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- 3 Biologics Working Party (BWP)

Concept paper on viral safety of plasma-derived medicinal products with respect to hepatitis E virus

Agreed by Biologics Working Party	March 2014
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Keywords virus safety, hepatitis E, plasma-derived medicinal products, blood products

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1. Introduction

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- 12 Hepatitis E virus (HEV) is a causative agent of hepatitis in many countries and of emerging concern in
- 13 industrialized countries. HEV is a non-enveloped, single-stranded, positive-sense RNA virus and a
- member of the family Hepeviridae. In developing countries, HEV (genotypes 1 and 2) is a major cause
- 15 of acute hepatitis, transmitted by the fecal-oral route and associated with contamination of drinking
- 16 water. In industrialized countries, HEV (genotypes 3 and 4) has been found to be more prevalent in the
- 17 human population than originally believed. HEV genotypes 3 and 4 infect not only humans but also
- 18 animals such as swine, wild boar, and deer. Zoonotic transmission of HEV genotypes 3 and 4 to
- 19 humans can occur by consumption of contaminated meat or meat products or by contact with infected
- 20 animals. These genotypes are generally less pathogenic than genotypes 1 and 2, although some
- 21 exceptions have been reported. Chronic infection with HEV genotype 3 is an emerging concern among
- 22 transplant recipients and may also occur in persons with HIV and certain hematologic disorders.

2. Problem statement

- 24 HEV infection is widespread and blood/plasma donors are often asymptomatic. Therefore, there is a
- 25 risk for viraemic blood donations. HEV has been recognized as a transfusion transmissible agent since
- 26 2004 and transfusion-related cases have been documented in several countries (United Kingdom,
- 27 France, Japan, Saudi Arabia, People's Republic of China). Recent analysis of blood and plasma
- 28 donations has identified HEV-infected donors in Germany, Sweden, and United Kingdom. In these
- 29 studies, frequency of viraemic donations ranged between 1:4000 and 1:7000. The duration of viraemia
- 30 is usually between 4 to 6 weeks, and the viral concentration can reach 7 log10 RNA per ml.
- 31 Consequently, HEV-RNA has been detected in plasma pools used for production of medicinal products.

3. Discussion (on the problem statement)

- 33 The published reports on frequency of viraemic blood donations and studies on plasma pools indicate
- 34 that plasma pools used as starting material for manufacture of medicinal products can be
- 35 contaminated with HEV. In addition there have been cases with post donation information, indicating
- that HEV-affected donations have entered plasma pools for fractionation.
- 37 This raises questions about the safety of the plasma-derived medicinal products. The Ph. Eur.
- 38 monograph for human plasma pooled and treated for virus inactivation (1646) is under revision to
- 39 include a test for HEV RNA (implementation date 1 January 2015). A WHO International Standard for
- 40 HEV for use in the standardisation of HEV NAT assays has been established. Manufacture of other
- 41 plasma-derived products includes process steps for inactivation/removal of non-enveloped viruses.
- However, their effectiveness against HEV is currently unclear. HEV is difficult to cultivate and current
- information about susceptibility of HEV to virus inactivation/removal steps used in the manufacture of
- 44 plasma-derived medicinal products is scarce.

4. Recommendation

- 46 Further information is needed on the safety of plasma-derived medicinal products with respect to HEV.
- 47 Therefore, an expert workshop will be organised in 2014 to address the relevant issues. The following
- 48 points should be addressed.
- Transfusion-associated infections and clinical experience with HEV-infections.
- Latest information on the epidemiology of HEV infection with focus on blood and plasma donors.

- Duration of viraemia and virus loads of blood and plasma donations.
- Potential testing methods for screening of donors and testing of plasma pools (NAT, reference materials).
- HEV-specific antibodies and neutralisation.
- Latest information about the development of cell culture systems for HEV and their feasibility for validation of virus inactivation/removal.
- Latest experience from studies on inactivation/removal of HEV.
- Relevance of model viruses for evaluation of virus inactivation/removal of HEV.
- Safety of solvent-detergent treated plasma.
- Risk assessment for plasma-derived medical products and implication for warning statements.
- Perspective from patients.
- 62 This workshop will provide the basis for deciding what further action may be needed, including the
- 63 possible update of current guidance on plasma-derived medicinal products and/or development of a
- 64 reflection paper specifically on viral safety of plasma-derived medicinal products with respect to
- 65 hepatitis E virus.

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5. Proposed timetable

The workshop is intended to take place on 28-29 October 2014.

6. Impact assessment (anticipated)

- 69 Viral safety of plasma-derived medicinal products needs to be kept under review as viruses are
- 70 identified that can be present in the plasma starting material. Initiating action with a workshop will
- 71 provide an effective means of bringing together and discussing the currently available information on
- this topic. This will then allow further actions to be identified.

73 7. Interested parties

- 74 Blood products working party (BPWP).
- Patient organisations (e.g. haemophilia patients (EHC, WFH), patients with primary immunodeficiencies
- 76 (EPPIC, IPOPI)).
- 77 Industry organisations (IPFA, PPTA) and manufacturers of plasma-derived medicinal products.
- 78 The workshop may also be of interest to ECDC and blood competent authorities.

8. References to literature, guidelines, etc.

- 80 Guideline on plasma-derived medicinal products, EMA/CHMP/BWP/706271/2010
- 81 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_quideline/2011/07/WC50010962
- 82 <u>7.pdf</u>

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- 84 Guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and
- package leaflets for plasma-derived medicinal products. EMA/CHMP/BWP/360642/2010 rev. 1
- 86 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/12/WC50011900
- 87 <u>1.pdf</u>