

# THE SOURCE

MAGAZINE OF THE PLASMA PROTEIN THERAPEUTICS INDUSTRY

WINTER 2015

## Working Together to Make a Difference

European Medicines Agency  
Haemophilia Registries Workshop

---

Predicting Immunogenicity by Integrated  
Modeling of Antigen Processing, MHC  
Presentation, and TcR Recognition

---

The Role of Government Entities  
in Access to Care





## Customized donor payment solutions for the Plasma Industry

At 3PEA, we understand that one size does not fit all. That's why 3PEA offers customized payment solutions to fit your unique requirements. Our solutions are designed to maximize donor acquisition and retention while reducing administrative time and costs.



DEPENDABLE - AGILE - RESPONSIVE

3PEA's comprehensive PaySign® prepaid solution can function either as a standalone web-based solution or fully integrated with existing donor management systems

No upfront costs

Customized reporting

Lower cardholder fees

FOR MORE INFO VISIT: [3PEA.COM/PAYSIGN](http://3PEA.COM/PAYSIGN) • [PLASMA@3PEA.COM](mailto:PLASMA@3PEA.COM) • 866.549.9126

#### GLOBAL BOARD OF DIRECTORS

**Baxalta Inc.** | Jacopo Leonardi

**Biotest AG** | Bernhard Ehmer

**CSL Behring** | Karen Etchberger

**Grifols USA** | David Bell

**Kedrion SpA** | Paolo Marcucci, Chair

**General Counsel** | Paul Rosenthal, Esq.

#### PPTA STAFF

**President & CEO** | Jan M. Bult

**Sr. Vice President,  
North America & Global Health Policy** | Julie Birkofer

**Vice President,  
Source & International Affairs** | Joshua Penrod

**Vice President,  
Global Medical & Regulatory Policy** | Mary Gustafson

**Executive Director, Europe** | Bruno Santoni

**Vice President,  
Legal Affairs & Global Operations** | John Delacourt

#### THE SOURCE STAFF

**Editor** | William Murray

**Managing Editor** | Rachel Liebe

Requests for permission to reprint should be directed to the editor at [thesource@pptaglobal.org](mailto:thesource@pptaglobal.org).

**THE SOURCE** is available as a PDF file at [www.pptaglobal.org](http://www.pptaglobal.org).

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. ©Plasma Protein Therapeutics Association 2014

#### DESIGN AND PRODUCTION

**B. Creative Group** | [www.agencybcg.com](http://www.agencybcg.com)

**THE SOURCE** is published quarterly by PPTA.  
147 Old Solomons Island Road, Suite 100  
Annapolis, MD 21401

**PHONE:** +1.202.789.3100

**EMAIL:** [thesource@pptaglobal.org](mailto:thesource@pptaglobal.org)



# WINTER 2015 Contents

## 3 IN MY VIEW

---

4 European Medicines Agency  
Haemophilia Registries Workshop

8 Predicting Immunogenicity by Integrated Modeling  
of Antigen Processing, MHC Presentation, and TcR Recognition

12 EMA Stakeholder Meeting Assesses Progress  
on Drug Shortages Initiative

17 Highlights From The European Haemophilia Consortium  
Annual Conference 2015

21 The Joint EU Member States Procurement  
of Rare Disease Medicines Initiative

24 The Role of Government Entities in Access to Care

---

## 29 INSIDE PPTA

29 International Plasma Awareness Week Wrap-Up

32 Business Forum Overview

---

## 33 MEET THE PPTA GLOBAL HEALTH POLICY STAFF

---

## 35 UPCOMING EVENTS

---

## 36 GLOSSARY



# Designed to Fit

It's one smooth ride, integrating seamlessly to fit your needs



Global leaders in the plasma industry trust ACCESS1 Health for custom software solutions that streamline operations, improve workflow and support regulatory requirements. ACCESS1 helps you accelerate with innovative, customized software created through close collaboration plus an in-depth understanding of plasma-specific challenges.

## **ACCESS1 revs up performance with sleek, innovative solutions for:**

Comprehensive logistics management software  
End-to-end product management

Algorithm-based decision optimization  
Regulatory adherence solutions



Get your operations and systems firing on all pistons. Contact us today to learn how we're helping other plasma companies and what we can do for you.

**877.321.2221 | [www.PlasmaSoftwareSolutions.com](http://www.PlasmaSoftwareSolutions.com)**





# In My View

BY JAN M. BULT, PRESIDENT & CEO

**“It is better to talk with someone rather than talk about someone”**

Recently, I spoke at a conference and heard two presentations about ethics. I find it very important to include the ethical dimension in our work, but there is an important condition: ethical discussions should be fact based and not only work with assumptions. The reason I write this is because one of the ethicists I heard was making statements about donor compensation that were very abstract. Later, he admitted that there was a big gap in his knowledge about the practicalities related to compensation. As usual, there were different views expressed with regard to the need (or not) for self-sufficiency for blood and medicinal therapies derived from human plasma. Based on some statements that were made on that day, I realized, not for the first time, that there are some things that are not right. It is amazing to me that some people feel they can talk about these topics as if they are abstract. At the end of the day, it is about how to make sufficient supplies of plasma protein therapies available to patients in clinical need. Our position on self-sufficiency has always been:

- Every country has the right and obligation to provide its population with safe and effective medicines
- Self-sufficiency is a goal
- Self-sufficiency is not a dogma
- Globally we need to talk about sufficiency

Though I heard some comments that were repeating nothing more than 40 year old opinions, I was encouraged by some private conversations which made me realize that opinions can be more aligned than what people might think.

What can be done better? In Europe there are regular meetings organized by the European Commission with national competent authorities to discuss various issues including plasma protein therapies and all its related components such as the collection of starting material

(plasma). Participants are chosen by the different Ministries of Health of the Member States. They can come either from governmental agencies or are invited experts.

Until now, the private sector manufacturers organized in PPTA or the private sector collection centers, organized in the European Plasma Collectors Committee have never been invited to these meetings as active participants or guests. On the other hand, public sector manufacturers, organized in the International Plasma Fractionation Association (IPFA), or public sector collections, organized in the European Blood Alliance (EBA) have, on occasion, been able to attend these meetings. That does not seem to be right.

I have nothing against IPFA or EBA members attending and participating. But why not use our members' expertise in such a complex area as well. Like I said before, **“It is better to talk with us than to talk about us.”**

And what about the patients' voice? We all remember the October 2013 “Rome Declaration” that had many recommendations to national governments to improve self-sufficiency. One of the recommendations went so far as to say... phase out in a programmed manner the industry that uses plasma from compensated donations (paraphrased)... If implemented, these measures would deprive more than two – thirds of the current supply of plasma protein therapies. Needless to say, this would have a devastating impact on patients whose lives depend on these therapies. The meeting where these issues were discussed was held without any representative of the industry and there was no voice for the end users of our therapies, the patients. Can you believe that? ●

**“It is better to talk with patients, than to talk about patients”.**

Jan M. Bult, PPTA President & CEO





# European Medicines Agency Haemophilia Registries Workshop

BY DOMINIKA MISZTELA

**T**he workshop was jointly organized by the European Medicines Agency's (EMA) Human Medicines Evaluation Division, the Blood Products Working Party (BPWP), the Paediatric Committee (PDCO) and the Pharmacovigilance Risk Assessment Committee (PRAC) in London, July 1-2, 2015.

Invited participants included members from academia, patient advocacy groups, European and U.S. regulators, EU registries' representatives from the European Haemophilia Safety Surveillance (EUHASS), PedNet Haemophilia Registry (PEDNET), UK National Haemophilia Database, the French Haemophilia registry (FranceCoag Network), German Haemophilia Registry/ Paul-Ehrlich-Institut (PEI), and industry members including PPTA.

The workshop was organized as part of the EMA-wide 'Cross-Committee Task Force on Patient Registries,' an EU collaborative framework for patient registries. The task force is developing a strategy white paper for registries to identify the tools needed to establish useful and sustainable registries and to set up registry initiatives which will be applicable across different disease areas. One of its key functions is to facilitate dialogues between Marketing Authorization Applicants (MAAs)/ Marketing Authorization Holders (MAHs), registry holders, academics, and National Competent

Authorities (NCAs) to enable collection and analysis of high quality data, to inform regulatory decisions, and ultimately, to inform the benefit-risk profile of medicinal products across Europe.

The workshop focused on how data collected in registries could be utilized in a more coordinated and efficient fashion with maximum benefit to public health. The workshop aimed to identify what regulators need from hemophilia registries and how to improve their usefulness based on the data collected.

#### **The main items discussed were:**

- Key data that regulators would like to see in registries.
- Assessment of current registries and whether they provide data that regulators are looking for.
- Evaluation of the rationale(s) for different approaches through particular well-functioning EU registry examples such as EUHASS and PEDNET.
- Assessment of whether collection of data from different registries in a similar fashion would allow combination of data and whether this is achievable with the national registries.

Currently, there are approximately 35 EU-wide registries for hemophilia and associated rare bleeding disorders



including EUHASS, PEDNET, Anti-Biopharmaceutical Immunization: prediction and analysis of clinical relevance to minimize the RISK Consortium (ABIRISK), UK National Haemophilia Database, the FranceCoag Network, and the German Haemophilia Registry/ PEI registry. Examples of international or world-wide registries are Survey of Inhibitors in Plasma Product Exposed Toddlers (SIPPET) and Global Emerging HEMophilia Practice (GEHEP) registry. In addition, multiple industry-initiated registries exist which were set up in parallel to clinical trials (CTs) and range from post-authorization study registries to patient diaries. Registries potentially represent a very useful public health tool to inform national Health Technology Assessments (HTAs) and health care providers on epidemiology, market access, procurement, and reimbursement. Furthermore, registry data can be requested by NCAs from MAAs/ MAHs and can be used as part of Risk Management Plans (RMPs) for pediatric studies/ pediatric investigational plans (PIPs), if they fulfil the relevant requirements. However, current registries are not well used. This is due to a high level of variation in the types of registries set up, the quality and amount of data collected, and the quality and information level of results produced. The main issue remains that the same patients are often entered in many registries simultaneously without adequate

consistency checks and follow-up, which leads to data overlap and double-counting. There is also a lack of common protocol and methodology for data collection, multiplication of efforts by different registry holders, inadequate scientific use of the data generated, and ultimately, limited benefit to the patient population. Moreover, registries often face issues with continuous financial sustainability and resources.

These issues were discussed in four separate sessions with presentations from regulators, clinicians, industry, patient organizations, and registry holders. Session one discussed the current status and current regulatory needs of hemophilia

---

The main issue remains that the same patients are often entered in many registries simultaneously without adequate consistency checks and follow-up, which leads to data overlap and double-counting.





Registries represent a useful tool to inform clinical drug and CT design, but have limited use and benefits due to low confidence in data and limited availability of data which are important for industry, such as pharmacoeconomics.

---

registries, including safety and immunogenicity, using Factor (F)VII and FIX as examples. The session addressed which data can be obtained from registries, and whether the data currently obtained from registries meet scientific and regulatory requirements.

Session two focused on EMA's 'Cross-Committee Task Force on Patient Registries' and provided an overview of European registries such as EUHASS, PEDNET, the UK National Haemophilia Database, and FranceCoag Network.

Session three provided insight into the industry's perspective on registries, with presentations from PPTA and the International Plasma Fractionation Association (IPFA), which centered on industry's experience with product-specific and with disease-specific registries, their advantages and disadvantages, how to strengthen the outcome of registries, and how industry can contribute to this process. In Session three, the following key points were highlighted: Registries, if well-kept can follow patients throughout life. However, as patients may receive multiple treatments over time, it is difficult for industry to interpret the data captured in registries. Access to individual patients' data is highly controlled and should be limited. In these instances this is ensured by Policy 0070 [EMA's Policy on publication of clinical data for medicinal products for human use (EMA/240810/2013)], where no single patient should

be traceable through the process of anonymization or pseudonymization, although varying levels of data protection and requirements for access to data and data ownership exist in different EU countries. Registries represent a useful tool to inform clinical drug and CT design, but have limited use and benefits due to low confidence in data and limited availability of data that are important for industry, such as pharmacoeconomics. In these instances, randomized, controlled CTs are preferred to registries as they have a higher level of scientific evidence, are carried out in accordance to GCP (Good Clinical Practice), and have regular monitoring and data quality assurance. Their drawbacks are high cost, difficulty in patient recruitment for rare disease indications, small sample sizes, and a relatively short follow-up period. Registries and databases, on the other hand, have lower quality data with issues such as confounding and missing datasets. In addition, data is not necessarily collected according to GCP standards. However, their advantage lies with larger sample sizes, easier recruitment, and lower cost. Furthermore, data collected in registries is considered to represent real-life data as opposed to a highly artificial CT environment. Industry supports consolidation of multiple registries into a few well-run and credible initiatives, with a basic protocol and a minimum dataset. It was highlighted that industry would like collaboration to be improved in



areas of data access, data transparency, and inclusion of research questions of interest to industry.

Session four presented patients' and academics' perspectives. Speakers from the World Federation of Hemophilia (WFH) and the European Haemophilia Consortium (EHC) highlighted patient groups' experiences with current registries, possible areas of improvement within the existing systems, and issues around access to data. Presentations from the European Association for Haemophilia and Allied Disorders (EAHAD) and the International Society on Thrombosis and Haemostasis (ISTH) reflected on current academic registry practice, their advantages and disadvantages, essential parameters to be collected, important questions to be investigated by registry data, data access, and suggested areas for improvement.

Workshop participants agreed that a number of essential elements need to be fulfilled in order for registries to be sustainable and useful. These include:

- A basic, generic European protocol laying down a minimum dataset for disease-specific registries should be set up so individual, national registries can collect data in a similar manner according to the same protocols and standards, which ultimately can be combined in an overarching EU-wide umbrella registry.
- National, country-level registries are needed to inform on country-specific issues and HTAs. However, these should be set up and maintained with a common protocol. For this national regulators should be empowered to harmonize registries on a national level.
- Ideally, all patients should be entered in a registry. However, difficulty remains in the design of an appropriate informed consent form, which would account for varying European requirements with regard to data protection, data confidentiality and privacy.
- The quality and amount of data would need to be continuously monitored and assured. The development of a unique patient identifier would reduce double-counting but issues remain with guaranteeing anonymity and an acceptable level of data protection across different EU member states.
- Improved funding and long-term sustainability of registries is desired as is assurance of compliance of centers and patients, scientific independence of registries, an improved transparency of and for all registry stakeholders, easier data sharing between different registries, and improved collaboration and open communication with industry.

#### **The following main consensus points were agreed upon during the meeting:**

1. Collaboration of all stakeholders is required, including patients, NCAs, industry, HTAs, and regulators.
2. Regulators need to further identify what data they wish to see in registries.
3. Registries represent one platform to study disease and should ideally be used in addition to CTs in the hemophilia setting. Ideally every patient should be entered in a registry and those who participate in CTs should remain entered in registries.
4. The development of a unique patient identifier to avoid double-counting is ultimately desired.
5. An agreement on a minimum dataset (such as parameters, dataset, confounders, minimization of bias, assessment of co-variants and variables) and a minimum protocol should be made, to inform the design and data collection in existing registries.
6. There is a need to harmonize national approaches and consolidate many registries into a few, well-functioning initiatives. With the development of a minimum dataset and a minimum protocol, data from national registries could be merged into an EU-wide umbrella hemophilia registry.

A large part of the discussion during the workshop centered around EMA's current Previously Untreated Population (PUP) requirement for marketing authorizations (MAs) for all existing and novel hemostatic products. Feedback from academic and industry clinicians indicates that it does not fulfil scientific or research objectives as PUPs may not be the appropriate population to study the development and assessment of immunogenicity. Moreover, given the small number of PUPs born in Europe, it makes conducting CTs with novel products difficult, delaying their market access to patients in Europe.

As a result, an additional consensus point was agreed during the workshop:

7. Based on the particular nature of the PUP population in the hemophilia setting, a review of the current EMA PUP requirement will be conducted in jointly by industry, academic and patient stakeholders and EMA.

One main consensus point was not agreed upon by the stakeholders: Anonymised data sharing for EMA and NCAs should be possible, upon request. •

---

**DOMINIKA MISZTELA**, PPTA Manager, Regulatory Policy Europe



# PREDICTING IMMUNOGENICITY

## by Integrated Modeling of Antigen Processing, MHC Presentation, and TcR Recognition

BY PEDRO PAZ

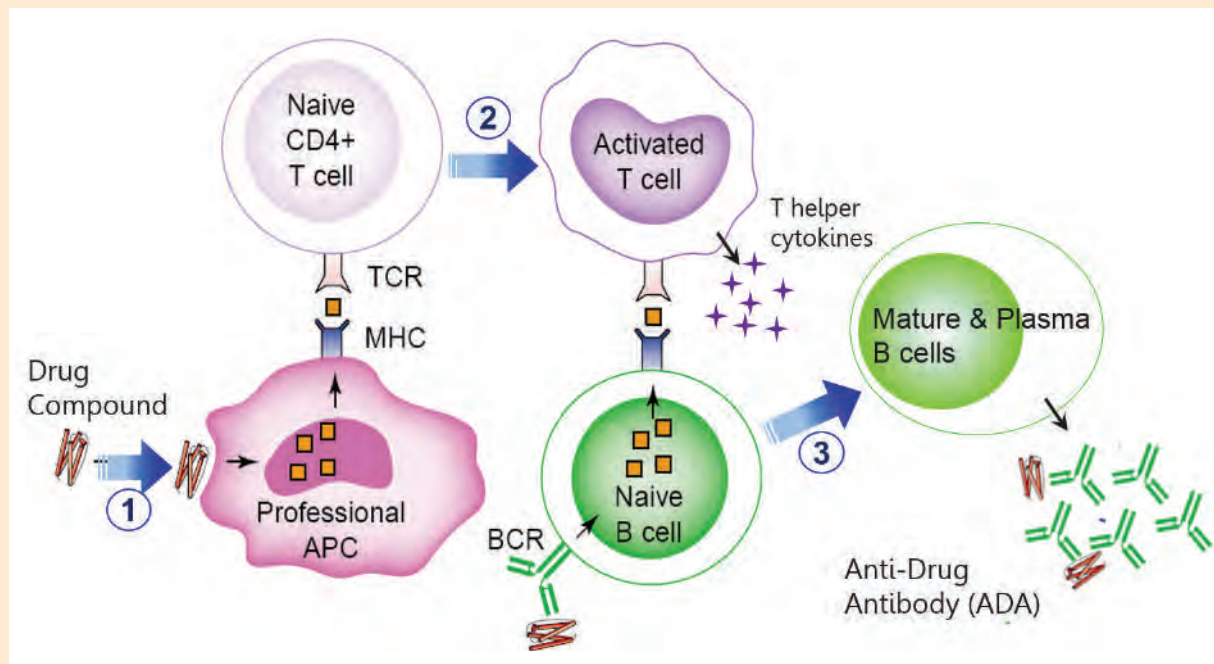
---

Our immune system performs a delicate balancing act of eliminating dangerous microbes that invade our body while leaving the uninfected tissues unharmed. Selective pressure of evolution, the genes we inherit from our parents, and our own unique encounters with substances such as viruses, bacteria, pollen or chemicals that activate the immune system (antigens), shape the immune response that becomes our main arsenal against the next pending attack. The key players in this defense system that patrol our tissues looking to respond quickly against antigens are the B and T lymphocytes.

---

B and T lymphocytes, also called B and T cells, respond by producing their unique classes of molecules (proteins) that recognize antigens. B cells secrete immunoglobulins (IgG) or antibodies that bind to antigens that exist outside our cells. T cells on the other hand express molecules on their surface, the T cell receptors (TCR) that bind small fragments called peptides from microbes which are able to invade cells. The T cell receptor acts as the switch that turns on or activates the T cells once it binds its target peptide. Peptides are produced in the cells through cutting of larger microbe/ antigen molecules by specific enzymes called the proteases, and are presented by proteins called the major histocompatibility complex molecules (MHC). MHC presentation of antigen peptides to T cells thus allows the surveillance and killing of cells that may be harboring microbes and evading antibody detection. In addition to eliminating infected cells, a subset of T cells (T helper cells, CD4+  $T_H$  cells) provide essential help during an antibody response by secreting factors called T helper ( $T_H$ ) cytokines that help the growth and development of mature B cells into long-lasting antibody-producing plasma B cells. Hence, B and T lymphocytes, upon sensing the presence of signals which trigger an immune response, activate





**FIGURE 1:** Steps in the immunogenic response against biotherapeutics (Drug Discov Today. 2004 Jan 15;9(2):82-90; 'Minimizing the immunogenicity of protein therapeutics', Authors: Chirino AJ, Ary ML, Marshall SA.)

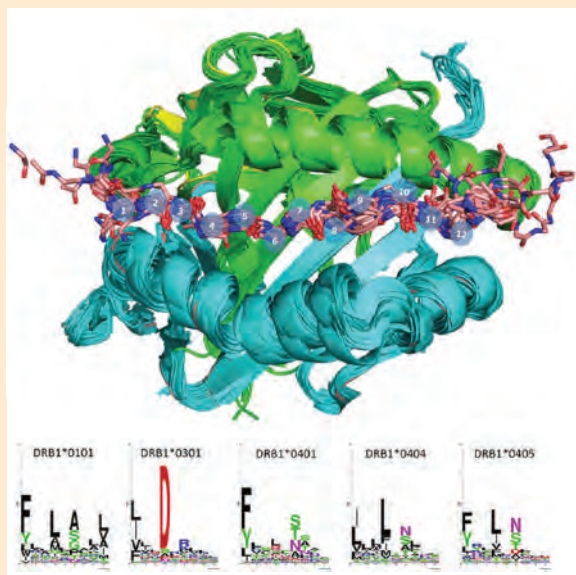
a tightly coordinated response that holds the balance between health and disease.

Antibodies against disease-causing microbes are clearly important in maintaining health; however the immune system does not discriminate between an immunogenic microbe and a potentially immunogenic drug compound. Approximately 25 percent of Hemophilia A patients treated with replacement factor VIII (FVIII) develop an immune reaction to their treatment in form of antibodies that inhibit the drug itself. The immune system of these patients successfully mounts an anti-FVIII response step-wise by: processing the FVIII drug and presenting it to the surface as part of the MHC-peptide complex; which activates FVIII-specific CD4+ TH cells to produce TH cytokines that; supports the development of B-cells that secrete anti-FVIII drug antibodies (ADA), as shown in the figure below. To date, inhibitor development remains the leading complication in treating hemophilia A patients with replacement FVIII.

So what factors contribute to the generation of ADA against replacement FVIII in Hemophilia patients? Key to this are the FVIII-specific TH cells that recognize the FVIII fragments processed and presented by a patient's MHC molecules. The FVIII peptides that bind MHC molecules for presentation to T cells are now called T cell epitopes. They are made in compartments inside cells, rich in specific proteases called cathepsins that cleave FVIII into short peptides

composed of 10-20 building blocks, or amino acids. The genes encoding the peptide-binding MHC molecules are highly variable, or polymorphic, with hundreds of versions or alleles already identified in humans. The polymorphisms found in MHC genes are predominantly clustered around the sequences encoding the groove of the MHC which binds the peptide. This groove restricts the FVIII peptide sequences presented to T cells. For example, as shown in Figure 2, the binding groove of the MHC DRB1\*0301 allele is highly selective for peptides containing the amino acid aspartate (D) as the fourth amino acid and with strong preference for leucine (L), isoleucine (I), valine (V), or phenylalanine (F) as the first amino acid. The binding motifs for many MHC alleles have been defined by mathematical and computational methods, or algorithms that predict peptide binding. These algorithms have been the basis for predicting the immunogenic potential of a given protein sequence.

While peptide presentation by MHC to TH cells is essential for immunogenicity, it is clearly not sufficient. The immune response requires FVIII-specific TCRs present on T cells to be engaged with the peptide epitope with sufficient affinity or binding strength. For this, the T cell has to be selected from a very diverse T cell repertoire that is present in every individual. Each of us possess a TCR repertoire formed early in fetal life in the thymus organ that is estimated to be between 20-100 million unique sequences. This repertoire,



**FIGURE 2:** Structure of peptide binding groove of MHC molecules and their binding motifs

The binding motifs for many MHC alleles have been defined by mathematical and computational methods, or algorithms that predict peptide binding.

which in principle can recognize the same number of unique T cell epitopes, is further refined by our individual experiences with antigens. These experiences generate a population of memory T cells that have previously encountered their epitope, and have been trained to respond even more quickly and stronger upon re-exposure to the same antigen. Like the interactions between the peptide and MHC molecule that stably cradle the peptide in the MHC groove, the TCR “switch” on the T cell surface also makes specific contacts with the peptide/MHC complex that activates the T cell. The structures of a number of TCRs switched on by their target peptide/MHC have been solved by techniques, such as X-ray crystallography, providing a structural framework of interactions that form the stable heterotrimer complex for T cell activation.

To improve on current computational methods that predict immunogenicity based solely on the strength of peptide binding to MHC, also known as MHC affinities, Bayer Pharmaceuticals together with the Andrej Sali lab in the Department of Pharmaceutical Chemistry at University of California, San Francisco (UCSF) have developed a computational, integrative structure-based approach called ITCcell for prediction of T-cell epitopes. The method combines information from the three stages of the immune response pathway: 1. Antigen processing, 2. MHC presentation, and 3. TCR recognition. First, the antigen sequence is dissected into peptides based on cathepsin cleavage profiles. Second, the method ranks the peptide that bind to a given MHC sequence based on a computed score of the structural model of the peptide-MHC complex. Finally, ITCcell determines whether or not any of the good scoring peptide-MHC complexes can bind to a given TCR, guided by known peptide-MHC-TCR complex structures as templates, and ranked based on a score of the best or most stable predicted ternary peptide-MHC-TCR structure.

To test the ITCcell method for T cell epitope prediction, five TCR sequences against known FVIII epitopes were plugged in the computer model. ITCcell predicted the Factor VIII epitope among 1.5 percent of the top scoring predictions for each of the five TCR sequences. In fact for two of them, the correct epitope was ranked first. For the remaining three TCR sequences, the rank of the correct peptide was 9, 24, and 34, out of 2,340 possible peptides. By comparison, epitope prediction using affinity-based computational methods such as NetMHC3.0 rank the correct epitope only as a weak binder.

Though the integrative computational modeling with ITCcell requires further validation and additional refinement, it is exciting to imagine the possibilities that this innovation might bring forward. Adding the TCR component along with the peptide/MHC fills a major void in the currently available immunogenicity prediction platforms. This method can only further enhance protein engineering strategies for de-immunizing FVIII as well as other biotherapeutics to reduce the risk of ADA development by predicting with greater fidelity the T cell epitopes that need to be modified to make them less immunogenic. Additionally, ITCcell may allow patients to be selected based on their TCR repertoire to identify which will benefit most from the therapy, or perhaps those which may be at high risk for developing inhibitors to FVIII. ●

**PEDRO PAZ, PhD**, Senior staff scientist, Immunoprofiling Group, Biologics Research US, Bayer HealthCare Pharmaceuticals



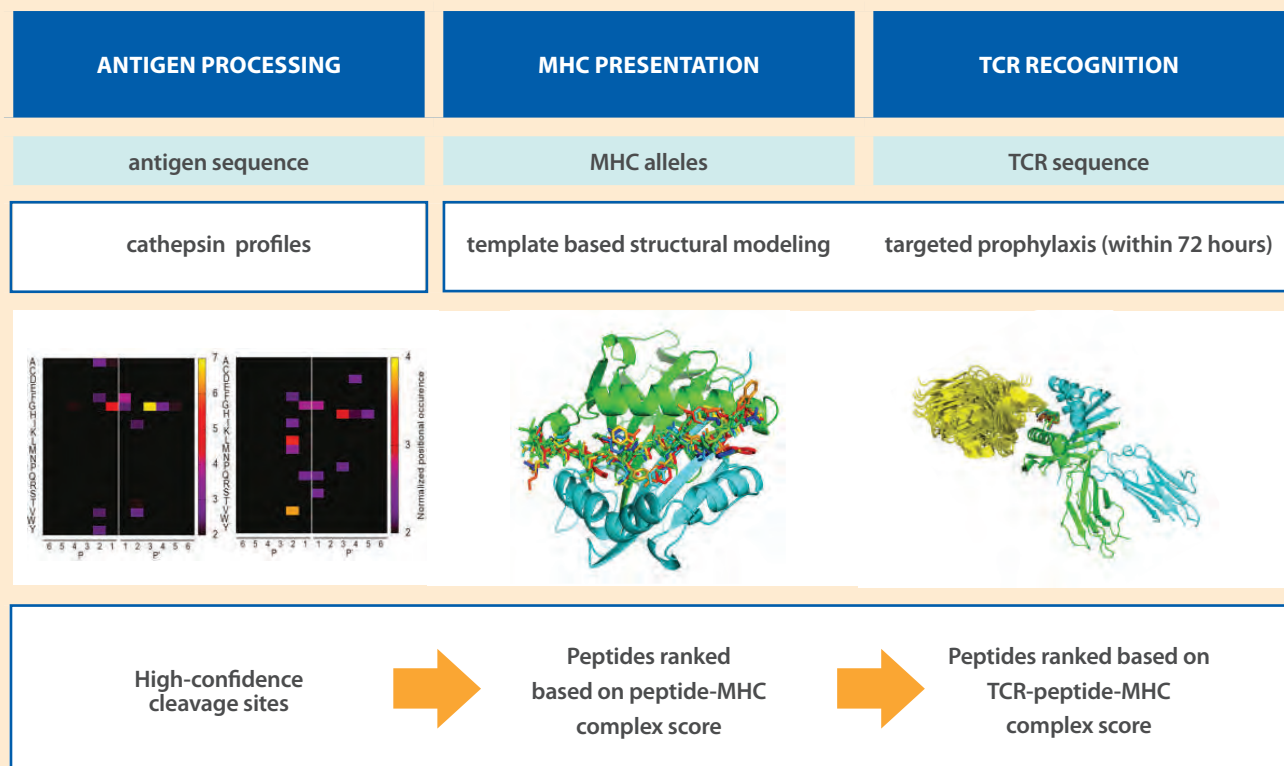


FIGURE 3: ITCell – an integrative structural modeling approach to predicting immunogenicity

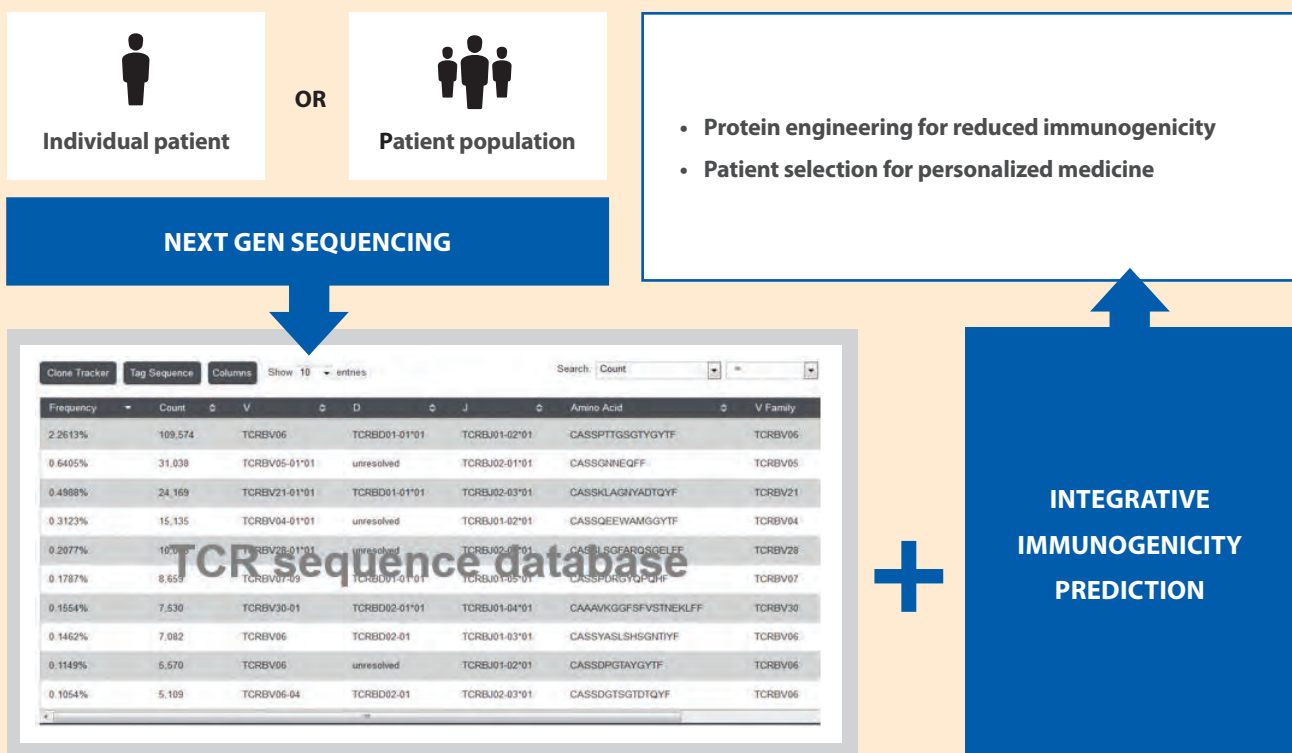


FIGURE 4: Potential applications for ITCell immunogenicity prediction



# EMA Stakeholder Meeting Assesses Progress on Drug Shortages Initiative

BY JOHN DELACOURT

---

In response to concerns regarding drug shortages, the European Medicines Agency (EMA) recently convened a meeting of impacted stakeholders. The “Stakeholder Meeting on Product Shortages Due to Manufacturing and Quality Problems: Developing a Proactive Approach to Prevention” was held at EMA headquarters in London on Oct. 9.

---

Though lacking in brevity, the title of the event did capture the essence of the exercise, which was to assess industry’s progress in developing “proactive” strategies for drug shortages prevention and communication. Although there is more work to be done, progress has been considerable with the meeting featuring the unveiling of a number of promising shortage preparedness tools.

## EMA’S DRUG SHORTAGES INITIATIVE

The issue of drug shortages is not a new one, but the current EMA initiative to address the problem began only three years ago, with publication of the Agency’s Reflection Paper on Drug Shortages,<sup>1</sup> as well as the related Implementation Plan.<sup>2</sup> Subsequently – in October 2013 – EMA convened a Drug Shortages Workshop that yielded two important outcomes. The first, and most directly important to the plasma protein therapies industry, was the Agency’s endorsement of PPTA’s proposal to launch a European Data Program similar in design to the Association’s existing North American shortage preparedness tool. That launch was completed in April 2014 and the program has remained in continuous operation since that time.

The second Workshop outcome was the formation, at EMA’s request, of two industry Task Forces to propose voluntary, proactive solutions to the shortage concerns identified by the assembled regulators, pharmacists, and patient representatives. One Task Force – led by the International Society for Pharmaceutical Engineering (ISPE) and the Parenteral Drug Association (PDA) – was charge with addressing the issue of drug shortages prevention.



The other – led by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Generic and Biosimilar Medicines Association (EGA) – was charged with addressing the issue of drug shortages communication. Because PPTA's European Data Program serves both a shortage identification and assessment function, on the prevention side, and as a means of drug shortages communication, PPTA was an active participant in both Task Forces over the next two years.

### NEW PREPAREDNESS TOOLS

The October 2015 Stakeholder Meeting provided an opportunity for the two Task Forces to present and explain their proposed solutions. Given the broad spectrum of potential causes of drug shortages, as well as the wide range of companies, products, and manufacturing approaches to be encompassed, the proposals tended to take the form of high level frameworks rather than specific systems to be implemented within a company or sector.

On the prevention side, two proposals were unveiled. The first – ISPE's "Drug Shortages and Prevention Plan"<sup>3</sup> – takes a systems-based approach. In addition to the work of the two Task Forces assembled by EMA, ISPE's plan relies on data gathered via the organization's 2013 Drug Shortages Survey. That data suggested that an effective shortages strategy must encompass both the organizational and technical issues that impact product quality. ISPE's plan proposes to achieve this end through a framework focused on six dimensions: corporate quality culture, robust quality systems, metrics, business continuity planning, communication with authorities, and building capability. This approach is intended to provide both industry and regulators with a road map to identify and resolve issues with manufacturing operations that may result in supply interruptions or shortfalls. Because the plan provides discussion points and industry examples in each chapter, it can also be used as a tool kit.

The second proposal on drug shortage prevention – PDA's "Risk-Based Approach for Prevention and Management of Drug Shortages"<sup>4</sup> – takes a product-based approach. PDA's plan asserts that drug shortages can be minimized through early assessment and evaluation in a structured way, and proposes harmonized terminology to facilitate a common understanding of shortage situations globally. The centerpiece of the plan is a risk triage model that combines simple procedures for assessing and controlling risks with a clear process for issue escalation to



Manufacturers' responsibility to communicate with other impacted groups – such as patients, physicians, and hospitals – though acknowledged as critical is addressed only peripherally. With respect to the communication between Manufacturing Authorization Holder (MAH) and regulator, however, the proposal contains a number of recommendations for optimizing both content and timing.



Although all parties agreed that drug shortages are a global issue, and that there is good coordination between EMA and the U.S. Food and Drug Administration in this area, complete harmonization at even the European level remains elusive.

---

management for decision making. The plan includes templates for both a Drug Shortage Risk Register and a Drug Shortages Prevention and Response Plan, which can be customized to the needs of an individual company or product line. Taken together, these components reflect the plan's central imperative that, as the risk to patients from a potential drug shortage increases, the level of rigor, effort, and cross-functional collaboration within an organization to address the risk should also increase.

On the communications side, the EFPIA/EGA-led Task Force submitted a proposal titled "Quality and Manufacturing Driven Supply Disruptions: Industry Communications Principles to Authorities."<sup>5</sup> As the title suggests, the proposal does not encompass all aspects of shortages communication, but rather focuses on the specific communication that takes place between industry and the relevant Competent Authorities when a potential supply disruption is identified. Manufacturers' responsibility to communicate with other impacted groups – such as patients, physicians, and hospitals – though acknowledged as critical is addressed only peripherally. With respect to the communication between Manufacturing Authorization Holder (MAH) and regulator, however, the proposal

contains a number of recommendations for optimizing both content and timing. These include: promoting more consistent and relevant reporting by MAHs, facilitating coordinated action between Competent Authorities, and providing standardized data to enable identification of root causes and prioritization of mitigation strategies.

### ISSUES STILL TO BE ADDRESSED

The optimism accompanying the discussion of these new preparedness tools was tempered somewhat by the presentations of two groups of pharmacists – the European Association of Hospital Pharmacists (EAHP) and the Pharmaceutical Group of the European Union (PGEU), which represents community pharmacists. EAHP stated that the problem of drug shortages continues to be pervasive, with 86 percent of survey respondents saying that shortages in their hospital are a problem in terms of delivering the best patient care. Consistent with this finding, 66 percent of respondents indicated that their work is affected by shortages on a daily or weekly basis. PGEU's own survey results provided a sense of the magnitude of this impact, with members reporting spending, on average, five hours per week on shortage-related issues.

As both the EMA and manufacturer representatives were quick to point out, however, these survey results reflect a problem that was identified early on: there is still no widely accepted definition of the term "shortage." Starting with the publication of its 2012 Reflection Paper, EMA has been clear that its efforts are directed exclusively at shortages resulting from manufacturing and GMP-compliance issues, as these are the issues squarely within the Agency's authority. Shortages resulting from other political, economic, and local issues – including reimbursement rates and parallel trade – likely account for a significant portion of the total, but are indistinguishable from a patient or pharmacist perspective. The Stakeholder Meeting participants did not agree on a specific solution to this problem, but did appear to reach a general consensus that developing different definitions, applicable to different levels of the supply chain, is the most promising route forward.

Another issue still to be addressed is adapting the shortage preparedness approaches discussed to a global framework. Although all parties agreed that drug shortages are a global issue, and that there is good coordination between EMA and the U.S. Food and Drug Administration in this area, complete harmonization at even the European level remains elusive. The meeting participants also acknowledged that a truly comprehensive preparedness strategy would need to account for the role of distributors and wholesalers.





One possibility that was raised is that an evaluation of shortage preparedness will become an element of EMA review of a Site Master File. Shortage preparedness could also be incorporated into the sections of Chapter 1 of the EU Guidelines to Good Manufacturing Practice on annual product review.

---

#### NEXT STEPS

It is not yet clear whether or how EMA will incorporate the proposals generated by the two industry Task Forces into new guidance or regulations in the area of drug shortages. One possibility that was raised is that an evaluation of shortage preparedness will become an element of EMA review of a Site Master File. Shortage preparedness could also be incorporated into the sections of Chapter 1 of the EU Guidelines to Good Manufacturing Practice on annual product review. In either case, companies could consult the tools developed by the two industry Task Forces as reflective of the Agency's expectations regarding shortage prevention and communication.

EMA has indicated that it will follow up on the Stakeholder Meeting by publishing a report and, presumably, an update of the 2012 Implementation Plan in early 2016. ●

#### References

1. EMA, Reflection Paper on Medicinal Product Supply Shortages Causes by Manufacturing/ Good Manufacturing Practice Compliance Problems, EMA/590745/2012 (Nov. 22, 2012), [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2012/11/WC500135113.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/11/WC500135113.pdf).
2. EMA, Reflection Paper on Medicinal Product Supply Shortages Causes by Manufacturing/ Good Manufacturing Practice Compliance Problems: Implementation Plan 2012-2015, EMA/708575/2012 (Nov. 23, 2012), [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2012/11/WC500135114.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/11/WC500135114.pdf).
3. ISPE, Prevention Plan (Oct. 2014), <http://www.ispe.org/drugshortagespreventionplan.pdf>.
4. PDA, Prevention Plan (2014), <https://store.pda.org/ProductCatalog/Product.aspx?ID=2577>.
5. EFPIA et al., Communications Plan (Dec. 2014), [http://www.efpia.eu/uploads/Industry\\_Communication\\_Principles\\_Principles\\_Dec2014\\_Final\\_v1.pdf](http://www.efpia.eu/uploads/Industry_Communication_Principles_Principles_Dec2014_Final_v1.pdf).

---

**JOHN DELACOURT**, PPTA Vice President,  
Legal Affairs & Global Operations

# One Company. Two Solutions.



**Haematologic  
Technologies  
Inc.**

## Products and services for hemostasis research

- Purified blood coagulation factors
- Antibodies
- Factor deficient plasmas
- Customized blood collection tubes
- R&D assay services

HTI is a manufacturer of highly-purified, native plasma proteins and associated products involved in the hemostatic system. Development of assays for research or destined for cGMP testing is also offered.



**[haemtech.com](http://haemtech.com)**



**Haemtech  
Biopharma  
Services**

## Testing and services for protein biotherapeutics

- Thrombin generation assays
- Immunogenicity testing
- Stability & release testing
- Host cell protein mitigation
- Immunoassay development

HBS is a cGMP-certified, QC testing laboratory that specializes in providing services for protein biotherapeutics manufacturers from drug inception through market release.



**[haemtechbiopharma.com](http://haemtechbiopharma.com)**



# Highlights From The European Haemophilia Consortium Annual Conference 2015

BY KARL PETROVSKY

The European Haemophilia Consortium (EHC) Annual Conference took place from October 1-4, 2015 in Belgrade, Serbia. Three hundred participants from academia, patient organizations, and industry attended this high level event.

The program consisted of scientific sessions and presentations as well as various company symposia. The scientific sessions covered hemophilia in Serbia, gene therapy, women and bleeding disorders, and complications in hemophilia, including the management of inhibitors and longer acting factors. Highlights included a dialogue on gene therapy, management of inhibitors, the EHC Inhibitor Network Initiative, and a debate on public tenders for factor concentrates versus clinical freedom.

## GENE THERAPY

Flora Peyvandi from the Angelo Bianchi Hemophilia and Thrombosis Centre in Milan presented on gene therapy. She started with the goal of gene therapy, which is to replace the dysfunctional gene with an exogenous functional gene to cure the disease phenotype. In 2012, more than 1800 clinical trials were conducted in 31 countries. Hemophilia is well suited for gene therapy approaches because there is a single gene defect (the FIX or FVIII gene) and the therapeutic goal is considered to be modest: an increase in plasma FIX/FVIII levels above one percent would be sufficient to ameliorate the bleeding phenotype and the efficacy can be assessed by validated routine laboratory assays.





Highlights included a dialogue on gene therapy, management of inhibitors, the EHC Inhibitor Network Initiative, and a debate on public tenders for factor concentrates versus clinical freedom.

There are significant differences regarding the development status of gene therapy in hemophilia A and B. So far it appears that gene therapy is emerging as a powerful and viable way to treat hemophilia B (HB). Encouraging results have been achieved in patients as a stable expression of FIX has been achieved through intravenous infusion of AVV8-hFIX in HB patients converting the phenotypes from severe to moderate/mild (Nathwani et al, 2011). Six clinical trials are presently being conducted in this area. However, the situation is different regarding hemophilia A gene therapy. Despite many efforts, this therapeutic target is more problematic for a variety of reasons: the larger factor VIII cDNA, the expression of FVIII is highly inefficient in achieving adequate levels of transgene expression, and the complication of anti-factor VIII immunity. Nevertheless, a new clinical trial for hemophilia A gene therapy recently began.

### MANAGEMENT OF INHIBITORS

Professor Makris, University of Sheffield, UK, described the management of congenital hemophilia inhibitors as consisting of the following elements: treatment of acute bleeding, the eradication of inhibitors, prophylaxis, and surgery. The regimen leading to inhibitor eradication via

Immune Tolerance Induction (ITI) remains as there is a controversy over whether high VWF containing plasma concentrates are better for ITI and whether ITI should be offered to adults with established inhibitors. According to Professor Makris, the definition of eradication of inhibitors is determined by the following elements: the inhibitor titre is no longer measurable (i.e., <0.6BU), the factor recovery is greater than 66 percent and FVIII half-life is greater than six hours. Makris comes to the conclusion that inhibitors are uncommon, their management is more difficult than standard hemophilia, there is a higher morbidity and mortality, treatments are more expensive, the evidence base is less than with the management of hemophilia without inhibitors, and finally, the inhibitors treatment should preferably be managed by comprehensive hemophilia care centers.

### EHC'S EUROPEAN INHIBITOR NETWORK PROGRAMME

EHC reported on the start of their European Inhibitor Network Programme conducted in liaison with the European Association for Haemophilia and Allied Disorders (EAHAD). The rationale for setting up the Programme is the substantial unmet need for more support for patients with inhibitors in Europe. The program is steered by a working group

consisting of hemophilia treators, patients, EHC/EAHAD, and many others. The objectives of the program are: to better understand patients with inhibitors, to stimulate research by getting more patients enrolled in clinical trials, to develop advocacy tools, to reach better education of payers (e.g. on limitations regarding randomized clinical trials), to collaborate with Council of Europe/European Directorate for the Quality of Medicines (EDQM) in order to reach a European Consensus of optimum care for hemophilia patients with inhibitors, and, eventually, to head towards a corresponding EDQM Resolution, such as the recent one from April 2015 on general hemophilia care principles. Since the main challenge for the EHC's national member organizations is the small number of patients with inhibitors in their groups, there is a big need to intensify collaboration amongst them. The roll-out of the results of EHC's Inhibitor Network Programme is planned for 2017.

### DEBATE ON NATIONAL TENDERS VERSUS CLINICAL FREEDOM

The EHC conference was the right place to debate this subject given that the EHC recently published their findings of a 38 country survey on tenders and procurement and the way coagulation factor concentrates are purchased. A debate at the Belgrade Conference was conducted between proponents of the tender and procurement model and supporters of the clinical freedom approach. Below are the main arguments from both sides:

The arguments forwarded by the proponents in favor of national tenders concept was that tenders are highly cost effective if they follow several rules. First they should be organized in two *phased* requirements: (1) safety, quality, and efficacy and (2) product price. Second, patients must actively be involved in tender committees in the setting of the tender process, along with other qualified health professionals. Generally, the tenders setting and outcome is considered as good as the qualification of the tender committee members. Tender systems for hemophilia products work well in developed countries like Ireland and in less developed, low health-budget countries. Tenders ensure sustainable, equal access of products to patients and they substantially enhance product affordability and counteract unreasonable pricing. If conducted as e-tenders in less developed, emerging countries, they can help eliminate financial malpractice.

The supporters of the clinical freedom approach versus tenders advanced the following arguments: One, clinical freedom ensures the most appropriate, personalized, professional treatment for hemophilia patients thus facilitating cost-effectiveness. Two, tender processes are



Since the main challenge for the EHC's national member organizations is the small number of patients with inhibitors in their groups, there is a big need to intensify collaboration amongst them.

.....

inappropriate, because most factor concentrates are not interchangeable, especially not regarding inhibitors. Tenders substantially restrict the product choice, which can turn out to be dangerous even if they are conducted in hospitals where tender management is unprofessional. The result of many tenders is that often the cheapest and not necessarily the most appropriate coagulation factor concentrate product is available. Tenders are not reflective of the cost of innovation. And importantly, the savings from the organization of product tenders are not allocated to governmental health budgets in order to improve hemophilia treatment care financing. ●

---

KARL PETROVSKY, PPTA Senior Manager, Health Policy

A woman with long brown hair, wearing a blue hospital gown, is lying in a hospital bed and smiling while using a tablet. In the background, another patient is lying in a bed, and medical equipment is visible.

# THE WORLD'S CITI. IT'S WHEREVER YOU ARE.

Every day, in cities around the world, people are doing amazing things. They're creating, innovating, adapting, building, imagining. What about a bank? Shouldn't we be equally ingenious? Strive to match our clients' vision, passion, innovation? At Citi, we believe that banking must solve problems, grow companies, build communities, change lives.

Citi® Prepaid Cards has used our passion and innovation to provide the plasma industry with a secure, easy payment answer for donor compensation. Citi Prepaid remains committed to our clients, just as our clients are committed to helping people live healthier, happier lives through research, therapy and treatment.

To find out more about Citi Prepaid Cards, please visit [citiprepaid.com](http://citiprepaid.com)





# The Joint EU Member States Procurement of Rare Disease Medicines Initiative:

BY KARL PETROVSKY

---

The Belgian/Dutch Ministry of Health approach and the Romanian/Bulgarian Ministry of Health approach

---

Everything started with the EU Commission setting up a “Joint Procurement Agreement on medical countermeasures for combating serious cross border health threats” in June 2014. This was a reaction to the uncoordinated response of EU Member States to the Ebola crisis and the earlier H1N1 pandemic of 2010 when EU Member States were competing with one another to get hold of scarce supplies of medicines. This resulted in panic buying and Member States felt that they were obliged to pay high prices for medicines. Communicable diseases and many other health threats do not respect borders and thus it was felt that better EU coordination is needed.

The EU Joint Procurement agreement was signed by 22 EU Member States, with France being the most recent one in September 2015. So far, the agreement is limited to vaccines and other medicines and equipment that address “serious cross-border health threats.”

However, in the current European climate of concern over the cost of medicines, the agreement is considered to be a model for much wider common action in buying pharmaceuticals, especially high cost and high volume medicines. For many European governments, high drug prices have an increasing influence on their policies with

These developments show that EU Member States' governments are now concentrating on ensuring equal accessibility of effective, high-cost drugs to patients and they are shifting away from considering industry interests, which generates innovation.

---

relation to non-discriminating accessibility to qualitative health care for patients, especially those suffering from rare diseases.

The EU Health Commissioner openly encouraged Member States to jointly procure costly medicines, which goes beyond the remit of the 2014 EU agreement.

#### THE BELGIUM/DUTCH INITIATIVE

The Belgian and Dutch Ministries of Health were first to start an initiative under this agreement, which set up first a Memorandum of Understanding and then an agreement in April 2015 to work together on negotiating prices for medicines for rare diseases, especially orphan drugs. Luxembourg recently joined the initiative. The Dutch-Belgian-Luxembourg effort is considered innovative because most EU member countries closely protect their sovereignty over pricing matters. Other countries (e.g. Austria and Italy) announced their intention to join later if the initiative proves to show positive results.

The Belgian, Dutch, Luxembourg plan is, at present, to run a pilot program with a few selected companies for the purchase of high cost, orphan medicines for rare conditions. However, the initiative is not targeting so called “Me-too” products. Both the Belgian and Dutch Ministers of Health have made it clear that they intend the agreement to go much further in aligning drug authorization and pricing processes across a broader range of products. The initiative goes well beyond jointly negotiating with the pharmaceutical industry. The three countries also want to exchange data, share registries, and coordinate assessment methodologies. They will also examine together which innovative drugs will be commercialized in the coming years and how they can best prepare. Currently, three companies participate in this pilot phase, where the governmental agencies are already concretely negotiating with industry.

#### THE ROMANIA/BULGARIA INITIATIVE

Bulgaria and Romania announced in June 2015 that they will set up a common initiative to jointly procure costly medicines. The framework for this initiative will be elaborated by a working group which will be published soon. The initiative

is open to incorporating other countries in the emerging markets part of the EU.

#### IMPACT AND CONCLUSION

These developments show that EU Member States' governments are now concentrating on ensuring equal accessibility of effective, high-cost drugs to patients and they are shifting away from considering industry interests, which generates innovation. When Luxembourg assumed the EU presidency in July of 2015, innovation was high on the agenda but it is oriented to serve patients first, and not in the sense that industry deserves to be rewarded for innovation.

The Netherlands, which will hold the EU presidency in the first half of 2016, has already indicated that it is keen to pursue the exploration of joint negotiation or joint purchasing of medicines, to get better value out of deals with the pharmaceutical industry.

Larger countries like Germany, the UK, and France are not currently a part of these efforts. One reason is that they want to keep “pricing sovereignty.” Germany, especially, sees the wider Joint procurement initiative as a strictly voluntary effort amongst the EU Member States. They do not see legal grounds in the EU Treaty to make mandatory that EU Member States organize joint drug pricing negotiations. And they insist that the EU Commission has no coordination role in this, not even in the voluntary version of it. The French Minister of Health recently explained such resistance, but she also gave an outlook: “Every country must remain sovereign in pricing... at least at this very stage in time. *We may move onto further integration (at EU level, sic) in the long run*, that may seem logical, but for some countries “there are a number of concerns”. (Kim Dixon, “Benelux joint medicine talks moving forward,” *PoliticoPro*, October 30, 2015)

Joint EU Member States procurement (or joint Member State price negotiation) of rare disease medicines will, for the time being, mostly attract small to middle market size Member States. It remains to be seen whether this initiative will be applied by other countries and, more importantly, whether it would be applied to plasma protein therapeutics. ●

---

KARL PETROVSKY, PPTA Senior Manager, Health Policy

# Collect with confidence and optimize operational efficiencies

At Haemonetics, we understand the pressures you face—from costs to increasing regulations to managing your supply chain. Our comprehensive portfolio of products and services is designed to support multiple facets of your operations, helping you achieve efficiencies and manage costs.



## Solutions for the global plasma industry

An ongoing commitment  
to **donor safety** and satisfaction

**Dedicated customer support,**  
training, and process improvements

A **reliable supply chain**  
helps ensure business continuity

Our **supply chain management model**  
streamlines ordering and fulfillment

To learn more about our full range of products, programs and services,  
contact your Haemonetics Account Manager or visit [www.haemonetics.com](http://www.haemonetics.com)





# The Role of Government Entities in Access to Care

BY JULIE BIRKOFER, KARL PETROVSKY, AND BILL SPEIR

Cost control mechanisms continue to permeate health care decision making and impact patient access to all forms and types of medical care, including plasma protein therapies. Perhaps, in some countries the economic downturn experienced seven to eight years ago has softened; but policy makers have not backed away from austerity measures.

Initiatives to reduce health care spending have been successfully implemented throughout the continuum of health care delivery. Markets have adjusted and patients have adapted to paying more but there is no end in sight to a global focus on cost cutting.

This global belief that the pot is shrinking, has resulted in several different payer mechanisms that are continually evolving to reduce costs. There seems to be a never ending stream of new ways to reduce costs and there is no end in sight. PPTA member companies have prioritized patient access to plasma protein therapies as a top tier within the Association. PPTA is able to strategically position its global health policy resources to ensure that patient access remains at the forefront of the Association's focus. Equally important is the fact that PPTA delivers the messages to key decision makers around the world that chronically ill patients with rare diseases depend on access to lifesaving plasma protein therapies and the plasma protein therapeutics industry is different from traditional pharmaceuticals.

PPTA has observed through the years the importance of stakeholders, patients, and physicians having a "seat at the table" when decisions are being made that may affect a rare disease patient's access to care. For instance, in the United States in 2008-2009, when comparative effectiveness



PPTA has observed through the years the importance of stakeholders, patients, and physicians having a “seat at the table” when decisions are being made that may affect a rare disease patient’s access to care.

research was being considered under the health care reform bill (Affordable Care Act), PPTA staff worked with patient organizations to assure that a Rare Disease Advisory panel consisting of patients, physicians, and clinical experts would be convened. The purpose of the Advisory Panel is to provide input to a new government entity (Patient Centered Outcomes Research Institute) when decisions are being made regarding access to care for rare disease patients.

In the states, when legislation is being considered that would impact access to care for a person with a bleeding disorder, such as hemophilia, the option exists in some states to put in place Hemophilia Advisory Boards. These Advisory Boards provide policymakers with input on the importance of access to the full continuum of care necessary to optimally treat an individual with hemophilia. In Europe, a process of national tenders is used in 19 countries to deliver plasma protein therapies to individuals with hemophilia. At a recent World Federation of Hemophilia Global Forum meeting, the importance of having physicians and patient organization representatives participating with the Health Ministry to make decisions about therapeutic availability was discussed. The point was made at the Global Forum that clinicians and patient representatives should be “formally involved” because they “understand the value of products as well as the cost.” It

was stated that “clinician and patient involvement [is] also cost effective” and that a “tender system [is] preferable to HTA led decision.” Tender systems also provide the opportunity for countries with smaller populations to band together under a tender to make treatment available. The benefits of a collaborative tender was discussed and the example was given in the “Baltic Countries – Lithuania, Latvia, Estonia.” “Estonia and Latvia – flawed tender process with no patient or clinician involvement. Collaborative tender would be beneficial if clinicians and patient organisations [were] involved.” The conclusion was made that the result of such a collaboration would be “lower cost, better selection process and higher per capita use.” PPTA has not made any conclusion with regard to tenders. It is also important to be aware that in some instances savings generated from a tender process are not necessarily returned to improve patient care. With regard to plasma protein therapies, all brands are unique and having only one therapy available is not optimal for treating patients. Tenders must take into account the unique nature of the therapies and acknowledge the fact that plasma protein therapies are not interchangeable. Tenders should strive to include multiple brands within a therapeutic class to treat patients.

The patient voice is powerful and when combined with the clinical expertise of a physician it becomes more formidable.



Austria is a strategically important country with the highest plasma collection volume per capita in the EU and hosts two important plasma manufacturers.

Hopefully this combination should lead to more informed decision making by policy makers and improved outcomes for patients.

## EUROPE

### UNITED KINGDOM

PPTA EU is working with all the plasma protein therapies (PPT) manufacturers in the UK as the government is trying to decrease the expenditures in healthcare due to the National Health Service's difficult financial situation. This can dramatically affect PPTs and patient access to care. In this case, we perform research in the global documents and arguments database so that we can develop our response. The final result of this action is yet to be seen, but when the industry develops a common position, the chances of being understood are much higher. In such cases, it's also important to communicate very closely with all stakeholders including patient advocacy groups.

### ROMANIA

Immunoglobulins, blood clotting factors, and albumin are subject to the application of the so called "Clawback Tax" on the basis of a law from 2011. This law requires all Marketing Authorization Holders that sell medicines reimbursed in Romania, either directly or via a local legal representative, have to pay 26.1 percent of the reimbursed turnover for such pharmaceuticals to the authorities. PPTA wrote a letter to the Minister of Health requesting the exemption of plasma protein therapeutics from the application of this tax. As a follow up to this letter, PPTA met with the authorities in Bucharest, Romania and plans to roll out a substantial action plan with the help of local consultants.

### AUSTRIA

The Austrian Ministry of Health (MoH) announced in October draft legislation that will come into effect in January 2016 imposing a mandatory rebate of between seven and fifteen percent on all medicines reimbursed in Austria. This comes on top of a governmental system which applies prices to plasma protein therapeutics much below the EU average. Austria is a strategically important country with the highest plasma collection volume per capita in the EU and hosts two important plasma manufacturers. PPTA's objective is to either stop the legislation or to obtain a carve-out of the plasma protein therapeutics sector due to the specificity of plasma-derived products. PPTA thus addressing the issue locally in order to counteract the law.

### POLAND

Immunoglobulins are considered by a recent law as equivalent medicinal products (biosimilars), based on the definition in the Reimbursement Act from 2011. Hence, a reimbursement level mechanism, similar to classical pharmaceuticals and their generic analogues, is applied to immunoglobulins without considering their inherent differences. In practice, this means that a decrease of reimbursement level by 25 percent is applied to immunoglobulins that are not first in market in Poland. PPTA has written a letter to the Ministry of Health arguing against the biosimilar classification.

### CYPRUS

PPTA acted against the new application of a law requesting the application for all plasma derived and recombinant analogue therapies of the 8.5 percent reduction of the wholesale price as per consequence of the revision of the Pharmaceutical Pricing Policy in Cyprus affecting



plasma protein therapies as from June 29, 2015. PPTA staff wrote a letter to the Cyprus Minister of Health requesting the exemption of plasma protein therapeutics from the mentioned reduction of the wholesale price.

## UNITED STATES

Basic economic theory shows that access to plasma protein therapeutics depends upon adequate reimbursement. This creates a difficult balancing act for state decision makers who must control costs while ensuring Medicaid recipients have access to health care. The fact that Medicaid is the fastest growing portion of most state budgets only makes the situation more complex.

The federal Medicaid statute codifies this theory by requiring states to “assure that payments are sufficient to enlist enough providers so that care and services are available under the plan at least to the extent that such care and services are available to the general population in the geographic area” 42 U. S. C. §1396a(a)(30)(A). This section is known as Equal Access rule.

The Equal Access rule will be tested when states begin changing their Medicaid pharmacy reimbursement to

.....

Basic economic theory shows that access to plasma protein therapeutics depends upon adequate reimbursement. This creates a difficult balancing act for state decision makers who must control costs while ensuring Medicaid recipients have access to health care.

meet the requirements of the Average Manufacturer Price (AMP) Rule (CMS 2345-P) that changes the way specialty pharmacies are reimbursed. The basic formula for Medicaid pharmacy reimbursement is ingredient cost of the drug plus a dispensing fee. Currently, ingredient cost is based on an estimated acquisition cost. The new rule will require states to base their ingredient cost on actual acquisition cost. It is expected that the ingredient cost component will be reduced as a result. The dispensing fee is also expected to change under the final rule.

The proposed rule added the word “professional” before dispensing fee. The federal government wrote in the proposed rule that they did this to make clear their “position that once the reimbursement for the drug is properly determined, the dispensing fee should reflect the pharmacist’s professional services and costs associated with ensuring that possession of the appropriate covered outpatient drug is transferred to a Medicaid beneficiary. **Therefore, as States change their payment for ingredient cost, we also propose to require States to reconsider the dispensing fee methodology consistent with the revised requirements.**”

In 2016, states will begin the process of amending their state plan amendments, statutes, and/or regulations to meet the AMP rule requirements. PPTA will take this opportunity to advocate for reimbursement that meets AMP rule requirements and is sufficient to ensure patient access to their medically appropriate plasma protein therapy. This will involve collaboration with PPTA, patient organizations, and specialty pharmacies.

In fact, the State Patient Access Coalition (SPAC), a coalition of specialty pharmacies and blood clotting factor manufacturers managed by PPTA, have been meeting with federal and state decision-makers about the need to have dispensing fees that accurately reflect what is done to properly deliver blood clotting factors. The AMP Rule has been discussed at recent Medicaid pharmacy directors’ conferences. Hemophilia products have been mentioned as needing a proper dispensing fee during these discussions. This is good news, but there will be a lot of work to do in 2016 to protect patient access to plasma protein therapies. ●

---

**JULIE BIRKOFER**, PPTA Senior Vice President,  
North America and Global Health Policy

**KARL PETROVSKY**, PPTA Senior Manager, Health Policy

**BILL SPEIR**, PPTA Senior Director, State Affairs



# Procleix

## Optimize your plasma testing



### **Procleix** Plasma Testing Solutions

By Hologic and Grifols

**For high-volume plasma testing operations, Procleix NAT solutions streamline and standardize testing across sites worldwide with:**

- A full menu for high-throughput plasma NAT testing (HIV-1, HCV, HBV, and Parvo/HAV)
- The ability to efficiently screen and discriminate on the powerful Procleix Tigris system
- The flexibility to accommodate growing volumes with minimal instrument and space requirements

Ask your local Grifols representative for further information or visit our website at [www.procleix.com](http://www.procleix.com).

## **GRIFOLS**

©2015 Grifols Worldwide Operations Limited. Procleix Tigris and Procleix Plasma Testing Solutions are trademarks of Grifols Worldwide Operations Limited; Tigris is a trademark of Hologic, Inc. This material may only be used in jurisdictions where the product(s) and/or indications mentioned in the material are approved. For a complete list, visit [www.procleix.com/approvals](http://www.procleix.com/approvals).

# Inside PPTA

NEWS FROM AROUND THE GLOBE

## ● International Plasma Awareness Week Wrap-Up

BY SONIA BALBONI

The plasma protein therapeutics industry celebrated its third annual International Plasma Awareness Week (IPAW) from Oct. 11-17. The goal of IPAW is to:

- Raise global awareness about plasma donation.
- Recognize the contributions of plasma donors in saving and improving lives.
- Increase understanding about lifesaving plasma protein therapies and rare diseases.

Beth Eacret, Vice President Plasma Operational Development, Grifols Plasma, describes the importance of IPAW:

*“We, as plasma collectors, have a responsibility to our donors, employees, patients, and the community to continually promote a greater understanding of what we do. IPAW allows us to **collectively** deliver one consistent message and expand the national and global reach during a specific time of year. The united approach has enhanced the opportunities to educate legislatures and increase public awareness of the critical role our donor s and employees play in saving and improving the lives of our patients.”*

Ms. Eacret is Chairperson of the PPTA committee responsible for organizing IPAW each year.

PPTA, its members, and partners organized events throughout the week honoring plasma donors. PPTA staff conducted Capitol Hill visits with all 50 United States Senate offices to educate lawmakers on the importance of plasma protein therapies and source plasma collection. A reception was held in conjunction with the Source Business Forum in Anaheim, California, marking the event. PPTA also held a symposium in Prague.

2015 marked the third consecutive year in which PPTA celebrated International Plasma Awareness Week in collaboration with its members and partners. On Oct. 15, the Europlasma Center in Prague (Czech Republic) hosted a get together to educate about plasma collection, the rare



**Dr. Pavel Valoušek, Spokesperson of Czech IG Plasma speaks to attendees about the history of Plasmapheresis in the Czech Republic**

diseases that are treated with plasma protein therapies, and to recognize the donors' important contribution to saving and improving lives.

PPTA President Jan M. Bult emphasized in his opening talk the importance of such an awareness week to motivate donors and to educate about the importance of plasma donation. Dr. Pavel Valoušek, Spokesperson of Czech IG Plasma, reviewed the history of Plasmapheresis in the Czech Republic, pointing out the challenging environment of the industry. Dr. Anna Šedivá of the Institute of Immunology at the Motol University Hospital, shared her experiences with Immunoglobulin therapy and the treatment of primary immunodeficiency (PID) patients. Miroslava Pastuchová, a PID patient who was only diagnosed in her late twenties, pointed out how much her life has improved with plasma protein therapies and whole heartedly thanked Lucie Obermannová, a young and committed donor, for her dedication.

Thirty-nine states and the District of Columbia issued proclamations recognizing IPAW. Additionally, the Honorable Doris O. Matsui (D-CA) entered a statement into the Congressional Record making special note of the occasion. PPTA also issued press releases in Austria, the Czech Republic, Germany, the United States, and the European Continent. ●

---

**SONIA BALBONI**, PPTA Senior Manager, Source & Standards





**IPAW was acknowledged on social media by patient organizations, companies, donors and patients using the hashtag “#IPAW\_2015”**

Patient organizations representing users of plasma protein therapies pledged their support and promoted International Plasma Awareness Week via websites, newsletters, social media, and outreach. Patient organizations not only worked to promote awareness about plasma and plasma protein therapies, but also highlighted the importance of plasma donation. PPTA would like to thank the 2015 IPAW Supporting Organizations for recognizing and celebrating IPAW: the Alpha-1 Foundation, GBS/CIDP Foundation International, Hemophilia Federation of America, the Immune Deficiency Foundation, the International Patient Organisation for Primary Immunodeficiencies, the Jeffrey Modell Foundation, the National Hemophilia Foundation, and the Platelet Disorder Support Association.

## Thank You From PPTA



**NATIONAL HEMOPHILIA FOUNDATION**  
*for all bleeding disorders*



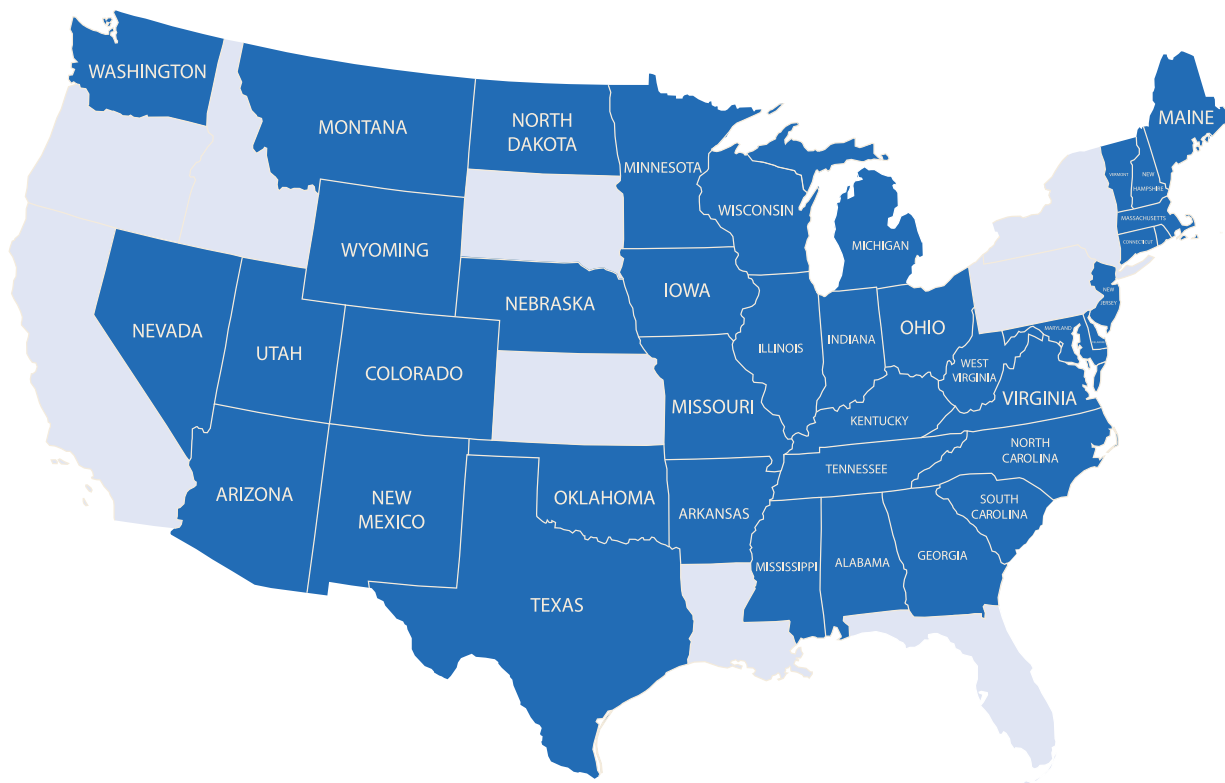


## Thank You From PPTA

Across the country, states issued proclamations and letters of support in recognition of the third annual International Plasma Awareness Week, Oct. 11 – 17, 2015. PPTA staff and member companies contacted gubernatorial offices to advocate for and raise awareness about plasma donation and plasma protein therapies. PPTA received 40 proclamations

from 39 states and the District of Columbia honoring the contributions of plasma collection centers and healthy, committed donors across the country.

PPTA would like to thank the following Governors for declaring International Plasma Awareness Week in their states:



ALABAMA	Robert Bentley	IOWA	Terry Branstad	NEBRASKA	Pete Ricketts	SOUTH CAROLINA	Nikki Haley
ARIZONA	Doug Ducey	KENTUCKY	Steve Beshear	NEVADA	Brian Sandoval	TENNESSEE	Bill Haslam
ARKANSAS	Asa Hutchinson	MAINE	Paul LePage	NEW HAMPSHIRE	Maggie Hassan	TEXAS	Greg Abbott
COLORADO	John Hickenlooper	MARYLAND	Larry Hogan	NEW JERSEY	Chris Christie	UTAH	Gary Herbert
CONNECTICUT	Dan Malloy	MASSACHUSETTS	Charlie Baker	NEW MEXICO	Susana Martinez	VERMONT	Peter Shumlin
DELAWARE	Jack Markell	MICHIGAN	Rick Snyder	NORTH CAROLINA	Pat McCrory	VIRGINIA	Terry McAuliffe
D.C.	Muriel Bowser	MINNESOTA	Mark Dayton	NORTH DAKOTA	Jack Dalrymple	WASHINGTON	Jay Inslee
GEORGIA	Nathan Deal	MISSISSIPPI	Phil Bryant	OHIO	John Kasich	WEST VIRGINIA	Earl Ray Tomblin
ILLINOIS	Bruce Rauner	MISSOURI	Jay Nixon	OKLAHOMA	Mary Fallin	WISCONSIN	Scott Walker
INDIANA	Mike Pence	MONTANA	Steve Bullock	RHODE ISLAND	Gina Raimondo	WYOMING	Matt Mead



## ● Business Forum Overview

BY SONIA BALBONI

During the Source Business Forum in Anaheim, California, more than 100 PPTA members listened to experts engage in presentations and a panel on donor safety and standards. The panel titled “Staying Ahead of the Curve: Donor-Centered Initiative,” featured discussions with:

- **John McVey**  
Senior Director, Quality and Regulatory Affairs,  
Baxalta Inc/BioLife Plasma Services
- **Ileana Carlisle**  
Vice President, Plasma Operations, Biotest  
Pharmaceuticals
- **Dr. Marilyn Rosa-Bray**  
Chief Medical Officer, Grifols Plasma Operations
- **Dr. Stephan Walsemann**  
Managing Director, KedPlasma GmbH

Updates were also given highlighting the accomplishments of Source Division expert committees in several areas, including IQPP standards, medical/regulatory, communications, and regional initiatives. PPTA president and CEO Jan M. Bult gave an overview of issues facing the industry and a provided a snapshot of what is on the horizon for the Association globally. Source Board of Directors Chairman Shinji Wada discussed important milestones reached by industry through work with the Association.

A reception was held following the event in recognition of the third annual International Plasma Awareness Week. ●

---

SONIA BALBONI, PPTA Senior Manager, Source & Standards

Updates were given highlighting the accomplishments of Source Division expert committees in several areas, including IQPP standards, medical/regulatory, communications, and regional initiatives.



Shinji Wada, Chair, PPTA Source Board of Directors (left) and Robert W. Reilly award winner Dr. Toby Simon.

### Robert W. Reilly Leadership Award

Dr. Toby Simon was awarded the annual Robert W. Reilly Leadership Award. He was recognized for his leadership in the industry, particularly in the areas of donor and patient safety and for his research in blood/plasma safety and availability. Dr. Simon is the Senior Medical Director, Plasma & Plasma Safety, Global Resources & Development for CSL Behring. He currently serves as the non-voting industry representative to FDA's Blood Products Advisory Committee and serves on various PPTA committees and Task Forces.



MEET THE

# PPTA Global Health Policy Staff



Sándor von Tóth  
Senior Manager, Germany



Brenna Raines  
Senior Manager, Health Policy



Krisztina Kozma  
Administrative Assistant

## Global Health Policy Team

*As the leading trade association representing the collectors of Source plasma and the manufacturers of plasma protein therapies, one of PPTA's top priorities is patient access to the lifesaving therapies. Earlier this year, PPTA's Global Board of Directors expanded its global footprint by focusing on the importance of worldwide patient access to plasma protein therapies. The Global Board of Directors made the strategic decision to create a Global Health Policy division within the Association to enhance the organization's effectiveness. This decision was made to highlight the sharp focus of the Association on access to care and to expand the Association's capabilities.*

*PPTA's Global Health Policy team consists of an experienced team of government relations and health policy experts. As you can see, PPTA staff has the talent and health policy expertise to have a positive impact on patient access issues. Lately, there has been an increasing number of attempts by government and national payers to control costs and utilization; all in an attempt to reduce costs. When payers make these decisions, typically all pharmaceuticals are lumped into one bucket; it's PPTA's mission to differentiate plasma protein therapies and highlight their tremendous value to and impact on patients.*

*PPTA's Global Health Policy team includes staff across the Association with a broad range of skills. Meet the team:*



Julie Birkofer  
Senior Vice President, North America  
and Global Health Policy



Bill Speir  
Senior Director, State Affairs



Pam Roberge  
Administrative Assistant,  
North America



Bruno Santoni  
Executive Director, Europe



Karl Petrovsky  
Senior Manager, Health Policy



Tom Lilburn  
Director, Government Relations



**QUALTEX®**  
LABORATORIES

QUALTEXLABS.ORG



## Your Testing Service Solution

### Services

- Infectious disease testing
- Nucleic acid testing
- Immunohematology reference lab
- Microbiology testing
- Specialty testing

### About QualTex

- Multiple laboratory sites
- 24/7/365 testing schedule
- FDA registered
- EU GMP certificate of compliance
- German Health Ministry certification
- ISO 9001:2008 certified
- Active research and development



### Locations

HEADQUARTERS – SAN ANTONIO  
6211 IH 10 West  
San Antonio, Texas 78201

ATLANTA  
4258 Communications Drive  
Norcross, Georgia 30093

888-QTX-LABS (789-5227)

A SUBSIDIARY OF

**BioBridge**  
GLOBAL





Barcelona, Spain

# Upcoming Events

## CONFERENCES & SYMPOSIUMS

### February

- 3 – 5** 9th Annual Congress of European Association for Haemophilia and Allied Disorders (EAHAD)  
*Malmö, SWEDEN*
- 17 – 20** 60th Annual Meeting of the Society of Thrombosis and Hemostasis Research  
*Muenster, GERMANY*
- 23** British Paediatric Surveillance Unit (BPSU) 30th Anniversary Rare Disease Conference  
*Birmingham, UK*
- 29 – Mar 3** Rare Disease Week on Capitol Hill 2016  
*Washington DC, U.S.*

### March

- 9 – 12** 3rd International Congress on Research of Rare and Orphan Diseases  
*Barcelona, SPAIN*
- 14 – 16** Orphan Drugs and Rare Diseases Global Congress  
*London, UK*
- 22 – 23** **International Plasma Protein Congress (IPPC)**  
*Barcelona, SPAIN*
- 31 – Apr 2** HFA Symposium  
*Las Vegas, Nevada, U.S.*

### April

- 3 – 6** 42nd Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT)  
*Valencia, SPAIN*

### May

- 4 – 7** 24th Biennial International Congress on Thrombosis  
*Istanbul, TURKEY*
- 26 – 28** 8th European Conference on Rare Diseases & Orphan Products  
*Edinburgh, UK*

### June

- 9 – 12** Congress of European Hematology Association (EHA)  
*Copenhagen, DENMARK*
- 14 – 15** **PPTA Plasma Protein Forum**  
*Washington, DC*
- 24 – 28** World Federation of Hemophilia (WFH) World Congress  
*Orlando, Florida, U.S.*



## GLOSSARY OF TERMS

**ABIRISK – ANTI-BIOPHARMACEUTICAL IMMUNIZATION:  
PREDICTION AND ANALYSIS OF CLINICAL RELEVANCE  
TO MINIMIZE THE RISK**

**ADA – ANTI-DRUG ANTIBODIES**

**AMP – AVERAGE MANUFACTURER PRICE**

**AVIS - ASSOCIAZIONE VOLONTARI ITALIANI SANGUE**

**BENELUX – BELGIUM, NETHERLANDS, AND LUXEMBOURG  
POLITICO-ECONOMIC UNION**

**BPWP – BLOOD PRODUCTS WORKING PARTY**

**CBER – CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

**CT – CLINICAL TRIAL**

**DSAI – DEUTSCHE SELBSTHILFE ANGEBORENE IMMUNDEFEKTE E.V.**

**EAHAD – EUROPEAN ASSOCIATION FOR HAEMOPHILIA  
AND ALLIED DISORDERS**

**EAHP – EUROPEAN ASSOCIATION OF HOSPITAL PHARMACISTS**

**EFPIA – EUROPEAN FEDERATION OF PHARMACEUTICAL  
INDUSTRIES AND ASSOCIATIONS**

**EGA – EUROPEAN GENERIC AND BIOSIMILAR MEDICINES  
ASSOCIATION**

**EHC – EUROPEAN HAEMOPHILIA CONSORTIUM**

**EMA – EUROPEAN MEDICINES AGENCY**

**EUHASS – EUROPEAN HAEMOPHILIA SAFETY SURVEILLANCE**

**FDA – U.S. FOOD AND DRUG ADMINISTRATION**

**GCP – GOOD CLINICAL PRACTICE**

**GEHEP – GLOBAL EMERGING HEMOPHILIA PRACTICE**

**HB – HEMOPHILIA B**

**HTA – HEALTH TECHNOLOGY ASSESSMENT**

**Ig – IMMUNOGLOBULIN**

**IPAW – INTERNATIONAL PLASMA AWARENESS WEEK**

**IPFA – INTERNATIONAL PLASMA FRACTIONATION ASSOCIATION**

**IQPP – INTERNATIONAL QUALITY PLASMA PROGRAM**

**ISPE – INTERNATIONAL SOCIETY FOR  
PHARMACEUTICAL ENGINEERING**

**ISTH – INTERNATIONAL SOCIETY ON THROMBOSIS  
AND HAEMOSTASIS**

**ITI – IMMUNE TOLERANCE INDUCTION**

**MA – MARKETING AUTHORIZATION**

**MAA – MARKETING AUTHORIZATION APPLICANTS**

**MAH – MANUFACTURING AUTHORIZATION HOLDER**

**MAH – MARKETING AUTHORIZATION HOLDERS**

**MHC – MAJOR HISTOCOMPATIBILITY COMPLEX**

**MOH – MINISTRY OF HEALTH**

**NCA – NATIONAL COMPETENT AUTHORITIES**

**NHF – NATIONAL HEMOPHILIA FOUNDATION**

**NHLBI – NATIONAL HEART, LUNG, AND BLOOD INSTITUTE**

**NIH – NATIONAL INSTITUTES OF HEALTH**

**PDA – PARENTERAL DRUG ASSOCIATION**

**PDCO – PAEDIATRIC COMMITTEE**

**PEDNET – PEDNET HAEMOPHILIA REGISTRY**

**PEI – PAUL-EHRlich-INSTITUT**

**PGEU – PHARMACEUTICAL GROUP OF THE EUROPEAN UNION**

**PID – PRIMARY IMMUNODEFICIENCIES**

**PIP – PEDIATRIC INVESTIGATIONAL PLAN**

**PPT – PLASMA PROTEIN THERAPY**

**PRAC – PHARMACOVIGILANCE RISK ASSESSMENT COMMITTEE**

**PUP – PREVIOUSLY UNTREATED POPULATION**

**RMP – RISK MANAGEMENT PLAN**

**SIPPET – SURVEY OF INHIBITORS IN PLASMA PRODUCT  
EXPOSED TODDLERS**

**TCR – T CELL RECEPTORS**

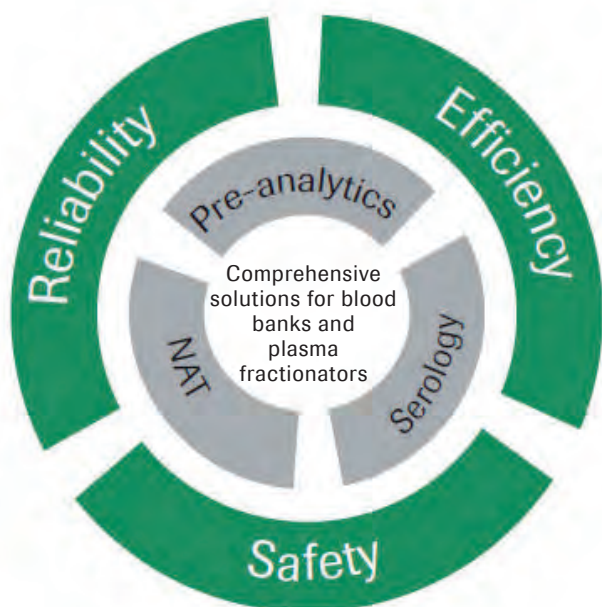
**T<sub>H</sub> – T HELPER**

**WFH – WORLD FEDERATION OF HEMOPHILIA**



## Roche Blood Safety Solutions

*Count on us, because patients are counting on you.*



### Providing Total Workflow Solutions that Raise the Standards of Performance

**Safety:** State-of-the-art assay sensitivity and genotype coverage allow reliable detection at the earliest stages of infection.

**Reliability:** With the highest reliability on the market, our ingenious technologies maintain workflow, minimize user interactions, prevent cross contamination, and provide full sample traceability.

**Efficiency:** High assay specificity coupled with innovative multi-dye technology reduce the need for retesting, while short turn-around times, automation, and uninterrupted workflow generate time savings and free staff for other tasks.

For more information, contact your local Roche Diagnostics representative.

COBAS and LIFE NEEDS ANSWERS are trademarks of Roche.  
©2015 Roche Molecular Systems, Inc. All rights reserved.  
[www.roche.com](http://www.roche.com)

\*The serology product range is not available for blood screening settings in all countries, including Canada, the Philippines, South Korea, and the United States. For complete information on local availability, please contact your local Roche representative.



THE AURORA™  
PLASMAPHERESIS SYSTEM



# Power and Productivity



Aurora is the automated system that streamlines plasma collection procedures, produces virtually cell-free plasma and provides an improved experience for both operators and donors.

- Intuitive touch screen display
- Data Management with Aurora provides easy, accurate data collection, remote procedure setup and paperless documentation
- Designed to improve plasma center efficiency

Find out more today at 1-800-333-6925  
or visit [www.fresenius-kabi.us](http://www.fresenius-kabi.us)