Plasma Protein Therapeutics Association

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DENGUE VIRUS AND PLASMA PROTEIN THERAPIES

The U.S. Centers for Disease Control (CDC) is warning Floridians, especially Key West residents, of a viral disease, Dengue fever, that is being spread by a mosquito species.

PPTA members are committed to providing safe and effective therapies. PPTA understands that people who rely on plasma protein therapies may have concerns about the possible transmission of Dengue virus through these therapies. PPTA considered available information on this virus and the available data clearly indicate that plasma protein therapies as manufactured by PPTA member companies provide high margins of safety against Dengue transmission.

Dengue fever is caused by Dengue virus (DENV), transmitted by mosquitoes, typically *Aedes aegypti*. DENV is an ssRNA positive-strand enveloped virus of the family *Flaviviridae*; genus Flavivirus. This genus includes the West Nile virus, Dengue virus, Tick-borne Encephalitis virus, Yellow Fever virus, and other viruses, most of them transmitted by ticks or mosquitoes. As a group, the Flaviviruses share a common size (40-65 nm), symmetry (enveloped, icosahedral nucleocapsid), nucleic acid (positive-sense, single stranded RNA approximately 10,000-11,000 bases), and appearance in the electron microscope. Dengue fever was first recognized in the 1780s.

DENV is contracted from the bite of e.g. the striped mosquito *Aedes aegypti* that has previously bitten an infected person (DENV replicates also in the mosquito, esp. in its salivary glands). The mosquito flourishes during rainy seasons but can breed in water-filled flower pots, plastic bags, and cans year-round. The virus is not contagious and cannot be spread directly from person to person. There must be a person-to-mosquito-to-another-person pathway.

Dengue is endemic in many countries in Asia, the Pacific, the Americas, Africa and the Caribbean. Regarding the United States until now there are sporadic cases and most of them were acquired elsewhere by travelers or immigrants (imported cases).

A Dengue virus infection can be asymptomatic or can result after a short incubation period of 3 to 10 days in mild to serious disease. While Dengue virus can replicate to high titers in the blood of infected persons, these high titers were predominantly measured in patients with severe illness. Thus, a seemingly healthy but asymptomatically infected plasma donor would be expected to carry at most a rather limited DENV load.

Over the years, PPTA member companies have generated an enormous amount of data regarding the inactivation of enveloped viruses, such as West Nile and Dengue viruses or BVDV of the Flaviviridae family generally used as a model virus. Since the early 2000s the US faced a significant West Nile virus (WNV) epidemic. In response to this

Boulevard Brand Whitlock, 114/5 · 1200 Brussels BELGIUM · tel : +32.2.705.58.11 · fax : +32.2.705.58.20
VAT: BE453 837 462 · e-mail: pptaeu@pptaglobal.be · www.pptaglobal.org
PPTA Offices in Brussels · Washington · Annapolis · Tokyo

development, PPTA member companies investigated the inactivation capacity of their manufacturing processes and found them to be effective against WNV and other related model viruses, supporting the validity of the model virus concept[1]. Given the taxonomical and physicochemical similarities of Dengue virus to other Flaviviruses used as model viruses in virus validation studies the data collected in those studies support the assertion that the clearance level for Dengue Virus is comparable. In 2009, PPTA published a collection of data on the inactivation of enveloped viruses by solvent detergent (S/D) treatment. This data collectively demonstrated the high robustness, reliability, and efficacy of this virus inactivation method[2,3]. Additional investigations also demonstrate that enveloped viruses are efficiently inactivated by commonly used inactivation methods [4,5].

It is important to note that since the introduction of effective virus inactivation and/or removal procedures, to the manufacturing process there have been no transmissions of known flaviviruses by plasma protein therapies. PPTA member companies remain vigilant in their efforts to ensure the safety of plasma protein therapies and will continue to monitor epidemiological developments in the USA and other countries where PPTA members source plasma to ensure that the industry responds to any potential threat if necessary.

References:

1 Kreil et al. West Nile virus and the safety of plasma derivatives: verification of high safety margins, and the validity of predictions based on model virus data. Transfusion. 2003;43:1023-1028.

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3 Dichtelmüller et al. Inactivation of lipid enveloped viruses by octanoic acid treatment of immunoglobulin solution. Biologicals 2002;30:135-142

4 Korneyeva et al. Enveloped virus inactivation by caprylate. A robust alternative to solvent-detergent treatment in plasma derived intermediates. Biologicals 2002;30: 153-162.

5 Stucki et al. Investigations of prion and virus safety of a new liquid IVIG product. Biologicals 2008;36:239-247