

THE SOURCE

MAGAZINE OF THE PLASMA PROTEIN THERAPEUTICS INDUSTRY

SUMMER 2017

Actions Today Impacting Tomorrow

Where Public Health and
Data Privacy Converge:
The Case of PPTA
Standards

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These statements are those of the author and do not necessarily reflect the opinion of PPTA or its members.

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In My View

BY JAN M. BULT, PPTA PRESIDENT & CEO

I will give you an example how (political) decision-making can have a serious impact on patient access to care; this time I will talk about the European rule for chemical compounds—REACH, which stands for Registration, Evaluation, and Authorization of Chemicals. The goal of REACH is to ensure a high level of safety for humans and the environment at both the production and consumer level. The rule applies for chemicals produced in or imported into the EU and exceeding a volume of 1,000 kg.

Currently, there are 12 chemicals that will be affected by this rule. One of them is 2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy]ethanol (Triton-X 100), in short Triton. Triton is a crucial agent in viral inactivation processes—it's widely available, well-tested, and applicable for a range of different and sensitive proteins, with a very high margin of safety.

The European Commission proposal introduces strict control as of 2018 with a sunset in 2020. It is always mindboggling to me that rules are developed without thinking through what the impact is beyond the goals that are supposed to be accomplished. I will try to explain what is going on here.

Everyone involved in our industry and the users of the therapies that are being manufactured knows that the differentiating factor between the therapies is the manufacturing process. The smallest change can make a difference in efficacy or tolerance of the therapy. For that reason, therapies are different and in many cases non-interchangeable. Though not all manufacturers use Triton, it is too simple to think that it just should be replaced. There are problems with that, as a matter of fact the impact of this ban is enormous.

From 2020 onwards, the affected companies have to file a lot of documentation to seek permission to use Triton under REACH and there is no guarantee that the permission will be granted. If no permission is obtained, the manufacturers have to change each process for each protein affected and each

manufacturing step that involves the use of Triton. Each of these steps require again a separate permission. Again, there is no guarantee that the permission will be granted.

If the permission is not granted, then the entire processes need to be re-developed! That includes efficiency of viral inactivation, checking the biological properties of the protein, yield, purity, and effect on patients, and can even include the need for new clinical trials in a rare disease patient population. Because of the small numbers of patients, it is already difficult enough to conduct clinical trials for new plasma protein therapies that are entering the market. All this work on potential alternatives has to be done within very short timelines.

Despite the extensive outreach to various organizations—like the European Medicines Agency, World Health Organization, European Commission, Association of British Pharmaceuticals Industries, UK Office of Life Sciences, Members of the European Parliament, members of the REACH committee and including non-member manufacturers, such as the International Plasma Fractionation Association, as well as patients groups—there was a disappointing outcome.

On March 23, 2017 the European Parliament ratified the REACH vote. This means that Triton needs to be authorized and will be phased out after 2020 unless specific authorization can be obtained. I am extremely puzzled by this for various reasons:

- Nowhere has there been any mention of the impact on the manufacturing of live-saving therapies when (unnecessary) alternatives have to be developed under extreme time-pressure. In fact, PPTA has extensively advocated to conduct impact assessment prior to the REACH vote and the decision in the European Parliament, however, this has not been considered by the European Commission.

I have always thought that members of the European Parliament (MEP) who vote must be able to do that by weighing the arguments and thinking about the ramifications of unintended consequences.

- The ban only affects industry (i.e., not academia) where every drop of used Triton needs to be accounted under robust control mechanisms.
- The main concern of Triton is its effects when degrading and presence in groundwater. It is incomprehensible that no assessment of the current level of Triton in European groundwater and control mechanisms used by the companies have been done or requested by regulators.
- The ban does not affect academia where controls are unlikely to be as robust as in our industry. So, when exemptions are possible, why not for this industry?
- When a suggestion was made to remove Triton from the list of 12, the response was that this may lead to other exemptions. So what, there is also an exemption for use by academia?
- The vote in the European Parliament was following party lines.

I have always thought that members of the European Parliament (MEP) who vote must be able to do that by weighing the arguments and thinking about the ramifications of unintended consequences. The best solution would be to have an exemption for the use of Triton in the manufacture of plasma protein therapies, the second best is to have a sunset date that allows for more time to develop alternatives.

I understand that MEP's need time to study all effects. I know that they have a busy agenda and have to deal with many other issues. I have a suggestion that may result in having more time that can be devoted on important issues.

Why not make a serious effort to stop the monthly traveling between Brussels and Strasbourg? Every month the entire Parliament moves from Brussels to Strasbourg for one week and moves back again. Month after month. This requires all 750 MEP's to travel to and stay in Strasbourg for one week, thousands of boxes with

documents have to be packed and unpacked. Separate trains are used as people movers and many trucks are packed and become document movers. All of this is done at the expense taxpayers and costs far more than 100 million euros per year. You may think what this has to do with the main topic? Well, here is an obvious excessive spending that cannot be stopped for political reasons and there is no political will to do something about it. At the same time, there seems to be enough political will to come down on a part of the industry that is very responsible with all the agents they use to manufacture safe lifesaving therapies. This does not seem right to me.

There is something else. The rule to ban Triton only applies to Europe. This means that there is no issue when Triton is used in other parts of the world. If you think that production can just be moved to avoid the problem, this is not true because of multiple reasons:

- Not all manufacturers have plants outside of Europe. There is a risk that some manufacturers may be forced to stop production.
- Several licenses are linked to one manufacturing site; therapies produced in another site (even with the same technology) then cannot be used.
- This ban moves us further away from regulatory harmonization.

I urge the policymakers to reconsider this ban. •



Jan M. Bult, PPTA President & CEO



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Where Public Health and Data Privacy Converge: The Case of PPTA Standards

BY JOHN DELACOURT, PPTA VICE PRESIDENT, LEGAL AFFAIRS & GLOBAL OPERATIONS

Recent changes in European data privacy law have created an opportunity for expansion of two PPTA standards—the National Donor Deferral Registry (NDDR) and the Cross Donation Check System (CDCS). In the past it was thought that implementation of these standards—both of which operate through the collection of information on individual plasma donors—would be impossible in Europe due to both strict data privacy requirements at the European level and widely varying rules at the Member State level. Passage of the General Data Protection Regulation (GDPR),¹ however, has brought additional clarity to the area of European data privacy law and now suggests a route forward.



PPTA'S VOLUNTARY STANDARDS

In order to fill gaps in regulation, as well as to encourage the implementation of “best practices,” PPTA and its members have developed voluntary standards programs for the industry. The International Quality Plasma Program

IN ORDER TO FILL GAPS IN REGULATION, AS WELL AS TO ENCOURAGE THE IMPLEMENTATION OF “BEST PRACTICES,” PPTA AND ITS MEMBERS HAVE DEVELOPED VOLUNTARY STANDARDS PROGRAMS FOR THE INDUSTRY.

(IQPP) governs plasma collection center practices and encompasses standards on subject matter ranging from donor education to the cleanliness, safety, and appearance of a center. Although PPTA strives to maintain uniform and truly “international” standards, in some cases, exceptions are necessary to accommodate different legal and regulatory environments. This is the case with the two database-driven IQPP standards—NDDR and CDCS—which, due to European data privacy law, are currently implemented in only the U.S. and Canada.

THE PURPOSE OF THE NDDR IS TO HELP ENSURE THE SAFETY OF PLASMA PROTEIN THERAPIES BY PREVENTING INFECTED DONORS FROM DONATING, THEREBY PREVENTING AN INFECTED DONATION FROM POTENTIALLY REACHING THE PLASMA POOL FROM WHICH FINAL PRODUCTS ARE MANUFACTURED.

NATIONAL DONOR DEFERRAL REGISTRY



Any plasma donor who **TESTS REACTIVE** for HIV, HBV, or HCV must be entered into a **NATIONAL DONOR DEFERRAL REGISTRY (NDDR)**. All donors are checked against the NDDR at each visit; those in the database are **UNABLE TO DONATE PLASMA**.



NATIONAL DONOR DEFERRAL REGISTRY

The NDDR is a database of donor test results—specifically, results showing that a donor has tested positive for one of a handful of blood-borne viruses.² The purpose of the NDDR is to help ensure the safety of plasma protein therapies by preventing infected donors from donating, thereby preventing an infected donation from potentially reaching the plasma pool from which final products are manufactured. The quality of plasma-derived therapies is protected by three “pillars” of product safety—donor screening, testing, and viral inactivation. The primary role of the NDDR is to enhance and strengthen the donor screening pillar, though it also protects collection center staff and other donors.

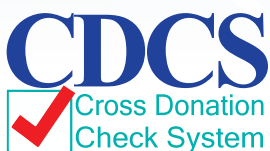
Although the use of database technology is of relatively recent vintage, the NDDR concept is not new. In fact, the NDDR has been in operation, in one form or another, since 1993. During that 24 year period, there have been dramatic improvements in information technology, such that a donor’s viral marker status—which used to be communicated by telephone and recorded manually—can now be recorded or confirmed by a collection center-NDDR interface that is direct and instantaneous. From the beginning, the program has been strongly supported by the U.S. Food and Drug Administration (FDA).³ This likely explains, in large part, why all 600+ U.S. plasma collection centers have adopted the NDDR standard.

Operation of the NDDR is relatively simple and straightforward. If a plasma donor tests positive for one of three viruses—HIV, Hepatitis B, or Hepatitis C—that individual’s name, and a limited amount of additional data necessary to confirm the individual’s identity, are entered into the database. On the screening side, whenever a new donor attempts to donate at a collection center, an NDDR check is run as part of the intake process. The result that comes back is either “match” or “not found.” If the donor is in the database (i.e., if his or her information results in a “match”) then, per the terms of the standard, that individual is permanently deferred and prevented from donating.



THE QUALITY OF PLASMA-DERIVED THERAPIES IS PROTECTED BY THREE “PILLARS” OF PRODUCT SAFETY—DONOR SCREENING, TESTING, AND VIRAL INACTIVATION.

Source: Thomas R. Kreil, Ph.D. (PPTA Pathogen Safety Steering Committee, Chairman)



CROSS DONATION CHECK SYSTEM

The CDCS is a database of donation dates.⁴ In contrast to the NDDR, which is intended to ensure the safety of the product, the purpose of the CDCS is to help ensure the safety of the donor. Both FDA and Member State health authorities in Europe limit the frequency of plasma donation for the simple reason that, while plasma is a renewable tissue, it takes time for the body to replace the donated volume. Although center personnel are required to educate donors regarding these frequency limits, there may still be situations in which individual donors attempt to donate too often. They may misunderstand how the frequency limits are applied or simply have forgotten about an earlier donation. Essentially, the CDCS is a means of ensuring that donors donate within the limits.

In its current form, the CDCS has only been in operation for two years but, like the NDDR, it was preceded by lower tech efforts. Prior to implementation of the CDCS database, centers located in close proximity to one another would exchange information by fax and would track donation frequency manually, using paper records. Consequently, moving to an electronic approach has not only improved reliability, but has substantially reduced the amount of center staff time required to manage the system. Like the NDDR, the CDCS is strongly supported by FDA and all U.S. centers are currently participating.

From an operational perspective, the CDCS is slightly more complex than the NDDR for the simple reason that the regulations governing donation frequency are more complex. The CDCS is currently configured pursuant to FDA's donation frequency rules. Essentially, plasma donor is prohibited from donating more than once in a single day

and more than twice in any 7-day period. A CDCS check, which takes place at the time of each donation, records the date of the current donation and examines the donor's recent donation history. If the current donation would exceed the frequency limits, then the donor is prevented from donating. Notably, the CDCS maintains only a rolling 7 days' worth of donation date information, as this is all that is required to ensure compliance with the frequency limits.

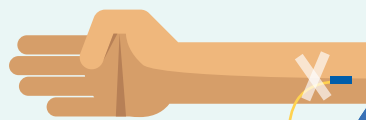
THE GENERAL DATA PROTECTION REGULATION

Data privacy in Europe is currently governed by the Data Protection Directive.⁵ However, in less than a year—on May 25, 2018—the Directive will be replaced by the GDPR in all Member States. Because it is a regulation rather than a directive, the GDPR should ensure a greater degree of uniformity in data privacy regulation across the EU. This is due to the fact that a regulation, as opposed to a directive, takes automatic effect and need not be implemented by national law. In the case of a regulation, opportunities for individual Member States to impose additional requirements as also more limited (though not completely non-existent).

The GDPR limits the ways in which “personal data” (i.e., any information relating to an identified or identifiable person) can be collected and used. Indeed, the GDPR specifies that processing of certain categories of “sensitive” personal data, including health data, is prohibited, subject to a few important exceptions. The GDPR applies to all data processors—regardless of whether based inside or outside Europe—that offer goods or services in the EU and/or monitor data subjects' behavior in the EU. Awareness of these requirements should be a top-level compliance priority, as failure to adhere to the GDPR can result in substantial penalties, including fines of up to €20 million (\$21.46 million) or four percent of annual worldwide turnover.

ALTHOUGH CENTER PERSONNEL ARE REQUIRED TO EDUCATE DONORS REGARDING THESE FREQUENCY LIMITS, THERE MAY STILL BE SITUATIONS IN WHICH INDIVIDUAL DONORS ATTEMPT TO DONATE TOO OFTEN.

CROSS DONATION MANAGEMENT



To protect the health of donors, CENTERS CHECK A NATIONAL DATABASE to make sure individuals do not donate plasma more than they should.



APPLICATION OF THE GPDR TO PPTA'S STANDARDS—PROBLEMS AND SOLUTIONS

With this background in mind, it is fair to say that, while expansion of NDDR and CDCS to Europe would need to be managed with the requirements of the GDPR in mind, those requirements do not appear to be an absolute bar. With respect to the technical security requirements, for example, the versions of these programs in place in the U.S. already incorporate firewalls and strong encryption. Likewise, the GDPR's requirements of anonymization and "data minimization" (i.e., collecting and processing only as much data as necessary) are built into both programs. For example, only the last four digits of the donor's national identification number (in the U.S., typically the Social Security number) are retained, and data minimization is incorporated by design. The NDDR is not an all-purpose storehouse of donor health information. Rather, it contains records on the three blood-borne viruses of greatest concern. Similarly, the CDCS is not a historical log of every single donation. Rather, it is a limited record of donation dates needed to ensure compliance with frequency limits that is regularly purged.

The fact that the GDPR, as a default rule, prohibits the processing of health information is a more significant, though not insurmountable, obstacle. The GDPR provides a number of specific legal bases for processing personal data, one of which is the performance of a task carried out in the public interest. Focusing on the core objectives of the standards thus appears to provide a clear route forward. Both NDDR and CDCS are designed to perform tasks in the interest of public health—NDDR by contributing to product safety and CDCS by protecting donor safety. The strong support of FDA and, it is expected, European health authorities as well, is a testament to this fact.

Even if this strong public health rationale were not present, there is another option. Collection and use of an individual's personal data is permitted when the individual provides consent. Because informed consent is already a part of the plasma donation process—the donor consents to venipuncture, acknowledges potential complications from the donation process, etc.—an additional consent regarding the collection and processing of personal health information would appear to suffice. The GDPR provides a number of specific requirements to ensure that the consent is "informed"—such as disclosure of what data will be collected, how it will be used, and how long it will be retained—but complying with these requirements should be, if not routine, at least an easy adjustment for collection centers that already value and prioritize donor education.

The one requirement that merits additional mention, and suggests that industry should not rely on the donor's consent alone as the legal basis for data processing, is

the right of erasure/right to be forgotten. As part of the informed consent, a collection center would also be required to disclose the donor's rights with respect to the collected data, including the right to *withdraw* consent. If consent is the only legal basis for collection, this would require the data processor to purge the data in question. This would potentially create issues for the CDCS because, in some Member States, donation frequency is defined in terms of a yearly cap. This would prevent implementation of the rolling 7-day data purge in place in the U.S. system.

In contrast, the problem is potentially more difficult with the NDDR, both because of the duration of retention (essentially indefinite) and the sensitivity of the data. It is certainly conceivable that some donors, when informed of a reactive test result, would withdraw consent to retention of information on their status as HIV, HBV, or HCV positive. If a substantial number did so, it would severely undermine the NDDR's donor screening function. It is not at all clear that such withdrawals of consent would be widespread, but the potential consequences of the right of erasure should be carefully evaluated. Right of erasure concerns also suggest that the primary public health function of both standards should be a point of emphasis with the data privacy authorities.

MOVING FORWARD

A more comprehensive legal review will likely be needed to ensure GDPR compliance. In addition to the issues outlined above, the fundamental question of how, and under what conditions, the two databases could be hosted outside the EU will need to be addressed. Because individual Member States are granted more flexibility with respect to health data, it will also be necessary to determine whether the data privacy laws of Germany, Austria, Hungary, and Czech Republic—where most source plasma collection centers are located—impose any additional requirements. Nevertheless, this initial analysis provides cause for optimism, and suggests that the prospects for expansion of NDDR and CDCS to Europe are strong. ●

References

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3. Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use, 80 Fed. Reg. 29842, 29854 (May 22, 2015) ("We recognize that the NDDR is a voluntary, self-regulating initiative by the Source Plasma Collection industry that is operated by a third party administrator. We agree it is an important industry practice to ensure the safety of plasma-derived therapies.")
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5. Directive 95/46/EC.



International Plasma Protein Congress 2017:

AN ONGOING DEBATE TO IMPROVE ACCESS TO CARE

BY SARA STEFANELLI, PPTA COMMUNICATIONS ASSISTANT, EUROPE

The 2017 International Plasma Protein Congress (IPPC) took place in Prague on March 14-15, with the participation of industry leaders, researchers, and patient representatives discussing the numerous challenges still hindering global, efficient access to care, but also presenting frontline projects on specific rare diseases and related therapies.

The two-day Congress opened with a focus on the hosting country—the Czech Republic—with an overview of its health care system by the new Deputy Minister of Health, Prof. Roman Prymula. Mr. David Bell (Grifols and Chairman of the PPTA Global Board of Directors) provided the Chairman's message, noting that PPTA's most important role is to educate patients, legislators, regulators, and the general public to ensure access to care for all who need it. He called for the industry to battle back against misperceptions and misinformation by speaking up about the industry and the safety of source plasma and the safety and efficacy of plasma protein therapies. Furthermore, the speakers provided some remarks on the challenges in the harmonization of the Czech Republic and the EU vision on health, as well as a summary of plasma production and pharmaceutical use in the Czech Republic. The session featured Prof. Jaroslav Zverina (Charles University in Prague); Dr. Miloš Bohoněk (Central Military Hospital–Military University Hospital Prague); Mr. Bruno Santoni (Plasma Protein Therapeutics Association [PPTA]); and Mr. David Bell. At the end of the session, the 2017 Hilfenhaus Award was presented by Dr. Oliver Schmitt (CSL Behring and Chairman of the PPTA Europe Board of Directors), and conferred to Prof. Henriette Farkas, M.D., Ph.D., DSc (Semmelweis University in Budapest).



From left to right: Mr. David Tsur (Kamada); Mr. Joshua Penrod (PPTA); Mr. Patrick Robert (Marketing Research Bureau); Dr. Pierre-François Falcou (PFF Consulting); Dr. Ranjeet S. Ajmani (PlasmaGen Bioscience).

The second session, moderated by Dr. Larisa Cervenakova (PPTA), examined various aspects of primary immunodeficiency (PID) diseases—outlining care and awareness initiatives in Germany, as well as strategies to optimize care organization and providing an overview of PID from Europe to Asia. Prof. Volker Wahn (University Hospital Charite in Berlin) presented on efforts to improve awareness of PID with German physicians through the FIND-ID project and the importance of early diagnosis and treatment. Prof. Esther de Vries (Tilburg University) talked about using the entire health care chain to optimize PID care including the use of data for building awareness and better diagnoses. Prof. Martin van Hagen (Erasmus University Medical Center in Rotterdam) provided a comprehensive overview of PID care in Southeast Asia including advances in genetic testing. He also discussed the increasing role of patient groups in Asia in helping to improve awareness of PID.

The Congress continued with a focus on the hemolytic disease of the newborn (HDN), from the description of the Rh disease and the use of hyperimmune plasma as therapy, to the challenges for universal eradication of HDN. The speakers represented members of industry and non-profit/academia who discussed challenges in Anti-D production, as well as challenges to reaching patients in the developing world. The speakers also addressed ways to ensure access to care for patients around the world. The session featured

Prof. Alvin Zipursky (Sick Kids Toronto); Dr. Kirsten Seidel (CSL Plasma); Prof. Vinod K. Bhutani (Stanford University); Mr. Lawrence P. Guiheen (Kedrion) and Prof. Gérard Visser (University Medical Center Utrecht).

Day one of the IPPC concluded with a patient-focused panel that addressed access to plasma protein therapies by examining specific geographic areas such as Central Europe, France, and Romania. Speakers included: Dr. Adrian Pană (Former Secretary of State in Romania); Ms. Martine Pergent (French PID patient association, IRIS); Mr. Brian O'Mahony (European Haemophilia Consortium); and Mr. Jan M. Bult (PPTA). Each of the speakers addressed the challenges and opportunities with working toward ensuring access to care and appropriate plasma protein therapies.

After a sponsors session about supply chain management for plasma and plasma protein therapies and the related challenges, which featured Mr. Eric Youssef (Merck) and Mr. Bruno Santoni, the sixth session concentrated on international developments with regard to plasma protein consumption across countries, the contrast in access to care worldwide and specifically to progress in Indian plasma products. The panel concluded with a presentation on how, through innovation, a small business that is locally focused can grow to one that has a global impact. The session featured Mr. Patrick Robert (Marketing Research Bureau); Dr. Pierre-François Falcou

(PFF Consulting); Dr. Ranjeet S. Ajmani (PlasmaGen Bioscience); Mr. David Tsur (Kamada); and Mr. Joshua Penrod (PPTA).

Session seven featured Mr. John Delacourt (PPTA); Ms. Cristiana Spontoni (Jones Day); Mag. Felix Patzak (Austrian Federal Office for Safety in Health Care); and Ms. Mary Gustafson (PPTA) and covered some regulatory aspects of the plasma protein therapeutics industry. First was a presentation on new trends in inspections. Of note is an initiative to use risk-based inspection planning that, through the use of control measures in inspection planning, could reduce the inspection burden while maintaining standards. Finally, there were presentations on the possible expansion of the National Donor Deferral Registry (NDDR) and the Cross Donation Check System (CDCS) to Europe. The panel concluded with an in-depth discussion of the EU General Data Protection Regulation and national regulations on personal data and their impact on the expansion of the NDDR and CDCS.

The closing session outlined how access to rare disease therapies can be supported through health-economic value; in particular, the discussion focused on reimbursement and the European Health Technology Assessment (HTA) harmonization project, underlining the pivotal role played by the patient's perspective in assessing such health-economic value. The session featured Prof. Maarten Postma (University of Groningen); Prof. Philippe Van Wilder (University of Brussels); Dr. Karen Facey (University of Edinburgh); and Dr. Irina Odnoletkova (PPTA).

As in each year, the 2017 International Plasma Protein Congress provided a fruitful platform of discussion, bringing together the varied stakeholders of the plasma industry and presenting unique and often challenging views on critical topics. During the closing announcements, Mr. Bruno Santoni thanked the sponsors, speakers, and attendees and encouraged all to attend IPPC 2018 in Budapest, Hungary. It was also announced that—thanks to the votes of all attendees—the 2019 IPPC will be held in Stockholm! ●



Top: Session three speakers listen to a presentation given by Prof. Gerard Visser (University Medical Center Utrecht). **(From left to right):** Prof. Alvin Zipursky (Sick Kids Toronto); Dr. Kirsten Seidel (CSL Plasma); Prof. Vinod K. Bhutani (Stanford University); and Mr. Lawrence P. Guiheen (Kedrion).

Bottom (from left to right): Dr. Karen Facey (University of Edinburgh); Dr. Adrian Pană (Former Secretary of State in Romania); Mag. Felix Patzak (Austrian Federal Office for Safety in Health Care); Ms. Martine Pergent (French PID patient association, IRIS).

The Hilfenhaus Award Conferred to Professor Farkas at the 2017 International Plasma Protein Congress in Prague

The 2017 Hilfenhaus Award was bestowed to Professor Henriette Farkas, MD, Ph.D., DSc, during the 2017 International Plasma Protein Congress for her work related to treating those suffering from Hereditary Angioedema (HAE) and working to improve treatments and patients' quality of life. She is a professor of allergology and clinical immunology at the Hungarian Angioedema Center at Semmelweis University in Budapest, Hungary.

Additionally, Prof. Farkas was the first person to start the treatment of HAE in Hungary. Her commitment earned her several awards and recognitions, e.g., the “Jendrassik Ernő” Medal and Award of Semmelweis University in 2005, the “L'Oréal-UNESCO Awards for Women in Science” in 2013 and the “For HAE Patients” Award of the International HAE Working Group in 2013. She is also member of many important bodies, such as the Committee of the Hungarian Allergology and Clinical Immunology Society, the Hungarian Professional College of Immunology & Allergology, the Medical Advisory Board of International Patient Organization for C1-Inhibitor Deficiencies, the International HAE Working Group, and the World Allergy Organization Steering Committee for Angioedema.

During the ceremony, Prof. Farkas gave a very clear overview of HAE, outlining the symptoms, the life-threatening consequences, the mechanism of activation of HAE, and different treatment options.

She then reported how access to care developed throughout the years in Hungary, evolving from a very stringent approach in the 1980s, to a mere hospital use in the following decade, and finally to self-administration in 2011. Prof. Farkas also presented the diverse activities carried out in the Hungarian Angioedema Center; it is the core of the regional HAE Network project, which aims at accelerating the proliferation of such centers in neighboring countries, as well as providing workshops and training courses. Finally, she presented some remarks on efficacy and safety of the therapy with plasma-derived C1-inhibitor, both in the short and in the long-term prophylaxis, specifically in pediatric and female patients. ●



Dr. Oliver Schmitt (CSL Behring and Chairman of the PPTA Europe Board of Directors) presents Prof. Henriette Farkas with the 2017 Hilfenhaus Award in Prague.

Her commitment earned her several awards and recognitions, e.g., the “Jendrassik Ernő” Medal and Award of Semmelweis University in 2005, the “L'Oréal-UNESCO Awards for Women in Science” in 2013 and the “For HAE Patients” Award of the International HAE Working Group in 2013.



Focusing on Primary Immunodeficiency Care

BY LARISA CERVENAKOVA, M.D., Ph.D, PPTA MEDICAL DIRECTOR

For many years, the plasma protein therapeutics industry has provided polyclonal immunoglobulin therapies as an intramuscular, intravenous, or subcutaneous treatment to patients with abnormalities in the immune system to fight viral, bacterial, fungal, and parasitic infections or to suppress autoimmune reactions. Most of these therapies are administered continuously throughout the patient's life—they are fundamental to the patient's survival, improve the quality of life, and contribute to a longer life. The International Plasma Protein Congress (IPPC) provides the opportunity to discuss various issues related to IgG use. Primary immunodeficiencies (PIDs) were one of the focus points at the IPPC, which took place in Prague this year. A session entitled “PID care” aimed at providing an update on diagnosis and treatment of this condition. It has been a pleasure to host three distinguished speakers: Professors Volker Wahn (Charité University, Berlin, Germany), Esther de Vries (Tilburg University, Netherlands), and Martin Van Hagen (Erasmus Medical Center, Rotterdam, Netherlands). The presentations covered topics related to epidemiology of PID, new detection approaches to establish correct diagnosis, health care chain to diagnose and treat patients, differences between Europe and Asia in diagnosing patients and providing care, importance of physician's education from various fields of medicine and role of patient organizations in finding new patients, advocating for access to medicine, and building and maintaining patient's databases.

PIDs AND THE IMMUNE SYSTEM

PIDs are disorders of the immune system that protects a person from foreign agents, such as infectious pathogens as well as allergens. The complexity of the immune system and the layers of protection involve close cooperation between the innate and adaptive immune system. Cell immunity and humoral immunity are the pillars of the adaptive immune system. Bone marrow and white blood cells, tissue macrophages, the complement system and antibodies—represented by five classes of immune globulins (IgM, IgG, IgA, IgD, and IgE)—and various cytokines are involved in recognition, processing, and elimination of foreign antigens and internal abnormal molecules. Sometimes, changes occur within the cells of the immune system, which phylogenetically have been developed to protect us from foreign attacks, and as a result, the immune system becomes impaired or it cannot function at all. Persons with different levels of impairment develop different conditions but sometimes impairment at any level of the cell development may lead to the same disease signs. Prof. de Vries stressed the difference between PID and secondary immunodeficiencies, which occur as a result of medical treatments with effects on the immune system or are associated with malignancies, infections (HIV, Epstein-Barr virus, etc), autoimmune diseases, or other disorders.

TIMELY DIAGNOSIS IS OF MAIN CONCERN

All speakers were concerned that not all patients with PIDs are diagnosed or timely diagnosed and treated. Prof. Wahn indicated that there are approximately five thousand patients with PID in Germany and less than fifteen hundred receive IgG treatment. Together with improved diagnosis, the number of new PID patients, including IgG treated, increases 5 to 10 percent per year. However, there are still delays in timely diagnosis and many individuals remain undiagnosed. Prof. de Vries stated that in the Netherlands, many patients do not reach the level of special care because many primary care physicians do not consider repeated respiratory tract infections to be a sign of a larger problem—immunodeficiency—which needs to be diagnosed and treated by the specialist, an immunologist. Because of that, many patients develop chronic lung diseases with irreversible organ damage. The situation is even more difficult in Asian countries according to Prof. van Hagen because of an insufficient infrastructure and absence of specialists who can diagnose PIDs.

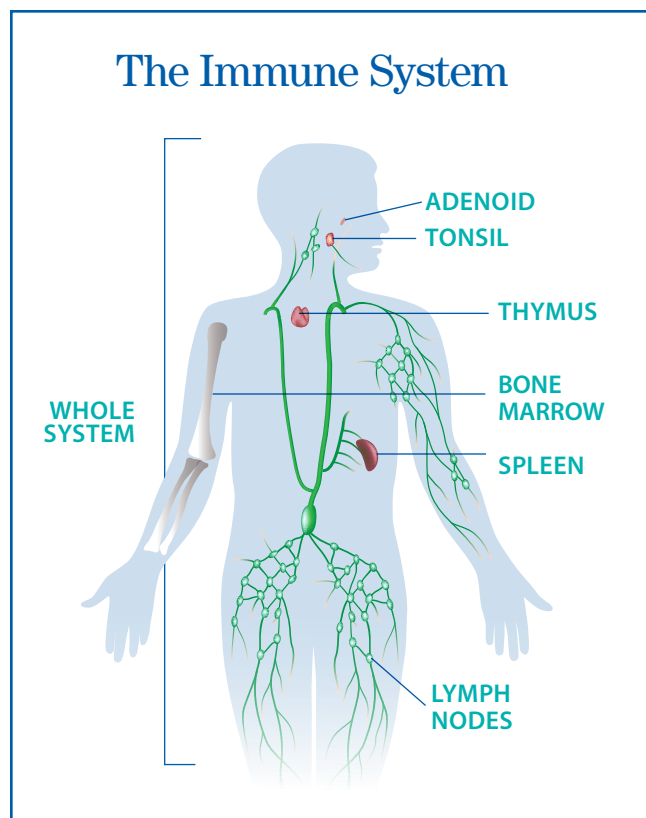
Prof. Wahn described the successful introduction in Germany of a screening for all newborn babies to detect Severe Combined Immunodeficiency (SCID), a PID which is characterized by a severe defect in both the T- and

B-lymphocyte. Children born with this condition suffer from serious infections (pneumonia, meningitis, skin rash, erythema, or sepsis) within the first few months of life, which can be life threatening if not treated. If a child gets infected with *Pneumocystis pneumonia* species, it can die within a day. Children with SCID cannot resist infection when vaccinated with live vaccines produced with weakened viruses (chickenpox, measles, rotavirus, or oral Polio) or bacteria (such as the *Bacillus Calmette-Guérin* vaccine against tuberculosis). Diagnosis of SCID is a contraindication for vaccination. Complications with fatalities occur when the diagnosis is not made and PID is not recognized early on before the vaccine is administered at 6-8 weeks of age. The diagnosis is made from a dried blood spot from a child's toe on filter paper and sent via regular mail for analysis. The testing involves detection of the presence of T-cell-receptor-excision-circles (TRECs) and in the case of B-cells, the presence of kappa-deleting-recombination-excision circles (KRECs), both of which can only be detected in mature cells. The absence of TRECs is a diagnostic marker for the absence of mature T-cells and subsequently SCID, whereas the absence of KRECs signals, for example, the diagnosis of X-linked agammaglobulinemia. As was discussed during the Q&A session during the IPPC, premature babies born as early as 28 weeks post-gestation present a diagnostic challenge which requires repeated testing after two weeks in order to confirm the diagnosis.

Other approaches—including FACS (Fluorescence-activated cell sorting) analysis to demonstrate the presence of T- and B-lymphocytes and to quantify distribution of various populations in blood of patients—significantly improve the diagnostic abilities in developed countries, according to Prof. van Hagen. However, these technologies are very expensive and cannot be used to the full extent in many Asian countries. Therefore, he—together with other colleagues—is working on developing a new, inexpensive diagnostic platform on a chip for testing patients against more than 300 monogenetic abnormalities associated with PIDs. He emphasized that proper early diagnosis will lead to correct and timely treatment of the patients.

TEN WARNING SIGNS OF PID AND PATIENT'S REGISTRIES

Prof. de Vries reminded the audience of the PID classification, highlighting the 10 warning signs of PID in children and adults. These signs include, among others, recurring otitis, bronchitis, sinusitis and pneumonias of viral or bacterial origin, gastrointestinal tract infections, other skin and systemic infections, low or absent



10 WARNING SIGNS

of Primary Immunodeficiency

- 1** Four or more new ear infections within 1 year.
- 2** Two or more serious sinus infections within 1 year.
- 3** Two or more months on antibiotics with little effect.
- 4** Two or more pneumonias within 1 year.
- 5** Failure of an infant to gain weight or grow normally.
- 6** Recurrent, deep skin or organ abscesses.
- 7** Persistent thrush in mouth or fungal infection on skin.
- 8** Need for intravenous antibiotics to clear infections.
- 9** Two or more deep-seated infections including septicemia.
- 10** A family history of PID.

Education material provided by the Jeffrey Modell Foundation (<http://info4pi.org/library/educational-materials/10-warning-signs>)

response to antibiotics, and a family history of PID. An immunodeficiency-related (IDR) score based on clinical information has been introduced by physicians in the U.S.¹ to help recognize PID in clinical practice. The majority of patients with PID have symptoms listed in the IDR score table, which can be used by general practitioners. Analysis of the large patient databases is seen by Prof. de Vries as the source for finding common signs and symptoms as signatures which can be used by primary care physicians to diagnose common variable immunodeficiencies (CVID) patients earlier. This is the reason she is involved in various projects which may help to address and resolve the diagnostic uncertainties among the first line of medical care.

IMMUNOGLOBULIN THERAPY FOR PID

Part of Prof. Wahn's talk was dedicated to X-linked agammaglobulinemia (XLA) but also highlighted the importance of distinguishing between immunoglobulinopathies and CVID and expressed concern about the results of the studies which analyzed data without distinguishing between these groups of patients.

Diagnosis of XLA is difficult to establish in neonates based on clinical signs according to Prof. Wahn because warning signs in the form of severe infection occur in infants and toddlers. The diagnosis often depends on pediatrician knowledge and experience. If the pediatrician is not able to recognize this condition, repeated infections can lead to lung damage with bronchiectasis or premature death in childhood. As a warning, Prof. Wahn presented an example of an 11-year-old patient with irreversible lung damage. This important study was performed in Italy² with enrollment of 73 male patients with XLA to assess the risk of development of bronchiectasis in relation to the age at diagnosis. The cumulative risk of developing chronic lung disease increased almost five-fold when the diagnosis was delayed from 5 to 15 years of age. The study authors observed a decrease in systemic infections, such as sepsis and meningitis/meningoencephalitis, which they attributed to optimal protection provided by high IgG trough levels due to IVIG replacement therapy. Prof. Wahn also pointed to the results of the early study performed during 25 years of observation by Liese and colleagues

at the University of Munich,³ which enrolled 29 patients with XLA who received immunoglobulin replacement therapy. The results clearly showed that patients who received high-dose IVIG (>400 mg/kg every three weeks) had a significantly high trough IgG levels which inversely correlated with the recurrence of pneumonia and the number of days spent in the hospital compared with patients receiving IVIG low-dose (<200 mg/kg every three weeks) or IMiG (100 mg/kg every three weeks) treatment. The days spent in the hospital were 0.7 versus 24.6 for trough levels 500-816 mg/dl versus 0-150 mg/dl, respectively. The better outcome was particularly evident when high-dose IVIG replacement therapy started before the age of five years. Prof. van Hagen noted that patients with CVID have a worse quality of life than cancer patients. This happens in a time when treatment in form of IgG therapies is available! All speakers voiced the need to change this situation.

ROLE OF PATIENT ORGANIZATIONS

Special attention was given to the role of patient organizations, including Jeffrey Modell Foundation, Immune Deficiency Foundation, European Society for Immunodeficiencies, FIND-ID (Netzwerk für Angeborene

Immunodefekte) in Germany, International Patient Organisation for Primary Immunodeficiencies, and the newly formed Asia Pacific Society for Immunodeficiencies. These important bodies play significant roles in helping to find PID-afflicted individuals and providing them with information on various aspects of this rare disease. It is also important to ensure access to available treatments, educate physicians, establish patient's registries and perform scientific analysis of available information, advocate on behalf of patients, and engage governments and industry in the various aspects of patients care and cure. •

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HTA

Health Technology Assessment and Plasma Protein Therapies: A Troubled Match

BY DR. IRINA ODNOLETKOVA, PPTA DIRECTOR, HEALTH ECONOMICS AND OUTCOMES

PLASMA PROTEIN THERAPIES: A SPECIAL TYPE OF PHARMACEUTICALS

Plasma-derived medicinal products comprise a special type of biologics. Since the introduction of the first large-scale method for separating therapeutic proteins from blood plasma with cold ethanol fractionation during World War II, the plasma protein therapeutics sector has experienced continuous growth.¹ In the past 70 years, the implemented business strategies resulted in developing new fractionation techniques, inventing alternative manufacturing methods—such as recombinant DNA technology, testing efficacy in new patient populations, and improving product safety and manufacturing efficiency. Today, plasma protein therapies (PPTs) are included in the World Health Organization's (WHO) "Essential Medicines List," which recognizes priority medicines based on the evidence of clinical efficacy and safety, with the purpose to ensure global health equity and meet the care needs of populations.²

PPTs are used for treating many chronic rare diseases, such as primary immunodeficiency (PID), hemophilia, chronic inflammatory demyelinating polyneuropathy, and

alpha-1 antitrypsin deficiency—and in some, there are no treatment alternatives. The global clinical need for PPTs for evidence-based indications is still largely unmet.³ Particularly in countries with low gross domestic product, patient access is often limited. However, developed economies—driven by budgetary constraints—have also been introducing cost containment measures, such as compulsory rebates and clawbacks, ignoring PPTs' manufacturing complexity and value for patients.

HEALTH TECHNOLOGY ASSESSMENT TO DETERMINE THE VALUE OF PLASMA PROTEIN THERAPIES

Approaches to the "value assessment" of health care interventions has been extensively debated by scientists and policymakers in past decades, without leading to a consensus. Health Technology Assessment (HTA)—used to determine the value of pharmaceutical products and to support national reimbursement decisions in Europe since the 90s—show inconsistencies in methods and conclusions. HTAs may be aimed at assessment of the level of therapeutic benefit (e.g., in Germany and France) or the level of cost-effectiveness

as applied in most European countries.⁴ Incremental cost-effectiveness ratio (ICER)—the outcome of such analysis—is typically calculated as a ratio between the additional cost imposed by the new therapy and the respective health gain expressed in quality-adjusted life years (QALYs), as compared to the best available treatment alternative. The application of a single ICER threshold in national reimbursement decisions is not common.⁵ The WHO recommends considering health technologies with an ICER below the value of the gross domestic product (GDP) per capita as very cost-effective, between one and three times GDP value as cost-effective, and not cost-effective if exceeding 3x GDP per capita.⁶ HTAs have also been increasingly used for the evaluation of PPTs, even though stakeholders caution that such analysis in many cases is inappropriate.⁷⁻⁸

The deficiencies of current HTA methods for assessing the value of PPTs are numerous.

EFFICACY AND COST-EFFECTIVENESS ASSESSMENT

First, in some conditions such as PID, absence of a treatment alternative can make HTAs an unethical evaluation method.⁹ The inability to conduct randomized trials and the evidentiary uncertainty caused by a limited number of observations, individual treatment responses and non-linear pharmacokinetic behavior of PPTs complicate bivariate judgement (effective versus not effective) based on short-term observations. The need for a methodological shift to adaptive trial designs, which allow for iterative evidence generation and a timely recognition of a drug's efficacy or lack thereof in certain subgroups, has been recognized.¹⁰ Conditional market entry schemes with post-launch evidence generation may offer a solution.

Second, measuring value through a mathematic calculation of cost per QALY has several limitations. Uncertainties in the clinical effect in small patient groups and subgroups, as well as high manufacturing costs result in high ICERs or infeasibility to calculate an ICER.¹¹ Moreover, the assumed neutrality of the QALYs (i.e., no matter who gains them) does not seem to be supported by societal preferences regarding health care resource allocation.¹²

PATIENT PERSPECTIVE AND OVERALL IMPACT ASSESSMENT

Third, current HTAs insufficiently involve the patient perspective. When evidence is scarce or uncertain and diseases are rare and complex, effective partnerships seem essential to determine the true added value of therapies and ensure that they are provided at the fairest possible price.¹³ Participation of patients should be considered in all phases of the project; in recent years, there has been greater recognition of the value of patient reported outcomes (PROs). Structural use of generic and disease-specific PROs in HTA is recommended but not consistently integrated in policy decisions.¹⁴ While clinicians admit to having limited expertise in handling patient perspectives,¹⁵ information from qualitative research, such as

patient interviews or focus groups, can provide policymakers with invaluable contextual information in order to understand the burden of a rare disease and how the treatment under assessment affects the patient.¹⁶

Fourth, next to the clinical and cost-effectiveness assessment, evaluation of the ethical, organizational, and societal impact of health technologies are recommended by the EUnetHTA's "HTA Core Model."¹⁷ However such methodologies are still in the early stages and barely applied in practice limiting the scope of information provided to decision-makers.

MANUFACTURING COMPLEXITY

Finally, the manufacturing complexity and specific dynamics of the plasma protein therapeutic sector are not considered in reimbursement decisions, particularly when reimbursement reductions are being applied. The manufacturing of plasma protein therapeutics is a highly-sophisticated process that takes about seven to twelve months from plasma donation to completion of the finished product. The process includes robust safety standards at each step, such as: donor screening, testing of each donation, plasma pooling and testing, protein purification, virus inactivation, and prion removal, etc. Because plasma is a biological product, rigorous testing and quality assurance occur throughout the manufacturing process.¹⁸ The cost structure of a plasma product is therefore completely different than that of small-molecule pharmaceuticals. The cost of collecting raw material (i.e., human plasma) can typically contribute to more than 60 percent of the overall cost of manufacture. In small molecule pharmaceuticals, introduction of a generic version of a drug has been shown to reduce price by up to 90 percent relative to the brand version. The manufacturer of a subsequent version of a PPT will have to devote time and invest in clinical trials, manufacturing, and post-approval safety monitoring similar to first-in-class PPT.¹⁹

An additional complexity that impacts the economics of plasma fractionation is that with each liter of plasma, a maximum protein output has to be achieved; while diversification of the product portfolio is essential for the business sustainability.²⁰ According to some analytics, if a fractionator would extract only one type of protein, their business would be uneconomic and at least a three-product portfolio is considered as necessary for a viable operation.²¹ Regional differences and variations in demand may affect the economic sustainability of the sector.

Further, the supply of plasma derived therapies is entirely dependent on the availability of healthy donors. Currently, free competition in the sector is disturbed by the "not-for-profit" fractionators that usually enjoy monopolistic protection by national authorities. This is based on the concept of self-sufficiency of plasma supply through voluntary unpaid donations.²² Low plasma supply in Europe remains a challenge when considering the growing global demand for PPTs.

In the past 10 years, many conceptual frameworks for the assessment of rare disease therapies have been developed²³ to overcome the limitations of contemporary HTA methods.

NEED FOR A NEW APPROACH TO VALUE ASSESSMENT OF RARE DISEASE THERAPIES

In the past 10 years, many conceptual frameworks for the assessment of rare disease therapies have been developed²³ to overcome the limitations of contemporary HTA methods. Most of the frameworks are a multi-criteria decision analysis (MCDA) and include a broader range of assessment elements than traditional HTAs, e.g., rarity and burden of disease, availability of treatment alternatives, level of health impact and uncertainty of effectiveness, vulnerability of patient population, manufacturing complexity, etc. However, application of these frameworks in reimbursement decisions remains limited.

In conclusion, timely diagnosis and treatment with PPTs has been shown to significantly prolong the life expectancy of people with rare diseases (e.g., PID and severe hemophilia) allowing those affected by these conditions to live normal and productive lives.^{24–25} However, current HTA methods are limited. This prevents information on the value of PPTs for patients and the complexity of their manufacturing and economics from being systematically captured. The result is inadequate information to policymakers. Patient associations caution that HTA's, which follow established rigid methodologies—may be used as a means to mitigate costs rather than a way to improve the quality of care in rare diseases.²⁶ Nowadays, some payers treat PPTs as if they were an easy-to-produce commodity. Alternative paradigms to assess “value for money” for interventions in rare diseases should be developed with high priority.²⁷ •

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Pharmacovigilance Legislation in the European Union: AN OVERVIEW OF LEGAL FRAMEWORK AND DEVELOPMENTS

BY DOMINIKA MISZTELA, PPTA MANAGER, REGULATORY POLICY EUROPE

INTRODUCTION - PHARMACOVIGILANCE SYSTEMS IN THE EUROPEAN UNION (EU)

Pharmacovigilance (PHV) is the science of drug safety. In practice, it is the collection, detection, assessment, monitoring, and prevention of adverse or undesired side effects, also known as adverse drug reactions (ADRs) associated with the use of marketed pharmaceutical products. The main aim of PHV is to treat patients safely and effectively by preventing harm and also by evaluating and minimizing the risk that may come from taking a particular medicine.

Some of the key PHV activities are:

- Data collection, evaluation, monitoring, and audit(s) on safety of medicines;
- Assessment of data for so-called ‘signals’—data which may indicate a possible change in the safety profile of drug(s);
- Proactive assessment of potential risk of drugs—expected or unexpected—as well as any actions and measures to minimize such risk(s) through so-called “risk management”;

- Timely and transparent information and communication to patients, health care professionals, the public, and pharmaceutical companies—for instance, by issuing advice or recommendations to modify, restrict, or even stop a treatment or medicine when the risk of taking it outweighs the benefit. This is then referred to as the “benefit-risk profile of a product which is no longer positive.”
- Timely and transparent information and communication to regulators in order to inform specific regulatory actions, such as requirements for additional monitoring of certain medicines.

In the EU, PHV is a key public health function.¹ PHV activities are shared between the individual Member States’ (MSs) National Competent Authorities (NCAs), the European Commission (EC)² and the European Medicines Agency (EMA).³ EMA has a key role in coordinating these activities through its expert committee on PHV, the Pharmacovigilance Risk Assessment Committee (PRAC).⁴ EMA is also responsible for managing any interactions with individual Marketing

Authorization Holders (MAHs), which, according to the EU legislation, have separate, specific obligations and responsibilities in terms of PHV.

LEGAL BASIS AND SCOPE OF PHV

The legal basis for PHV for medicines for human use in the EU is laid down in Regulation (EC) No 726/2004⁵ and its 2010 amendment through Regulation (EU) No 1235/2010,⁶ including advanced therapy medicinal products (ATMPs).⁷ They specifically cover the procedures for authorization of centrally authorized medicinal products, such as submission and granting of marketing authorization (MA), as well as their supervision once on the market; Directive 2001/83/EC⁸ deals specifically with provisions for nationally authorized medicines. Directive 2010/84/EU⁹ further increased patient protection and streamlined operational PHV processes by providing legal framework on how to produce, distribute, and use medicines, as well as for the submission of data on medicines by MAHs.

In fact, the legal requirement for data submission on medicines by MAHs, maintenance of submitted medicinal product information and notification to EMA of any new information or variation is a key concept of the 2010 pharmacovigilance legislation,¹⁰ following the so called “Article 57 requirement (Article 57(2) of Regulation (EC) No 726/2004.”¹¹

In 2012, the EU PHV legislation underwent a major overhaul through Directive 2012/26/EU,¹² applicable since October 2013, which provides guidance on notification and assessment of safety issues, and Regulation (EU) No 1027/2012.¹³ On March 7, 2013, the EU Commission adopted the Commission Implementing Regulation (EU) No 520/2012,¹⁴ which describes how to practically implement the PHV legislation. It also allowed, for the first time, the direct reporting of ADRs to NCAs by patients. It also covers, for instance, medication errors and overdose(s). It is probably best known for the introduction of the so-called “Black Symbol,” a black inverted triangle (▼)¹⁵ together with a short sentence explaining that the medicine is under additional monitoring (see Figure 1). The additional monitoring requirement applies to:

- All products authorized in the EU after Jan. 1, 2011, including biosimilar medicines;
- Products of biological origin—for instance vaccines or those derived from human blood or plasma, and which are authorized in the EU after Jan. 1, 2011;
- Provisionally licensed products, whereby the MAH for the medicine is required to submit additional data or studies.

The medicine remains on the ‘list of medicines under additional monitoring’¹⁶ for five years or until the PRAC decides to remove it. The entire list is reviewed monthly; at the time of writing this article the most recent list is from March 29, 2017.¹⁷

The 2010/12 Legislation and the Implementing Regulation is often referred to as the “New pharmacovigilance

legislation in the EU.” It is regarded by many as the biggest development and change to the regulation of human medicines in the EU since 1995.

GOOD PHARMACOVIGILANCE PRACTICES (GVP) AND GUIDELINE ON GVP

Guidance and instructions for MAHs, EMA, and NCAs on how to apply the new PHV legislation is given in the “Guideline on Good Pharmacovigilance Practices (GVP).” It describes a set of practical measures for PHV processes on how, when, and what to report and includes details on monitoring and surveillance—for instance through inspections and audits—as well as how to manage and minimize risk for patients.

The GVP consist of Modules (Modules I-XVI), Annexes (I-III) and population-specific considerations.¹⁸ The first seven modules came into force on July 2, 2012, following a public consultation between February and April 2012. As of April 2017, there are twelve modules and two addendums (I, II, III, IV, V, VI, VII, VIII, VIII Addendum I, IX, X, XV, XVI, XVII Addendum I), with three more modules planned for 2017.

The population-specific considerations include vaccines (I) and biological medicinal products (II) with three more population-specific considerations to be developed in 2017 (pregnancy and breastfeeding, pediatric population, and geriatric population). Additional information, such as definitions, templates, and additional guidance is covered in three Annexes (I; IIa; IIb; IIIa; IIIb; IIIc; IIId; IIIf, IIIf).

MOST RECENT UPDATES TO PHV AND GVP

In 2014, the EU Commission adopted a Commission Delegated Regulation (EU)¹⁹ on post-authorization efficacy studies (PAES). These are specific studies which are conducted in order to add additional or complementary efficacy data on an authorized medicine. This may be due to improve the scientific understanding of the medicine, such as real-life situations, or because some data can only be gathered post-authorization, such as the long-term effect(s) of a certain drug.

Since the initial publication of the first seven modules of GVP in June 2012, additional modules were released and revised following public consultation. The most recent revisions include Module V to amend requirements of risk management plans, Module IV to clarify the definition of a PHV audit, Module VI on reporting of adverse reactions, and Module IX on signal management.

On March 30, 2017, the EMA published the latest revision (Revision 2) of Module V and Revision 2 to Module II, which includes the new Article 57 database²⁰ and pharmacovigilance systems master file.

The timelines of all GVP public consultations and release of final documents can be found on EMA’s GVP webpage.

SUMMARY/CONCLUSIONS AND FUTURE CHALLENGES



Figure 1: Introduction of the "Black Symbol"

The Commission Implementing Regulation (EU) No 520/2012 was adopted March 2013 and is probably best known for the introduction of the so-called "Black Symbol," a black inverted triangle (▼)¹⁵, together with a short sentence explaining that the medicine is under additional monitoring.

PHV systems in the EU have developed considerably since its inception through Regulation (EC) No 726/2004 and Directive 2001/83/EC; with more developments to follow in the coming years with the advancement of research and science and an increasing number of newly developed and more complex medicines—medicines designed for specific patient populations or specific situations. These may have unknown and unpredictable adverse effects on human health.

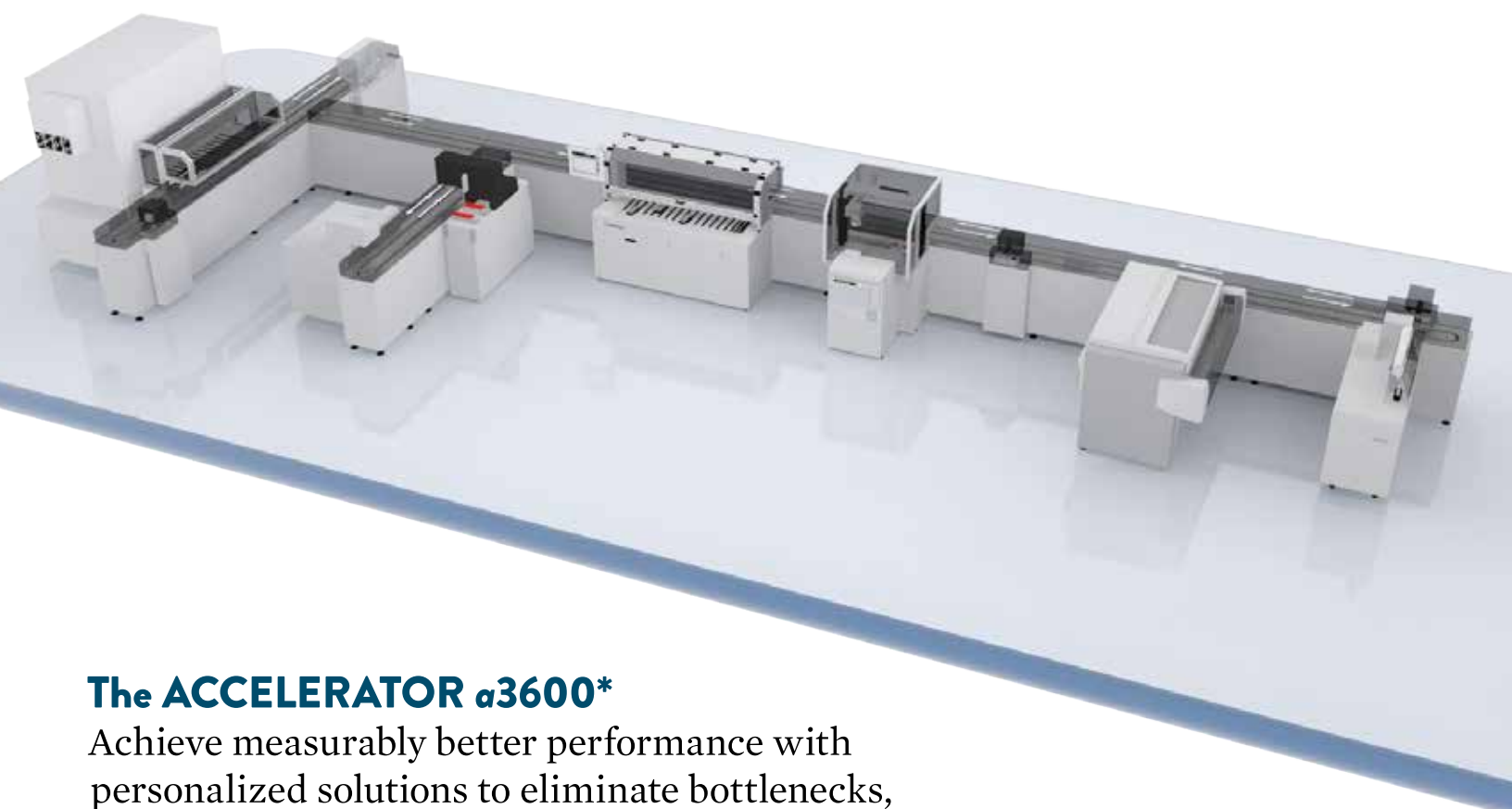
PPTA member companies recognize that minimizing the potential harm that may arise from medicines is essential and take proactive actions such as transparency, communication, and patient involvement, and through providing timely, high quality safety data and proactive risk-management. ●

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The Need for Plasma in Asia

BY JOSHUA PENROD, PPTA VICE PRESIDENT, SOURCE & INTERNATIONAL AFFAIRS
JULIA FABENS, PPTA MANAGER, INTERNATIONAL AFFAIRS

Asia has far and away the largest population of any continent, at 4.43 billion,¹ and a rising standard of living.² The percent of gross domestic product that most Asian countries are able to dedicate to health care is rising as well.³ These factors, combined with a modest population growth rate (1.04 percent)⁴ across the region, amount to one irrefutable fact—the clinical need for plasma protein therapies in Asia will increase. It is important that steps be taken in order to accommodate that clinical need, and advance the idea of Asia as a critical partner in a goal of global sufficiency of plasma.

Looking at numbers of people with hemophilia A (PWH) and primary immunodeficiency (PID) show the stark gap between the numbers that might be statistically expected and how many have been identified. In India alone, we might expect to see 131,105 PWH, but the World Federation of Hemophilia reports that 14,508 PWH have been identified. In China, those numbers are 137,122 and 11,837, respectively. The estimated numbers of patients with a PID, compared to identified patients, are even bleaker. In India, we might expect to see 11,539, while 500 have been identified. A 2016 South East Asia Primary Immunodeficiency Network (SEAPID) study of Indonesia, Malaysia, the Philippines, Singapore, Thailand, and

Vietnam shows that of an expected 46,461 patients with a PID, 489 have been identified.

What do these disparate numbers mean for the need for treatment in Asia? They mean that as health care systems and diagnosis improve and citizens are increasingly able to afford better medical care, previously unidentified patients will be diagnosed, which is a wonderful thing. It is important, however that there is a sufficient ability to procure the critical therapies they require. While there is a desire in many Asian countries to facilitate additional supply of plasma for fractionation, countries face a variety of hurdles to robust collection.

China, for example, has very strict regulations on collections, and while PPTA applauds China's efforts to maintain a safe supply of plasma, some of the measures taken put an undue burden on collection without any safety benefit. First and foremost among those is a prohibition against the use of recovered plasma, which means that much important plasma is lost as a result. Total demand for plasma to fully supply the Chinese market was 12,000 tons in 2016, while Chinese collection centers collected 5,480 tons.⁵ Some of that shortfall is made up by albumin sales from foreign companies, but significant clinical need remains unmet. An additional restriction requires that

We believe that through educating policymakers, doctors, patients, and industry leaders, and providing support wherever possible for those looking to help advance this goal, there is no reason that Asia cannot become an even more active contributor to the world's supply of plasma for fractionation.

plasma collection centers be owned by a fractionation company, which prevents the development of independent collectors which are a crucial piece of the systems enjoyed in the U.S. and European countries.

On the other hand, India's plasma collection is limited by a prohibition against the collection of source plasma. The country currently collects a small amount of recovered plasma—the Marketing Research Bureau estimates around one percent of the world's supply of plasma for fractionation in 2015, or around 425,000 liters. However, with the world's second largest population, also with an increasing standard of living, India has the potential to make a great impact on the world's supply of plasma should a well-regulated and safe source plasma collection system form in that country.

The Japan Blood Product Organization provides around 910,000 liters of plasma in 2015 to domestic manufacturers for processing into PPTs.⁶ However, there is limited incentive to collect more due to the inclusion of PPTs in the Export Control Order, which prohibits their export, as well as the export of source plasma. An official report issued by a Ministry of Health task force in October of 2016 suggested removing PPTs from the Export Control Order and allowing the export of products made from “surplus” blood components on humanitarian grounds. While not concrete progress toward free trade in plasma, it is certainly a step in the right direction. Other challenges involving appropriate diagnosis and treatment of patients in Japan also warrant consideration, such as awareness of rare diseases, treatment, and the possibilities for suitable reimbursement policies that take such rare disease dynamics into account.

Indonesia is another country with great ambition but significant barriers to effective plasma collection. It was chosen as the pilot country for the 2013 World Health Organization (WHO) and European Commission project for enhancing the availability, safety and quality of blood products in low- and middle-income countries.

As part of that project, three major fractionators reviewed Indonesia's current plasma collection practices and found a number of areas where critical deviations from established practices were observed.⁷ However, more recent projects being developed in Indonesia may point the way to a more effective approach, with a new memorandum of understanding between the Indonesian Red Cross and PT Bio Farma. The Indonesian Ministry of Health has also recently approved PT Bio Farma to manage the production of immunoglobulins and albumin from plasma collected by the Indonesian Red Cross.⁸

PPTA tirelessly advocates for global sufficiency in plasma for fractionation. The countries mentioned here, as well as many others throughout Asia, show that there is certainly a strong regional will to contribute to that goal. We believe that through educating policymakers, doctors, patients, and industry leaders, and providing support wherever possible for those looking to help advance this goal, there is no reason that Asia cannot become an even more active contributor to the world's supply of plasma for fractionation. ●

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Access to Care: Differentiating the Plasma Protein Industry

BY TOM LILBURN, PPTA SENIOR DIRECTOR, GOVERNMENT RELATIONS

It's widely understood that human physiology is complex, intricate, and evolving over time. Delicately balanced proteins mediate system responses, with feedback mechanisms that adjust other complicated systems, working 24 hours a day, 365 days a year.

Factory-like processes grow bone, produce blood and proteins, and replicate many different cells needed for survival—all within a self-regulating biological sphere that lasts for many decades. Medical innovations in medicine have allowed us to find a way to reach into these complex biological systems and provide patients with proteins which their own bodies may be missing. The very nature of this biological material means the resulting plasma protein therapies are difficult to produce and different from other small molecule drugs.

The starting point for plasma protein therapies is the human body itself. Complex, large proteins that are necessary for proper blood clotting and the prevention of infections by antibodies are contained in plasma—the liquid portion of blood. Plasma cannot be made in a laboratory nor can it be made by combining chemicals; plasma-derived therapies can only be made from individuals who donate their plasma. More than 600 U.S. plasma collection centers—each with 50-100 employees—collect, process, freeze, and ship plasma donations to PPTA member manufacturing centers. In order to treat some rare diseases for one year, it can take more than 1,000 plasma donations.

The collection process is highly regulated by the United States Food and Drug Administration (FDA) and plasma therapies are the only pharmaceutical for which the starting material must be licensed. The FDA then, in a second and separate regulatory process, approves the final product. Traditional pharmaceuticals only have approval of the finished product. More than 35 million plasma donations each year must be qualified, in addition to the finished product.

The limitation of a finite source of biological starting material affects every step of the collection and manufacturing process. Preparing a therapy often takes between seven to twelve months from donation to final product release. The complex manufacturing process sets plasma protein therapies apart from chemical pharmaceuticals and other biologics whose processes are



“Because not all patients respond the same to each medication, it is the responsibility of the coordinating expert physician to work with each patient to define the optimal medication(s) for that particular patient.”



“It is unacceptable to limit availability of augmentation therapy in any way and especially to a single product.”

much more condensed and whose direct manufacturing costs are a significantly smaller portion of the overall cost: 14 percent for pharmaceuticals versus 57 percent for plasma proteins.

Integral to the story of why plasma proteins are so different are the patients they treat. Each disease group for which plasma protein therapies are indicated is considered rare, by definition having fewer than 200,000 patients afflicted. The total number of patients treated with plasma protein therapies in the U.S., across all disease groups, is slightly below 100,000. Disease groups such as hereditary angioedema patients only have about 5,000 patients on treatment. Larger, yet still rare, disease groups—such as bleeding disorders or primary immunodeficiency diseases—have between 30,000-40,000 patients taking plasma protein therapies.

While clinically different and small in number, what these patients all have in common is that they need these missing proteins to survive and thrive. In addition, these patients’ diseases are genetic and chronic requiring lifelong treatment. In 1971, the 10-year survival rate for patients with common variable immune deficiency was only 37 percent, but by 2008—with the use of plasma proteins—it had increased to 90 percent. Hemophilia patients in the beginning of the 20th century only lived till 13 years of age, but in 2017 have a normal life expectancy of 77 years. Unlike some other disease treatments that have short duration improvements or modest increases in survival, patients treated with plasma proteins can live healthy lives, contribute to society, and ease the burden of their protein deficiency on their families and the health system. According to a recent study by the Jeffrey Modell Foundation, the economic impact of diagnosing and treating a primary immunodeficiency disease and treating with immunoglobulin therapy represents an average savings of more than \$55,000 per year.

The uniqueness of plasma proteins is directly connected to the complexity of their processing during the manufacturing process. Manufacturing differences in fractionation,

stabilization, purification, and inactivation processes are unique to each brand and can result in clinically distinct products.

Plasma protein therapies can differ in terms of formulation, purity, half-life, immunogenicity, osmolality, pH, and sodium or sugar content. Due to these differences, patients experience varied efficacy, tolerability, and clinical outcomes between products. Patients who are stabilized and doing well clinically often are unwilling to risk switching product; nor do expert clinical guidelines support doing so. The American Academy of Allergy, Asthma and Immunology states, “IVIG is not a generic drug and IVIG products are not interchangeable. A specific IVIG product needs to be matched to patient characteristics to insure patient safety.”

Lastly, plasma proteins are different from many of their small molecule cousins because of the heightened need and constant vigilance from evolving threats to the availability of plasma. As a biological material with a finite human supply, any degradation in the collection process from natural disasters to transportation interruptions can affect production. Strict adherence to all collection and manufacturing standards—both those from the FDA (collection and manufacturing) and stringent PPTA industry standards, such as the International Quality Plasma Program and the Quality Standards of Excellence, Assurance and Leadership program ensure plasma protein safety. Plasma protein therapies’ safety protocols are constantly evolving due to new and emerging pathogens, the most recent being the Zika virus.

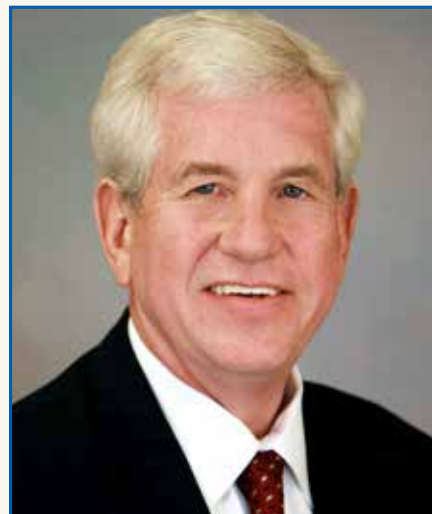
Today’s highly regulated, complex, lengthy, and capital-intensive collection and manufacturing processes for plasma proteins produce lifesaving therapies. From the screening of donors at collection centers through the long journey of frozen plasma to manufacturing sites, each step is precise, regulated, and necessary. Rare disease patients rely on PPTA members to make these safe treatments from plasma proteins that are worlds apart from the larger pharmaceutical pill industry. ●

Inside PPTA

MEET THE PPTA STAFF

Thomas B. Lilburn

SENIOR DIRECTOR, GOVERNMENT RELATIONS



Q How long have you been with PPTA?

I joined PPTA in April of 2015, but actually have known PPTA and some of the staff and worked with the organization for more than 20 years. The organization has grown, but the people in the industry are still great to work with.

Q What do you focus on in your role as Senior Director, Government Relations?

My efforts are directed at ensuring access to plasma protein therapies in the U.S. in the federal arena. Most policies—set legislatively by the U.S. Congress or administratively by the Health & Human Services Department—affect whether patients can access their medicines. Even commercial payers look to federal agencies as they set their policies. Building meaningful working relationships with congressional committees and individual Members of Congress is essential to having a voice to advance and protect the interests of our industry.

Q Tell us about your background?

I graduated with an undergraduate degree in biology and after a side trip as a Marine Captain and a subsequent MBA, I worked in the broader brand pharmaceutical industry for over three decades. Like many, I started as a representative calling on physicians, “carrying a bag” as it’s often referred to by my colleagues. I was involved in the early launch of Gamimune-N, and with experience in management, product marketing, managed care, and public affairs—plus an interest in government—I was asked to develop and manage a national state affairs program for Bayer. That’s when I first met the Association folks—Jan M. Bult and Julie Birkhofer—during some tumultuous times, sitting on a PPTA steering

committee. The experience of sitting on the other side of the desk has been invaluable in understanding the needs and problems facing the industry. Eventually I was asked to go to Washington, D.C. and work on federal issues like Medicare Part D, importation, and the Affordable Care Act.

Q What is most rewarding about working in this industry?

The ability to actually meet and know patients who truly benefit from the therapies our members make. These aren’t lifestyle drugs or elective surgeries. These are lifesaving medicines for real people who—without the innovation, dedication, and entrepreneurship of our members—would suffer great harm.

Q Who has been an inspiration to you in your life?

A teacher. During my 9th grade in high school, I had an irascible, bombastic science teacher that could explain science in an unconventional way that piqued your interest—it started with you asking questions about how things worked and not stopping until you’ve found the answer. I’ve been fascinated and involved in science, in one way or another, ever since.

Q Tell us something that may surprise us about you?

I used to have long hair and drive a 3-wheeled Harley Davidson “chopper” with racing slicks and no mufflers. ●



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In celebration of PPTA's 25th Anniversary, PPTA is hosting a black-tie gala in conjunction with the Plasma Protein Forum in Washington, D.C. ●

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Upcoming Events

CONFERENCES & SYMPOSIUMS

June

- 22-25** 22nd Annual European Hematology Association (EHA) Congress
Madrid, Spain
- 23-25** 26th Annual Alpha-1 National Education Conference
Chicago, United States

July

- 8 – 13** XXVIth Congress of the International Society on Thrombosis and Haemostasis (ISTH)
Berlin, Germany

August

- 24 – 26** National Hemophilia Foundation (NHF) 69th Annual Meeting
Chicago, United States

September

- 11 – 12** International Plasma Fractionation Association (IPFA)/Blood Centers of America (BCA) 3rd Global Symposium on The Future for Blood and Plasma Donation
Atlanta, United States
- 11 – 14** European Society for Immunodeficiencies (ESID): Autoimmunity & Inflammation in PID; Beyond the Paradox
Edinburgh, United Kingdom
- 23** Guillain-Barré Syndrome (GBS) Foundation International Regional Conference
Chicago, United States

October

- 8 – 14** International Plasma Awareness Week (IPAW)
- 19** PPTA Business Forum
Las Vegas, United States

November

- 8 – 10** International Primary Immunodeficiencies Congress (IPIEC): Focus on Diagnosis and Clinical Care
Dubai, United Arab Emirates
- 8 – 10** 10th World Federation of Hemophilia (WFH) Global Forum on Research and Treatment Products for Bleeding Disorders
Montreal, Canada

December

- 9 – 12** 59th American Society of Hematology (ASH) Annual Meeting & Exposition
Atlanta, United States

2018

February

- 16 – 17** ICI 2017: 19th International Conference on Immunology
London, United Kingdom

March

- 13 – 14** PPTA International Plasma Protein Congress (IPPC)
Budapest, Hungary

GLOSSARY OF TERMS

ABRA – AMERICAN BLOOD RESOURCES ASSOCIATION

ADR – ADVERSE DRUG REACTION

ARTICLE 57 DATABASE – DATA SUBMISSION ON MEDICINES

ATMP – ADVANCED THERAPY MEDICINAL PRODUCT

CDCS – CROSS DONATION CHECK SYSTEM

CVID – COMMON VARIABLE IMMUNODEFICIENCY

DAE – DONOR ADVERSE EVENT

EC – EUROPEAN COMMISSION

EEA – EUROPEAN ECONOMIC AREA

EMA – EUROPEAN MEDICINES AGENCY

EMA – EUROPEAN AGENCY FOR THE EVALUATION
OF MEDICINAL PRODUCTS

EU – EUROPEAN UNION

FACS – FLUORESCENCE-ACTIVATED CELL SORTING

FDA – UNITED STATES FOOD AND DRUG ADMINISTRATION

GDP – GROSS DOMESTIC PRODUCT

GDPR – GENERAL DATA PROTECTION REGULATION

GVP – GOOD PHARMACOVIGILANCE PRACTICES

HAE – HEREDITARY ANGIOEDEMA

HDN – HEMOLYTIC DISEASE OF THE NEWBORN

HTA – HEALTH TECHNOLOGY ASSESSMENT

ICER – INCREMENTAL COST-EFFECTIVENESS RATIO

IDR – IMMUNODEFICIENCY-RELATED

IG – IMMUNE GLOBULIN

IPPC – INTERNATIONAL PLASMA PROTEIN CONGRESS

IQPP – INTERNATIONAL QUALITY PLASMA PROGRAM

KREC – KAPPA-DELETING-RECOMBINATION-EXCISION CIRCLE

MA – MARKETING AUTHORIZATION

MAH – MARKETING AUTHORIZATION HOLDER

MCDA – MULTI-CRITERIA DECISION ANALYSIS

MEP – MEMBERS OF THE EUROPEAN PARLIAMENT

MS – MEMBER STATES OF THE EU

NCA – NATIONAL COMPETENT AUTHORITY

NDDR – NATIONAL DONOR DEFERRAL REGISTRY

PAES – POST-AUTHORISATION EFFICACY STUDY

PHV – PHARMACOVIGILANCE

PID – PRIMARY IMMUNODEFICIENCY

PPT – PLASMA PROTEIN THERAPY

PPTA – PLASMA PROTEIN THERAPEUTICS ASSOCIATION

PRAC – PHARMACOVIGILANCE RISK ASSESSMENT COMMITTEE

PRO – PATIENT REPORTED OUTCOME

PWHA – PEOPLE WITH HEMOPHILIA A

QALY – QUALITY-ADJUSTED LIFE YEARS

REACH – REGISTRATION, EVALUATION,
AND AUTHORIZATION OF CHEMICALS

SCID – SEVERE COMBINED IMMUNODEFICIENCY

SEAPID – SOUTH EAST ASIA PRIMARY
IMMUNODEFICIENCY NETWORK

TREC – T-CELL-RECEPTOR-EXCISION-CIRCLE

WHO – WORLD HEALTH ORGANIZATION

XLA – X-LINKED AGAMMAGLOBULINEMIA



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