EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CHMP/BWP/744742/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Reflection paper on viral safety of plasma-derived medicinal products with respect to *Hepatitis E* virus' (EMA/CHMP/BWP/723009/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Thomas R. Kreil, Baxalta
2	European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) - Hepatology Committee: Björn Fischler, Stockholm and Dominique Debray, Paris, on behalf of the group. Other members of the committee: Ulrich Baumann, Hannover (chair), Antal Dezsofi, Budapest, Nedim Hadzic, London, Loreto Hierro, Madrid, Joerg Jahnel, Graz, Valerie McLin, Geneva (secretary), Valerio Nobili, Rome, Francoise Smets, Brussels, Henkjan Verkade, Groningen
3	International Plasma Fractionation Association (IPFA)

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1. General comments - overview

Stakeholder no.	General comment	Outcome (if applicable)
1	This reflection paper refers partially to data generated by the Baxalta Global Pathogen Safety group. We would like to request citation of the manuscript which reports these findings in great detail, which has been accepted for publication in 'Transfusion'.	Accepted. Citation of scientific publication has been added.
1	Suggestions for formatting are made	See individual points below.
2	Thank you for giving us the opportunity to respond to this well written and detailed report. We agree on the complexity of the issue. Our group concluded though that universal screening for hepatitis E plasma-derived medicinal products is in the best interest of our patients and should become obligatory. Hepatitis E is well documented be a significant cause of acute and chronic disease in the at risk population. It seems evident that HEV RNA is detected in a certain proportion of plasma donations. Also, of all the described methods for virus elimination, only filtration seems reasonably efficient. Thus, we would argue that compulsory HEV RNA testing should in fact be added, if the intention is primarily to avoid harming the patient. The data presented in the already quoted paper by Hewitt PE *et al.* (Lancet 2014) as well as the content of the editorial by Pawlotsky JM in the same issue are important for our decision. The alternative of screening	The clinical risk of HEV infections and the data from Hewitt *et al*. (Lancet 2014) have been considered in the reflection paper. The latter study and the Editorial from Pawlotsky in the same issue considered transmission cases from transfused blood components such as red blood cells, platelet concentrates or plasma and underline a transmission risk from these products. However, transmission of HEV via these non -virus-inactivated blood components is not in the scope of reflection paper. This reflection paper considers only medicinal products derived from pooled plasma. It is important to underline that requirements for inactivation and/or removal of viruses have been set out for these products. It is agreed that defining specific risk populations for HEV infections remains difficult considering that the scientific knowledge on the clinical picture of HEV infection is still evolving and under discussion. The paediatric aspects (points 1-4) raised in these comments have been considered in the specific list of points below.

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	only products meant for immune-compromised patients could at least theoretically be considered with regard to cost-effectiveness and sufficient availability of blood donors. However, our group agreed on the aim to fully eliminate HEV from blood products, to eliminate known and controllable risk factors to the vulnerable population of children in need for blood products. See also our comment below, concerning line 490. In addition, some specifically paediatric aspects of the infection are lacking: 1. The risk of vertical transmission and subsequent severe infection in foetuses and neonates. 2. The greater risk of HEV induced severe liver disease in infants 3. The risk of person to person transmission among household contacts and in nurseries. 4. Data on incidence, treatment and outcome of HEV chronic infection in organ and stem cell transplanted children.	
3	IPFA appreciates the publication of the discussions of the expert meeting on the viral safety of plasma-derived medicinal products with respect to hepatitis E virus. This draft document generally reflects the discussions held at EMA in 28-29 October 2014. However, IPFA would like to propose some	See specific points below.

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	amendments, as you would find below, reflecting in a more precise way the details of the technical discussion, as well as stating again the lack of specific case report of HEV transmission via fractionated medicinal plasma-derived products.	

2. Specific comments on text

Line number	Stakeholder number	Comment and rationale; proposed changes	Outcome
28, 58-59, 96, 511, footnote	1	Comment: according to the International code of virus classification and nomenclature of ICTV, IX-Rules for Orthography: 3.40 Species names are printed in italics and have the first letter of the first word capitalized. Proposed change (if any): *Hepatitis E virus*	Agreed. The proposed change has been made.
98	2	Proposed addition: In acute infections during the third trimester of pregnancy the risk of transmitting the virus to the fetus or postnatally to the newborn infant ranges between 50 and 100%, with a high risk of lethal outcome. Reference Khuroo J *et al*. Viral Hep 2009	Partially agreed. This statement is only valid for infections with HEV genotype 1 and not for infections with genotype 3 (or 4). The text has been modified as follows for clarity: *Hepatitis E virus* infection with genotypes 1 and 2 can lead to high mortality among pregnant women in developing countries. In acute infections during the third trimester of pregnancy the risk of transmitting the virus to the fetus or postnatally to the newborn infant ranges between 20 and 100%, with a high risk of lethal outcome (Verghese and Robinson, 2014). However, no serious infections of pregnant women with genotype 3 have been observed, so far.
110	2	Proposed change: In general, reduction of immunosuppression at the time of acute infection can help to	Agreed. The text has been changed accordingly:

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		clear the virus. However, it may not be feasible or could be dangerous for solid organ transplant recipients due to the risk of acute rejection, for recipients of haematopoietic stem cell transplantation because of the risk of Graft-Versus -Host-Disease (GVHD), or patients with other diseases such as autoimmune hepatitis because of the risk of relapse and acute liver dysfunction.	….In general, reduction of immunosuppression can help to clear the virus ~~(e.g. kidney transplants)~~. However, it may not be ~~an option for specific~~ feasible or could be dangerous for solid organ transplant recipients (~~e.g. heart, liver) or it can be dangerous at~~ due to the risk of acute rejection, for recipients of haematopoietic stem cell transplantation because of the risk of Graft-Versus-Host-Disease (GVHD) ~~risk~~, or patients with other diseases such as autoimmune hepatitis because of the risk of relapse and acute liver dysfunction.
134, 444	1	Comment: word missing ('the') Proposed change (if any): 'from **the** UK' and 'As far as **the** patient'	Agreed. The text has been changed.
137 - 144	3	Comment: The analysis of blood components which transmitted HEV should not only consider the HEV RNA concentration but also the infused volume (total RNA HEV infused) which for certain components (such as plasma) can be quite high.	Agreed. However the cited study from Hewitt *et al.*, does not provide all the information. The Paragraph has been modified where possible: …In one case there was evidence for transmission by SD-plasma containing 41.4 IU/ml HEV RNA where a patient received 13 units of 200ml
193	1	Comment: writing of 'in vitro' inconsistent	Agreed.

Line number	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): *in vitro* in italic	
181, 455	1	Comment: unit missing Proposed change: 'up to 10^7 IU HEV-RNA **per ml**'	Agreed.
203	1	Comment: full-stop missing Proposed change: reported in France**.**	Agreed.
209-212	3	Comment: The lipid "pseudo-envelope" of HEV protects from neutralisation. However some (upstream) steps can remove this "envelope" which allow for neutralisation of plasma-derived HEV by anti-HEV IgG. Proposed change: please add: "Depending on the manufacturing process with possible impact on the physical state of the virus particles (associated or not to lipids) antibodies can contribute to some degree to prevention of transmission of HEV".	Paragraph has been modifies as follows: Antibodies ~~might~~ can contribute towards reduction of HEV infectivity in product intermediates, however, this depends, to some extent, on the impact of the manufacturing process on the physical state of the virus particles and their association with lipids or not.
210	3	Comment: Data from LFB (ref: line 776 in appendix) show that antibodies can neutralise to some extent HEV in an IgG intermediate product. Proposed change: Antibodies ~~might~~can contribute towards…	Agreed. See modification above.
217-218, 280, 345-347, 351	1	Comment: according to the International code of virus classification and nomenclature of ICTV, IX-Rules for Orthography: 3.39 …'virus Orders, Families, Subfamilies and Genera are printed in italics and the first letter of the names	Agreed.

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		are capitalized.' Proposed change: *Hepevirus* genus in the family *Hepeviridae*. …'*Picornaviridae* or *Parvoviruses*…', members of the *Picornaviridae* instead of *Picornaviruses*	
236-238	3	Comment: Partitioning steps often involve both removal and inactivation mechanisms for reduction of infectivity of viruses (ex: ETOH fractionation, chromatography…) which limits the use of NAT for the investigation of these steps. Please consider removing precipitation and chromatography from the list. Proposed change: "…removal), e.g. for manufacturing steps such as nanofiltration~~, precipitation/~~ or depth filtration~~, or chromatography~~. NAT…"	It is agreed that, partitioning steps sometimes involve both removal and inactivation mechanisms for reduction of infectivity of viruses and that a NAT assay might therefore underestimate the virus reduction capacity of a partitioning step where there is additional virus inactivation (or neutralisation). However, a properly conducted NAT study is still considered useful for estimating the virus reduction by partitioning. An advantage is that a NAT study might help to separate virus reduction by partitioning from virus reduction by inactivation or neutralisation. Another advantage of NAT, is that such studies are much more feasible than studies involving infectivity assays for HEV. No change of the text is considered necessary.
258-260, 270, 318, 331, 341, 343, 348, 351, 370, 475	1	Comment: according to the International code of virus classification and nomenclature of ICTV, IX-Rules for Orthography: 3.40 Species names are printed in italics and have the first letter of the first word capitalized.	Agreed.

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		Proposed change: *Hepatitis A virus*, *Encephalomyocarditis virus, Canine parvovirus, Porcine parvovirus, Minute virus of mice, Parvovirus B19, Feline calicivirus, Murine norovirus, Cutthroat trout virus, Parvovirus*	
286	1	Comment: addition of reference Proposed change: …'was comparable to reduction of model viruses (Farcet *et al*., 2015)….'	Agreed.
300-301	3	Comment: Same comment than Lines 236-238 Please consider removing the NAT evaluation of the "precipitation step" Proposed change: "~~Virus partitioning at precipitation steps can by studied by NAT assays.~~"	Not agreed, see comment above.
310	1	Comment: addition of reference Proposed change: …'instead of albumin (Yunoki et al., 2008; Farcet et al., 2015).'	Agreed to include Farcet reference.
314	3	Comment: None Proposed change: Please add in the comment on line 314 that "The lipid-associated HEV particles have been shown to be more resistant to pasteurization (ref appendix Yunoki: line 834 "non-detergent treated…")	Agreed. Modified text: … It seems therefore that albumin has a stabilizing effect on HEV. Recent studies indicate that the lipid-associated HEV particles may be more resistant to pasteurisation (Yunoki *et al*., 2016).

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315	1	Comment: addition of reference Proposed change: …'most heat-resistant HAV strains (Farcet et al., 2015).'	Agreed.
343, 404	1	Comment: HAV or EMCV are listed as examples of a *Picornavirus*, however these are both members of the family *Picornaviridae*. Proposed change: …'usually includes a *Parvovirus* and a member of the *Picornaviridae* such as HAV or EMCV.' and …'to remove effectively *Parvoviruses* and/or members of the *Picornaviridae* (e.g. HAV, EMCV)…'	Modified text: ….these filters usually include viruses from the *Parvoviridae* (e.g. MVM) as well as the *Picornaviridae* (e.g. HAV or EMCV) families.
350	1	Comment: addition of reference Proposed change: …'has been experimentally confirmed (Yunoki *et al*., 2008; Farcet *et al*., 2015) and others.'	Agreed. Modified text: …'has been experimentally confirmed (Yunoki *et al*., 2008; Farcet *et al*., 2015) and others.
355	1	Comment: addition of reference Proposed change: …'were applied to filters (Farcet *et al*., 2015).'	Unnecessary here.
Line 372	1	Comment: FCV is a *Vesivirus*, in the family of the *Caliciviridae* Proposed change: …'low pH than FCV, a member of the *Caliciviridae*, which was investigated…'	Agreed.
Line 379	1	Comment: data for partitioning of HEV and for the model	Modified text:

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		viruses FCV and HAV are available and could be mentioned here - addition of reference Proposed change: …'extrapolated to HEV but removal for HEV, HAV and FCV was seen to be similar in the case of affinity chromatography of a Factor VIII product (Farcet *et al*., 2015).'	The results obtained with model viruses can therefore not be readily extrapolated to HEV In one study, similar reduction of HAV, FCV, and HEV was observed by FVIII affinity chromatography (Farcet *et al*., 2016).
412-413	3	Comment: same comment than Line 210 Proposed change: … antibodies ~~might moderately~~can contribute towards…	Agreed.
419	3	Comment: same comment than Lines 137 - 144 Proposed change: please consider adding: "In addition, the volume of component transfused needs to be considered as the total amount of particles transfused is the determining point for transmission".	Same response as to comments on Lines 137-144. It is not considered necessary to add this sentence here as the calculation of infectious doses has been clearly outlined.
428-430	3	Comment: A review of the French cases of potential post-transfusion transmissions was performed after the meeting and is in full support of the validity of the infectious dose concept. Proposed change: ~~Although, t~~The infectious dose represents a significant factor for risk assessment, ~~it has to be~~ keeping ~~t~~ in mind that it can be associated with ~~a considerable~~ variability depending on the individual scenario. ~~The overall experience with transfusion-transmitted~~	The proposed modification is not agreed. Although a certain number of TTI cases has been analysed, the overall experience is still considered limited.

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		~~HEV infection is still limited.~~	
446	2	Proposed addition: …, although it is well established that HEV can lead to chronic infection in immune deficient patients resulting in graft loss in solid organ transplant and graft versus host disease in haemaptopoietic stem cell transplant recipients.	Partially agreed. HEV is not the causative agent of graft versus host disease (GVHD) in haemaptopoietic stem cell transplant recipients; however, it may complicate the therapy of GVDH. Modified text: …. although it is well established that HEV can lead to ~~prolonged~~ chronic infection in immune deficient patients, occasionally with severe complications in solid organ transplant recipients, and where immunosuppression is reduced due to HEV infection, graft versus host disease may be a consequence.
486		Comment: It is important to remind everyone in the conclusion of the safety of PDMP regarding the HEV transmission risk. Proposed change: Please consider adding: "To date there has been no specific case report of HEV transmission via fractionated medicinal plasma-derived products. However recognizing the clear evidence for contamination of…."	The lack of transmission cases has been already clearly expressed in this Section (see lines 475-480 or lines 501-503 of the draft reflection paper). It is not considered necessary to reiterate such statements in the same section.
490	2	Comment:	See general comment above.

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		These patients would be hard to define in detail since the risk is not limited to transplant recipients but also applies to quite large groups of patients receiving immunosuppressive treatments for pediatric autoimmune liver disease, inflammatory bowel disease, and rheumatoid disease and also patients with underlying chronic liver disease, infants and pregnant women at risk of acute liver failure.	
515	2	Specific references on paediatric hepatitis E needed. Suggestion: Verghese VP. Clin Infect Dis 2014;59(5):689–97 ESPGHAN Position Statement: Hepatitis E in childhood – in preparation.	Agreed.
529-530	1	Comment: addition of reference Proposed change: Farcet MF, Lackner C et al (2015) Hepatitis E virus and the safety of plasma products: investigations into the reduction capacity of manufacturing processes. Transfusion Epub 2015 Sept 24. DOI 10.1111/trf.13343	Agreed.
531	1	Comment: reference has been published in Journal Proposed change: …'Lancet 384,1766-1773.'	Reference has been updated.
790	1	Comment: correction of reported preliminary data Proposed change: …'(up to >4.**3** $\log_{10}$)'	Has been changed accordingly.