



BY ALBRECHT GRÖNER,
HERBERT DICHELMÜLLER
AND ILKA VON HOEGEN

PATHOGEN SAFETY

EXPERIENCES WITH KNOWN AND UNKNOWN PATHOGENS

GLOBALIZATION IS NOT LIMITED TO THE FLOW OF INFORMATION, GOODS, CAPITAL AND PEOPLE

across political and geographic boundaries, but also includes the distribution of pathogens into new geographic areas and populations. Today, plasma protein therapies have an excellent safety record with no proven pathogen transmission for multiple decades. This is extremely important for recipients of plasma protein therapies, who often depend on these medicinal products during the course of their entire lives. This article gives an insight into the experience of manufacturers of plasma protein therapies with pathogens of different origin.

How Manufacturers of Plasma Protein Therapies Ensure the Safety of the Products

The examples for emerging viruses given above have to be considered on a case by case basis. In the case of WNV and B19V, there was an abundance of experience with the viruses themselves or relevant model viruses belonging to the same family. The available data provided a well-founded level of assurance pertaining to the efficiency of virus reduction/inactivation procedures in the manufacturing process of plasma protein therapies. PPTA member companies performed extensive studies on the inactivation of WNV demonstrating that WNV behaves ex-

actly as expected for a flavivirus. Based on these compiled data on WNV and other flaviviruses, it could be demonstrated that WNV does not impair the safety of plasma protein therapies. Regulators came to the same conclusion.

SARS initially caused world-wide concern because of the unknown nature of the pathogen. Shortly after the outbreak of SARS the causative agent was identified as a coronavirus. Coronaviruses are enveloped viruses which are believed to cause a significant percentage of all respiratory infections, e.g. common colds in human adults. Available data demonstrate that coronaviruses are efficiently inactivated through established

manufacturing processes for plasma-derived proteins, reassuring patients, physicians and regulatory authorities on the safety of plasma protein therapies. In the case of SARS, PPTA member companies performed individual studies to demonstrate the efficiency of their virus inactivation/removal steps.

The examples described provide reassurance that model viruses allow a fairly accurate prediction how pathogenic viruses of the same family behave with regard to virus inactivation through established inactivation methods.

Enveloped viruses are more susceptible to inactivation pro-



cesses than non-enveloped viruses. There are a number of established and efficient methods to remove or inactivate non-enveloped viruses, such as nanofiltration, chromatographic methods, the cold ethanol fractionation process or pasteurization and dry heat.

In 2000, PPTA introduced a voluntary standard for Parvovirus B19 as an additional safeguard. The standard can be found on PPTA's website www.pptaglobal.org.

Spongiform encephalopathies, such as vCJD, are caused by abnormal prion proteins and follow a completely different paradigm than diseases caused by viruses or bacteria which contain genetic

PPTA Member Companies and Regulators Remain Vigilant Against Known and Unknown Pathogens

A Known Pathogen

Specific climate conditions can facilitate the spread of a virus, for example in the case of West Nile Virus (WNV) that caused an unprecedented epidemic in the U.S., starting in 1999 in the New York City area. WNV was known in Africa, the Middle East and Southern Europe. WNV mainly infects birds, but is known to infect humans in certain circumstances, and other species. The main route of human infection is through the bite of an infected mosquito.

Increase of understanding of a known pathogen

Parvoviruses are non-enveloped viruses; human parvovirus B19 (B19V) was first isolated in 1975. B19V is normally spread via the respiratory route and is considered a childhood disease ("fifth disease") but can under certain circumstances cause clinically significant diseases (Erythema infectiosum, hepatitis, myocarditis, arthritis). In humans, a number of new parvoviruses besides B19V have recently been identified, e.g. PARV4, which has been isolated from patients with Acute Viral Infection Syndrome,

or Bocavirus, which has been isolated by screening of respiratory tract samples. The pathogenicity and clinical relevance of these two parvoviruses is at the moment unclear. Therefore, PPTA member companies and regulators remain vigilant.

An Unknown Pathogen

Unknown viruses are (previously undiscovered) zoonotic viruses, or any infectious disease that can be transmitted from non-human animals to humans or from humans to non-human animals, entering the human population. For example when the first cases of Severe Acute Respiratory Syndrome (SARS) were recognized the cause of the disease was unknown. Soon the causative agent was identified as SARS coronavirus (SARS-CoV) This virus caused nearly a pandemic between the months of November 2002 and July 2003, with a case-fatality rate of 9.6% worldwide (World Health Organization Reference). SARS represents a true emerging infection. Other members of the family of Coronaviruses have been known for a long time and are easily inactivated by established methods.

An Unknown Form of a Known Pathogen

Creutzfeldt Jakob Disease (CJD) was first described in the early 20th century and occurs roughly in one per million humans per year. Variant Creutzfeldt Jakob Disease (vCJD) is caused by abnormally folded prion proteins. Infection occurred initially by consumption of bovine spongiform encephalopathy (BSE) infected beef. Today, there are four known transmissions through blood transfusions. In 2009, a patient was described who died of causes unrelated to vCJD. A post-mortem biopsy found abnormal prion protein in his spleen. As of today, no conclusion has been established about the route of transmission in this case. Transmission of abnormal prion proteins from human-to-human has been described for related forms of the disease, but vCJD represents an example of an interspecies transmission of abnormal prion proteins through oral intake of contaminated beef.

“Based on these compiled data on WNV, it could be demonstrated that WNV does not impair the safety of plasma protein therapies as concluded also by regulators.”

information. In this case the disease is caused by the abnormal prion protein, which is able to replicate but contains no genetic information. PPTA members conducted many investigations including a collaborative study to demonstrate the prion inactivation by sodium hydroxide (NaOH) for sanitization of production equipment (Bauman et al., 2006). The aim of this study was to ensure patients and regulators on the efficacy of common cleaning and sanitization procedures. Other studies demonstrated that the manufacturing process has the capacity to remove prions (if they would be present) from the plasma. An overview of publications is listed in the Committee for Proprietary Medicinal Products (CPMP) Guideline on the investigation of manufacturing processes for plasma-derived medicinal products with regard to vCJD risk (CPMP/BWP/CPMP/5136/03)

Other PPTA initiatives to reassure patients and other stakeholders were workshops on specific pathogen related topics. For example, PPTA held specific events on selected topics in 2002, 2005, 2008, and 2009 in conjunction with the annual International Plasma Protein Congress. The aim of these events was to ensure a continuous and transparent communication and information exchange among all interested parties.

How Can the Industry be Best Positioned to Respond to Emerging Pathogens?

The infrastructure for dealing efficiently with a spreading epidemic ideally needs to be in place before the arrival of the virus. The U.S. experience has shown that it is difficult enough for one country under the same regulatory jurisdiction to implement the different measures necessary to deal with the epidemiology. Just imagine what it needs to achieve this on a global basis. Different countries have different regulatory frameworks, different communication practices and a different perception of risk. PPTA member companies must comply with these different requirements worldwide. It is generally accepted that plasma is global and plasma protein therapies are unique medicinal products provided to patients worldwide. Consequently, a har-

monized global approach would be needed to react timely and efficiently to new emerging pathogens.

In 2004, PPTA launched the Emerging Infectious Diseases (EID) Roundtable. The EID Roundtable included policymakers from regulatory and standard setting organizations, representatives of patient groups, international experts in print media, bioethics and risk management, and scientists, with the goal to begin a dialogue to improve global communications related to decision making in the face of EID threats. In the second Roundtable in 2005 it was reaffirmed that only a harmonized approach can avoid negative impact on availability of plasma protein therapies. Education of patients and physicians about the difference in risk between components for transfusion and fractionated, virus inactivated plasma protein therapies is key to sensible decision making and risk mitigation.

PPTA's dedicated group of scientists from all member companies, the Pathogen Safety Steering Committee (PSSC) diligently survey the literature and other publicly available data in order to post safeguards against the potential risk of transmitting emerging pathogens. In general, bacteria, fungi, and parasites transmissible by blood are not considered relevant for plasma-derived products as these pathogens can be removed by sterile filtration which is a prerequisite for all plasma protein therapies. Other pathogens as viruses and prions are evaluated constantly and thoroughly for potential epidemiology in the donor population (including donor deferral measures), for a potential virus load in the plasma of an apparently healthy donor and for virus reduction capacity of the manufacturing processes, employing relevant viruses and relevant model viruses in order to perform a risk assessment regarding the safety of plasma protein therapies.

REFERENCES

Bauman PA, Lawrence LA, Biesert L, Dichtelmüller H, Fabbrizzi F, Gajardo R, Gröner A, Jorquera JI, Kempf C, Kreil TR, von Hoegen I, Pifat DY, Petteway SR, Cai K. *Critical factors influencing prion inactivation by sodium hydroxide. Vox Sang.* 2006;91:34-40

“Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003”. WHO. http://www.who.int/csr/sars/country/table2004_04_21/en/index.html. Retrieved 2008-10-31



ALBRECHT GRÖNER and HERBERT DICHELMÜLLER are members of PPTA's PSSC. ILKA VON HOEGEN is PPTA's Senior Director, Quality and Safety