

IPFA Position Paper on

ZIKA virus and the safety of plasma-derived medicinal products

Zika virus is a mosquito-borne *flavivirus* that was first identified in Uganda in 1947¹. Two epidemics were reported in the Yap Isles in 2007 and in French Polynesia in 2013-2014. In April 2015, locally-acquired cases of Zika virus infection have been reported in Brazil and in December, the Brazilian Ministry of Health estimated that 440,000–1,300,000 suspected cases of Zika virus infection had occurred in Brazil in 2015². The virus also reached Colombia and other countries in South and Central America including the Caribbean in late 2015. To date 26 countries and territories in the Americas* have confirmed autochthonous circulation of Zika virus with an estimated 1.5 million cases of infection³.

IPFA has always regarded the safety of patients as a priority and continue to be vigilant regarding emerging new threats. A review of available information on this virus and of manufacturing processes of plasma products manufactured by IPFA members supports the view that Zika virus does not represent a risk of transmission through the use of plasma products.

Zika virus infection

Zika virus (ZIKV) is a member of the *Flaviviridae* family, genus *flavivirus*. *Flaviviridae* are spherical, enveloped, RNA viruses, 40-60 nm in size. This family also includes Hepatitis C virus (HCV- genus *hepacivirus*), West Nile virus, Dengue Virus, Yellow fever virus (YFV) and Japanese encephalitis virus as other members of the *flavivirus* genus.

Like most *flaviviruses*, Zika virus is transmitted by mosquitoes, primarily *Aedes aegypti*. *Aedes albopictus* mosquitoes (also called Tiger mosquito) also might transmit the virus. Both mosquitoes are found throughout much of the Americas (including parts of the United States) and also transmit Dengue and Chikungunya viruses. In addition to mosquito-to-human transmission, Zika virus infections have been documented through intra-uterine transmission resulting in congenital infection, intrapartum transmission, sexual transmission, blood transfusion[†], and laboratory exposure⁴.

An estimated 80% of persons who are infected with Zika virus are asymptomatic^{5,6}. The most common symptoms of Zika virus disease are fever, rash, joint pain, and conjunctivitis (red eyes) that are easily confused with other diseases like Dengue and Chikungunya. Incubation lasts from 3 to 12 days. The illness is usually mild with symptoms lasting from several days to a week. Severe disease requiring hospitalization is uncommon. Neurological complications linked to Zika virus infection, like Guillain-Barre syndrome, have been reported in Brazil and French Polynesia. A possible link between Zika virus infection in pregnant women and microcephaly of the foetus has been under investigation in Brazil since October 2015 when the Brazilian Ministry of Health reported an unusual increase in cases of microcephaly following the Zika outbreak⁷.

* Barbados, Bolivia, Brazil, Colombia, Costa Rica, Curaçao, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Nicaragua, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, US Virgin Islands, Venezuela

† 2 confirmed transfusion cases recently reported in Brazil

Zika virus is considered an emerging infectious disease with the potential to spread to new areas where the *Aedes* mosquito vector is present. As of 12 February 2016, no autochthonous cases of Zika virus infection have been reported in EU Member States[‡]. However, imported cases of recent travelers in affected countries/territories were reported in several EU countries[‡].

Safety of plasma-derived medicinal products

All plasma-derived products manufacturing processes include validated and effective inactivation/removal steps that cover enveloped viruses such as *Flaviviridae*. Virus validation data, using Bovine Viral Diarrhea Virus (BVDV), a recommended model for HCV, or YFV and existing data concerning the inactivation/removal of viruses of the same family, such as the West Nile virus or Dengue virus, confirm the effectiveness of *virus inactivation* treatments towards enveloped viruses, namely Solvent–Detergent treatment, pasteurization[§], low pH treatment and Dry-Heat treatment^{**}, as well as *removal* of these viruses through nanofiltration (filters of 15-20 nm or 35 nm pore sizes). Moreover, existing data confirm that a number of purification steps in manufacturing processes also contribute to virus reduction. Plasma products manufacturing processes include 2 (sometimes 3) effective reduction steps for enveloped viruses such as Zika Virus. Since the implementation of these inactivation/removal steps in the manufacturing processes of plasma products, there has not been one report of a transmission of an enveloped virus (including viruses of the *Flaviviridae* family), supporting the conclusion that Zika virus will be inactivated by these measures as well and that no additional measures are required upon collection of plasma specifically destined to the manufacture of plasma products.

Altogether, it can be concluded that Zika virus does not represent a risk of transmission through the use of plasma-derived medicinal products.

References:

¹ Dick GW, Kitchen SF, Haddock AJ. Zika virus. I. Isolations and serological specificity. *Trans R Soc Trop Med Hyg* 1952;46: 509-20.

² European Centre for Disease Prevention and Control (ECDC); 2015. <http://ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-zika-virus-first-update-jan-2016.pdf>

³ World Health Organization – Zika situation report (12 February 2016) <http://www.who.int/emergencies/zika-virus/situation-report/who-zika-situation-report-12-02-2016.pdf>

⁴ ECDC: Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome. <http://ecdc.europa.eu/en/publications/Publications/zika-virus-americas-association-with-microcephaly-rapid-risk-assessment.pdf>

⁵ CDC. Zika virus: 2016. <http://www.cdc.gov/zika/index.html>.

⁶ Duffy MR, Chen TH, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009;360:2536–43.

⁷ Ministério da Saúde (Brazil). Ministério da Saúde investiga aumento de casos de microcefalia em Pernambuco

[‡] Austria, Denmark, Finland, France, Germany, Ireland, Italy, Malta, Netherlands, Portugal, Slovenia, Spain, Sweden and the UK

[§] heating of the solution at 60°C for 10 hours

^{**} heating of lyophilized product at 80°C for 72 hours

[Internet]. 2015 [cited 2016 Feb 08]. Available from:
<http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20629-ministerio-da-saude-investigacao-aumento-de-casos-de-microcefalia-em-pernambuco>

⁸ ECDC : http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/epidemiological-situation.aspx#sthash.mPwTYrjd.dpuf