30 May 2024
EMA/CHMP/BWP/245922/2024
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'CHMP Reflection paper on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products - Revision 3' (EMA/CHMP/BWP/303353/2010 Rev 3)'

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

Stakeholder no.	Name of organisation or individual
1	European Haemophilia Consortium (EHC)
2	Plasma Protein Therapeutics Association (PPTA)
3	International Plasma and Fractionation Association (IPFA) (ref. IP-19-140)
4	1. Department of Health and Social Care, Government of the United Kingdom of Great Britain 2. Scottish Government 3. Welsh Government
5	Joint UKBTS Professional Advisory Committee representing UK Blood Services (NHSBT, SNBTS, WBS and NIBTS)
6	David B. McIntosh MA. (Oxon) Chartered FCIPD. MIHM. FRSA. Chair, for and on behalf of: United Kingdom Plasma Action, UKPA
7	United Kingdom Primary Immunodeficiency Network (UKPIN)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The decision to update the Position Statement is welcomed. This revision provides an excellent summary of the current literature. The review of the position for sCJD in the light of current knowledge is considered appropriate. The summary of this document usefully brings together the current knowledge on transmissible spongiform encephalopathies (TSEs) that is of relevance to CJD and plasma-derived and urine-derived medicinal products. Comparing this summary with the summary of the 2011 Position Statement, the following differences are noted: 1. On the basis of findings since 2011, there is now a concern that sCJD could be present in plasma from donors incubating sCJD. (Lines 69-76.) 2. At the time of the 2011 Position Statement, there was no evidence that sporadic, genetic or iatrogenic forms of human TSEs had been transmitted from person to person through exposure to plasma products. Since then, two plasma product recipients in the UK have been diagnosed with sCJD. A causal link between the treatment with plasma products and the development of sCJD has not yet been established and there is a possibility that both cases may reflect a chance event in the context of systematic surveillance of CJD in large populations. (Lines 182-189.) 3. The 2011 Position Statement stated that recall of plasma-derived medicinal products is not justified where a donor is later confirmed as having sporadic, genetic or iatrogenic CJD. In the current revision, this recommendation is now qualified by 'provided the manufacturer has demonstrated using	Partly Accepted. The sections on prion reduction and batch recalls have been reworded.

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	appropriate methodology, that the process includes steps which significantly minimize the risk of prion contamination of the final product.' (Lines 79-83) 4. The current revision states: 'Taking account of the available data concerning potential contamination of blood donations with vCJD or CJD agents, assuring an adequate prion reduction capacity of the manufacturing process is considered crucial for the TSE safety of plasma-derived medicinal products.' (Lines 97-99.) 5. Concerning the 2004 Guideline on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with regard to vCJD Risk, the current revision states that since its publication, the methods for prion detection, the knowledge about infectivity in the prion area in general and prion infectivity in the blood have significantly evolved. Experimental studies highlighted the fact that prion removal capacity may vary directly according to the spiking preparation (dispersion and TSE agents strains) particularly for steps based on retention mechanisms. (Lines 106-110). In view of these differences from the 2011 Position Statement: i) Is there a need to revise the 2004 Guideline on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with regard to vCJD Risk? Any revision should presumably include a change to the title e.g. from 'vCJD Risk' to 'Human TSE Risk'. ii) For plasma-derived medicinal products where the overall prion reduction capacity of the manufacturing process seems limited or questionable, should manufacturers be required to undertake further investigations using appropriate methodology taking account of a revision of the 2004 Guideline? iii) Italy has a policy to recall batches of plasma-derived medicinal products where a donor is later confirmed as having sCJD. Will Member States	

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	follow the Position Statement's recommendation not to recall batches of plasma-derived medicinal products where a donor is later confirmed as having sporadic, genetic or iatrogenic CJD, provided the manufacturer has demonstrated using appropriate methodology, that the process includes steps which significantly minimize the risk of prion contamination of the final product?	
2	PPTA's Pathogen Safety Steering Committee (PSSC) considers this document a reasonable and appropriate update of the statement. PPTA's PSSC prepared an assessment of the most recent scientific publications on CJD and TSEs for the BWP Secretariat's perusal; some updates of the literature and evidence cited in the statement are suggested.	Partly accepted. The information provided has been considered. Suggestions have been considered below.
3	IPFA is grateful to have the opportunity to comment on the Draft revision of the CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products. The document represents the updated knowledge for the ongoing evaluation of the risk of transmission of vCJD by PDMPs. IPFA have 2 general comments: Comment 1: With regards to the updated knowledge, a lot of data has come out in the last 10 years or so regarding the probable implication of PrP containing exosomes in the pathogenesis of prion diseases via blood (i.e. presence of prions on the surface of exosomes in blood and plasma). In the context of the importance of the spike preparations for evaluating the elimination efficacy of the manufacturing process studies, we consider that the updated guideline should also include this set of data as it constitutes relevant data concerning the conceivable nature of prions in blood. Examples of data regarding this issue are provided in Appendix 1 (below)	Partly accepted. Information about infectivity in blood/plasma and spike has been added. Role of exosomes in propagation of the disease is still hypothetical. Updated knowledge has been considered and recommendations have been revised.

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	Comment 2: IPFA would like to point out that the main information from the updated knowledge is that data on the vCJD epidemiology and the risk associated with blood (and plasma), including blood infectivity, is in favor of a lower risk than previously estimated (which is quite reassuring), but it does not seem to be reflected in the updated recommendations of the guideline. **APPENDIX 1:** **General comment 1: List of references** Hartmann A, Muth C, Dabrowski O, Krasemann S, Glatzel M. Exosomes and the Prion Protein: More than One Truth. Front Neurosci. 2017 Apr 19;11:194. Cervenakova L, Saá P, Yakovleva O, Vasilyeva I, de Castro J, Brown P, Dodd R. Are prions transported by plasma exosomes? Transfus Apher Sci. 2016 Aug;55(1):70-83. Berrone E, Corona C, Mazza M, Vallino Costassa E, Faro ML, Properzi F, Guglielmetti C, Maurella C, Caramelli M, Deregibus MC, Camussi G, Casalone C. Detection of cellular prion protein in exosomes derived from ovine plasma. J Gen Virol. 2015 Dec;96(12):3698-3702. Properzi F, Logozzi M, Abdel-Haq H, Federici C, Lugini L, Azzarito T, Cristofaro I, di Sevo D, Ferroni E, Cardone F, Venditti M, Colone M, Comoy E, Durand V, Fais S, Pocchiari M. Detection of exosomal prions in blood by immunochemistry techniques. J Gen Virol. 2015 Jul;96(Pt 7):1969-74. Saá P, Yakovleva O, de Castro J, Vasilyeva I, De Paoli SH, Simak J, Cervenakova L. First demonstration of transmissible spongiform encephalopathy-associated prion protein (PrPTSE) in extracellular vesicles from	

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	plasma of mice infected with mouse-adapted variant Creutzfeldt-Jakob disease by in vitro amplification. J Biol Chem. 2014 Oct 17;289(42):29247-60. Ritchie AJ, Crawford DM, Ferguson DJ, Burthem J, Roberts DJ. Normal prion protein is expressed on exosomes isolated from human plasma. Br J Haematol. 2013 Dec;163(5):678-80. Bellingham SA, Guo BB, Coleman BM, Hill AF. Exosomes: vehicles for the transfer of toxic proteins associated with neurodegenerative diseases? Front Physiol. 2012 May 3;3:124	
4	On the 9 September 2019, the UK Department of Health and Social Care, in parallel with the Welsh and Scottish Governments, made a joint announcement highlighting changes to specific variant Creutzfeldt Jakob disease risk reduction measures in the UK, approving the use of domestic plasma and pooled platelets for patients born on or after 1 January 1996, and for the use of domestic plasma for patients with Thrombotic Thrombocytopenia Purpura. There has been no UK position change regarding the use of plasma, sourced in the UK, for the manufacture of plasma-derived medicinal products through fractionation and the cautionary approach in the position statement is endorsed. The full UK Government written ministerial statement may be found at: https://www.parliament.uk/business/publications/written-questions-answers-statements/written-statement/Commons/2019-09-09/HCWS1821/	Comments noted.

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	The full report detailing the scientific rationale of this policy change, developed by the independent Advisory Committee on the Safety of Blood, Tissues and Organs may be found at: https://www.gov.uk/government/collections/sabto-reports-and-guidance-documents	
5	The position statement notes that 'residence in the UK is a recognised risk factor for vCJD and has led to the UK deciding no longer to fractionate from UK plasma'. This decision was made 20 years ago in 1998 because of the perceived risk to recipients and the risk of plasma product shortages engendered by the need to withdraw multiple batches of products if many donors later developed vCJD, at a time when the potential scale of the epidemic was very uncertain. The understanding of the risk to patients of plasma sourced from UK donors is changing with more data and the passage of time since the original decision, in particular the absence of evidence of transmission of vCJD by blood components or plasma products since the introduction of universal leucodepletion in the UK in 1999. This is evidenced by the recent risk assessment carried out for the UK Department of Health and Social Care (DHSC). The Department has periodically carried out a risk assessment on the predicted number of future infections with vCJD that could occur from blood transfusion. The latest was carried out in 2018 under the supervision of the Advisory Committee for Dangerous Pathogens Transmissible Spongiform Encephalopathy (ACDP TSE) subgroup. This expert subgroup and the full ACDP committee are hosted by, but independent of, DHSC England. The risk assessment was used by a Working Group of the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) to review the	Comments noted.

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	continued need for importation of plasma (FFP and cryoprecipitate) for those born after 1995. They concluded that this precautionary measure was no longer required and that UK plasma could be used for all patient groups because of the reduction in risk (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/829906/SaBTO_PC_report.pdf). The position statement supports the continuation of exclusion of donors in other countries who have spent one year in the UK, so as 'to be consistent with the UK decision to no longer fractionate from UK plasma'. Following on from the revised risk assessment and SaBTO decision to cease importation of plasma, however, the Republic of Ireland have recently announced that they are to stop exclusion of donors who have spent time in the UK. The statement also seems to acknowledge that the current risk in the UK is low, as it does not require batch recall if information becomes available post-donation that a donor would have been excluded because of UK residency (lines 775-6). The paper discusses the situation in France where 27 cases of vCJD have occurred, approximately one tenth of the number in the UK. Despite this, France, following periodic risk assessments which have acknowledged that the estimated total eventual size of the outbreak has reduced, has continued to fractionate plasma over the last 20 years and there have been no transmissions of vCJD through blood components or plasma products. Like the UK, they leucodeplete all blood components (including plasma intended for fractionation). There is good evidence of transmission of vCJD by red cell components though none since universal leucodepletion was implemented in 1999. The evidence of transmission through fractionated plasma products is weaker and there is data supporting the reduction of infectivity by steps in the manufacturing process.	

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	The statement contains information about prevalence studies in the UK. The most recent (Appendix III) found evidence of prion accumulation in samples originating from both before and after the BSE epidemic, but raises questions about the specificity of these findings due to poor correlation with the known dynamics of the BSE epidemic and clinical vCJD outbreak in the UK. Unfortunately, no such studies have been done in other countries so there is no negative control population. The incidence of vCJD in the UK is now very low (one case in the past 5 years) so the risk of having to recall manufactured batches has receded, which was one of the reasons for introducing the ban in 1998. Concluding remarks, lines 695-8, states 'Country-based exclusions may appear unjustified in the sense that the vast majority of donors who will be excluded will not develop the disease. There is a lack of spare plasma capacity to make up for shortfalls if countries that are major producers of plasma-derived medicinal products discontinue the use of nationally collected plasma for fractionation'. Given that there is a recognised shortage of plasma for fractionation in Europe and indications that the risk of vCJD transmission in the UK has significantly reduced, we consider it imperative to repeat a risk assessment of the risks of UK plasma to recipients of plasma products, as has been done by the French authorities one- to two-yearly from 2000 to 2009. If the risk assessment concludes that the risk is significantly lower than previously assumed, then the UK Blood Services would suggest that the position statement be flexible enough to allow UK plasma back into the supply chain.	

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6	**1 Introduction** 1.1 These general comments and the specific notes in the following section of this form relate to Variant Creutzfeldt Jakob Disease in the context of the safe use of UK donors' plasma for the production of plasma-derived medicines, relating mainly to sections 2, 4, 6, 7 and 9 of EMA/CHMP/BWP/303353/2010 Rev 3. The comments here are supported by two supplementary memoranda appended hereto (Ref. UKPA Short.Form.Memorandum. 904/ B/21.10.2019 and UKPA.Memorandum.904/C/25.10.2019) that it is hoped the EMA will accept as part of this contribution to the consultation exercise. 1.2 United Kingdom Plasma Action (UKPA) is an independent not-for-profit organisation representing concerned clinicians, patients and blood donors in the UK, where shortages of immunoglobulin and other plasma products are already causing difficulty and are in grave danger of worsening, against a background of global plasma shortage. At the same time, thousands of litres of UK donors' plasma are being excluded from the supply chain instead of being used in medicines manufacture. It is clear that this plasma could be of significant help in alleviating plasma product shortages if reinstated to the supply chain. 1.3 The general global reliance on United States exports for supplies of plasma products currently poses serious risks to the rest of the World; risks that are likely to get worse rather than improve in the coming months and years, unless decisive steps are taken to avoid that happening. In view of this, and in the light of a significant body of new evidence in relation to the safety of both raw material and product, the UKPA team and the organisations and individuals we represent see an up-to-date reassessment of the balance of the risks involved to be an urgent priority for health services and regulatory authorities in the UK	Comments noted.

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	and throughout Europe. We are hopeful that the EMA/CHMP will be able to take a lead in these matters, to help minimise overall risks to health and to life, for the benefit of all. 1.4 The matters referred to herein relate to Variant Creutzfeldt Jakob Disease in the context of the safe use of UK donors' plasma for the production of plasma-derived medicines. This is the specific area of concern to UKPA and the clinicians, patients and blood donors that we represent. Recognising that the work of the CHMP and the field covered by the position statement covers a much wider area than the narrow specialism of vCJD in relation to UK donors' plasma and plasma products, the UKPA team hopes that our specialist interest and the resulting comments that we offer here may be of value to the CHMP and to the EMA in their ensuing further work, following the completion of this stage of the consultation exercise. **2 General Comments on EMA/CHMP/BWP/303353/2010 Rev 3** 2.1 Our observations here fall into two categories – 2.1.1 references to studies and events that post-date the EMA/CHMP work described in the position paper and which we believe bring a significant new perspective to the assumptions and findings therein; and 2.1.2 other general observations relating to the context and content of the draft paper. 2.2 In relation to the most recent relevant findings (from work completed too late to have any bearing on the drafting of the EMA/CHMP position paper) we believe that chief among these are 2.2.1 the findings of the Irish Blood Transfusion Service expert committee that re-examined that country's long-standing blood related vCJD	

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	precautions during the Spring and Summer of 2019 and reported in September 2019; and 2.2.2 the findings of the UK expert committee on the Safety of Blood, Tissues and Organs (SaBTO) that also reported in September 2019. These of course both came too late to be included in the draft position paper, but are highly relevant to it. They are touched upon here below and can be studied more fully at the sources referenced. 2.3 The Irish Blood Transfusion Service (IBTS) convened a special meeting of its medical advisory committee in April 2019 to consider the evidence relevant to the potential blood-born vCJD risk in the UK. It was agreed that up-to-date evidence justified an in-depth review of the position with respect to the level of risk and such precautionary measures as might or might not still be appropriate in 2019/'20. After further investigation and analysis, the IBTS decided, in September 2019, that the previous permanent deferral policy in relation to UK donors and UK residency or visitation should be discontinued. 2.4 As reported in the Irish Press at the time, IBTS chief executive, Andrew Kelly stated that "The evidence now available allows the IBTS to overturn this deferral and reinstate those donors." Pointing out that the original deferral policy was introduced as a precautionary measure at a time when there was great uncertainty about the BSE/vCJD outbreak, IBTS medical and scientific director, Professor Stephen Field, said that "The number of cases of vCJD to date and the predicted number of future cases have been significantly lower than has been anticipated." (https://www.irishexaminer.com/breakingnews/ireland/irish-blood-transfusion-reverses-15-year-long-uk-donor-deferral-policy-949941.html)	

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	2.5 The Irish work on reassessing the vCJD risk, and taking appropriate action to reflect the new balance of risk that emerged from that work, is echoed by the recent investigation by the UK expert committee on the Safety of Blood Tissues and Organs (SaBTO). The SaBTO Paediatric Components Working Group has conducted an in-depth study into the current appropriateness or otherwise of the previous precautionary policy in relation to certain aspects of the clinical use of UK donor blood components as risk reduction measures against vCJD. The work was completed and a report issued in March 2019. The SaBTO recommendation was that on the basis of an up-to-date assessment of the potential risks and costs involved, both in maintaining the old vCJD precautions and in their discontinuation, the preferred option should be discontinuation of the precautions. (https:/ /www.gov.uk/government/collections/sabto-reports-and-guidance-documents) 2.6 The UK Department of Health and Social Care accepted the SaBTO recommendations on the basis of a number of factors, including a significant shift in the balance of risk, and announced the termination of the previous UK precautionary measures on the 9th of September 2019. In making her announcement to the British House of Commons, Caroline Dinenage, Minister of State, commented as follows "Over the last 15 years, accrued scientific evidence has indicated that the risk of vCJD through the transfusion of UK plasma or platelets is much lower than initially thought; there have been no known transfusion transmissions of vCJD from any blood components since the leucodepletion process was introduced. In March 2019, the independent Advisory Committee for the Safety of Blood, Tissues and Organs (SaBTO) reviewed the scientific evidence and operational practices, engaged with stakeholders, and recommended that some specific risk reduction measures, requiring the use of imported plasma and apheresis	

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	platelets for individuals born on or after 1 January 1996 and/or with TTP, be withdrawn." (https://www.theyworkforyou.com/wms/?id=2019-09-09.HCWS 1821.h) 2.7 The UKPA team notes that these two important developments, coming to light as they have done at dates after the date of drafting of EMA/CHMP/BWP/303353/2010 Rev 3, bring new insight to the analysis. They will no doubt have a significant effect on the end results after the consultation process is complete and the various contributions to it have been collated. Both the Irish and UK developments recognise and underline the now widely accepted fact that the current vCJD risk to UK donors' blood and blood components, including plasma, has fallen significantly since these matters were last the subject of review. This is reinforced by other findings mentioned below, in the specific UKPA comments on the relevant sections of the position paper and in the UKPA Memoranda appended hereto (Short Form Memorandum 904/B/21.10.2019 and Memorandum.904/C/25.10.2019.) 2.8 The mass of pharmacovigilance data from UK plasma product manufacture and issue in the years before the exclusion of UK donors' plasma (ie pre-1999) further supports the conclusion that the actual vCJD risk in the UK is very much lower than previously thought. For instance, more than 2.5 million grams of immunoglobulin made from UK donors' plasma were administered to patients during the critical years in the 1980s and '90s when the BSE/vCJD crisis was at its height. No cases or suspected cases of this immunoglobulin causing vCJD transmission have ever been recorded, neither at the time, nor in the 20 years since the end of the period; 36 years on from the earliest administrations of these products to patients during the most critical vCJD era. (Ref. UKPA.Memorandum.904/C/ 25.10.2019; and also	

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	https://www.cjd.ed.ac.uk/sites/default/files/PID%20Study%20Steering%20Group%20 report_2019.pdf) 2.9 In addition to the clean slate for UK immunoglobulin, it is of added interest to note that, with the exception of one controversial case of abnormal prion protein found in one tissue sample from a deceased haemophilia patient who had died of other causes, the records show no cases of vCJD infection in recipients of any other plasma derivatives obtained from UK donors' plasma at any time; neither during the critical years at the height of the BSE/vCJD crisis, nor in the many years since. This would appear to vindicate the position taken by the European Committee for Proprietary Medicinal Products (CPMP) in February 1998, that a batch of a plasma derivative should be recalled if it had been manufactured with a donation from a person who was subsequently diagnosed with vCJD (press release CPMP/201/98, Feb 25th 1998); in contrast to the decision of the UK Government at the time to ban altogether the preparation of plasma derivatives from UK donors' plasma (UK Department of Health, press release 98/182, 17th July 1998). With hindsight, the CPMP's decision on the matter would seem to have accorded more accurately with the requirements of the situation – giving hope that the EMA/CHMP may once again take the lead in these matters at this current time. 2.10 In addition to the relevant pharmacovigilance data in relation to the absence of vCJD in UK-plasma-derived medicines administered to patients in the 1980s and '90s, there is also a huge mass of accumulated data confirming the consistent absence of any reported vCJD transmissions from the transfusion of red cell concentrate or other fresh blood components in the UK over the 20 years since (post the introduction of leucodepletion). This, taken together with other evidence now available has exposed a highly significant gap between the emerging empirical reality and the old risk estimates still sometimes being	

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	applied to the analysis of these issues. There would certainly now seem to be very good grounds for a close re-examination of those risk assessments in the light of an up-to-date understanding of the clinical and epidemiological realities of 2019/'20. 2.11 In addition to drawing attention to the above reasons why the UKPA team, along with many others, notes a recognised reduction in the risk that vCJD poses, we would also respectfully point out that the whole context for the vCJD/UK plasma content in EMA/CHMP/BWP/303353/2010 Rev 3 has changed dramatically in recent years. This aspect, of changed background, context and risk environment, is the key thrust of the second category of general comments that the UKPA team would like to contribute to this consultation. We believe that this has changed in ways that significantly affect the balance of argument that underlies the draft position paper in its current form; and in ways that are not dealt with or recognised therein. 2.12 Whereas original vCJD risk estimates and policy decisions in relation to UK blood donors' plasma could be formulated on the assumption of a zero or near-zero risk alternative (plentiful supplies of safe and efficacious plasma products available via importation, in reliably predictable quantities) the background to current decision-making is now much less benevolent. The practical alternatives to the use of UK blood donors' plasma are all now based on the importation to the UK of plasma products that are dependent on a global plasma supply that is now very far from reliably plentiful. Indeed, global supply is running well short of the level required to fulfil all clinical demand/patient need. This is true even in the United States which is the World's number one supplier of plasma and plasma products (@ circa 70% of total global demand.) 2.13 The effects of this shortage are acutely felt in the availability of immunoglobulin – of which shortages are already being experienced, with	

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	rationing being necessary to eke out supplies. Many patients are therefore receiving less medicine than their prescribing clinicians would like them to have; less indeed, often, than the patients need. Some patients, with conditions that do not entitle them to top priority when immunoglobulin is in short supply are having to go without altogether. Throughout the UK, clinicians and their patients are suffering from and becoming increasingly concerned about this state of affairs. Sadly however, the current unsatisfactory situation is by no means the most serious risk that the UK and other fellow European countries are now facing in this area. 2.14 The even more concerning risk is the danger that an event or events in the United States (whether epidemiological, commercial, political or due to other unpredictable phenomena) could, at any time, interrupt global supplies of immunoglobulin and other plasma products so much as to cause catastrophic shortages/outages in clinical areas where no practicable alternative effective treatments exist. This is a very real and present danger. Clearly, were it to befall us it would have the most serious consequences in terms of morbidity and mortality – not only in the UK, but all over Europe and indeed globally. In summary, the World is far too dependent on one country, the United States, for its vital plasma product supplies. All the relevant bodies and organisations concerned, globally, but particularly in Europe, must surely understand themselves to be duty-bound to work together to lower this serious strategic risk. The re-acceptance of UK blood donors' recovered plasma to the supply chain is of course only one small step along the right road, but it would certainly make a good start. 2.15 The UKPA team and the doctors, patients and donors that we represent submit these and the attached comments as a contribution to the present consultation exercise in the hope that they may be of assistance in the policy	

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	and guidance review process. We feel confident that the EMA/CHMP will rise to the challenges involved and will play a full part in averting present and future dangers; securing a safer and more reliable future for the citizens of Europe in the whole field of immunotherapy and related medicine.	
7	This CHMP position statement appears to simply accept the previously recommended exclusion of UK donors for plasma derived products based on the UK deciding to not fractionate UK sourced plasma. UKPIN is working with other agencies in the UK to re-open this debate since there has been approval from Safety of Blood, Tissues and Organs (SaBTO) and the government in the UK on lifting the restrictions on use of fresh frozen UK sourced plasma. UKPIN urges you to consider this approach in light of the evidence rather than current (out of date) policy.	Comments noted.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 51 & 52	6	Comment: Unfortunately, in this fast moving space the wording drafted here is already well out of date. We suggest that it should be up-dated as below - Proposed change: "Much of the scientific information has already been updated. However, there may be further developments available since the date of drafting. Any such will be included in the final review, post-consultation and the regulatory recommendations reviewed accordingly."	Partly accepted. The whole section has been revised considering the actual data.
52-54	1	Comment: There is a change to the regulatory recommendation for batch recalls. The 2011 Position Statement stated that recall of plasma-derived medicinal products is not justified where a donor is later confirmed as having sporadic, genetic or iatrogenic CJD. In the current revision, this recommendation is now qualified by 'provided the manufacturer has demonstrated using appropriate methodology, that the process includes steps which significantly minimize the risk of prion contamination of the final product.' (Lines 79-83) Proposed change (if any): Remove 'batch recalls' from line 54 as the regulatory recommendation has been modified:	Partly accepted. The whole section has been revised considering the actual data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		However, there is no change in the regulatory recommendations regarding exclusion, potential testing of donors, **and** the need to evaluate the prion reduction capacity of the manufacturing process ~~and batch recalls~~.	
62 - 65	6	Comment: It is true that residence in the UK has long been a recognised risk factor for vCJD. However, the position on this has now changed significantly. The recommendations in this regard require to be up-dated, in line with the recent work done and the decisions taken in Ireland and the UK and other evidence, referenced elsewhere in this submission and its attachments. Proposed change: "In view of the mass of evidence gathered since the last review and in line with the recent decisions of the Irish Blood Transfusion Service, the exclusion policy for donors who have spent a cumulative period of 1 year or more in the UK between the beginning of 1980 and the end of 1996 be excluded from donating blood/plasma for fractionation should be the subject of urgent further review."	Partly accepted. The whole section and recommendations have been revised considering the actual data.
73	1	Comment: 'seeding activity' only appears here in the document. We would suggest that this term is avoided as it is not clear for the non-expert reader.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): and some cases of vCJD and sporadic CJD have been found with equal amounts of abnormal prion protein ~~or seeding activity~~ in peripheral tissue.	
73-79	3	Comment: This study concerns the intracerebral injection of plasma from clinically-infected patients into transgenic mice (Tg340) that overexpress human PrP approximately 4 times selected as a very sensitive sCJD model. This study situation is far from the human situation of PDMPs (made from pools of plasma not containing sCJD clinically-infected donations), where injection is performed intravenously. The limit of this study and of the model should be emphasized in this section. Proposed change (if any): Modify line 75 to: Although this data should be evaluated with precaution (intracerebral injection, overexpressing transgenic mice selected for their high sensitivity to sCJD, plasma from clinically-infected sCJD patients), these findings ~~raise a concern that sCJD~~ show that a certain level of infectivity (not necessarily to a level infectious for man) could be present in plasma from donors incubating sCJD.	Partly accepted. The summary section has been reworded. The limitations outlined in this comment have been considered in the main text Section.
108	3	Comment: Edit	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): please correct spelling of word "infectivty"	
121	3	Comment: Edit Proposed change (if any): please correct spelling of word "sJD" to "sCJD"	Accepted.
130	3	Comment: Proposed change (if any): we propose to add the word "worldwide" at the end of this phrase.	Partly accepted. The sentence has been rephrased indicating the worldwide occurrence of CJD.
170 & 171	6	Comment: We understand that it has been very difficult to achieve a satisfactory comprehensive update, in view of the amount of evidence either not yet in existence at the date of drafting, or perhaps unavailable to the drafters. It is noticeable for instance that the reference list has many references dated prior to 2011 but few with more recent dates. This is a possibly unavoidable but definitely serious drawback. Proposed change: "The purpose of the final revision will be to update the position statement fully, taking account of the most recent scientific developments since the last revision in 2011. While every effort has	Partly accepted. The outlined limitations have been recognized but the proposed text is not considered suitable for inclusion into the reflection paper after the public consultation phase.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		been made to bring the position up to date at the time of drafting, it is recognised that new items of information, including contributions to the consultation process, are likely to bring new perspectives on the data and the conclusions to be drawn. These will be assimilated during the post-consultation review process and included in the final position statement, as appropriate."	
174	3	Comment: concerning the word (v)CJD, shouldn't it be CJD instead? There is new information on both v and s CJD. Proposed change (if any):	Accepted.
175	3	Comment: The study in question shows the presence of prion infectivity in plasma, but not really that the samples are infectious for man. This should be more explicit. Proposed change (if any): replace "be infectious" by "contain prion infectivity"	Accepted.
187-188	3	Comment: regarding the words "has not yet been established", there may never be such a demonstration. Proposed change (if any): please remove the word "yet"	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
199	3	Comment: regarding the words "May 2016", this should be updated before final publication of the guideline. Proposed change (if any):	Accepted.
199 and 215	1	Comment: It would be helpful to have an update on vCJD figures for the final position statement as the figures given date from 2016. Proposed change (if any):	Accepted.
202	3	Comment: Proposed change (if any): Please remove "the" before the word "USA"	Accepted. (This text is no longer part of the updated text.)
206	3	Comment: reference to Canadian case is missing at the end of the phrase. Proposed change (if any): "have been reported as most likely infected when living outside of the USA and Canada"	Accepted.
215-216	3	Comment: Same comment than line 199 (update)	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed Change (if any):	
218-219	3	Comment: regarding the words "in order to try and obtain" please modify Proposed change (if any): "in order to try to obtain"	Accepted.
229 - 232	6	Comment: The quoting of these statistics in this way at this time is surely less than wise. The bald comment that the risk levels quoted "are higher than predictions from modelling of the clinical data" hardly does justice to the true position. The central thread that runs through all modern discussion of these matters is that previous theories and predictions about vCJD risk have been found, and continue increasingly to be proven, to be well adrift from the observed reality. It is not therefore to some suggested deficiency in reality that attention must be drawn, but to the patent deficiencies of previous theories and predictions and the need to update them Proposed change: "The estimates of risk arrived at from earlier studies have proven to be significantly adrift from the emerging facts. These historic estimates of alleged risk are therefore due for an in-depth re-analysis. It is intended that this will be addressed as a post-consultation follow-up exercise in which the established clinical and epidemiological	Partly accepted. It is agreed that these estimates are historic. The wording has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		facts will be re-analysed, along with the results of reliable experimental studies, to guide new risk assessments where these are possible."	
236 - 237	6	Comment: It is hard to see why it is felt appropriate to say here - "It should be noted that plasma-derived medicinal products have not been manufactured from donations collected in the UK since 1998" without adding any qualifying comments. The statement seems to imply unquestioning acceptance of this policy. It would surely seem wiser, as part of an up-dating review process, to emphasise the need to re-visit anything as long-standing, ever-controversial and increasingly risky as the UK donor plasma exclusion policy. Certainly, any up-dating of policies and recommendations in this area must be expected to include a long cool look at any such policy in the light of the evidence accumulated over the last 20 years and the growing risks attached to maintaining out-of-date policies in a changing world. Proposed change: "Whereas plasma-derived medicinal products have not been manufactured from donations collected in the UK since 1998, it should be noted that the necessity for this precaution has come increasingly into question. It stands in sharp contrast for instance to the policy adopted in France at the same time and with the CPMP recommendations also	Partly accepted. The paragraph has been reworded. The additional text proposed regarding the ban on UK-sourced plasma being reviewed is not found relevant to the estimates described in this section of the Reflection paper. The recent changes regarding the ban on UK-sourced plasma have been addressed elsewhere in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		made in 1998. The policy is now under review in the UK and the up-dated EMA/CHMP recommendations that emerge from the present consultation exercise will take account of the UK findings."	
263 - 268	6	Comment: It is not altogether accurate to say that the referenced UK prevalence studies of appendix tissues derived from individuals before, during and after the BSE epidemic have recently been published[29]. The most recent was published three years ago; and three years is a long time in the developing story of vCJD. The draft as it stands does mention some of the uncertainties surrounding the appendix studies, but given that the position paper is intended as an up-to-date review of relevant new scientific developments, it would seem altogether more appropriate to put these studies more clearly into perspective. Given the importance previously placed on the results of these studies and their former assumed relevance in previous risk assessments and policy decisions, it is important to note – and to emphasise - the growing gulf between those assessments and the emerging facts. Proposed change: "The appendix studies that formed a significant part of the background to previous risk assessments and to the establishment of earlier anti-vCJD precautions remain controversial and should ideally be the subject of further follow-up studies. In the meantime it is very difficult to reconcile the	Partly accepted. The reference on the Appendix III study has been updated and the interpretation has been reworded in light of the current epidemiology.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		potential risk levels previously indicated by these studies with the epidemiological and clinical experience on the ground. That gulf clearly requires further investigation.”	
268	3	Comment: please correct “immunohistochemistry n” by “immunohistochemistry in” Proposed change (if any):	Accepted.
269	1	Comment: Reference 29 does not provide information on ‘various interpretations are possible’ of the Appendix III survey but refers to ACDP's August 2016 Updated position statement on occurrence of vCJD and prevalence of infection in the UK. Therefore, please consider adding reference to this position statement. Proposed change (if any): Add sentence with a reference: The survey results have been considered by the Advisory Committee on Dangerous Pathogens TSE Sub-Group and a position paper detailing the conclusions of the committee has been published[ref] Reference: Advisory Committee on Dangerous Pathogens TSE Subgroup Updated position statement on occurrence of vCJD and prevalence of infection in the UK	Partly Accepted. References have been updated with the recently published study results and the paragraph has been reworded reflecting the current epidemiological data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		https://app.box.com/s/hhhhg857fjpu2bnxhv6e/file/91796156506 NEW REF Rev#5	
269	3	Comment: The ending of this paragraph is abrupt. It might be appreciable to provide a short conclusion on the possible interpretations including a statement on the prevalence of vCJD in the UK population and also whether the risk period for transmitting BSE could or needs to be extended. Proposed change (if any):	Accepted. See previous comment.
270-291 (Section 3. Human tissue distribution of infectivity/ abnormal prion protein)	2	Comment: See additional reference for new infectivity data: **Distribution and Quantitative Estimates of Variant Creutzfeldt-Jakob Disease Prions in Tissues of Clinical and Asymptomatic Patients.** Douet JY, Lacroux C, Aron N, Head MW, Lugan S, Tillier C, Huor A, Cassard H, Arnold M, Beringue V, Ironside JW, Andréoletti O. Emerg Infect Dis. 2017 Jun;23(6):946-956. doi: 10.3201/eid2306.161734. NEW REF Rev#6	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
286	3	Comment: Edit Proposed change (if any): "~~Infectious~~ vCJD infectivity was detected in spleen but not in the brain from a~~n~~ subclinically vCJD-infected individual"	Accepted.
287-288	1	Comment: The sentence 'While PrP^{TSE} and infectivity are occasionally found in the spleen of sporadic CJD, the levels of PrP^{TSE} are lower than in vCJD' does not appear to be supported by line 283 where it states that recent data show equal amounts of of PrP^{TSE} in lymphoreticular tissues from vCJD and sporadic CJD. (It is also noted that the reference for the sentence at line 287-288 has been omitted in this revision.) Proposed change (if any): Please consider clarifying the text.	Accepted.
298	3	Comment: Please add a space "bybioassay" Proposed change (if any): "by bioassay"	Accepted.
303-304	3	Comment: The reference 48 does not refer to "buffy coat infectivity being washed off cells". We think this is not the right reference. Proposed change (if any):	Accepted. Sentence has been removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
333	3	Comment: concerning "the efficacy to transmission" Proposed change (if any): "the efficacy <u>of</u> transmission"	Accepted.
340-342	3	Comment: The sheep model used in this study concerns the PG127 scrapie strain which is a "rapid" strain with short incubation periods and its infectious potency is most likely overestimated with regard to the vCJD strain (as suggested by the much lower infectivity observed in the BSE in sheep model - McCutcheon 2011). This should be emphasized here as a caution. Proposed change (if any): … transfusion is still sufficient to transmit the disease in a proportion of the recipients[53]. <u>However this data, obtained with a rapid scrapie strain (PG127) should be taken with caution with regard to its relevance to the risk of vCJD transmission.</u>	Accepted.
354	3	Comment: Edit Proposed change (if any): Please insert a "(" in front of the word "PMCA"	Accepted.
355	3	Comment: Edit	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): please correct the word "Wetsern" by "Western"	
360	3	Comment: Edit Proposed change (if any): Please replace the word "resulted" by "was"	Accepted.
361	3	Comment: Edit Proposed change (if any): please delete the first "both"	Accepted.
361	3	Comment: We think the reference 63 is not the right reference. Proposed change (if any): Please modify to references 54 and Mathiason CK, et al. Infectious prions in the saliva and blood of deer with chronic wasting disease. Science. 2006 Oct 6;314(5796):133-6.	Accepted.
373 - 374	6	Comment: These three confirmed and one possible transfusion transmitted infections with vCJD date from the period before the introduction of routine leucodepletion in the UK (1999). It should also be pointed out that in the 20 years since the UK plasma	Partly accepted. Paragraph has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		ban in 1999, UK patients have received over 58 million units of red cell concentrate and other fresh components of UK blood donations with zero cases of vCJD transmission recorded. (Ref. UKPA Memorandum 904/C 25th Oct. 2019 – appended here.) Proposed change; "…Taken together, these instances have always been taken as strong evidence that vCJD is transmissible through blood transfusion. That this is so, at least theoretically and at least in the case of non-leucodepleted blood donations, remains the most probable conclusion. However, the mass of clinical evidence now available shows that post the introduction of leucodepletion in 1999, there have been no reported cases of vCJD transmitted in this way anywhere in the UK. As this zero transmission finding relates to over 58 million units of fresh blood components administered to patients over the relevant period, it would seem that the actual transmission risk through this route is very much smaller than had previously been thought/estimated on the basis of small scale studies of this kind."	
375 - 383	6	Comment: It should be noted here that the case cited is controversial. Its findings have never been replicated in any other studies. Also, it conflicts with a mass of pharmacovigilance data on UK donor sourced plasma products that we respectfully suggest should also be referenced, for balance. (Ref. UKPA Memorandum 904/C 25th Oct. 2019 – appended). The	Partly Accepted. Text slightly modified to also accommodate the comment from stakeholder #3 (See below).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		reference also fails to mention that the implicated FVIII product was of intermediate purity and not subject to the additional purification and pathogen clearance steps now applied to modern plasma derived coagulation factor products. Taken properly in context, it would also seem appropriate to point out that other routes of exposure to vCJD (eg dietary) cannot be excluded and may indeed, with hindsight, be more likely. Proposed change: "While this case may represent a warning that some plasma-derived products might contain residual prion infectivity, it should also be noted that it is the only case of its kind so far reported and has always been somewhat controversial. Its implications conflict with the pharmacovigilance data for UK-plasma-derived products and the surveillance studies conducted by the UK National CJD Surveillance Centre; both bodies of evidence indicating an absence of any vCJD transmission through that route."	
380	3	Comment: According to the publication, a total of 26 samples were tested (4 + 22). Proposed change (if any): Please modify the value "24" to "26"	Accepted.
375-383	3	**Comment 1:** We think that it is important to mention that the patient was also exposed to other possible routes of infection for vCJD: via the food chain,	Partly accepted. The text has been modified. (See also comment #6 above).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		transfusion with donor red cells, surgical and invasive endoscopic procedures. **Comment 2**: the conclusion that the most probable source of infection was non-implicated batches of FVIII in the Peden 2010 article was not re-evaluated following the publication of Gregori et al, 2011[1] which convincingly showed that based on the human situation of vCJD transmission through RBCC and BSE-infected blood transfusion studies in the sheep model, vCJD infectivity in blood and blood components would be significantly lower (by more than 2 logs) than previously estimated . Indeed, although in the 2009 document "vCJD Risk Assessment Calculations for a Patient with Multiple Routes of Exposure"[2], it was concluded that a lower blood infectivity hypothesis would not impact the relative risk levels associated to implicated batches versus non-implicated batches, this assessment did not put in the balance the other probable sources of infection for the haemophiliac patient (see comment 1 above). To our knowledge, the impact of the lower infectivity estimate in blood (and plasma) (Gregori et al, 2011[1]) on the relative risk linked to other sources of exposure, for which no change in the infectivity level estimates is anticipated, has not been considered and might need to be discussed in this paragraph.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		References: 1- Gregori et al, 2011, *Estimation of variant Creutzfeldt-Jakob disease infectivity titers in human blood*, Transfusion NEW REF Rev#8 2- *vCJD Risk Assessment Calculations for a Patient with Multiple Routes of Exposure*, Peter Bennett and Jenny Ball, Health Protection Analytical Team, UK, 5th June 2009 NEW REF Rev#9 3- Proposed change (if any):	
392-394	3	Comment: reference 74 does not contain the information described here. Wrong reference? The reference 74 relates to the injection of spleen and brain homogenized tissue into humanized mice. There is no injection of RBC, plasma or WBC. Proposed change (if any):	Accepted. The reference has been corrected.
410	3	Comment: We believe it's important to always keep in mind that the transgenic mice are PrP overexpressing mice.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): add the word "overexpressing" here: *human PrP* overexpressing *transgenic mice*	
430 (5. Detection techniques)	3	Comment: correction proposed Proposed change (if any): a space is missing between "PrP^{TSE}" and "is"	Accepted.
430-431	3	Comment: concerning "Whilst moderately abundant" Proposed change (if any): please delete the "moderately"	Accepted.
449	3	Comment: Proposed change (if any): Missing word in "that there several". Please correct to "that there are several"	Accepted.
476 – 477 (6. Leucoreduction)	6	Comment: The statement that "there is no compelling scientific evidence to date for the introduction of leucoreduction of plasma for fractionation" could be misunderstood. Elsewhere in the draft paper it is, quite rightly, emphasised that leucodepletion is a wise precaution for red cells and other fresh blood components. This means of course that the	Partly accepted. The statement in lines 467 to 477 refer to plasma for fractionation. The proposed additional sentence has not been included. It should be noted that leucocyte content in plasma is less than

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		leucodepletion of whole blood is highly recommended and that all the derived components downstream of that filtration will also benefit from the risk reduction that is thereby achieved. One can only assume that the statement on lines 476 and 477 must be intended only to refer to discreet leucodepletion of plasma. If so, it would be appropriate to make this clear. Proposed change: ”Taken together, there is no compelling scientific evidence to date for the introduction of separate leucoreduction steps, or other methods aiming at removal of cells and debris, specifically for plasma for fractionation as a precaution against vCJD transmission. The question should be further explored by suitable experiments. It should be noted however that in view of the likely reduced risk benefits afforded to leucodepleted whole blood, recovered plasma from leucoreduced whole blood donations may nevertheless be thought preferable from a vCJD safety point of view to recovered plasma from non-leucodepleted donations.”	in non-leucoreduced whole blood or non-leucoreduced cellular blood components that have been implicated so far with human transfusion transmitted infections. A significant portion of prions in blood is still associated with cell free plasma and will not be removed by leucodepletion. Therefore, emphasis should be put on the prion reduction at subsequent down-stream purification steps. The wording in the paragraph has been modified.
486	3	Comment: concerning “endogenous validation experiments” Proposed change (if any): would “endogenous infectivity experiments” be more precise / appropriate?	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
586 (8. Urine)	3	Comment: Proposed change (if any): please delete "with" in "and sheep ~~with~~ at preclinical"	Accepted.
587	3	Comment: "scrapie" written twice Proposed change (if any): please delete the second "scrapie"	Accepted.
606 – ff (Section 9. Recommendations) (Section 9.1 Sporadic, genetic and iatrogenic CJD and plasma-derived medicinal products	2	Comment: The issue of genetic forms could be addressed if the patient has a confirmation of a negative result with the genetic testing.	Not accepted. The issue has not been understood. If the sick (or deceased) donor is tested negative for genetic markers, genetic disease is excluded but further differentiation between variants, sporadic (and iatrogenic) CJD needs to be performed.
624-625 9.1. Sporadic, genetic and iatrogenic CJD and plasma-	2	Original text: *'Therefore, the CHMP recommendation that recall of plasma derived medicinal products is not justified where a donor is later confirmed as having sporadic genetic or iatrogenic CJD or risk factors…'*	Partly accepted. Additional guidance on cases where it is not possible to confirm such cases has been added in Section 9.2.4

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
derived medicinal 606 products		**Comment:** **In some cases, post-mortem neuropathologic confirmation tests were not carried out due to the lack of tissue donor's availability. Therefore, a possible action to be taken could be to add/give in the guideline a clear indication that the donor should agree on post-mortem confirmatory tests to exclude vCJD (in form of a statement similar to an "informed consent")**	
634 9.2. Variant CJD and plasma-derived medicinal products	3	Comment: spelling mistake Proposed change (if any): replace "vJCD" for "vCJD"	Accepted.
636 – 638 9.2. Variant CJD and plasma-derived medicinal products	6	Comment: We suggest that this is an overstatement of the case. We do not believe that the epidemiological evidence of human to human transmission of vCJD by blood transfusion in section 4.2 and elsewhere is best described as "strong". Given the tiny numbers in the quoted evidence and against the perspective of over 58 million units pf red cell concentrate and other fresh blood components transfused in the UK without any vCJD transmission at all – even at the height of the UK BSE/vCJD crisis – "strong evidence" hardly seems entirely appropriate.	Partly accepted. The epidemiological evidence is considered valid. The sentence has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "There is some epidemiological evidence of human to human transmission of vCJD by blood transfusion (see Section 4.2). However, the clinical and epidemiological data from the UK experience during and since the worst of the BSE/vCJD crisis reveal an absence of any observed infection down this route, since the introduction of leucodepletion. (Note: 58 million units transfused; zero cases of vCJD transmission reported – cf UKPA Memorandum 904/C 25th Oct. 2019.)"	
638 – 640 9.2. Variant CJD and plasma-derived medicinal products	6	Comment: The statement here that "the most likely route of infection in the patient with haemophilia was receipt of UK plasma products" is not altogether uncontroversial. Given the much larger number of samples from the patient's spleen that tested negative as against positive (25 to 1) it does not seem to be entirely clear that the patient can confidently be said to have been CJD positive at all. If the patient was positive (or at least one small part of the spleen was positive) for vCJD, the question as to whether that was due to FVIII or some other phenomenon must surely be admitted to be an entirely open question. Further, bearing in mind the pharmacovigilance data from many hundreds of tonnes of UK donor recovered plasma that were safely fractionated and administered to patients throughout the height of the UK BSE/vCJD crisis (Ref. UKPA Memorandum 904/C 25th Oct. 2019) the whole	Partly accepted. Section has been reworded. However, the proposed wording is considered too detailed for the conclusion section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		issue is surely worthy of more careful re-consideration. Proposed change: "In addition, abnormal prion protein was detected in one tissue sample in a patient with haemophilia treated with high doses of intermediate purity factor VIII (of a kind since superceded by more highly processed and purified clotting factor). Estimates of the relative risks of exposure through diet, surgery, endoscopy, blood transfusion and receipt of UK sourced plasma products suggest that any preclinical infection in the patient with haemophilia may possibly have been caused by receipt of UK plasma products. However, as there are no other cases that confirm this possibility and in view of the absence of actual reported cases of clinical vCJD transmission by any plasma products, including none in the UK in relation to significant quantities of products produced from UK donors' recovered plasma during the height of the UK BSE/vCJD crisis, this suggestion remains controversial."	
638-643	2	Comment: The Agency should consider adding reference for UK-sourced immunoglobulins: **No evidence of asymptomatic variant CJD infection in immunodeficiency patients treated with UK-sourced immunoglobulin.** Helbert MR, Bangs C,	Not accepted. References are not found appropriate for the conclusion section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Bishop M, Molesworth A, Ironside J. Vox Sang. 2016 Apr;110(3):282-4. doi: 10.1111/vox.12358. Epub 2015 Nov 3.	
Lines 645 and ff. (Section 9.2.1 Exclusion criteria, a consideration of country-based exclusion)	2	Comment: Would the Agency comment on the U.S Food and Drug Administration's recent amendment to their CJD guidance? Amendment to "Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products; Guidance for Industry". December 2017' referencing Geographic exposure risk of variant Creutzfeldt-Jakob disease in US blood donors: a risk-ranking model to evaluate alternative donor-deferral policies. Yang H, Huang Y, Gregori L, Asher DM, Bui T, Forshee RA, Anderson SA. Transfusion. 2017 Apr;57(4):924-932. doi: 10.1111/trf.13971. The FDA's current FDA policy states that deferral option focusing on the three highest risk countries (France, Ireland and the UK, bearing in mind that in the meantime, UK residency has been removed as a risk factor in Ireland as of the 07 October 2019, please see details below)	Partly accepted. The section on country-based exclusion criteria has been revised considering the actual data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
648-49	3	Comment: This phrase is ambiguous "Therefore, other approaches are considered in order to try and identify donors who may present a higher risk". Proposed change (if any): We propose to replace by "Therefore several measures have been taken in order to exclude donors who may present a higher risk"	Partly accepted. The section on country-based exclusion criteria has been revised considering the actual data.
650 - 651	6	Comment: The statement here is unfortunately quite seriously misleading. To say that residence in the UK has long been recognised as a risk factor for vCJD is of course accurate. To add that it "has led to the UK deciding no longer to fractionate from UK plasma" really is not. "Has led" implies a recent decision, whereas the decision was in fact taken way back in 1998/'99. Its continued application today is precisely one of the matters that requires careful attention in this present up-dating review. The Irish Blood Transfusion Service's recent decision to discontinue its previous vCJD precautions based on UK residence is a good example, both of a commendably open-minded approach to up-dating these matters and of the kind of careful re-assessment of the relevant risks that is now required and justified. Now that these Irish deliberations, together with the recent UK SaBTO recommendations are available for scrutiny, it is to be hoped that they will be included in the further review process that will	Partly accepted. The section on country-based exclusion criteria has been revised considering the actual data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be undertaken by the EMA/CHMP teams post the consultation phase of the present exercise. Proposed change: "Residence in the UK has for many years been a recognised risk factor for vCJD. In 1998/'99, when very little was known about vCJD, the UK government took the precautionary decision to no longer fractionate from UK plasma. However, these matters are now under review. The Irish Blood Transfusion Service recently undertook a comprehensive study of the situation, resulting in Ireland discontinuing its previous precautionary exclusion of UK donors and Irish donors with a history of UK residence. In the UK also, some precautionary measures in relation to fresh UK donors' blood components have already been discontinued and further changes are under discussion with clinical and patient representative groups. These will be taken into account in the further review of EMA/CHMP recommendations in the period post the current consultation (after 31st October 2019)."	
651-652	2	Original text: '*Residence in the UK is a recognised risk factor for vCJD and has led to the UK deciding no longer to fractionate from UK plasma.'*	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The statement does not reflect the current risk for UK residency. The is no risk factor for someone currently resident in the UK compared to someone who was resident 15 years ago. Also, this statement does not take into account the most recent decision of the Irish Blood Transfusion Service (IBTS) Medical Advisory Committee from 09 September 2019: Permanent deferral policy for individuals that had been resident in the UK, including Northern Ireland and the Channel Islands, for a cumulative period of one year or more between 1 January 1980 and 31st of December 1996 (as well as deferral in place for a number of selected surgical procedures) will no longer be applicable and donors will now be eligible to donate from 7th October 2019. (https://www.giveblood.ie/Can-I-Give-Blood/Keeping-Blood-Safe/vCJD/vCJD.html)	
652	3	Comment: concerns "fractionate from UK plasma" Proposed change (if any): delete the word "~~from~~"	Accepted.
657 - 663	6	Comment: Again, this whole paragraph has been overtaken by events. The recommendations are no longer appropriate.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: It would seem best to omit this recommendation from future drafts.	
667 - 668	6	Comment: It is surely pertinent to point out that a 2019 recommendation that is based on a desire to be consistent with a UK decision taken as long ago as 1998/'99 seems unlikely to have the soundest up-to-date rationale. It is notable that one has to go back 16 years (to 2003) to discover the ancient roots of this approach. It surely has no place in a review designed to update recommendations in the light of the latest evidence. Proposed change: It would seem best not to carry this paragraph forward to future drafts.	Accepted.
669	3	Comment: concerns "fractionate from UK plasma" Proposed change (if any): delete the word "~~from~~"	Accepted.
653-670	2	Original text: 'Exclusion of donors based on cumulative period of time spent in the UK' With the most recent decision of the IBST, this statement would benefit from re-assessment. As already mentioned in the paragraph above, the PSSC would recommend considering the recent decision of the IBTS to remove the deferral for people	Partly accepted. The section on country-based exclusion criteria has been revised considering the actual data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		who had spent 12 months or more in the UK between the years 1980 and 1996 along with certain surgical / dental procedures.	
686 - 688	6	Comment: The difference in exclusion recommendations for the UK and France seems to be based on old evidence and must surely be due for an up-date. The drafted observations on national vCJD prevalence should surely be viewed as sound justification for further review rather than as conclusions purportedly justifying new recommendations. Proposed change: "The historic differences of approach in the UK and France with respect to donor exclusion were based on earlier understandings of possible vCJD risk levels. As these are now being up-dated, so too will be final EMA/CHMP recommendations in relation to exclusion after the current consultation process is complete."	Partly accepted. The section on country-based exclusion criteria has been revised considering the actual data.
714 - 715	6	Comment: The statement that it is not appropriate to recommend the introduction of plasma leucoreduction for the safety of plasma-derived products is presumably aimed at specific policies for plasma for fractionation. It may be best to make this clear. Proposed change: As above.	Not accepted. It is not necessary to modify the text in this section given the scope of this document (i.e. plasma-derived medicinal products).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 742-743 and Point 3, Flow-diagram, page 20	2	*Original text:* *'If such a correlation is not established (e.g. a novel step) and the step is considered critical for removal of infectivity for the specific product (e.g. it is the only step for removal), the investigations should be confirmed using an infectivity assay for the critical step(s). (Flow diagram, step 3)'* *Comment:* *The PSSC would recommend performing infectivity assays for critical steps such as where it is the only removal step. Whilst the PSSC acknowledges the need to perform such infectivity assays, there should be the option of a waiver of the requirement for infectivity assays where biochemical methods such as Western Blotting have been shown to be effective at detecting prion protein and have been validated. The latter should not be the only recourse in order to provide data on 'critical process steps' and it is possible that the such steps may be hard to define in some processes.*	Partly accepted. It is agreed that infectivity assay may only be necessary in specific cases, however the scientific principle outlined so far is not wrong. The sentence has been sightly rephrased.
Lines 764-765. Section 9.2.4 Recall of batches where information becomes	2	Original text '*In view of the lack of adequate information on vCJD, it is prudent to recall batches of plasma-derived medicinal products where a donor to a plasma pool subsequently develops vCJD. Recall should also*	Partly accepted. The section has been modified in order to add guidance on the situations outlined in the comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
available post-donation		*include medicinal products containing plasma-derived products as excipients (see also 9.2.5).'* Comment: The guideline does not provide indications on the actions to be followed from reception of Transmissible Spongiform Encephalopathies (TSE) Notification to the confirmed post-mortem diagnosis: in some European countries a temporary ban of use of plasma-derived medicinal products (PDMPs) is applied/requested by the relevant national Competent Authority in case of notification of suspected CJD (e.g. possible or probable sporadic CJD) until the exclusion of vCJD is confirmed by post-mortem autoptic results. Proposed change (if any): ***The recall or quarantine of PDMP is not justified in case of notification of post donation information concerning already processed units from a subject with a suspected TSE pathology for which the post-mortem autoptic results are not yet available and there are no data (epidemiological, clinical, diagnostic tests*) indicating a suspect case of variant CJD.*** ***On the contrary, if there are epidemiological, clinical tests signs typical of a variant form, it is recommended as a precautionary measure to recall batches of plasma-derived medicinal***	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		products. Recall should also include medicinal products containing plasma-derived products as excipients, whilst final post-mortem diagnosis is pending. **Comment:* EMA guideline should ***recommend or indicate the criteria (clinical diagnosis/possible tests if adequate neuropathological specimens are unavailable)*** **to better discriminate a sporadic/classical CJD from a suspected variant form.**	
772-773-774	2	Look-back to identify the fate of donations should be taken as far as possible. Regulatory authorities, Official Medicines Control Laboratories (OMCLs), surveillance centres and the supply chain should be informed of all batches of product and intermediate implicated whether or not supplies of the batch are exhausted. Comment: EMA guideline should specify in which cases the look-back has to be conducted as far as possible. Proposed change (if any): Look-back to identify the fate of donations should be taken as far as possible ***in case of confirmed variant CJD*** *or* ***suspected variant CJD***. Regulatory authorities, Official Medicines Control Laboratories (OMCLs), surveillance centres and the supply chain	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should be informed of all batches of product and intermediate implicated whether or not supplies of the batch are exhausted. **Alternative/ suggested wording:** ***In case of notification of post donation information concerning a subject with a suspected TSE pathology for which the post-mortem autoptic results are not yet available and there are no data indicating a suspect case of variant CJD, or in case of confirmed sporadic, genetic or iatrogenic CJD, lookback should be not to exceed 5 years from the notification date.***	
Lines 777-788 (Section 9.2.5. Albumin used as an excipient or in manufacturing processes)	2	Comment: Please note that, according to the PSSC's knowledge, no cases in relation to use of any medications with albumin being an excipient have been reported.	Partly accepted. It is correct that no such cases have been reported. The implicated plasma products (i.e. FVIII) have been discussed in Section 4.2 of the Reflection paper. No modification is necessary in this section.
789-790	2	Original text: '*Use of substitutes for plasma-derived albumin used as an excipient or in manufacturing processes is* *encouraged and should be considered as a long-term approach.'*	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment: This statement is problematic as one of the most widely used alternative excipients, Hydroxy Ethyl Starch shows evidence of adverse reactions in certain patient populations and EMA's PRAC has recommended its suspension in January 2018 (https://www.ema.europa.eu/en/news/prac-recommends-suspending-hydroxyethyl-starch-solutions-infusion-market)	