ	Plasma Protein Therapy
PID	Primary Immunodeficiency
TSE	Transmissible Spongiform Encephalopathy
QSEAL	Quality Standard of Excellence, Assurance and Leadership
who	World Health Organization

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N.V. Asahi Kasei Bioprocess Europe S.A. N.V. Asahi Kasei Bioprocess Europe S.A. Cologne Technical Center Gottfried-Hagen Strasse 20 51105 Cologne Germany Phone: +49-221-995007-0 +49-221-9950077-10 Fax: planova_de@om.asahi-kasei.co.jp

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