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IPFA Position Paper

on the Safety of Plasma-Derived Medicinal Products

with respect to Hepatitis E Virus risk

Medicinal plasma-derived products (PDMP) have today an unprecedented level of safety with respect to the risk of transmission of pathogenic agents. The manufacturing processes of plasma products include very efficient and robust virus *inactivation* steps, such as Solvent Detergent treatment or pasteurization, against enveloped-viruses that include HIV, HCV and HBV. Moreover these processes include today additional virus *reduction* steps for mitigating the risk associated with the transmission of non-enveloped viruses which are also efficient against enveloped viruses. Combined with NAT testing of blood/plasma donations, these measures confer medicinal plasma-derived products very high safety margins with respect to the risk of transmission of these highly pathogenic viruses and are considered effective for all marketed products (EMA/CHMP/BWP/360642/2010 rev 1).

With regard to the risk of transmission of non-enveloped viruses such as HAV and Parvovirus B19, tremendous effort has been invested by the plasma product industry for improving the safety of plasma products with respect to this remaining risk of transmission as these viruses could potentially escape certain virus *inactivation* steps. In this context, as B19 infection is relatively frequent in donor populations and can lead to very high viremia, implementation of NAT testing dramatically reduced the potential B19 load in plasma pools for manufacture. In parallel, thanks to intense research and development efforts, additional virus *reduction* steps have been introduced which are efficient against non-enveloped viruses such as filtration on small pore size retentive filters whose efficacy is highly predictable according to the size of the agent. Today most of the plasma products include efficient virus *reduction* steps and there has been no report of virus transmission, including HAV and B19, by modern PDMP since the implementation of these measures.

Recently, concern was raised about the risk of transmission of HEV by PDMP following the description of cases of HEV transmission in recipients of blood components and of virally-inactivated plasma. Due to the development of assays for the detection of this virus, its prevalence and circulation in the general population and in blood/plasma donors have been confirmed in industrialized countries. HEV is not an emerging virus: as a zoonosis, the main source of infection is through contaminated food or water. HEV infection is most of the time unapparent. However, HEV is a causative agent of acute hepatitis and it can lead to severe complications in certain populations such as immunocompromised patients or patients with pre-existing liver disease. HEV infection in developing countries can also lead to fulminant hepatitis in pregnant women. Despite the historical circulation of HEV, there is no report of its transmission to date associated with the use of a plasma-derived medicinal product and pharmacovigilance data as well as risk analysis of PDMP support the view that they are safe with respect to this risk.

Risk analysis of PDMP towards a new risk requires that possible exposure to the risk through the use of PDMP on one hand and risk reduction through existing measures on the other hand be reviewed in light of up-to-date knowledge. When data is missing, efforts should be devoted to

generate new information. Regarding exposure, a number of studies in various countries show that the presence of HEV (RNA) in blood (plasma) donations is not an infrequent event. Due to the exposure to HEV in a significant part of the donor populations, plasma pools also contain HEV antibodies which may contribute to the safety of plasma products by neutralization. HEV viremia is usually low to moderate, several orders of magnitude lower than B19 viremia, which limits the potential benefit of NAT-testing pools of plasma for HEV in comparison to the efficacy of virus reduction steps in manufacturing processes of PDMP.

Risk reduction of HEV relies on the efficacy of manufacturing processes in inactivating or eliminating non-enveloped viruses taking into consideration the specific features of HEV such as sensitivity to physical treatments or size of the virus. In addition to present knowledge regarding non-enveloped virus reduction in manufacturing processes, experimental models have been developed for the evaluation of PDMP manufacturing processes and data are becoming available which document the efficacy of certain virus reduction steps. Viruses such as HAV and CPV/PPV have many similar properties to HEV, which for certain steps makes them suitable models of HEV. Available data allow assessing risk according to the principles described in the Guideline for medicinal plasma derived products EMA/CHMP/BWP/706271/2010. However a major limitation of the risk assessment model is that genome copy numbers of the virus are used for estimating the exposure and the reduction of infectivity through manufacturing processes. This likely overestimates the residual risk, if any, probably by several orders of magnitude. In this context, available data regarding HEV infectivity in relation to viral load provide clues to the true safety margins of PDMP.

IPFA considers that taken together, available information and risk assessment for PDMP, according to the current state of knowledge, support the safety of patients receiving PDMPs regarding the HEV transmission risk and that implementation of additional regulatory measures such as pool NAT testing or product specific validation studies will not partake to improving safety for patients.

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