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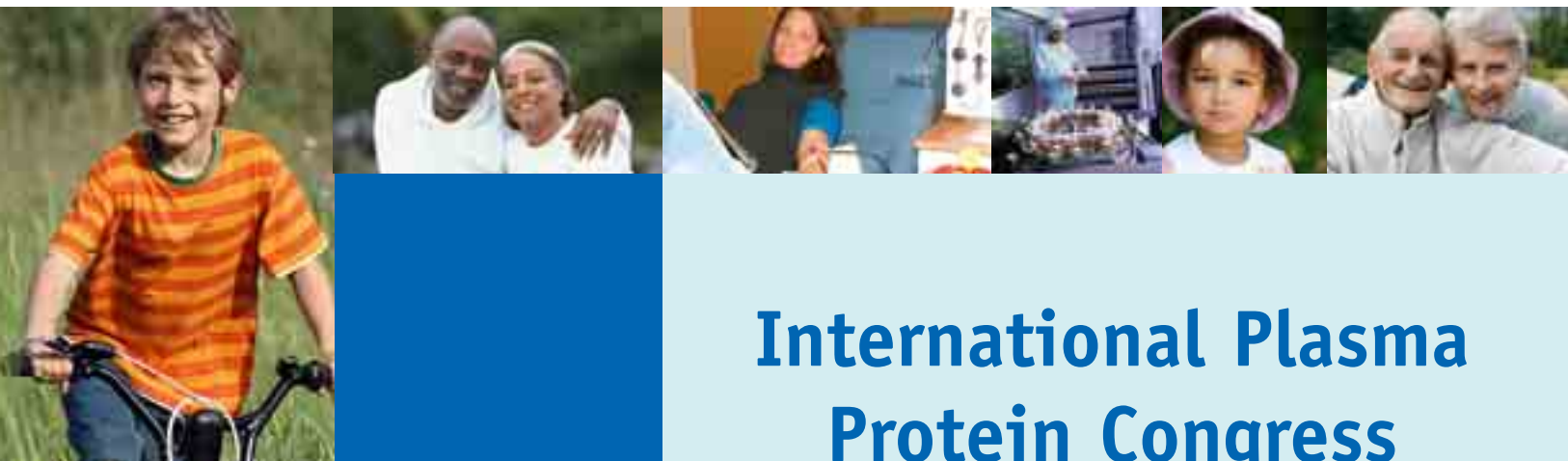
The Newsmagazine of the Plasma Protein Therapeutics Industry



Physical therapy in hemophilia
Interview with Paul Brown
2007 Stakeholder meeting

IPPC

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Managing Editor: . . . Alexandra de Mello-Gouveia

Editor: Johan Prévot

The Source is published 4 times a year by PPTA,
147 Old Solomons Island Road, Annapolis, MD,
21401. Phone: +1.202.789.3100
e-mail: thesource@pptaglobal.be

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In my View

THE IMPORTANCE OF STAKEHOLDER RELATIONS

Almost 15 years ago, two former heads of companies came to the conclusion that it was necessary to form an industry representative association. These two gentlemen were Dr. Otto Schwarz from Immuno and Ralph Galustian from Bayer. Not only were the issues this industry was dealing with very complicated, there was hardly any relationship with the stakeholders and many hemophilia patients had very disturbing experiences with using plasma protein therapies.

Otto Schwarz, as the first Chairman, helped the industry realize how important working together is, which was not easy in the beginning. The next Chairman was Ralph Galustian. He realized that talking alone was not enough, but a critical mass was needed to get started. He convinced the other industry members to make available a budget that would allow for the building of a strong association. My predecessor Robert W. Reilly was tasked with this.

A further development came with the Chairmanship of John Sedor from Armour. He led the industry to develop a strategic plan and focus

on the 4 key issues. The most important were to work on the Stakeholder confidence in Quality and Safety of the plasma protein therapies and in parallel work on the Credibility and Image of this industry.

After developing the strategic plan, the new Chairman Jan Turek (Bayer) helped the organization to develop their objectives and have measurable outcomes in all the defined strategic priorities.

His successor was Thomas Glanzmann from Baxter BioScience. He understood that there was no room for complacency when it comes to Quality and Safety and helped the industry to raise its bar in these critical areas. Our standard programs were enhanced and became a cornerstone of the association activities.

Ruedi Waeger (Aventis Behring) took over and in the middle of the industry changes, helped to restructure the Association to become a strong industry representative. Further alignment and streamlining helped to improve organizational excellence.

The current Chairman Peter Turner from CSL Behring is leading the

industry to demonstrate the value it is delivering to all stakeholders. He is doing that now very successfully in his fourth and last year as Chairman.

It is remarkable to see how much better the industry is listening to and communicating with its stakeholders in good and challenging times. We value the input of our stakeholders and hope they value our contributions. We want and will continue this.



Jan M. Bult / President, PPTA

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Interview with Paul Brown



The Source spoke with Paul Brown, M.D., Chairman of the FDA Transmissible Spongiform Encephalopathy Advisory Committee (TSEAC), 1997-2001, and Senior Investigator at the National Institutes of Health, Bethesda, Maryland, until 2004.

What are prions, what is their natural function and what is their involvement in prion diseases?

Prion is an acronym for “proteinaceous infectious particle”. It is a protein made by virtually every cell in the body, but its function is still unknown. Speculations include facilitating transport of salts across the cell membrane, participation in transfer of impulses between nerve cells, influence on diurnal rhythm, and even a role in the phenomenon of memory. What is important in the context of disease is that this protein is susceptible to misfolding into an abnormal configuration that aggregates into clumps of what is called amyloid, which is deposited in affected tissues (especially the brain), injuring cells and, eventually over a period of months to years, leading to illness and death.

We now recognize a number of disorders in the category of ‘protein misfolding diseases’, including not only the various forms of prion disease but also diseases like Alzheimer’s Disease (AD), Parkinson’s Disease, and a few more esoteric brain diseases. Each one of these diseases is caused by a different body protein that is susceptible to misfolding and clumping into amyloid, but only prion diseases have been shown to be transmissible, and thus ‘infectious’. It is possible that in the future, one or more of the other misfolded protein diseases may, under certain conditions, be found to be transmissible, but no such evidence exists today.

How would you describe the current situation regarding BSE and vCJD?

Both diseases are in decline nearly everywhere in the world where they have occurred, and no new countries are being added to the list. In the UK, where they first appeared,

fewer than 100 cattle were diagnosed with BSE this past year (2006), and only one new human case of primary vCJD. We will continue to see occasional cases of vCJD with very long incubation periods, but the feared ‘second wave’ of cases is less and less likely as time passes. There are precedents for making this statement: the epidemics of cannibalistic kuru, and growth hormone-associated CJD were both characterized by double ‘peaks’ related to the genotypes of the infected individuals – earlier in patients homozygous at codon 129 of the ‘prion gene’, and later in heterozygous patients. However, in each instance there was major overlapping of the two curves – that is to say, the heterozygous wave began well before the homozygous wave disappeared. This has not happened in vCJD: after more than 10 years, there are still no heterozygous cases of primary vCJD.

There is one other recent observation in cattle that could possibly bear on human CJD. For years BSE was thought to be caused by a single prion strain, but it now turns out that so-called ‘atypical strains’ are also occurring, often in apparently healthy older animals. Molecular analysis has shown some similarity between one of the atypical strains and one uncommon subtype of sporadic CJD, and a cause and effect relationship has been suggested, but it will take years of continued testing and observation to answer the question.

In the UK tonsils and appendices were tested for the presence of infectious prion protein to determine the vCJD prevalence. What is “prevalence” and why is there still no conclusive result?

Prevalence in this context is defined as the number of infected individuals in a given unit of population (usually a million) at a given point in time. In the UK tonsil/appendix study, three positive appendices were discovered in a study of several thousand samples. Two were codon 129 valine homozygotes, the third could not be determined. Estimated prevalence for the entire UK population yielded the frightening result that thousands of people could be incubating vCJD, an observation completely at odds with the actual number of cases of vCJD that have occurred in the UK. The only way to align these divergent observations is to consider that all codon 129 methionine homozygotes have already contracted the disease, and that the other genotypes are still in the incubation phase of disease, or

perhaps are carriers of the infection who will never become ill. The study was totally anonymous so that no information is available on the age or background of the individuals whose samples tested positive, without which we cannot meaningfully evaluate the data.

Do you believe that BSE or vCJD imposes a threat to the blood and plasma supply in the US?

Although the USDA approach to bovine testing means we will never truly know the scale of BSE in the US, I doubt it is a serious problem, despite at least two endogenous cases. Assuming a negligible BSE problem, any vCJD problem would be correspondingly negligible.

Following the UK and other European countries, the US FDA has recently presented their prion risk assessment for plasma-derived Factor VIII products. For the lay person, the purpose and relevance of a risk assessment is often difficult to comprehend. Could you please explain your interpretation of the FDA's risk assessment?

The typical risk assessment considers sets of assumptions based on both experimental and epidemiological data and then hedges its conclusions. The risk assessment of Factor VIII is a good illustration. Experimental data (in rodents) about levels of infectivity in plasma and plasma fractions, together with infectivity reductions associated with various processing steps was one element in the assessment. The other element was the statistical probability that any given batch of plasma would have a contribution from a donor who would later develop vCJD, the dose over time of administered FVIII, and the fact that there is as yet no case of CJD linked to the administration of FVIII. The FDA concluded that "the actual risk of vCJD infection from pdFVIII is likely to be very low". I agree.

appropriate system. Ideally, such studies should be conducted in parallel using both endogenous and exogenous infectivity models: exogenous 'spikes' of high infectivity to determine how great a reduction is possible, and endogenous blood (low infectivity) as a check on the validity of the result.

What are animal models? What is their relevance to the situation in humans?

Animal models are a 'default' solution to the problem of being unable to use humans for harmful studies (for example, disease transmission experiments). The next best thing is great apes, the most closely related species, but this is also out of the question because of ethical concerns and the extremely high costs associated with such experiments. Susceptible monkeys are the next choice and they are used in some places in the world. Outside of monkeys it is difficult to determine which species of animal is more relevant, a sheep, a mouse or a hamster. Rodents are typically used because they are small, inexpensive, and have shorter survival periods after being infected. We all recognize that, even when using primates, we cannot be absolutely sure that the results of our experiments are applicable to humans.

Why are scientists after all these years of research still only speculating about the level of infectivity in human plasma?

The reason is that humans cannot be used in experiments, and we cannot assume that the level of infectivity in experimentally infected rodents, sheep, or even primates can be translated to humans. The level of infectivity in brain tissue from primates with CJD is about 100-fold lower than the levels in rodents, and it is plausible to suppose that the levels of infectivity in blood would also be lower. Blood from rodents has been repeatedly shown to have a

"Plasma protein therapy is a low-risk or no-risk situation"

What is the difference between endogenous and exogenous infectivity?

In the context of blood infectivity, endogenous means that an animal is infected either naturally or experimentally and then goes on to produce its own circulating (infectious) blood. Exogenous means that an external source, or 'spike', of infectivity (for example, a small amount of brain homogenate) has been added to normal blood. The distinction is important because infectivity in the brain may not be in the same form as infectivity in circulating blood. In consequence, experimental results on exogenously infected blood (for example, processing steps for plasma proteins) are based on an 'artificial' and perhaps inap-

maximum level of about 10 infectious doses per ml (= 4500 infectious doses in a 450 ml unit of blood). If human blood has 100-fold lower levels, we might expect a maximum of about 45 infectious doses in a unit of blood. This is all speculative, but we may soon get some additional information about levels of infectivity in sheep infected with BSE, which will be interesting to compare with rodents.

What is the difference between an immunological (in vitro) assay and a bioassay (in vivo)? Why is a bioassay also called an infectivity assay?

Bioassays are measurements of infectivity, either in animals or more recently in tissue cultures. In vitro assays measure

some correlate of infectivity, most often the prion protein, which usually (but not invariably) correlates with infectivity. It is thus an excellent 'clue' to the associated presence of infectivity, and is widely used by virtue of its comparative cost, and the speed with which a result can be obtained (days instead of months or years). However, if it is really critical to measure infectivity, we are still obliged to perform expensive and time consuming bioassays, because failure to detect the prion protein may not mean the absence of infectivity (some in vitro methods are comparatively insensitive), or conversely, detection of the protein by an ultrasensitive method may actually exceed the limits of transmissibility.

Is there a difference between the risk when receiving a blood transfusion or a plasma protein therapy?

A huge difference. Blood transfusion is a high risk situation (at least from vCJD blood). Plasma protein therapy is a low-risk or no-risk situation. We know that, compared to white cells, plasma contains much lower levels of infectivity, that Cohn fractionation of plasma further reduces infectivity, and that additional processing into plasma protein products eliminates any infectivity that might have been present in the Cohn fractions.

Do recipients of plasma derived protein therapies have to worry about contracting vCJD through these products?

I think not, but I could be wrong. Historically, when crude cryoprecipitate was used as the source of FVIII, there was a risk that infectivity in plasma (if present) could contaminate the cryoprecipitate and thus be administered to hemophilia patients. However, in recent times, the cryoprecipitate routinely undergoes further processing steps that significantly reduce any infectivity that might be present. For example, chromatography columns used in processing have been repeatedly shown to eliminate about 1000 infectious doses per ml of processed product, and as noted above, there is no realistic possibility that blood could contain that high a level of infectivity. Similar considerations apply to other plasma protein products. However, it is also possible to argue that blood transfusions from patients incubating vCJD are indisputably infectious, and evidence from laboratory studies does not necessarily translate to the real world where conditions are not so tidy and well controlled. Unfortunately, the records of 'who got what' (recipients of different batches of plasma products) are too imperfect to be able to evaluate connections (if any) between individual recipients and particular batches of plasma-derived therapeutic proteins.

Can prion diseases be transmitted through sexual contact?

As far as we know the answer is no. There are two routes of infection which seem not to occur, one of which is venereal and the other is respiratory. Decades of searching have turned up but a single instance of CJD in spouses, and they were thought to be an example of statistical coincidence rather than transmission from one spouse to the other. Surely, the absence of spousal CJD pairs among thousands and thousands of cases of sporadic CJD argues strenuously against venereal disease transmission.

Many diagnostic companies are developing tests to detect abnormal prion proteins in blood donors. Can these proteins be detected before the onset of symptoms? If these proteins are detected in an asymptomatic individual, is it certain that this person will develop vCJD?

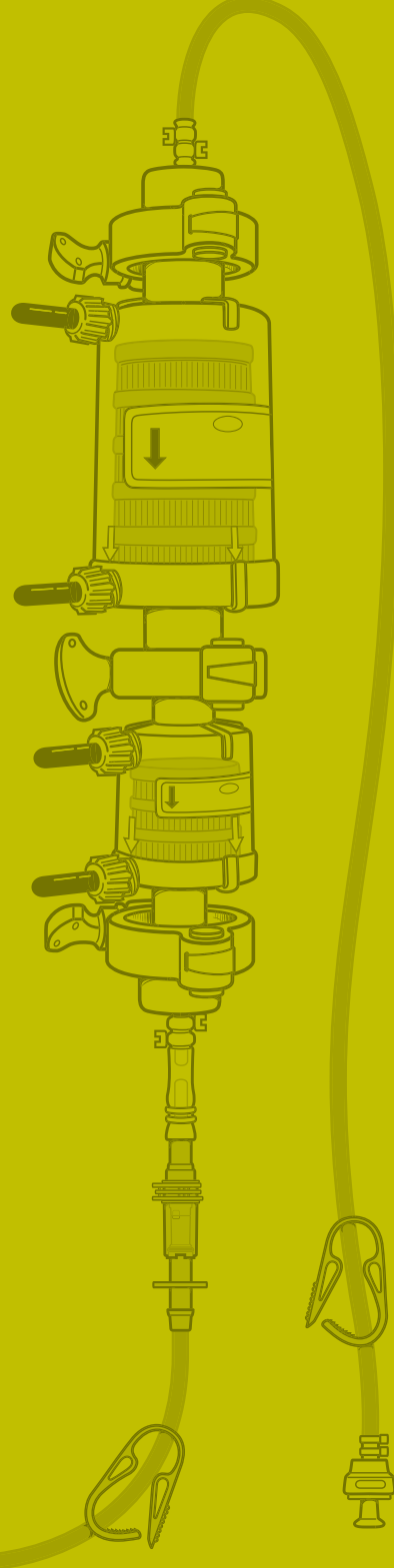
A couple of years ago the prospect was upbeat in that at least a dozen companies were developing tests with promising preliminary results. However, many of them have run into unexpected methodological difficulties when testing human plasma, and in consequence, the prospect today is less optimistic. Currently, a method that amplifies very low levels of protein before applying a detection technique appears to be the method of choice, but this could change in coming months, as various laboratories using different methods move ahead in this common goal to develop a practical pre-clinical screening test. Even if such a test were available, however, there are two key questions for which we do not have the answers: we do not yet know whether blood which tests positive for prion protein is capable of transmitting disease; and we also do not know whether the donor of such blood will develop CJD. Both questions require answers before any test is put to use.

Is there a cure for vCJD?

Some very interesting studies have recently been initiated using both immunotherapy (vaccine) and chemotherapy (drug) approaches, and although we still seem far from anything resembling a practical form of treatment, a breakthrough could happen at any time. The important matter is that people are again doing serious research to develop a prevention or cure, not only for vCJD, but for all forms of TSEs.

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Physical therapy in hemophilia

By P. de Kleijn

The role of physical therapy in hemophilia

The physical condition of people with Hemophilia A and B depends largely on the availability of clotting factor, which varies widely worldwide. The amount of and manner in which physical therapy is indicated is closely related to this. Physical therapy in hemophilia globally is divided into: prevention, function recovery after (acute) bleeds, retention of activity and participation with hemophilia arthropathy and chronic synovitis, and pre- and post-operative support. These facets are all incorporated into the International Classification of Functioning, Disability and Health (ICF) [1], in which the consequences of a disease or condition are described in terms of Body, Activities and Participation. This is affected by environmental and personal factors. The availability of Factor VIII and IX falls in the environmental factors category, as do the size of a country and the accessibility (in terms of distance and time) of a treatment center. A good example of personal factors is coping behavior: the manner in which an individual deals with his/her condition. The ICF's use has increased considerably in clinical practice in recent years [2-4].

Physical therapy in bleeds

The physical therapist guides the patient to strive for optimal function recovery after an intra-articular bleed, for example, has stopped. The treatment plan occurs in steps, with functional milestones for the patient to aim for [5]. These steps are, for example in the case of a considerable knee bleed: mobilizing from bed to chair; going to the bathroom independently; resuming household chores; starting school or work and, finally, beginning sports and leisure activities. At first, physical therapeutic intervention is aimed at physical limitations. Each subsequent goal can only be attained if certain conditions are met, for example less pain and swelling, better stability of the joint and more muscular strength.

Generally known and promoted by the World Federation of Hemophilia (WFH) is the RICE protocol: Rest, Ice, Compression and Elevation. According to the ICF chart, recovery starts at the body level, but afterward at the activity level. Functionally speaking, the patient must actively be able to stabilize his knee before sitting on the

side of the bed, otherwise a repeat bleed is likely. Functional goals differ per country. Crossing the street at a crosswalk in Europe is different than in India; a "floor sitting community" requires more knee bending than sitting on our Western chairs. Functional milestones as such are not independent; the total protocol after an intra-articular bleed should consist of preventative measures, acute phase, phase after bleeding is stopped and evaluating measures [6]. A stopped bleed followed by optimal functional recovery is the best prevention for the next bleed!

Prevention

The road to prevention is easily made. In addition, recommendations for the general education of children, which needs to include children being regularly active. This facilitates normal motor development, where kids can participate in gym classes, play outside with kids their own age and chose a sport.

Although this topic can be discussed by social workers with parents of children with hemophilia, the physical therapists are the ones who can link this to normal motor development, can contact physical education teachers and advise parents and children when it comes to well-considered choosing of an appropriate sport.



P. de Kleijn presenting at the 2006 EHC Congress in Sofia

Another preventative measure is acquiring crutches, even before there is a bleed, and actually learning to use them. Once the bleed happens, a knee joint can be considerably relieved by proper use of crutches. Also making contact

with relevant people, such as family, neighbors, teachers and sports instructors can work preventatively. These people should not panic in case of a bleed, but be able to act adequately.

Communicating with a patient about the start and end of a bleed is necessary from a treatment point of view, as well as from a prevention perspective. Knowing when a bleed is coming is very important if clotting factor is available: consequences to the joint in the long term will be less the quicker the factor gets administered. It is, however, also important to discuss with a patient when a bleed is stopped. It is vital for doctor, nurse and physical therapist to let the patient indicate this. Objective signs, such as decrease of pain, swelling, warmth and increase in motion and activity, are used for verification. This way, a patient learns to understand his body better.

The path of functional milestones is only complete when the patient can resume all activities from before the bleed. Research shows that this should not happen too fast [7], especially with children, since their cartilage damages more easily [8]. One task of the treatment center should be the evaluation of the most recent bleed(s), together with patient and family. It would be unwise not to learn from your mistakes, but unfortunately this evaluation is often not performed.

Physical therapy in hemophilic arthropathy and chronic synovitis

Immediately following a bleed, the body does everything it can to clean up blood residue and a synovial reaction follows. If this persists longer than three months, we speak of chronic synovitis and physical therapy occurs in combination with a solid factor policy: daily administration

functional therapy is often interrupted by residual bleeds and little progress is achieved. The synovitis in itself cannot be suppressed by physical therapy, so the support after stopping a bleed becomes even more important.

One or multiple bleeds can lead to damage of the joint cartilage, also known as hemophilia arthropathy. This looks similar to secondary arthrosis [11] and is a slowly progressing process [12]. Characteristics are the appearance of the initial pain after (long-term) weight pressure, as well as a decrease in range of motion and number and duration of activities. It is important to regularly consult the patient and use objective data to follow the clinical process. This is not the case in many hemophilia treatment centers, where the patient only goes in case of a bleed (ad hoc policy). The basis of treatment with physical therapy is knowing and following the clinical process and maintaining the balance between burden and the burden limitations.

Physical therapy does not help the arthropathy as such, but focuses on optimal (physical) functioning during all phases of the process. The basis of physical therapy is exercise therapy. It is better to let patients do mostly functional exercises and not the ever classic exercises because of non-compliance. This improves as the patient is in less pain. It is a myth to think that physical therapy can achieve this in a direct way. A solid pain schedule and accurate coordination between patient, physical therapist and hemophilia treator is the key to success. Warmth can be applied or manual traction used for relaxation. Each patient who has less pain, has less avoiding behavior [13] and is capable to exercise more functionally to build achievable results into their personal activity schedule. For example, exercise needs to be done beforehand if there is not enough

“A stopped bleed followed by optimal function recovery is the best prevention for the next bleed!”

of clotting factor [9]. This is impossible in many countries and synoviorrhesis is an option in that case; unfortunately it depends on the cost aspect which medicine is eligible per country [10]. The knee with chronic synovitis is the most well known picture that people associate with hemophilia. With synovitis, pain is not the primary issue, but the warm swelling and instability and symptoms are often communicated too late. Progress by means of exercise and

strength, hydrotherapy can help if the burden on joints is too much, but everything is geared to arrive at functional exercise therapy quickly.

Multi-disciplinary treatment and pre- and postoperative physical therapy

The WFH promotes comprehensive care as the optimal treatment strategy in the treatment of people with

hemophilia, essentially a must in all chronic cases. The rehabilitation doctor can be consulted when functional goals are not achieved and the person cannot maintain an appropriate quality of life. Functioning can improve with a brace, ankle tube or orthopedic shoes. The physical therapist and rehabilitation specialist work very closely in this process. If the results are not satisfactory, the rehabilitation specialist will advise the patient to visit an orthopedic surgeon. The most common indication is joint replacement, or at least an arthrodesis in the case of an ankle, besides osteotomy, arthroscopic synovectomy or other operations. The process of pre- and post operative physical therapy was highlighted in a separate session during the WFH World Congress last year and described in the “State of the Art” edition of Haemophilia [14].

Research and development

One needs solid data to objectify results: in order to obtain these you need reliable and validating measuring instruments. The measuring instruments also need to be responsive if you want to follow a patient over time. Literature [15] shows: “Reliable clinimetric instruments, validated for patients with haemophilia, and sensitive to change, are relatively sparse in the literature, and performance instruments are not reported at all”.

Although disappointing in terms of ‘evidence’ for physical therapeutic intervention in hemophilia patients, recent developments are more hopeful. A Hemophilia Activity List (HAL), a condition-specific instrument that measures the activities of hemophilia patients in a reliable and valid way, was recently developed [16]. The origin of this questionnaire is in the answers given by 162 people with hemophilia. The list is patient friendly and translated into multiple languages

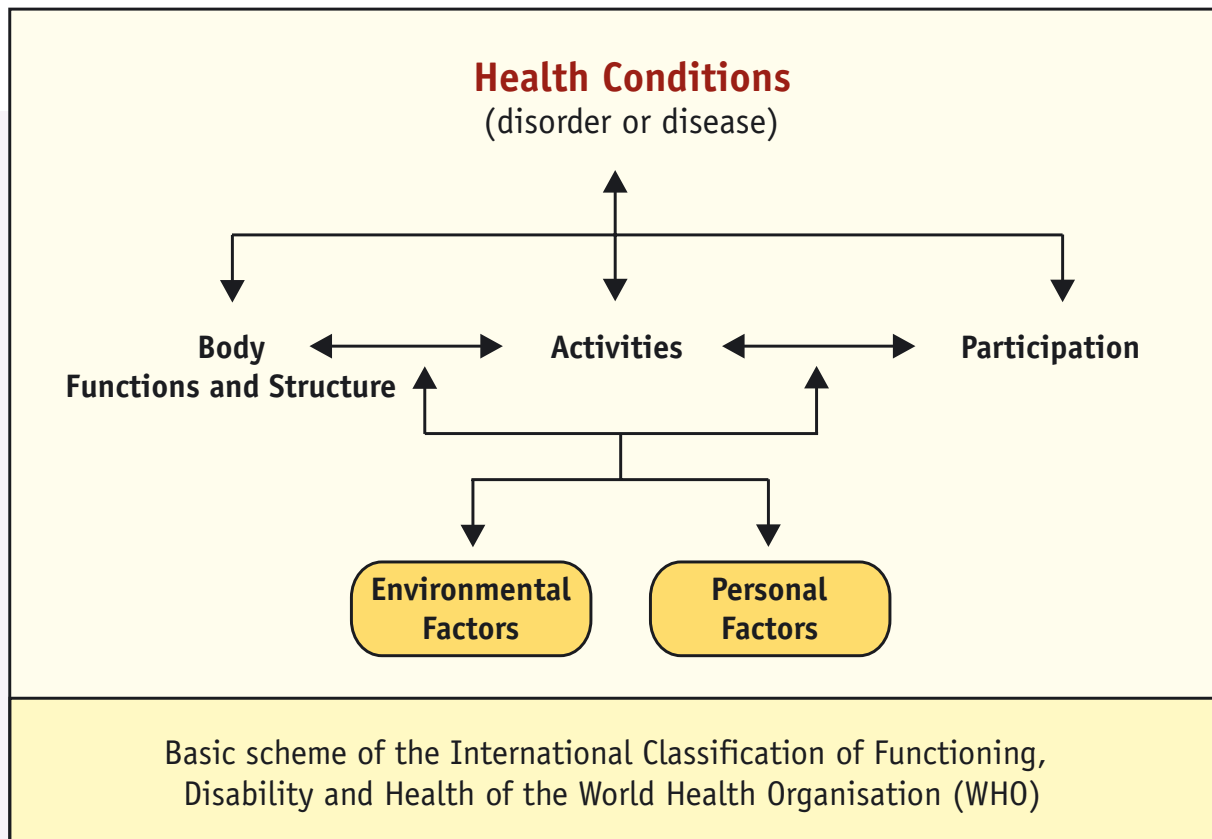
Conclusion

Optimal physical therapy is used sporadically to guide people worldwide, even though each medical doctor realizes the importance of physical therapy in hemophilia.

It is therefore of great importance that, besides research and obtaining evidence, implementation is actually taking place.

P. de Kleijn

If you would like to know more, please contact P.deKleijn@umcutrecht.nl or F.R.vanGenderen@azu.nl



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Stakeholder Meeting 2007

by Julie Birkofer

PPTA continues the tradition of holding Stakeholder Meetings with the leadership from the patient groups who represent the community of plasma protein therapy (collectively, “plasma-derived and recombinant analogs”) users, industry and representatives from government agencies. The first meeting of 2007 occurred on January 10 in Washington, DC. Highlights from the meeting included:

- vCJD update from a leading industry scientist and researcher
- Opportunity for dialogue and open discussion on FDA's risk assessment on plasma derived FVIII
- Focused advocacy on access to full-range of therapies from qualified providers;
- The importance of definitions of “Care” - medical and pharmaceutical; and due process protections.

These meetings are an integral part of the Association's advocacy strategy and constantly emphasize the benefits of working together to assure patient access to life sustaining plasma protein therapies. Sometimes it's difficult to narrow down the many issues facing the community to allow for meaningful discussion in a day's meeting. But, with input from Stakeholders and broad participation, these meetings prove very productive. Here are a few of the highlights from the recent meeting:

TSE Update

These meetings provide a unique venue for dialogue between the Association and its Stakeholders. Thomas R. Kreil, Ph.D., chair of PPTA's Pathogen Safety Steering Committee, was invited to speak at the meeting to answer questions raised by stakeholders after the December 15, 2006 Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) meeting. Dr. Kreil's remarks focused on clarifying PPTA's presentation of industry clearance studies on plasma-derived Factor VIII (pdFVIII). Dr. Kreil delivered the presentation that he made to the TSEAC; however, he expanded the presentation in key areas, supplied an in depth review of each slide with background and more detailed information, and provided stakeholders the opportunity to ask questions on each point presented. Dr. Kreil stated the pdFVIII manufacturing processes remove prions and that individual reduction factors depend on the specific manufacturing process, the number of steps investigated, and experimental design. He also stressed

that the level of risk is unknown but likely low as has been demonstrated by FDA's risk assessment as well as others, and that there is no evidence of transmission by pdFVIII products. Dr. Kreil emphasized that industry continues to work diligently on this issue. He explained the importance of individual company manufacturing processes, and the complex inter-relationship of processes to products. Changes to processes require careful deliberations. He stressed that adding additional steps to one process would in fact change the product and possibly its effectiveness, as well as, possibly resulting in unexpected changes to other products. Stakeholders expressed appreciation for taking the time to clarify the previous presentation and stated they welcome opportunities to learn about the fractionation process.

The North American Data Gathering Program

PPTA staff again reviewed improvements to the data reporting system, which will be visible on the PPTA web site (www.pptaglobal.org) in February 2007 when the January 2007 data becomes available. The “traffic light” style reporting system will be removed in February as it is not the best indicator of U.S. distribution. The PPTA web-based information system will provide monthly charts (beginning February 2007) for each of the five (5) therapy groups captured by the Data Collection Program (IVIG, Albumin 5% and 25%, Recombinant FVIII and Plasma Derived FVIII.) Based on extensive research into a new system, it was determined that the aggregate distribution data are the most reliable and useful data points in attempting to determine the status of total U.S. supply of plasma protein therapies. PPTA staff noted at the meeting the record increases in IVIG distribution. As this article goes to print, over 32,000 kg of IVIG were distributed in the U.S. in 2006 as compared to 28,000 kg in 2005.

Stakeholder Toolkit

PPTA staff presented the Stakeholder Toolkit, in response to Stakeholder requests for information on plasma protein therapy manufacturing processes and available resources. The toolkit has been designed to be a working document that will continue to evolve to further meet the needs of Stakeholders as an educational vehicle. Additions to the toolkit were suggested (i.e., a glossary of terms is under development and a chart that describes the fractionation process is attached). Updates to the toolkit will be

announced and made available on the Stakeholder page of Association website (<http://pptaglobal.org/en/stakeholder.cfm>). Stakeholders are asked to continue to provide comments and recommendations on the toolkit to Diana Krueger at dkrueger@pptaglobal.org.

European Update

Recognizing that PPTA is a global organization and that consumers worldwide depend upon access to plasma protein therapies, PPTA's Senior Manager Public Affairs provided an overview of stakeholder outreach activities in Europe. The Plasma Protein Users Group (PPUG) is the main vehicle for stakeholder relations (patient groups, physicians and industry) in Europe. The PPUG was created in 2004 and the goal of this platform is to share information and determine common actions. Members of the PPUG include the International Patient Organization for Primary Immunodeficiencies (IPOPI), World Federation of Haemophilia (WFH), European Haemophilia Consortium (EHC), European Federation for Alpha-1 Antitrypsin Deficiency (Alpha Europe), Guillain-Barré Syndrome/CIDP Support Group, Idiopathic Thrombocytopenic Purpura (ITP) Support Association, as well as the European Organization for Rare Diseases (Eurordis). Leading physicians representing the European Society for Immunodeficiencies (ESID), the International Union of Immunological Societies (IUIS) and the Hemophilia community also attend the meetings. In addition to actions related to EU Health Policy developments, the main achievements of the PPUG have been the creation of a web-based patient group toolkit (<http://www.patientgrouptoolkit.org>) as a means to help facilitating the development of national patient groups and the coordination of a joint submission for the reinstatement of immunoglobulins on the World Health Organization's (WHO's) Model List of Essential Medicines. The submission which is led by IPOPI and IUIS was submitted to WHO in October 2006. Since then it has been available for public review on the WHO website and has received wide support from stakeholders from across the world. The submission will remain on the WHO website (<http://mednet3.who.int/EML/expcom/expcom15/rein-statement.htm>) for public review until January 31, 2007. Letters of support can be sent directly to WHO secretariat at: emlsecretariat@who.int. The WHO Expert Committee on the Selection and Use of Essential Medicines will meet in March 2007 to decide which drugs will be included in the 15th edition of the Model List. The next meeting of the PPUG will be held in Vienna on March 5, 2007.

State Quality of Care Initiatives

PPTA staff provided some introduction and background on state quality of care initiatives. To set the context for the discussion, PPTA reported the results from the November elections with the emergence of Democratic majorities in the House, Senate as well as among State Governors and State Legislatures; as well as Attorneys General. Specifically, there are now 28 Democratic Governors and 22 Republicans. In the state legislatures, 23 are Democratic controlled, 16 are Republican controlled and 10 are split. PPTA staff also discussed a recent survey of State Medicaid Directors who are the top Medicaid official in each state. The survey found that 18 Directors indicated that Universal Coverage proposals were possible in their respective states and 16 Directors reported their intentions to file State Plan Amendments to their existing Medicaid programs.

Reports were received by several representatives of the consumer organizations. Several consumer representatives shared tactics that are being either considered or implemented to assure patient access to plasma protein therapies. For example, the National Hemophilia Foundation is exploring the feasibility of creating advisory boards in states to include consumers, physicians, and state officials. These boards should serve the needs of the consumers and capitalize on the more serious issues. Several consumer representatives stressed the importance of recruiting volunteer advocates in the states to impact public policy. Other consumer groups are focusing on disease management programs. Another tactic that is very effective in making the case to policy makers for patient access is to provide them with data. One national organization reported on their patient survey and noted that similar data from physicians would soon be available. Recently, one organization was able to generate more than a hundred letters were submitted by patients challenging a policy in Arizona. This is a real life example of grassroots advocacy really working to assure patient access. On issues that impact patient access to lifesaving plasma protein therapies, it definitely takes a village – we must all work together on behalf of patients.

PPTA PLASMA PROTEIN FORUM 2007

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5 -6 JUNE 2007
AT THE HYATT IN RESTON, VA

Agenda

2007 Plasma Protein Forum
Forum June 5-6, 2007
Hyatt Regency Reston, Reston, Virginia

Day 1 / Tuesday, June 5, 2007

7:00 a.m. - 8:00 a.m.	Registration/Continental Breakfast
8:00 a.m. - 8:05 a.m.	Welcome/Opening Remarks
8:05 a.m. - 8:30 a.m.	Chairman's Message
8:30 a.m. - 9:00 a.m.	Keynote Address Overview of Plasma Protein Therapeutics Market: Global Trends
9:00 a.m. - 9:45 a.m.	
9:45 a.m. - 10:15 a.m.	BREAK
10:15 a.m. - 11:30 a.m.	Bleeding Disorders: Fundamentals of Access
11:30 a.m. - 1:00 p.m.	Luncheon Special Presentation: "What is Resilience?" [Sponsored by Talecris Biotherapeutics and Roche Diagnostics]
1:00 p.m. - 2:15 p.m.	Balancing the Perfect with the Practical: IVIG Analytes
2:15 p.m. - 3:30 p.m.	A Day in the Life of a Center Manager
3:30 p.m. - 3:45 p.m.	BREAK
3:45 p.m. - 5:00 p.m.	Alpha-1 Proteinase Inhibitors: Treating Rare Disorders
5:00 p.m. - 7:00 p.m.	Reception - Exhibit Hall Presentation of the Robert W. Reilly Leadership Award The Reception features the presentation of the 2007 Robert W. Reilly Award, which recognizes an individual whose outstanding leadership and positive contributions to the industry have demonstrated unquestionable professional character, ethics and commitment to the advancement of the plasma protein industry.

Day 2 / Wednesday, June 6, 2007

7:00 a.m. - 8:00 a.m.	Registration and Continental Breakfast
8:30 a.m. - 8:35 a.m.	Welcome
8:35 a.m. - 8:45 a.m.	Opening Remarks
8:45 a.m. - 9:30 a.m.	Keynote Speaker
9:30 a.m. - 11:00 a.m.	Immunoglobulin: Lifesaving Plasma Therapy
11:00 a.m. - 11:15 a.m.	BREAK
11:15 a.m. - 12:30 p.m.	Source Plasma Collection: A snapshot of the Future
12:30 p.m. - 2:00 p.m.	NETWORKING LUNCH / Exhibit Hall
2:00 p.m. - 3:15 p.m.	Audit Q and A
3:15 p.m. - 3:30 p.m.	Closing Remarks

Donor profile

It's All About Relationships and People: Forty years of Life Saving Service

When Raymond Guillory and Gordon Buffington were approached in 1967 by Ray St. Peter about the possibility of becoming donors with Blood and Plasma Research of Beaumont, Texas, they had no idea it would be the beginning of a life-long relationship with a new family and fellowship of an elite community of donors. Eager to do their part for the greater good of mankind, they began a journey of helping families and have become two quiet heroes through forty years of loyal and dedicated giving.

Mr. Raymond, a construction lineman from Sulphur, Louisiana, had donated whole blood at the Beaumont Blood Center for the family member of a co-worker and had been identified by the Blood Center as having a red cell antibody, the Anti-D. St. Peter informed him that this antibody in his plasma was needed by Ortho Diagnostics for use in manufacturing a vaccine that would help save newborn babies. Being a family man himself, Raymond very much wanted to help, but was somewhat skeptical of this

procedure known as plasmapheresis, of doing it twice each week, and of receiving red blood cells from someone else to increase the strength of his antibody. He telephoned his doctor to inquire about the safety of the program, and his doctor indicated that the procedures were safe and that this would be a good thing for him to do.

Raymond donated his first unit of plasma in January, 1968 and was the very first donor collected by the newly founded Blood and Plasma Research, Inc. of Beaumont, Texas. Being sent all over the country to work made it difficult for Mr. Raymond to donate twice each week, every week, so the center arranged to collect his plasma on weekends when he was available. Raymond began working for the City of Vinton in 1975 and began driving eighty miles, round trip, to Beaumont twice each week to donate after work. Since he retired from the City in 1994, Raymond's expertise is still very much in demand, for he continues to work for various companies and government agencies, as needed, and has worked especially hard since Hurricane Rita in September, 2005.

Raymond has always been an avid gardener, and the Blood and Plasma staff have benefited heartily from his talent. Squash and cucumbers are common items of his generosity during the summer while turnip and collard greens from his garden grace the staff dining tables in the winter. Spending time with his children, grandchildren and great grandchildren is one of the things he cherishes most, but he still tries to make time for a little hunting and fishing now and then. Raymond celebrated his fiftieth wedding anniversary in 1999, and his wife, Gussie, is as familiar a face to Blood and Plasma Research as he is. At age 74, and with such a busy life, Raymond is still committed to the cause and, when he comes to donate, one can be assured that Miss Gussie will come, too.

When asked why he decided to become a donor, Raymond replied, "to help better humanity". He has reaped benefits however, that he never would have imagined. He got to know the staff and other donors right away, and friendships of a lifetime were born. Raymond and the Blood and Plasma staff have shared many life experiences together including the births of grandchildren and great grandchildren as well as the untimely death of one of the Guillory's sons. In addition to the close friendships made with the Blood and



Donors Raymond Guillory and Gordon Buffington under the portrait of the center founder Ray St. Peter

Plasma owners and staff, one of the many others he has made during his years of service to Blood and Plasma is that with fellow donor, Gordon Buffington.

Although Gordon didn't have the antibody needed for Rh immune globulin, he was informed by St. Peter that he was a good candidate for developing it and that his plasma was needed for manufacturing Rh immune globulin. After being immunized several times and developing the Anti-D, Gordon, too, donated his first unit of plasma to Blood and Plasma Research in January of 1968.

Gordon retired from Texaco in 2000, but continues to be very active. He loves to travel and has a powered parachute which he takes around the country to fly at various events. He also collects and enjoys shopping for antiques. His most recent toy, however, is a red 1939 Chevy street-rod. He raises cattle as a hobby, and he enjoys spending time with his children and grandchildren. Gordon is famous for making the best Cajun gumbo and never fails to share his bounty with the Blood and Plasma staff.

When asked how being a plasma donor has affected or impacted his life, Gordon says he has been enriched by associating with the people there. He says that being with the staff is like being with his grandchildren. Even new donors eventually get the hang of it and fit in, he notes.

Why does Gordon still donate? "Because of the need," he insists. He also feels that donating is good for him; that it helps keep him young and in good physical shape. He says, too, that going into the center is like seeing and being with family several times a week.

Since 1968, Raymond and Gordon have witnessed the many changes which have occurred in the plasma center over the decades, as a result of new diseases and improved technology, and have watched the industry evolve into its current complexity. When asked their feelings about the changes, Gordon and Raymond both say that the changes have been for the better. They have seen improvements good for both donors and staff, and Gordon even expounded on the improved quality of the product! Both of these gentlemen really appreciate the simple things, however, such as the one venipuncture technique performed now, as opposed to the four that were required

for plasmapheresis in 1968, along with the automated pheresis procedure. Their stories wouldn't be complete though, without adding that with the colorful personalities of their Cajun backgrounds (Gordon says by association, only!), the Blood and Plasma donor room never lacks for fun.

With thirty-nine years of donating plasma for Rh immune globulin, Raymond Guillory and Gordon Buffington have silently and anonymously touched the lives of thousands of families world-wide. Their dedication is to help people; they believe that it is an opportunity and a responsibility, with no hourly parameter governing their willingness and generosity. And Raymond and Gordon continue to come and maintain the relationships developed over the decades, unique kinships that will keep them and others donating for years to come.

Fortunately, the world at Blood and Plasma Research revolves around people like Raymond Guillory and Gordon Buffington. The success of Blood and Plasma Research can only be attributed to the dedication and devotion of donors such as Raymond and Gordon, who continue to give of themselves for the sake of others. Sharing the past forty years with them has been a time of growing together, with mutual respect and common goals that bond for life, and it is an honor and a privilege to have and serve friends such as these. They, truly, are family.

We would like to thank Kristi Lovelady from Blood & Plasma Research, Inc., Beaumont, Texas for contributing this inspirational story.

Interview with Thierry Brouwer

The Source spoke with Thierry Brouwer, coordinator of the GBS Foundation for the French-speaking community in Belgium. Thierry is 47 years old and is an IT analyst. He suffered from acute Guillain-Barré Syndrome (GBS) 18 years ago and was hospitalized in intensive care, with a respiratory aid. He was treated by plasmapheresis as immunoglobulins were not yet known in the treatment of GBS in Belgium. Thierry fully recovered from GBS.

Please explain what Guillain-Barré Syndrome (GBS) is:

GBS is a rare, paralyzing auto-immune disease. It is an inflammatory disorder which is characterized by a dysfunction of the immune system whereby the white cells attack the myelin sheath around the peripheral nerves leading to a slowdown of nerve signals.

Patients with GBS feel very weak and when nerves cannot send signals efficiently, muscles begin to lose their ability to respond to the brain's commands, thereby leading to paralysis. It will often start with the extremities of the body, fingers for example but paralysis can become much wider.

The particularity of GBS is that most patients will recover without sequels recurrence but while the prognosis is quite optimistic, symptoms can be overwhelming impressive.

The axonal form of GBS is a more serious type of the disease which manifests itself in a similar way than acute GBS but where chances of recovery are slimmer.

There is also Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), sometimes referred to as 'chronic GBS'. CIDP patients will not experience symptoms as badly as acute GBS patients and weakness appears more slowly. However, despite periods of remission, full recovery is not possible.

What is the role of the GBS Foundation for the French-speaking community of Belgium?

The main role of the Foundation is to bring moral support to patients and their families. The Foundation also puts GBS patients in contact with former GBS patients who have recuperated their capacities (which is the case for 80-90 % of GBS sufferers).

The Foundation also visits and establishes an open dialogue with people with GBS and their close ones. We try to understand their needs, to give them hope but to also not hide the difficulties of treatment. It is very important for us to provide them with all the necessary information so that they can understand the illness.

It is also important for the Foundation to have a relationship established with treaters and the medical community so as we can be well informed about which patients are sick and when.

Once an admitted patient agrees, the treater contacts the Foundation so that we can provide support. The Foundation's website (<http://users.skynet.be/gbs/>) also provides patients with information and is a source of communication.

The Foundation is also a member of the GBS/CIDP Syndrome Foundation International. For more information please visit: <http://www.gbsfi.com/>.

Please give us an idea of the number of people with GBS in Belgium.

It is very difficult to provide a response as the illness manifests in different forms. Some patients are only very mildly affected and do not need any treatment. I would estimate that in the most serious form of the illness Belgium has a half a dozen people with GBS.

What treatment options are available for people with GBS?

The first question we need to address is what do we mean by treatment? We also need to consider how to alleviate the pain and the secondary effects of the disease. After this has been considered, the treatment to halt the disease needs to be established.

In the acute form of the disease, there are three phases: the onset of the first symptoms, the peak of the disease, and lastly the progressive recovery. Two treatment options are available: plasmapheresis and immunoglobulins.

Some patients respond better to one treatment, some to the other. However, it seems that administrating both treatments at the same time does not accelerate the

recovery therefore; one or the other is used. It is difficult to judge which treatment works better for which patient. Especially in the case of the acute form where it is almost impossible to determine which treatment will work better and therefore the treater decides which treatment to administer.

Medical publications also refer to the use of corticosteroids in the treatment of GBS but this has shown to be ineffective.

People with GBS experience serious problems with pain and discomfort and therefore adequate knowledge by medical personnel is very important.



How has life improved for GBS sufferers in the past years?

I believe that the comfort of life for people with GBS has greatly improved as a result of progress in the domain of pain relief treatments. Nurses and treaters have also acquired an increased knowledge of the illness which helps them provide better therapy for patients.

Another aspect of comfort is that the duration of the illness must be reduced. There are two 'schools of thought' on treatment for GBS, either with immunoglobulins or plasmapheresis.

From a logistical view point, immunoglobulins have the advantage of being much easier to administer. Intravenous administration is a very simple procedure. On the other hand, plasmapheresis requires more material; the patient must be displaced and at times a supply of blood is needed. Therefore, some patients find plasmapheresis more cumbersome however; I personally believe that neither treatment is more painful than the other.

What are the principle problems faced by people with GBS?

The main problem is the emotional trauma linked to the uncertainty of what the future holds. Whilst we know that the syndrome can be most probably cured there is the uncertainty of when this will be achieved.



In addition, there is the physical impact of paralysis, the pain, the side effects of the medication which in some cases can cause drowsiness, the possibility that some patients who experience paralysis in their lungs have difficulties communicating because their respiratory system is affected, bedsores and the dependence on medical apparatus.

In some cases diagnosis is not directly made. This can be very dangerous. It is difficult for a General Practitioner (GP) to detect GBS directly as many of the first symptoms are benign and common. Unfortunately, the health of people with GBS declines very quickly after this first visit to their GP and many of them end up directly in hospital. It is very rare for a GP to make an immediate diagnosis except if the patient is in an advanced stage of the disease and is suffering from serious symptoms particular to GBS. The most dangerous outcome is if a patient does not seek medical attention fast enough or is misdiagnosed. In the most serious case, if a patient waits too long to seek treatment, the risk of paralysis and immobility can be fatal. However, this has never happened in Belgium where health-care is well developed. The most efficient way to detect GBS is via a lumbar puncture; however, this is very difficult for a GP to execute.

How do you see the future for GBS patients?

It is important to continue the education of medical staff so they better understand GBS and can provide better support and care for GBS patients. In general, this is not a problem in university hospitals. However, with treatment with immunoglobulins, which is easier to administer, an increasing number of smaller hospitals are providing care for GBS patients but a lot of the personnel have little or no understanding of the condition.

Medical science has made tremendous progress in the past years and needs to continue to do so. We need to acquire a better general understanding of auto-immune diseases and of the human immune system.

Through my contact with patients, I believe the trend shows a decrease of GBS and I hope this will continue. I think this can be attributed to the introduction of new treatments, the increased use of immunoglobulins and the realization that cortico-steroids are not very efficient. Treatment is a very important factor but it is equally important to know when to administer it and in what quantities.

The European Variation Procedures

By Dr. Ilka von Hoegen

The European Regulatory System for Changes to Marketing Authorisations

When the Commission's regulations (EC) No 1084/2003 and (EC) No 1085/2003 came into force in June 2003, the hopes of manufacturers of biological and plasma protein therapies for relief from unnecessary regulatory requirements were disappointed. Instead of simplifying and streamlining the regulatory requirements and reducing the financial burden, the conditions for biological therapies were in many cases even more restrictive than before: in 19 cases changes to the manufacturing process of biologicals are exempted from Type I variation procedures and categorized as Type II, the lengthiest and most complex variation procedure, whereas under the previous regulations (EC) No 541/95 and (EC) No 542/95, respectively, only 6 exemptions were defined. Thus, the variation procedures are creating a regulatory environment in Europe that is increasing the regulatory burden, consuming resources of regulatory authorities as well as industry's on less than critical issues without affecting the safety or efficacy of the medicinal product. Soon after the new regulations came into force, PPTA and other associations representing manufacturers of biological medicinal products urged the European Commission to change the regulatory situation for these therapies to encourage innovation and continual improvement to their manufacturing processes. Due to the rapid development or improvement of biological therapies in accordance to the state-of-the-art there has been a significant increase in the number of variations being submitted under either the centralized or mutual recognition procedure. Consequently, today the costs of variation processes are the most significant line item in the budget of all regulatory departments.

In 2006, the Commission announced their intention to revise the regulations and invited industry to submit their views on how the current system should be improved. In their consultation paper "Better regulation of pharmaceuticals: Towards a simpler, clearer and more flexible framework on variations" the Commission acknowledges

that the framework on variations must strike the right balance between protecting health and supporting innovation. It is equally crucial that the administrative workload entailed by the framework still enables competent authorities to focus on the substantial issues, related to the scientific monitoring of medicines and the protection of public health.

The Commission recognizes that significant simplification could be achieved through harmonization of regulatory requirements for changes to purely national authorization, which represent the vast majority of marketing authorizations in the European Union. However, inclusion of purely national authorizations within the scope of the revised variations legislative framework would require a change in the co-decision legal basis. Since such a process requires the approval of all 27 EU Member States, the Commission wisely decided to follow a two step approach in which the amendments not requiring a change in the legal basis are adopted independently.

In addition to the practical feed-back from industry, Member States competent authorities and the EMEA, the revision was deemed necessary because of the finalisation and adoption of the Q8 (Pharmaceutical Development) and Q9 (Quality Risk Management) guidelines of the International Conference on Harmonisation (ICH). The concepts laid down in these guidelines, also taking into account the ongoing work on the Q10 (Quality Systems) guideline, could not be appropriately implemented into the European regulatory framework without amendment to the variations regulations. The Q8 guideline encourages companies to develop an enhanced scientific understanding of their products and processes to reduce the intensity of oversight for subsequent changes. In addition, the concept of "design space" allows introduction of changes within the pre-approved design space without notification or regulatory approval. The Q9 guideline provides principles and examples of tools for quality risk management, which is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product throughout its lifecycle. Q10 addresses robust quality systems that facilitate implementation of Q8

and Q9, thus enabling the realization of the benefits of the concepts contained within these two guidelines. In the Q8/Q9/Q10 environment, a company should be able to establish the three essential components to facilitate self-management of change: enhanced product and process understanding, demonstrable ability to apply quality risk management tools and, robust quality systems. The recognition of the ICH guidelines is of particular importance in terms of international harmonization in view of the globalization of the pharmaceutical market.

In the new system proposed by the Commission, Type IA variations would not require any prior approval and would be submitted in the annual report (“do and tell”) except for specific administrative changes, for example a change of address of the manufacturer. On the other hand, line extensions Type IB or Type II variations would require prior approval. At present, a change which is neither a line extension, nor a Type IA/IB change is by default a Type II variation. Thereby, any change which may not raise any major health issue not clearly foreseen in the annexes to the current variations regulations is subject, by default, to the lengthiest and most complex variation procedure. In the new proposal, changes, which are not laid down in the annexes would be handled, by default, as Type IB variations (“Tell, wait and do”) unless the concerned competent authorities objects to the classification within the defined time frame.

Most importantly, for biological manufacturers, the Commission is considering reclassification of variations for biological medicinal products from Type II to Type I, either IA or IB, depending on the nature of the change. Such a reclassification from the lengthy and costly Type II variations would significantly reduce the financial and regulatory burden for manufacturers of biological products. Unfortunately, the full list of proposed reclassifications based on the Annexes of the current variations regulation submitted by PPTA in 2004 is only partially taken into account in the Commissions proposal.

Regulation (EC) No 1085/2003 applies not only to variations to the terms of centralized marketing authorizations, but also to variations to the terms of a Plasma Master File (PMF) and of a Vaccine Antigen Master File (VAMF). However, this extrapolation may not appear entirely clear

from a legal point of view, since the term variation is defined as an amendment to the marketing authorization dossier, and not to the PMF/VAMF. The Commission intends to clarify the legal applicability of the variations regulation to the VAMF/PMF and to introduce the requirement for a Type IB variation for the so-called 2nd step, which is the inclusion of a new PMF/VAMF in a given marketing authorization, after the dossier has been approved by the EMEA in a centralized procedure. PPTA strongly believes that the 2nd step procedure for the PMF should be omitted, because by definition all EU Member States have to approve the dossier in the centralized procedure and there is no obvious reason for a second evaluation on national level. This procedure would represent an expansion of the shared assessment concept, which has already been used successfully in other areas.

In 2005, the Commission announced the “Better Regulation” policy initiative, whose primary goal is to ensure – whenever possible – that Community legislation is made clearer, simpler and more flexible. The revision of the variations regulations provides a concrete illustration of this policy in the area of pharmaceuticals. In particular, manufacturers of biological and plasma protein therapies would benefit significantly from the proposed changes with the caveat that in two areas the Commission’s proposal appears halfhearted to go to the full length of possibilities, one being the limited reclassification of variations from Type II to Type IA/IB and the other one to omit the second step procedure in the PMF approval process.

- 1) *Commission Regulations (EC) No 1084/2003 and (EC) No 1085/2003 concerning the examination of variations to the term of a marketing authorization for medicinal products for human use and veterinary medicinal products either granted by a competent authority of a Member State or falling within the Scope of Council regulation (EEC) No 2309/93*
- 2) http://ec.europa.eu/enterprise/regulation/better_regulation/index_en.htm

The Alabama Experience

States continue to attempt to address their budget deficits by focusing on health care expenditures. Rising prescription drug costs continue to account for a large portion of those increases. Although, PPTA recognizes the fiscal dilemma faced by the majority of states, the Association in unison with its stakeholders has long maintained that doing so should not be at the expense of patient access to lifesaving plasma protein therapies (collectively, “plasma-derived and recombinant analogs”). PPTA and its stakeholders are ever vigilant that changes in reimbursement in state Medicaid programs do not diminish access to plasma protein therapies and also maintain access to providers that deliver comprehensive quality care.

A recent example of a State in economic trouble turning to health care expenditures for relief is Alabama. Although Alabama’s latest attempts to control costs could have impacted the bleeding disorders community, it is important that the community responded because such precedents that could negatively impact patient access must be vigorously opposed and, in the best interest of preserving patient access, defeated. It is also important to constantly focus on differentiating plasma protein therapies from traditional pharmaceuticals in all aspects of the continuum

and Human Services (HHS) to provide discounted prices on covered outpatient drugs to a list of “covered entities.” In fact, the 340B program was created to encourage pharmaceutical manufacturers to offer discounts to these covered entities that are outside the Medicaid program and thus not able to obtain Medicaid rebates under a Medicaid Rebate Agreement.

Under this 340B Drug Pricing Program, a manufacturer enters a Pharmaceutical Pricing Agreement with HRSA in which it agrees to charge covered entities no more than the “PHS ceiling price” for its products.

WORKING TOGETHER FOR PATIENT ACCESS

On November 28, 2006 the Pharmacy Director of Alabama Medicaid sent a letter to hemophilia distribution providers announcing a change in the reimbursement methodology for hemophilia factor concentrates. This methodology would have been based upon Public Health Service (PHS) pricing. PPTA and stakeholders contended to the agency that implementing a reimbursement mechanism preventing providers who do not have access to PHS pricing from the 340B drug discount program from servicing Medicaid beneficiaries would not be in the best interest of Alabama Medicaid beneficiaries and not consistent with the purpose and intent of the 340B program.

"It is also important to constantly focus on differentiating plasma protein therapies from traditional pharmaceuticals in all aspects of the continuum of care."

of care. Such as orphan populations served, fragile, rare often chronic diseases; lack of interchangeability among therapies, no generic alternatives; importance of maintaining the sanctity of the physician/patient relationship; the lengthy and cost intensive manufacturing process and robust regulatory environments to name a few.

BACKGROUND

Section 602 of the Veterans Health Care Act of 1992 (“VHCA”) enacted the 340B Drug Pricing Program. That statute requires drug manufacturers, as a condition for federal funds to be available to purchase their products under both Medicaid and Medicare Part B, to enter into an agreement with the Secretary of the Department of Health

Beneficiaries receiving services from Alabama Medicaid and other government health care programs should not be denied timely access to the treatments they need to keep them alive and functioning. Utilizing PHS pricing could cause numerous providers of hemophilia therapies to decide to discontinue providing hemophilia therapies to their patients. Such approaches may result in single source provider situations. PPTA working in conjunction with stakeholders has long maintained the policy that single source provider arrangements adversely affect access to the full range of therapies. Specifically, the single provider may choose to furnish a limited selection of therapies. According to the Medical and Scientific Advisory Council of the National Hemophilia Foundation, access to the full



range of licensed hemophilia therapies is essential for optimal treatment (MASAC Recommendation #168; Regarding Access to Care for Patients with Bleeding Disorders). Delayed access to the appropriate clotting factor for the patients' unique condition can cause painful and crippling injury to a hemophilia patient's joints and organs. Such complications also often lead to increased costs for medical assistance programs for hospital, skilled nursing and other specialty services.

Patients and their physicians make informed decisions regarding the particular therapy they will utilize. Hemophilia therapies are not interchangeable and open access to all products should remain unimpeded. Each therapy has been approved by the federal Food and Drug Administration (FDA) for specific clinical indications. These are branded therapies, with no generic substitutes. Different therapies may require different dosages and regimens, and may be appropriate only for specific populations. Further, the effectiveness of particular therapies may vary with different populations or with specific individuals. Failure to maintain open access to this full range of licensed therapies could result in the adverse health outcomes discussed above.

OUTCOME – ACCESS RESTORED

On January 5, 2007, the Medicaid Agency stated in a letter to interested parties that "in response to the comments we have received regarding this proposed rule, the Agency will not move forward at this time with the proposed hemophilia reimbursement change." This was a victory for the whole community. Additionally, as other states choose to pursue similar reimbursement changes this year, the actions undertaken in Alabama by industry, patients, and providers represent a blueprint for the community.

1) 42 U.S.C. § 1396r-8(a)

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www.bindingsite.co.uk



Meet PPTA Staff



My name is Cathy Izzi. I am PPTA's Director of Member Services. Although PPTA prepares to celebrate its 15-year anniversary (from its beginning as IPPIA), I have been serving the plasma protein industry's trade

association since 1982, and will be celebrating my 25 years of service later this year.

Member Services encompasses a wide range of services to both our members and our staff. Currently in my role, I primarily focus on human resources, office management and training for Association staff. My role also includes assisting with outreach to the Source membership, including production of Source Essentials, e-newsletter. Over the years, Member Services has focused on publications and training for members and plasma collection center staff. The Member Services role is continually changing and evolving in response to Association activities and needs. It is likely one of the most dynamic staff roles in this regard and one that has kept my interest for nearly 25 years.

Tell us about your background?

My educational background is primarily in the arts: music, dance, and graphic arts. I participated in a local dance company in the early 80's, and have enjoyed performing as a jazz vocalist with Izzi Does It since 1999 beside my husband of nearly 24 years. We have a 16-year old son who keeps us busy and who is promising to be a talented guitarist.

Starting out at with ABRA in 1982, there was a staff of three: Robert W. Reilly, James Reilly, and myself. I quickly assumed various functions from administrative assistant to newsletter production to meeting coordination. I then became Manager, Special Projects. This included administration of the IQPP program, publications, and meetings and workshops. As the needs of the Association grew, so did the job function. Additional staff was hired to take on some of these functions as well as additional Association services. I became involved in working with the

Association's Education Committee to continue the development and facilitation of the Center Managers Workshops and other specialized workshops for industry personnel.

As Director, Member Services, I had a greater role in overseeing the Plasma Forum logistics for several years and continued to develop newsletters and writing content for the Association publications. I continued to assist the Director of Communications in these areas until the opportunity for the internal Member Services role became available. In this role, I am often consulted for a variety of logistical and historical information on Association services. I am always flattered that staff continue to seek out my guidance and am always pleased to accommodate their request for the benefit of the Association and its membership.

What is your proudest professional achievement?

At this time, it's that I've been serving in one industry association for 25 years. I have to credit part of my longevity to the incredibly talented, dedicated and good-hearted people whom I've worked with over the years, staff and members alike; and, of course, to the variety of opportunities available within Association management services for the industry. Probably the most challenging and satisfying achievement was working with the Association's Education Committee and developing the Centers Managers Workshops into a credit-based continuing education program. I believe that the program helped to model and add value to programs developed by industry companies for their in-house training. The need for such industry-wide training then shifted to more global communications needs which were implemented through the Association's communications plan by dedicated staff.

What is most rewarding about working in this industry?

I think you will receive very similar answers from most staff – the end all of industry activities and efforts is that companies are producing life-changing and life-saving therapeutics for people in need worldwide. It is truly a people-to-people industry, and being exposed to the passion of our members toward this goal is refreshing.

News

The 110th Congress commenced on January 4th with the new Democrat majority firmly in place. As anticipated there are many health care related initiatives that Speaker of the House Nancy Pelosi (D-CA) has set for the first '100 legislative hours' including the introduction of H.R. 4, Medicare Prescription Drug Price Negotiation Act of 2007, that requires the Secretary of the Department of Health and Human Services ("HHS") to negotiate with pharmaceutical manufacturers the prices that may be charged to prescription drug plan sponsors and Medicare Advantage organizations on the behalf of Medicare beneficiaries.

The new Austrian Minister of Health, under new Austrian SPÖ Federal Chancellor Alfred Gusenbauer, will be Andrea KDOLSKY (ÖVP-Conservatives), 45, MD, now President of the Lower Austrian Hospital Holding which is amongst the biggest Austrian Clinics Holding. Kdolsky has a degree in anaesthesiology and intensive medicine, with additional expertise in hospital management.



The European Commission's Pharmaceutical Committee held its 61st meeting on the 5 December 2006, in Brussels, chaired by Martin Terberger, head of Unit Entr/F/2-Pharmaceuticals. A meeting report has been published and provides a brief summary of the outcome on the different agenda topics. To view the report please visit: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/12_2006/Pharm_541.pdf

The European Pharmacopoeia / European Directorate for the Quality of Medicines (EDQM) of the Council of Europe has become the "EDQM & HealthCare". The Council of Europe has decided to apply the EDQM's expertise in consultation and networking activities at the European and world level to two new areas of great importance: blood transfusion and organ transplantation. The blood transfusion work programme is based on three main principles: no commercial use of products of human origin, voluntary, non-remunerated donations and protecting the health of donors and recipients. Additionally, as from Tuesday 2 January, postal, internet and e-mail addresses for the EDQM & HealthCare will be changed. The telephone and fax details remain the same. For more information please visit: http://www.edqm.eu/site/page_685.php

In Japan, the panel concerning manufacturing systems for plasma therapeutics endorsed this week the interim report from the Working Group on the self sufficiency of albumin and IVIG which has been established under the panel. The report proposes specific measures taken by healthcare professionals and by manufacturers, including contract manufacturing, for the promotion of self sufficiency. The panel agreed that the second round of the Working Group will start in February 2007 and the topics would be: measures for the specific immunoglobulins, contract manufacturing using domestic plasma, export of plasma therapeutics derived from domestic plasma and measures for stabilizing the blood business.

In Japan, the Demand and Supply Committee of Plasma Therapeutics provisionally accepted the 2007 Demand and Supply Plan. The target volumes of recovered plasma, domestically collected for fractionation, will be set at 970,000 liters, which is increased by 40,000 liters

compared to the previous year. The 2007 Demand and Supply Plan will be officially authorized in March 2007. Japan needs 1,6000,000 liters for albumin products.

The European Medicines Agency (EMA) Management Board has adopted the 2007 work program and budget. The work program for next year has been structured to accommodate a number of planned developments, especially the entry into force of new EU legislation on pediatric medicines (expected in early 2007), which will increase the Agency's role in encouraging the availability of safe and effective medicines for pediatric use. The second major development will be the accession to the EU of Romania and Bulgaria, from 1 January 2007. This will bring the number of countries participating in the work of the Agency up to 30. The Management Board also adopted the 2007 budget, totaling €154,538,000 (2006: €138,676,000). For more information please visit: <http://www.emea.eu.int/pdfs/general/manage/mbpr/51738606en.pdf>

In Australia, the Plasma Fractionation Review Report was published, which Australia agreed to assume following the Australia-United States Free Trade Agreement (AUSFTA). The review was designed to identify any issues that may arise if Australia introduced increased competition into the provision of plasma fractionation services for Australia. To view a press release on this issue please click on: [http://www.health.gov.au/internet/ministers/publishing.nsf/Content/COFCD37A22EC8436CA257245000AE646/\\$File/abb161.pdf](http://www.health.gov.au/internet/ministers/publishing.nsf/Content/COFCD37A22EC8436CA257245000AE646/$File/abb161.pdf). To view the published report please click on: <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/plasma-fractionation-review-overview.htm>

The revised version of the Monograph on Human Plasma for Fractionation was adopted by the European Pharmacopoeia Commission at its 126th Session (21-23 November 2006). The monograph will be published in the 6th Edition of the European Pharmacopoeia in June 2007 and implemented on 1 January 2008. Until then, the current monograph requesting freezing at -30°C still applies. The new text requests the freezing of plasma for fractionation to a core temperature of -25°C within 12 hours. Plasma used only for the recovery of stable products can still be frozen at -20°C .

A study from the Medical Research Council, published in the Lancet medical journal, reports on the details of the UK's third case of variant Creutzfeldt-Jakob disease (vCJD) associated with blood transfusion. The case highlights the risk faced by other recipients of vCJD infected blood and suggests that blood transfusion is an effective route of transmission for vCJD.

A fourth case of variant-Creutzfeldt-Jakob disease (vCJD) associated with a blood transfusion was recently diagnosed in the UK. This latest patient has been diagnosed with vCJD about nine years after receiving a blood transfusion from a donor who later went on to develop vCJD. A transfusion from the same blood donor was also associated with one of the previously identified cases. The patient is still alive and is under specialist care. All four cases relate to the transfusion of blood components: no cases have been reported relating to treatment with plasma products. To view the press release from the UK Health Protection Agency please visit: http://www.hpa.org.uk/hpa/news/articles/press_releases/2007/070118_vCJD.htm

The Blood Steering Committee in Japan, accepted on January 17 to discontinue ALT testing for source plasma for fractionation. The member companies and PPTA worked closely together using the good work that had been done in Europe. The committee recommended that ALT testing for blood and blood components should be continued.

Calendar of Events

March 5

PMF Round Table
Vienna, Austria

March 6 - 7

International Plasma Protein Congress
Vienna, Austria

March 27-30

27th International Symposium on Intensive
Care and Emergency Medicine
Brussels, Belgium

April 19-20

Canadian Hematology Meeting
Buenos Aires, Argentina

May 3-6

WFH 10th Musculoskeletal Congress
Stresa, Italy

May 8-12

5th Plasma Product Biotechnology Meeting
Elba, Italy

May 18-20

20th Annual Conference of the European
Haemophilia Consortium, Parma, Italy

June 5-6

Plasma Protein Forum
Reston, U.S.

June 23-27

XVII Regional Congress of the ISBT,
Europe, Madrid, Spain

July 6-12

XXI ISTH Congress
Geneva, Switzerland

September 14-16

40th Biannual Congress of ESPHI
(European Society of Pediatric Hematology
and Immunology)
Athens, Greece

September 28-30

The 3rd World Congress of Alpha1 Patients
Rome, Italy

November 10-13

XVIII Regional Congress of the ISBT, Asia
Hanoi, Vietnam



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**AsahiKASEI
GROUP**

NORTH AMERICA

Asahi Kasei Medical America
Long Island Branch
1600 Stewart Ave., Suite 602
Westbury, NY 11590, USA
Tel: 877-752-6682 (toll free, USA & Canada)
Fax: 516-620-3135
planova_us@om.asahi-kasei.co.jp

EUROPE

Asahi Kasei Planova Europe
Paepsem Business Park
Boulevard Paepsem 22
1070 Brussels, Belgium
Tel: +32-2-526-0501
Fax: +32-2-526-0550
planova_de@om.asahi-kasei.co.jp

ASIA

Asahi Kasei Medical
Planova Division
9-1 Kanda Mitoshicho
Chiyoda-ku, Tokyo 101-8482, Japan
Tel: +81-3-3259-5723
Fax: +81-3-3259-5725
planova_jp@om.asahi-kasei.co.jp



Join colleagues and counterparts

5th Plasma Product Biotechnology Meeting 2007

May 8th–12th
Hermitage/Biodola
Elba, Italy

PPB07 will continue the tradition first established in 1999 of bringing together experts and newcomers to the plasma fractionation industry in a small and informal setting, where everyone has ample opportunity to meet, discuss, and exchange ideas. Combine this with a unique opportunity to visit Kedrion Biopharmaceuticals, Italy's major plasma fractionator, just north of Pisa.

As in previous meetings, the chairperson will develop each main session based on issues prioritized by participants through their contributions. The sessions below will cover key issues on the route from initial recovery to production of approved plasma products.

- Submission of abstracts for oral presentations – January 26th, 2007
- Submission of abstracts for poster presentations – April 8th, 2007
- Watch the website to see the program develop. www.bo-conf.com/ppb07

Keynote lecture	
Therapeutic Plasma Proteins: If You Were Not in the Business Already Would You Enter It?	Alberto Martinez, CEO, Talecris Biotherapeutics, USA
Focus lecture	
Application of Process Analytical Technologies	Andrew Chang, Senior Director, PharmaNet Consulting, USA
Session	Chairing
Manufacturing	Johan Vandersande/Po-Shing Wah, Baxter Bioscience, USA
New Approaches to Quality	Tim Hayes, American Red Cross, USA
Pathogen Safety Issues	Bernard Horowitz, Bernard Horowitz Consulting, USA
Clinical Studies	Darryl Maher, CSL Limited, Australia
Recombinant Plasma Proteins	Joseph Bertolini, CSL Limited, Australia
Innovations in Plasma	Claudia Nardini, Kedrion SpA, Italy