UK Plasma for Fractionation

Review of Safety Profile

Commissioned and approved by the UK Blood Services Forum:

NHS Blood and Transplant

Gwasanaeth Gwaed Cymru Welsh Blood Service

Northern Ireland Blood Transfusion Service

With input from international scientific experts and representatives, including:

PPTA Plasma Protein Therapeutics Association

IPFA international plasma and fractionation association

JPAC

CSL Behring

EPODIN

IPOPI International Plasma Protein Organisation

MRB Marketing Research Bureau

eba European Blood Alliance

Executive summary

This paper provides an overview of the safety profile of plasma donated in the United Kingdom (UK). It is intended to inform the Member States of the European Union (EU) and European Economic Area (EEA), and any other interested party, on the safety profile of UK plasma in the context of vCJD and with respect to its fractionation in the EU for the manufacture of plasma-derived medicinal products (PDMP). It is also intended to assist the plasma industry when considering fractionation of UK-sourced plasma, and to encourage the European Medicines Agency (EMA) to use the latest information in concluding its updated guidance.

Among the many safeguards to prevent the transmission of vCJD through blood components and PDMPs was a ban on the use of UK plasma for the production of all PDMPs, which the UK introduced in 1999. Meanwhile, many non-UK countries implemented deferrals for blood donors, who lived or received a transfusion in the UK.

Cases of vCJD in the general population have been far fewer than had been predicted when precautionary safety measures were introduced more than 20 years ago. Since the introduction of leucodepletion in 1999, and accounting for the incubation period, more than 40 million UK-derived blood components have been issued in the UK with no reports of transfusion-transmitted (TT) vCJD. In February 2021, the UK Government made the decision to permit the manufacture of immunoglobulin from UK plasma.

Following separate reviews that concluded no significant difference in the risk posed, the United States (US), Australia and Ireland have, between 2019 and 2022, lifted their deferrals of blood donors with a history of living in the UK, and the US also accepts donations from people previously transfused in the UK All these reviews conclude that the risk of transmission of vCJD from UK plasma is not significantly different from the risk from any other source of plasma for the manufacture of PDMPs.

Further, the updated US position means that plasma and products imported from the US into Europe may already contain UK plasma, making the current European position inconsistent - a development that also supports a review in Europe. There is rising demand for PDMPs and Europe is facing a threat of shortage in the supply of plasma-derived immunoglobulins to treat patients. Europe (including the UK) depends on US plasma imports for more than 38 % of its need and the EU has an annual shortfall of 3.8 million litres of the plasma needed to manufacture PDMPs for European patients, whilst the clinical need for PDMPs is increasing by approximately 6% per year.

Industry and patient groups are clear that the use of UK plasma would bring significant benefits to European patients and the resilience of the European plasma supply chain, by releasing pressure on the system with the additional source of plasma. Inclusion of UK plasma donations is also supported by ethical considerations, namely that ensuring an adequate supply of PDMPs will save patients' lives.

We conclude that UK plasma for fractionation is as safe as plasma from other sources and urge all blood regulators to take account of this safety profile when considering fractionation of UK plasma. In addition, we suggest that blood regulators review and revise their guidelines on the deferral of donors who have lived in, or received a transfusion in, the UK.

Abbreviations

ACDP TSE	Advisory Committee on Dangerous Pathogens - Transmissible Spongiform Encephalopathies subgroup
BSE	Bovine spongiform encephalopathy
CHM	Commission on Human Medicines (UK)
CHMP	Committee for Medicinal Products for Human Use (EU)
DHSC	Department of Health and Social Care (UK)
EBA	European Blood Alliance
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EFS	Établissement Français du Sang
EU	European Union
FFP	Fresh frozen plasma
IPFA	International Plasma and Fractionation Association
IgG	Immunoglobulin G
IVIg	Intravenous immunoglobulin
LFB	Laboratoire Français du Fractionnement et des Biotechnologies
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NHS	National Health Service (UK)
NHSBT	NHS Blood and Transplant (UK)
NCJDRSU	National CJD Research & Surveillance Unit (UK)
PDMP	Plasma-Derived Medicinal Products
PPTA	Plasma Protein Therapeutics Association
PRF	Prion Reduction Factor
SaBTO	Advisory Committee on the Safety of Blood, Tissues and Organs (UK)
TT	Transfusion-transmitted
vCJD	Variant Creutzfeldt–Jakob Disease

1. Background and aim

1.1. This paper considers the current position regarding the use of plasma donated in the United Kingdom (UK) for fractionation. It considers the safety profile of UK plasma, risk reduction measures, the latest UK and international decisions, the view of industry and patient groups and the supply difficulties and demand needs that make reconsideration of these matters so urgently important.

1.2. Its aim is to inform the Member States of the European Union (EU) and European Economic Area (EEA) on the safety profile of UK plasma with respect to its fractionation in the EU, for the manufacture of plasma-derived medicinal products (PDMP) for use in the UK and, where possible in other countries where patients are in need.

1.3. This paper has been developed on behalf of the UK Blood Services Forum with input from international scientific experts and representatives from the European Blood Alliance, the Plasma Protein Therapeutics Association (PPTA) Global Pathogen Safety Working Group, the International Plasma and Fractionation Association (IPFA), CSL Behring, the National CJD Research and Surveillance Unit, Marketing Research Bureau and the European patient organisations EPODIN and IPOPI. For a full list of contributors, please see Acknowledgements on Page 35.

2. European Union Agencies' positions

2.1. The European Medicines Agency (EMA) is an agency of the European Union (EU) in charge of the evaluation and supervision of medicinal products. In July 2022, the European Commission issued the draft proposal for a Regulation on standards of quality and safety for substances of human origin (SoHO) intended for human application, repealing Directives 2001/83/EC and 2002/98/EC. The proposed Regulation encourages EU Member States to "promote the donation of SoHOs, including plasma, of high quality and safety, thereby also increasing self-sufficiency in the Union".

2.2. The Committee for Medicinal Products for Human Use (CHMP) is the EMA committee responsible for human medicines. The Biologics Working Party (BWP) provides recommendations to the EMA's scientific committees on all matters relating directly or indirectly to quality and safety aspects relating to biological and biotechnological medicines.

2.3. While the EMA has not issued an official position on UK plasma, there is a 2018 CHMP position statement, awaiting review after consultation, on Creutzfeldt-Jakob disease (agreed by the Biologics Working Party). This position statement has been pending review since 2019 (EMA, 2018).

2.4. The 2018 CHMP position statement recommended that: "… *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 are excluded from donating blood/plasma for fractionation*." and *"Since UK donors are excluded from donating plasma for the manufacture of plasma-derived medicinal products in the UK, it is consistent to exclude donors who have spent long periods in the UK.".* This statement has been superseded by the UK MHRA decision to accept UK plasma for the manufacture of immunoglobulins (MHRA 2021)

2.5. Whilst acknowledging the 27 French cases of vCJD, the paper does not recommend the exclusion of donors who have spent any cumulative length of time in France.

2.6. In August 2021, the European Centre for Disease Prevention and Control (ECDC) an EU agency aimed at strengthening Europe's defenses against infectious diseases published a risk assessment entitled "*The risk of variant Creutzfeldt-Jakob disease transmission via blood and plasma-derived medicinal products manufactured from donations obtained in the United Kingdom*" (ECDC 2021). The document notes that the risk of vCJD infection is decreased by plasma fractionation but refers to the absence of a suitable, validated screening test for blood donors, and states that this makes it difficult to assess the residual risk for transmission.

2.7. The ECDC risk assessment reaches the following options for response, with the suggestion that EU/EEA countries consider the risks and benefits of using or handling UK plasma: "*In order to determine whether the use of immunoglobulins and other PDMPs produced from UK plasma would pose an increased threat, EU/EEA countries may consider assessing their endogenous risks, evaluating product-specific data packages (including the prion-reduction capacities of applied fractionation procedures), and balancing the assessed threat with the supply need for PDMPs and source plasma in their country. Until such data are available, EU/EEA countries may consider, as a precautionary measure, preventing the use of immunoglobulins and other PDMPs derived from UK plasma, as well as the fractionation of UK plasma in EU/EEA facilities*". This statement remains unchanged after the July 2022 clarification regarding the scope of the risk assessment being limited to labile blood components. (ECDC, 2021; updated 11 July 2022).

2.8. To assist EU/EEA countries in addressing these suggested options for response this paper covers the following points:

- **Epidemiology of vCJD:** More than two decades have passed since the precautionary measures were put in place. There have been no reported transfusion transmissions by red cells since leucodepletion was introduced in 1999 and no transmissions reported anywhere, ever, through platelets or plasma components. Neither have there been any documented cases of vCJD in the UK population previously treated with UK-sourced immunoglobulin, nor have there been in France, where there were cases of vCJD; leucodepletion and other blood safety measures were implemented and domestic plasma continued to be fractionated and PDMPs administered over the last 25 years. In countries where a review of the risk of transfusion-transmission of vCJD has been conducted (eg, the USA, Ireland and Australia), there has been found to be no significant increase in risk posed by the receipt of blood or blood products from UK donors. (See Section 3.)

- **Risk reduction steps:** There are numerous risk-reduction steps including donor selection, the leucodepletion of plasma, and in the plasma fractionation process. The manufacturing process of PDMPs includes highly effective prion reduction steps and mathematical modelling has shown that PDMPs derived from UK plasma will present an extremely low risk of vCJD. (See Section 9)

- **EU patient need and benefit:** There would be significant benefits to EU patients and the resilience of the European plasma supply chain from allowing the re-entry of plasma from the UK into manufacturing of PDMPs

for the UK market. This will increase the proportion of plasma of European origin available for the production of PMDPs for UK and European patients and will improve the strategic independence of the European plasma supply. This will enhance stability in the supply of essential medicines for patients who depend on treatment with PDMPs. (See Section 4)

3. A history of vCJD in the UK

3.1. In response to the emergence of bovine spongiform encephalopathy (BSE) and vCJD, the UK implemented several safety measures to prevent the spread of vCJD through the food chain, blood transfusion and treatment with PDMPs. This included a ban on the use of UK plasma for the manufacture of all PDMPs, which was implemented in 1999 (MHRA, 2021).

3.2. Since 1995, 178 patients with definite and probable vCJD have been reported in the UK. Of these, 123 are definite, neuropathologically confirmed, deaths from vCJD, and 55 are deaths from probable vCJD (without neuropathological confirmation).

3.3. Four instances of probable TT vCJD have been noted, resulting in three clinical cases of vCJD and one asymptomatic infection in a recipient with post-mortem confirmation of abnormal prion protein deposition in the spleen.

3.4. A fifth individual, who had haemophilia, and had received many doses of Factor VIII concentrate, was found to have abnormal prion in his spleen at post-mortem after he died from an unrelated cause in 2008. He had received treatment with the intermediate purity Factor VIII concentrate 8Y, two batches of which included a donation from a single donor who subsequently died of vCJD in 1997 (the relevant treatments being given in 1994 and 1996). (Peden et al, 2010). This individual had had several RBC transfusions between 1998 and 2007, the earliest of which was probably not leucodepleted, but none from vCJD-implicated donors and the Factor VIII treatment was considered the probable cause of the vCJD infection. However, this remains the only case implicating Factor VIII and the causal connection is not proven. (Peden 2010). See Section 8.4 for a discussion of the prion reduction factor (PRF) associated with the manufacture of PDMPs, which for the 8Y product has been reported as 4 logs lower than that of other PDMPs (Roberts, 2012).

3.5. The UK haemovigilance organisation Serious Hazards of Transfusion (SHOT) reports that there were "*three vCJD incidents prior to the introduction of leucodepletion* [in 1999] *and other measures taken by the UK Blood Services to reduce the risk of vCJD transmission by blood, plasma and tissue products*". SHOT also notes that "*a further prion case died but transfusion was not implicated as the cause of death. The outcome was assigned to major morbidity instead because although there was post-mortem evidence of abnormal prion proteins in the spleen the patient had died of a condition unrelated to vCJD and had shown no symptoms of vCJD prior to death.*" (Serious Hazards of Transfusion, 2021).

3.6. There is a well-established UK CJD surveillance system that employs multiple, overlapping case identification methods, with particular subsystems relating to possible blood/blood product-related cases. It is unlikely that a significant number of cases have been missed, a view supported by published studies (Majeed et al 2000, Urwin et al, 2016, Davidson at al, 2014, Kanguru et al, 2022, Verity et al, 2019).

3.7. vCJD has not been reported in anyone in the UK born after 1989 (the year major dietary protection measures were introduced) and there have been no new cases of TT vCJD since 2007. It should be noted that the transmissions associated with red blood cell transfusions occurred prior to the introduction of leucodepletion in 1999 (National CJD Research & Surveillance Unit, 2020).

3.8. Since the introduction of leucodepletion, more than 58 million UK-derived blood components have been issued in the UK, 40 million of which were issued more than eight years ago (the approximate incubation period for TT vCJD) with no reports of TT vCJD (SHOT report 2021).

3.9. There have been no reports of vCJD transmission via plasma or platelet transfusions. There have been no reported cases of transfusion-related transmission anywhere else in the world even though some countries, such as France, have had cases of vCJD.

3.10. France has had the second-highest number of vCJD cases (27) after the UK (Brandel & Knight, 2018), but has continued to collect and fractionate plasma using nanofiltration after the beginning of the outbreak. The Établissement Français du Sang (EFS) collects around 850,000 litres of leucodepleted plasma for fractionation each year, which is provided to the Laboratoire Français du Fractionnement et des Biotechnologies (LFB). EFS also issues three million blood components each year (EFS, 2020). There have been no reported transmissions of vCJD by LFB-produced PDMPs or EFS-produced blood components.

4. UK position on the safety of UK plasma

4.1. Since the first appearance of vCJD, the UK Department of Health and Social Care (DHSC) has periodically carried out a risk assessment on the predicted number of future infections and associated deaths due to vCJD that could occur from the transfusion of blood components. It combines assumptions based on the latest understanding of the disease and experimental data, including studies to determine the number of individuals who may have the disease but have not developed clinical symptoms, and the results of animal experiments, with the number of deaths due to vCJD that have occurred.

4.2. There was considerable concern regarding the potential length and magnitude of the outbreak, with Garske and Ghani (2010) predicting that there could be 10 cases per year in the 2020s, however the reality has been very different (see Figure 1). Since 2011, when there were five cases, there have only been two further cases, one in 2013 and one in 2016; the first year that zero deaths due to vCJD were recorded was 2012 (NCJDRSU, 2022).

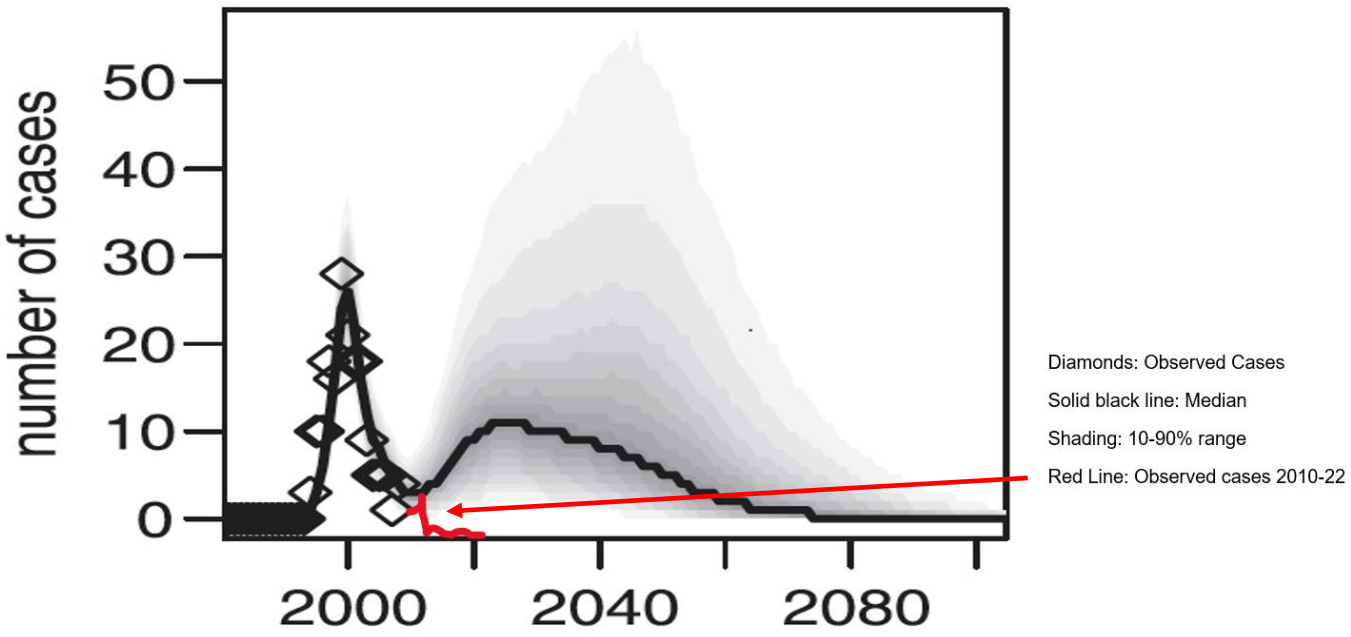

Figure 1: Modelling from 2010 predicting a significant second peak of infections. The actual number of cases has been much smaller (adapted from Garske & Ghani, 2010)

4.3. As more time has elapsed without any further cases of TT vCJD being recorded, the projected number of future deaths has been revised downwards.

4.4. In addition, there is now a better understanding of the disease and studies on animals have shown that all components may carry some infectivity and that leucodepletion is an important risk reduction measure for all blood components, although it does not remove risk entirely (McCutcheon et al 2011, Douet et al 2014). The risk assessment was reviewed in 2018 by the Advisory Committee on Dangerous Pathogens (ACDP).

4.5. Following the review of the risk assessment, in 2019 the UK advisory committee on the Safety of Blood, Tissues and Organs (SaBTO) considered some of the risk reduction measures that were in place to mitigate the risk of transmission of vCJD to paediatric patients. These measures included the importation of Fresh Frozen Plasma (FFP) and the use of apheresis (single donor) platelets for patients born after 1996. Modelling was performed by analysts at DHSC and reviewed by independent experts on the ACDP TSE SubGroup. The analysis showed that the risk of transmission of vCJD by UK FFP was extremely low, on average one in every 5.2 million units of UK plasma transfused. This could result in a further one to two clinical cases due to plasma transfusions over the next 50 years (in the worst case 15 extra cases) (SaBTO, 2019). The requirement to import FFP for this patient group was removed and UK FFP is now provided for these patients.

4.6. In 2020, prompted by the supply risks described in Section 7 and the perceived diminishing risk, the MHRA reviewed the evidence on the safety of UK plasma for use in the manufacture of immunoglobulins. Evidence for the review was gathered through stakeholder consultation (which included manufacturers, patient associations, government organisations, and prion experts) and mathematical modelling of the risk.

4.7. In October 2020, this evidence was presented to the Commission on Human Medicines (CHM), a committee of the MHRA that advises ministers on the safety, efficacy, and quality of medicinal products. The CHM "*deliberated on whether the removal of the ban would pose a risk of increased transmissions and clinical cases of vCJD [and] concluded that* ***the risk of vCJD cases arising from the use of UK plasma for the manufacture of immunoglobulin medicinal products would be negligible****. The CHM also noted the clinical need for immunoglobulin products for patients with immunodeficiency and certain autoimmune conditions"*. (MHRA 2021)

4.8. In February 2021, the ban was lifted on the use of UK plasma for manufacture of immunoglobulin for use in the UK (MHRA, 2021). The CHM advised that UK-sourced plasma is acceptably safe for the manufacture of immunoglobulin medicinal products for the treatment of UK patients, provided that all relevant risk-mitigation measures already in place for blood components for transfusion (the use of leucodepletion, deferral of high-risk donors and traceability between donor and recipient) are applied to UK-sourced plasma for the manufacture of immunoglobulins. There are plans to conduct further reviews of other PDMPs, such as albumin, and further approvals are expected in due course.

5. International perspectives on geographic deferral of donors

5.1. The deferral of donors based on time previously spent in the UK has been recently reviewed in three jurisdictions. In each case the decision has been taken to remove the deferral following analysis of the risk posed by vCJD. There are no known examples of the deferral being maintained following a review of the risk assessment.

5.2. United States

5.2.1. In May 2022, the US Department of Health and Human Services, Food and Drug Administration (FDA), Center for Biologics Evaluation and Research, updated its guidance around the safety of UK plasma. The new guidance *"removed previous recommendations to defer blood donors for (1) geographic risk of possible exposure to CJD for time spent in the UK from 1980-1996 and (2) receipt of a blood transfusion in the UK from 1980-present. This guidance also recommended the requalification of individuals previously deferred for these geographic risk factors, provided they meet all other eligibility requirements*." (FDA, 2022).

5.2.2. The FDA decision to rescind the deferral of blood donors transfused in the UK, was based on the absence of a significant difference from donors in the United States, where no endogenous cases of vCJD have been reported. This strongly supports the assessment that the safety profile of UK plasma is not significantly different from any other source plasma for the manufacture of PDMPs.

5.2.3. Further, the FDA noted that it was "[changing its] *geographic deferral recommendations for vCJD risk based on new information in the risk assessments published by UK's SaBTO and MHRA. These risk assessment models, which FDA has independently evaluated, demonstrate that, in the UK, the current risk of vCJD transmission by blood and blood components would expose transfusion recipients to no or minimal additional risk of vCJD in the future, and, for blood components that are leukocyte reduced, the possible risk is even further reduced*" (FDA, 2022).

5.2.4. This change has also created a paradox where PDMPs manufactured from US plasma could be used in the UK or Europe, having been derived from donations from individuals who are currently not allowed to donate in the UK and EU countries due to previous residency or receipt of a transfusion in the UK. This makes the current European position inconsistent. If, following this change, US imports are considered to remain acceptable, it would appear reasonable that PMDPs derived from UK plasma should also be considered acceptable.

5.3. Australia

5.3.1. In April 2022, the Australian Therapeutics Goods Administration (TGA) overturned its ban on former UK residents donating blood in Australia due to the perceived risk of vCJD. The ban had been in place for two decades. This followed McManus and colleagues' review of the Australian Red Cross Lifeblood policy of deferring donors who had either been resident in, or travelled through, the UK. They concluded that the removal of the deferral would have no negative effect on the safety of the blood supply and would be a safe and effective strategy to increase the donor base (McManus et al, 2022).

5.3.2. Following the lifting of the ban, Australia's LifeBlood noted: "[we are] *delighted to have received a decision from the Therapeutic Goods Administration, which will enable people who lived in the United Kingdom between 1980 and 1996 to donate blood. We look forward to having more to share once planning for implementation is complete, including a date for when we expect to welcome new donors*." (Australian Red Cross Lifeblood, 2022a).

5.3.3. The lifting of the ban on UK donors meant that 21,000 new donors signed up to become blood and plasma donors (Australian Red Cross Lifeblood, 2022b).

5.4. Ireland

5.4.1. In 2019, Ireland overturned its deferral of donors who had previously resided in the UK. A comprehensive review of the risk of vCJD associated with blood transfusions was conducted by the Irish Blood Transfusion Service (IBTS) in 2019. Prior to this, donors that had possibly been exposed to vCJD via blood transfusion, surgical instruments and residency in the primary BSE endemic area (UK, Northern Ireland and the Channel Islands) during the period from 1 January 1980 until 31 December 1996 could not donate.

5.4.2. The IBTS Medical Advisory Committee met on 13 May 2019 and decided that "*the current deferral 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, would be no longer be applicable and donors will now be eligible to donate.*

6. Patient, blood establishment and industry perspectives

6.1. Patient and European Patient Organisation for Dysimmune and Inflammatory Neuropathies (EPODIN)

6.1.1. According to the European Patient Organisation for Dysimmune and Inflammatory Neuropathies (EPODIN), “Patients with dysimmune and inflammatory neurological diseases (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, Lewis-Sumner syndrome etc), suffer a major and sometimes irreversible loss of autonomy in the absence of the appropriate first-line treatment based on PDMPs. A significant proportion of patients die prematurely. The chronic nature of many of these diseases requires a regular and continuous supply of plasma, which can only be obtained through the careful mobilisation and organisation of the European blood and plasma supply chain.”

6.1.2. EPODIN also notes that, “The health independence of Europe and its countries is also a concern for European patients. Indeed, the plasma collected on our continent is very insufficient to meet the needs of patients for whom care is delayed or suspended due to the lack of access to PDMPs. In some European countries with still fragile health systems, patients sometimes have no access at all to these essential therapies. It is essential for the UK to collect plasma to treat its most vulnerable population. Countries such as France, a nation of comparable size that has also had to deal with vCJD and BSE in the 1990’s, has chosen to maintain plasma collection to enable PDMP supply to patients.”

6.1.3. Finally, EPODIN is of the view that “Europe cannot remain indefinitely dependent on American plasma and continue to treat, in a suboptimal way, hundreds of thousands of European patients who are dependent on PDMPs due to a lack of sufficient supply of plasma "raw material". It is essential that the United Kingdom contributes to the European ambitions of blood plasma collection while (i) the needs of the patients continue to grow, and (ii) industrial plasma fractionators assure the safety of their products.” (EPODIN, 2022).

6.2. PLUS, the Platform of Plasma Protein Users

6.2.1. The Platform of Plasma Protein Users (PLUS), is a consortium of seven patient organisations representing people living with treatable rare plasma-related disorders such as haemophilia, primary immunodeficiencies and alpha1 anti-trypsin deficiency among others. Together, these organisations represent the views of more than 110,000 people living with treatable rare plasma-related disorders in Europe.

6.2.2. PLUS, in email correspondence, have stated: "*Each European country should collect more [plasma], so that they can contribute to a regional effort to increase plasma collection so as to contribute to the global sufficiency of PDMPs.[…] The data presented [herein] […] shows that plasma donated by the citizens of the UK and the Republic of Ireland is as safe a raw material for the development of PDMPs as any plasma donated anywhere else in Europe."*

6.3. International Plasma and Fractionation Association (IPFA)

6.3.1. IPFA represents mainly not-for-profit organisations engaged in the collection of plasma and fractionation of it into PDMPs. IPFA´s members represent both blood organisations collecting plasma and manufacturers (fractionators) who produce PDMPs.

6.3.2. A key strategic priority for IPFA is to mitigate the risk of dependency of supply of plasma from any single country or region – also known as 'strategic independence of plasma'. Given the current dependency on US plasma for the global plasma supply, IPFA promotes Europe's strategic independence of plasma in order to avoid the risk of shortages in case of adverse events in the US plasma supply (IPFA, 2022).

6.3.3. In December 2021, IPFA and the Plasma Protein Therapeutics Association (PPTA) issued a joint letter to the ECDC regarding the ECDC risk assessment of UK plasma. In the letter, the two organisations challenged the ECDC conclusions, noting that, "*in its current form the Risk Assessment does not provide robust, evidence-based advice on the risks that the use of plasma and blood from UK donors poses to the safety of manufactured human IGs, taking into account any risk-reduction measures that could be applied during donation, processing or manufacturing.*

6.3.4. PPTA and IPFA encouraged the ECDC *"to consider an impact assessment based on risk-benefit balance, the attention to important data which are relevant for an appropriate assessment of the risk and evidence on effectiveness of manufacturing process to remove prions*." (PPTA & IPFA, 2021).

6.3.5. The ECDC has clarified that the "*assessment of variable industrial processes and their impact on the microbial safety of the medicinal products is beyond the remit of ECDC. Any references to manufacturing included in the Risk Assessment were included merely to provide context, and were not subject to further analysis, for the reasons detailed herein'"* PPTA and IPFA have requested that ECDC updates its literature review and assessment to include manufacturing processes and cleaning (PPTA & IPFA, 2021).

6.3.6. In August 2022, IPFA encouraged the EMA/BWP to update the 2018 CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products, following the UK plasma risk assessments and up to date scientific data.

6.4. European Blood Alliance

6.4.1. In 2022, the EBA, an association of not for profit Blood Establishments, with 28 members (including observers) throughout the European Union, EFTA States and United Kingdom, published on its website a statement emphasizing that *"Increasing plasma collection by not-for-profit blood establishments in Europe is a priority for the European Blood Alliance (EBA), to safeguard the supply of safe PDMPs and blood components for patients in Europe while preserving donor health.",* and stated that *"EBA notes the change in deferral criteria in countries in which these risk analyses have been performed and calls on all European stakeholders to assess the analyses, with a view to perform a similar risk analysis and, where pertinent, to consider updating their own deferral criteria regarding blood and plasma donation.*

6.5. Plasma Protein Therapeutics Association (PPTA)

6.5.1. PPTA represents the private sector manufacturers of plasma-derived and recombinant analog therapies, collectively known as plasma protein therapies and the collectors of Source plasma used for fractionation.

6.5.2. Following the lifting of the UK ban PPTA, in February 2021, *"welcome(d) the decision of the UK government to lift a two decades old ban on the use of UK-donated plasma for the manufacture of immunoglobulins, following a scientific review conducted by the Medicines and Healthcare products Regulatory Agency"* (Liebe, 2021a).

6.5.3. The PPTA noted that*, "For too long, patients in the UK have relied on U.S. plasma donors for the manufacture of plasma-derived medicines (…) The need for plasma is now more urgent than ever, so this decision by the UK government will help increase the overall availability of these lifesaving medicines"* and that*, "Increasing plasma collections wherever possible is essential to meet the growing clinical need for plasma-derived medicines. Accordingly, PPTA eagerly anticipates the publication by the European Medicines Agency of its assessment on the safety and use of UK plasma for manufacturing of PDMPs"* (Liebe, 2021a).

6.6. A Fractionator view

6.6.1. CSL Behring has provided a fractionator's view on UK plasma. CSL Behring "*welcomes initiatives like the MHRA review to lift the ban on fractionation of UK plasma for use in the manufacture of PDMPs as it sought to examine and re-assess standards based on accurate scientific reasoning. It is important that the rules governing plasma donor selection, testing and manufacturing processes are regularly reviewed to ensure they are consistent with the latest scientific evidence, whilst maintaining highest quality and safety of source plasma. Millions of people around the world rely on plasma-derived therapies as lifesaving and life-sustaining treatments, and these people need and deserve a regulatory framework which ensures safe and efficacious treatments, as well as an adequate supply of source plasma that is needed to produce them.*"

6.6.2. CSL Behring is of the view that "*Safety of PDMPs against TSE relies on plasma donor selection and TSE reduction capacity of manufacturing processes which have been investigated by manufacturers of PDMPs. These extensive studies conducted by manufacturers and an examination of the latest available literature show that manufacturing processes include adequate prion reduction steps with the capacity to reduce experimental TSE agents. (Cai et al, 2013) There is strong experimental evidence and mechanistic knowledge that manufacturing processes of PDMPs can be considered as a significant safety pillar to complement low risk donor population to assure safety of PDMPs. (Lee et al, 2001; Stenland et all, 2002)*"

6.6.3. Finally, CSL Behring notes that "*Donor selection criteria should be regularly reviewed and revised based on current scientific evidence to avoid unnecessary constraints in plasma supply with no added patient safety benefit."*

7. Rising patient demand for plasma derived medicinal products

7.1. The EU has a shortfall of 3.8 million liters (or 30%) of the plasma needed to manufacture PDMPs for European patients, with clinical need for PDMPs increasing ~6% per year (Liebe, 2021b). Europe (including the UK) depends on US plasma imports for more than 38% of its need (Liebe 2021a; Marketing Research Bureau 2022).

7.2. There are risks associated with this reliance on importation. The global plasma shortage has been exacerbated by the COVID-19 pandemic, due to a fall of 20% in plasma collection throughout the US in 2020 owing to donor deferrals and pandemic-related restrictions. By 2022, although in recovery, most of the industry has not reached pre-pandemic plasma collection figures.

7.3. Further, the US currently operates on a paid donation model with US donors able to donate plasma twice per week. Concerns have been raised about the high frequency of plasma donations in the US and potential adverse health impacts on donors. Should the FDA reduce its allowable donation frequency, this would significantly reduce the amount of plasma available to the EU.

7.4. The total IVIg usage in Europe (inclusive of the UK) is 64 tons per annum, and 50 tons per annum for the EU (excluding the UK). In 2020, France was the largest IVIg market, followed by Germany and Italy. For all plasma-derived products, the five largest countries (Germany, France, Italy, Spain and the United Kingdom) made up over 60% of the total market while their population constituted 41% of the region. In the least developed countries in the region, immunoglobulins do not drive the market because the cost of chronic immunoglobulin therapy is beyond the means of most patients, and it is not purchased in large volumes by their governments, primarily due to cost and availability (Marketing Research Bureau, 2022b).

7.5. It is estimated that up to 350,000 EU patients may rely on IgG. Accurate estimates are difficult as IVIg is prescribed to treat a wide array of indications ranging from primary to secondary immunodeficiencies, and neurologic, hematologic and dermatological conditions. In order to manage the restricted supply, some EU countries have established IVIg usage guidelines or “priority list of indications” to offer guidance and limit the IVIg prescribed (Marketing Research Bureau, 2022b).

7.6. Factors such as economic situations, health care policies, influence of patient advocacy groups, insurance and other socio-economic factors also vary across EU countries, impacting the number of official IVIg patients. This is reflected in IVIg consumption per capita rates across European countries. For example, in 2020, the IVIg consumption per capita was highest in Switzerland with 224 kilograms per million people, while the lowest was in Georgia with 0.3 kilograms per million people (Marketing Research Bureau, 2022b).

7.7. In England, the NHS Immunoglobulin Database reported that in 2021 around 20,000 patients in England relied on IVIg, indicating perhaps another 4,000 in the rest of the UK (NHS, 2021). Due to the limited supply, the UK's National Health Service (NHS) has implemented prioritisation measures to allocate immunoglobulins to patients with the highest clinical need.

7.8. The UK needs ~1.5M litres of plasma per year, and the target is to reach 30% self-sufficiency by 2025. In the scenario where 45% self-sufficiency is achieved there would be a reduction in the European plasma demand gap from 38% to 33% (see Figure 2).

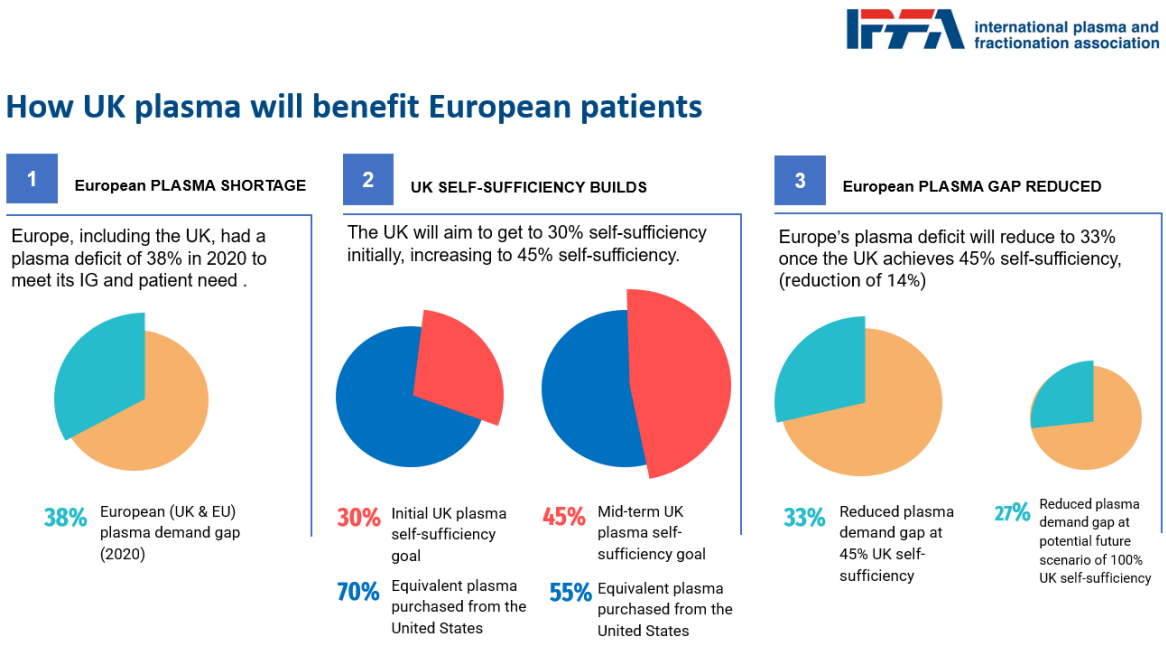

Figure 2: The indirect benefit to European patients of the use of UK plasma for UK patients (IPFA, 2022)

8. Plasma risk reduction methods

8.1. The MHRA sets out two main approaches used to further reduce the risk of transmission of diseases by PDMPs. The first is *"controlling the quality of the starting material to ensure that only low-risk material enters the manufacturing process"* and the second is "*controlling the manufacturing process to ensure that it provides a sufficient level of safety to accommodate the use of UK-sourced plasma."* The review also stated that *"relevant risk-mitigation measures already in place for blood components for transfusion (the use of leucodepletion, deferral of high-risk donors and traceability between donor and recipient) should be applied to UK-sourced plasma for the manufacture of immunoglobulins."*

8.2. Donor selection criteria

8.2.1. The MHRA suggests controlling the quality of the starting material, which "*could include donor deferral (e.g. based on medical history, age) or starting material/pool testing (if a suitable test becomes available).*"

8.2.2. Donor selection criteria in the UK are stringent and are kept under close review by both the Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) and SaBTO. The criteria currently exclude individuals who have received human pituitary-derived hormones, grafts of human dura mater or cornea, sclera or other ocular tissue, are identified as being members of a family at risk of inherited prion diseases, persons who have been told that they have been put at increased risk from surgery, transfusion or transplant of tissues or organs, and persons who have been told that they may be at increased risk because a recipient of their blood or tissues has developed a prion-related disorder (JPAC, 2022).

8.2.3. Persons who are known to have received an allogeneic tissue or blood transfusion since 1980 are also deferred from donation in the UK although it is likely that this measure will be reviewed given the US FDA decision to now accept donations from people who received transfusions in the UK (see section 5.2.4).

8.2.4. SaBTO and UK Blood Services considered additional donor selection criteria around donor age, exploring the possibility of sourcing a sustainable blood supply from donors born after 1996, when human food chain regulations were sufficiently tight to exclude the possibility of BSE contamination. The post-1996 donor cohort became eligible to donate in 2013 in small but growing numbers so the proposal was to target blood from these donors to the most vulnerable recipients. However, this strategy was found to present an increased risk of transmitting other infections such as Epstein Barr Virus, Cytomegalovirus and Parvovirus B19 (SaBTO, 2014).

8.2.5. The picture was further complicated by the outcome of the "Appendix III" study which found no significant difference in the prevalence of abnormal prion protein staining between any of the appendix survey populations, which included the post 1996 birth cohort. The ACDP acknowledged that these results were difficult to reconcile, concluding that *"There could be some "background" prevalence in all groups, plus some additional prevalence associated with BSE in the most highly-exposed population."* and going on to say that "*whichever interpretation is adopted, the contrast between the prevalence of abnormal prion protein and the number of clinical vCJD cases seen to date suggests that only a few of those with this protein abnormality will develop any symptoms of prion disease*." (Advisory Committee on Dangerous Pathogens TSE Subgroup, 2016).

8.2.6. Regarding "testing of the starting material or pool testing", despite considerable efforts over more than 20 years to develop a blood donor screening assay for vCJD, this has not progressed to the stage where it is sufficiently reliable or practical to be used by blood services and there appears to be little current activity in this area (Edgeworth et al., 2011; Seed et al., 2018). If a fractionator's risk assessment indicates that it would be worthwhile to test the manufacturing pool then the Protein Misfolding Cyclic Amplification (PMCA) assay could be contemplated (Giaccone & Moda, 2020).

8.2.7. The UK has very strong systems in place for donor-to-patient traceability for blood components. The collection of plasma for fractionation is being performed by UK Blood Services to the same standard. When a fractionator is appointed, their plasma master file will require details of all constituent donations to each manufacturing pool allowing full traceability between each individual donation, the relevant pool of donations and all resulting products manufactured from that pool.

8.3. Leucocyte depletion

8.3.1. The removal of the majority of leucocytes from blood components is standard practice in the UK following its implementation in 1999, and will remain in place for plasma for fractionation. It is widely acknowledged that this has been a major contributory factor to the reduction of transfusion-transmission of infections. The CHMP Position Statement comments that *"Despite widespread exposure to potentially contaminated blood transfusions in the UK, Europe and the wider world, confirmed cases of vCJD resulting from exposure to contaminated blood or blood products are small. This may be partly attributed to the rapid introduction of leucodepletion."* (EMA, 2018).

8.3.2. In its review of IG manufacture, the MHRA found that "*leucodepletion decreases the risk of infection by a factor of ~5 and the risk of clinical case by a factor of ~3.5*" (MHRA, 2021). Leucodepletion has been found to have many other benefits such as the reduction of HLA alloimmunisation, adverse transfusion reactions and disease transmission, and its use is a basic assumption in the modelling used in several previous safety reviews and recommendations such as the SaBTO reviews of Cytomegalovirus (CMV) testing and Human T-cell Lymphotrophic Virus (HTLV) testing (SaBTO, 2018).

8.3.3. The number of donations that are pooled prior to the fractionation process has previously been considered to be proportionate to the risk of contamination of the pool with a pathogen. Pool sizes can range from less than 100 to upwards of 100,000. However, where prevalence of the pathogen is very low, the larger pool size may be considered to contribute a dilution effect that reduces the likelihood of an infectious dose being present in the final products. It should be noted that the modelling in this paper assumes dilution rather than dispersal of infectious prion, consistent with the approach by the MHRA in their risk assessment (MHRA, 2021).

8.4. Manufacturing processes and prion reduction factors

8.4.1. The second approach in the MHRA report *"...could include mandating leucodepletion, the use of prion or nano-filters, specific combinations of numbers of donations and prion reduction factor to ensure an acceptable risk. Additional measures could relate to traceability of the source plasma and effective methods for cleaning manufacturing equipment."* The areas not already covered are discussed below.

8.4.2. Regulatory authorities require manufacturers of PDMPs to carry out ‘product-specific investigational studies’ and to critically evaluate their manufacturing processes to determine the prion reduction factor (PRF) specific to each individual PDMP (e.g., CHMP 2004). Although the physical and biochemical characteristics of prion agents suggest that they could well be removed by separation technologies used in, or compatible with, the preparation of PDMPs (Foster, 1999), suitable experimental data are required to determine the extent to which this is achieved in practice.

8.4.3. There are many variables and limitations to the experimental studies such as the source of the infectious material (endogenous material from an infected animal or exogenous material ‘spiked’ into the relevant matrix eg plasma), the species and strain of the infectious material (eg hamster-adapted scrapie or mouse-adapted BSE), and the detection method (eg *in vivo* determination of infectivity (ID50) or *in vitro* determination of abnormal prion protein by Western Blot etc).

8.4.4. Steps in the plasma fractionation process that have been examined using these procedures include precipitation steps employed in the preparation of immunoglobulin and albumin by ethanol fractionation of plasma, depth filtration processes used in the preparation of immunoglobulin and albumin, chromatographic processes used in the preparation of albumin, immunoglobulin and coagulation factors, and nanofiltration of protein solutions, including immunoglobulin and coagulation factors (see sections 7.5 and 7.6) are also adsorption and/or precipitation steps used in the preparation of lower purity Factor VIII concentrates.

8.4.5. The PRFs claimed by one manufacturer ranged from 4.8 log to greater than 11 log for a range of PDMPs (Roberts et al, 2012), another reported 12.9 log reduction for an IVIg preparation (Goussen et al., 2017) and manufacturer responses quoted in the MHRA risk assessment for IVIg range from 4.8 log to 10.5 log and from 7.3 to 9.4 for hyperimmune immunoglobulin (MHRA, 2021). For a comprehensive review of processes and PRFs see Cai et al 2013, and Flan and Arrabal, 2007.

8.4.6. However, when multiple steps are used in the manufacture of each PDMP, and where each step may have been demonstrated to have a PRF, the overall PRF for the product is not calculated as the sum of each individual step as this may risk ‘double counting’ if the basis of separation is the same eg precipitation. Using the PRF of the most effective step (which range from 1.8 to 6.8 logs in these publications) or ‘combined steps’ studies is a suitably cautious approach.

8.5. Prion filters and nano-filters

8.5.1. Filters containing specific ligands for prion protein were developed for use with individual blood donations but were never implemented in the UK (or elsewhere) as no clear benefit in the reduction of endogenous infectivity was demonstrated in independent studies (EMA, 2018). A medicinal plasma product is available that uses an affinity ligand gel prion reduction step in its manufacture, but no claim is made for any degree of prion reduction.

8.5.2. Nanofiltration using 15 or 20 nm filters is used as a viral reduction step in the manufacture of many PDMPs and has been effective in the removal of prion infectivity using various preparations of scrapie brain homogenate as spike models and *in vitro* and *in vivo* read out (Roberts et al, 2012, Cai et al, 2013). However, the nature of the spike material may influence the performance of the filter, and concentration polarisation at the filter surface may mean that the scaled-down models of the manufacturing process may not give realistic results. Therefore, it may be reasonable to use spike preparations with different physico-chemical properties and include in the modelling the lowest prion reduction factor (PRF) demonstrated.

8.6. Cold ethanol precipitation and other steps

8.6.1. Cold ethanol precipitation steps, which constitute the upstream part of albumin and immunoglobulin purification processes, provide robust prion removal capability in experimental studies using various spike models and *in vitro* and *in vivo* read out (Lee et al, 2001; Gregori et al, 2004; Cai et al, 2013).

8.6.2. Other purification steps employed in manufacturing processes of PDMPs (including immunoglobulins and coagulation factors) such as chemical precipitation steps, low pH depth filtration and chromatography steps further contribute to the prion reduction capacity of manufacturing processes of PDMPs (Stenland et al, 2002; Stucki et al, 2008; Gröner et al, 2012; Cai et al, 2013).

8.7. Summary of prion reduction during manufacturing

8.7.1. Based on currently available experimental studies from manufacturers of PDMPs, it is estimated that PDMPs have greater than 4 log (or 10,000 fold) manufacturing process reduction of the vCJD agent (FDA TSEAC Draft Risk assessment, 2006; Cai et al, 2013).

8.8. Cleaning of manufacturing equipment

8.8.1. There is a theoretical risk that, should prions causing vCJD be present in a pool of plasma, they may contaminate the manufacturing equipment such as stainless-steel tanks, tubing and chromatography columns. There is experimental evidence from animal models that shows prions in brain homogenates can adhere to steel and can transmit disease, but the models' relevance to human prions in blood may be questionable - the amount of prion infectivity would be very much lower and being in a protein-rich matrix could inhibit binding. Nonetheless, sanitisation of manufacturing equipment is a regulatory requirement for inclusion between batches and the current use of sodium hydroxide or other reagents has been shown to be effective for stainless steel decontamination and regeneration of chromatography resins (Gröner et al., 2004; Bellon et al., 2013). Manufacturers of PDMPs perform small-scale studies to demonstrate the effective reduction of experimental prion agents by the cleaning regimen of manufacturing lines (EMA, 2004; Käsermann et al, 2003; Gröner et al., 2004; Bellon et al., 2013). Therefore, no additional cleaning or sanitisation methods are necessary when processing UK plasma.

9. Consideration of the relative risk of UK plasma

9.1. In January 2017, a working group of SaBTO was established to advise whether the risk reduction measures for TT vCJD of a) importing plasma and b) using apheresis platelets for individuals born on or after 1st January 1996 and for patients with thrombotic thrombocytopenic purpura, should be maintained, withdrawn for some individuals, or withdrawn altogether.

9.2. As part of the analysis to support that advice, the working group estimated that using UK plasma for these transfusions would create a small additional transmission risk; on average for every 5.2 million units of UK plasma transfused there may be one additional death due to vCJD.

9.3. The risks per unit of plasma used to derive medicinal PDMPs will be different from this for two main reasons: pooling of multiple units of plasma and prion reduction during fractionation.

9.4. The calculations provided show that the risk from each unit of donated plasma is lower when that unit is used to make PDMPs through fractionation, than when it is transfused. In particular, we show that a unit of plasma that is used for fractionation, with a 4-log prion reduction factor, is over 7,000 times less likely to lead to a vCJD transmission than if that unit was used for transfusion. This suggests that there would be less than one death from vCJD for every 36.4 billion units of plasma that are fractionated (assuming at least a 4-log prion reduction).

9.5. An infected unit of fresh frozen plasma given during transfusion has the following likelihood of transmitting vCJD where p is the prion dose measured in ID50s, and L is the level of leucodepletion.

$$1 - 0.5^{\frac{p}{L}} \qquad [1]$$

9.6. An infected unit that undergoes fractionation for the creation of PDMPs has the potential to infect more people as it will feed into a large pool. However, it will also be diluted amongst other donated plasma units and will undergo prion reduction.

9.7. The expected number of transmissions caused by a unit of plasma that undergoes fractionation is:

$$U * (1 - 0.5^{\frac{p}{L*U*10^{R}}}) \qquad [2]$$

9.8. U is the number of units of product created per batch, and R is the log prion reduction. The first U accounts for the number of recipients exposed to the unit, whilst the U in the exponent accounts for the prions from this donation being diluted by being spread across U units of product.

9.9. For positive values of x that are less than 1, the following holds:

$$x * 0.5 \leq 1 - 0.5^{x} \leq x * \ln(2) \qquad [3]$$

9.10. The right inequality holds for all positive x whilst the left holds for x less than 1. Since there have been no identified cases of transmission from leucodepleted blood products, it is believed that transmission rates for leucodepleted units are significantly below 50%. This is sufficient that p/L < 1 and so the risk from transfusion of an infected unit of FFP is at least:

$$\frac{0.5 * p}{L} \qquad [4]$$

9.11. Whilst the expected number of transmissions caused by a unit of plasma that undergoes fractionation is at most:

$$\left| \frac{p}{L * 10^{R}} * \ln(2) \right| \qquad [5]$$

9.12. By looking at the ratio of risk (dividing [4] by [5]), we see that plasma that undergoes fractionation causes approximately $0.7*10^{R}$ fewer transmissions.

9.13. For a 4-log prion reduction this is a 7,000-fold reduction. This means that if there is predicted to be one death from vCJD for every 5.2 million units of fresh frozen plasma transfused, there would be less than one death from vCJD for every 36.4 billion units used in fractionation.

9.14. It is predicted that approximately 1.1 million units of plasma will be collected each year in the UK, meaning that there may be one death from vCJD transmission every 33,000 years.

9.15. It is important to note that there is considerable uncertainty in this modelling and these numbers should be viewed with caution. However, it is clear that the probability of TT vCJD through the use of UK plasma for fractionation is extremely low.

10. Ethical considerations of the use of UK plasma for PDMP manufacture

10.1. The main ethical argument in favour of allowing the use of UK plasma donations for the production of PDMPs is that increasing the supply of PDMPs seems necessary to avoid shortages, and thus to avoid adverse effects for patients whose health relies on PDMPs. Given the extremely low risk of vCJD-transmission through UK-sourced PDMPs demonstrated in this paper, this health benefit is expected to outweigh any adverse health effects.

10.2. Whilst it was appropriate, on a precautionary basis, to cease the fractionation of UK plasma in 1999, maintaining this policy under current circumstances cannot be justified by appealing to the precautionary principle. Application of the principle must be consistent and proportionate, which implies that it cannot be used to justify the action of retaining the ban that will, in any credible scenario, cause more serious harms through restricting PMDP supply than it would prevent (Kramer et al. 2017b, 2017c).

10.3. Over the last 23 years it has been found that the risk is much smaller than had been feared, while the deferral policy increases the risk that the supply of essential blood products will be inadequate and that some patients will suffer serious consequences as a result. An evidence-based approach may now be taken to trade-off these risks.

10.4. This is consistent with Watkins et al (2012) who note: *"revision or removal of safety initiatives needs to be considered if operational experience or new scientific evidence leads to a changed view... This is particularly the case of initiatives introduced on a precautionary basis before comprehensive evidence on the level of risk being available."* In this case, the trade-off is between two risks, and Wilson et al (2018) specifically consider vCJD donor deferral measures when discussing the removal of precautionary policies. They note that this can be politically challenging, especially when the theoretical risks may still be perceived, but discuss the potentially harmful consequence of maintaining these precautionary policies, not only resulting in the short-term loss of blood donors but reducing the capacity to introduce policies to address future risks. They conclude that intermediate approaches, as with the original vCJD precautionary measures (eg importing plasma for transfusion to younger recipients), and the current proposals (eg using UK plasma for PDMPs only for UK patients), can be an appropriate way to deal with transfusion medicine issues where the trade-off is between risk-risk rather than risk-benefit.

10.5. When considering removing a safety measure, one should ask whether such a policy would be implemented today, based on the latest evidence. In this case, it is unlikely that UK plasma would be excluded, given that it would make no tangible safety improvement to the safety profile demonstrated herein, whilst causing the potential harm of restricted availability for patients in need of PDMPs. Removing safety measures may be more politically sensitive than deciding not to implement them, but it is doubtful that there is any ethical difference (Kramer et al 2017a).

10.6. Manufactured medical products like PDMPs are rightly expected to meet high safety standards. There can nevertheless be valid ethical arguments not to apply every safety measure that would further reduce small residual risks (Verweij & Kramer 2018). Allowing UK plasma donations is supported by such an ethical argument, namely that ensuring an adequate supply of PDMPs will save patients' lives, and therefore does not conflict with manufacturers' ethical responsibility.

10.7. Following the relaxation of safety measures, it would be appropriate to retain surveillance to ensure that any unintended effects will be identified promptly.

11. Conclusion

11.1. More than two decades have now passed since the precautionary measures were put in place following the outbreak of vCJD. There have been no reported transfusion transmissions by red cells since leucodepletion was introduced in 1999 and no transmissions reported anywhere, ever, through platelets or plasma components. Neither have there been any documented cases of vCJD in the UK population previously treated with UK-sourced immunoglobulin nor have there been in France, where there were cases of vCJD but leucodepleted domestic plasma has continued to be fractionated.

11.2. In countries where a review of the risk of vCJD transmission has been conducted, there has been found to be no significant difference in the risk posed by the receipt of blood or blood products from UK donors, than from any other donors. The UK now permits the use of domestic plasma for transfusion, and for the manufacture of immunoglobulin. There are many measures in place to prevent transmission of infections by PDMPs but the possibility of transmitting infective agents cannot be totally excluded - this applies to known pathogens but also to unknown or emerging viruses and other pathogens.

11.3. In the United States, where no endogenous cases of vCJD have been reported, the deferral of blood donors transfused in the UK was also lifted based on the absence of significant difference in risk. This fact strongly supports the assessment that the risk of transmission of vCJD from UK plasma is not significantly different from that posed by any other source plasma for the manufacture of PDMPs. Further, the updated US position means that plasma and products imported from the US into Europe may already contain UK plasma, making the current European position inconsistent - a development that also supports a review in Europe.

11.4. It is appropriate to review the precautionary safety measures considering 23 years of epidemiological evidence that suggest the absence of additional risk, and it is ethical to do so given the opportunity to provide significant benefit to patients currently in need of treatment.

11.5. The demand for PDMPs is increasing and there would be significant benefits to EU patients and the resilience of the EU plasma supply chain should fractionation of UK plasma into PDMPs be permitted. This would reduce dependency on importation, improving strategic independence and benefiting patients who depend on treatment with PDMPs, which can currently be restricted based on supply, not need.

11.6. This paper provides detailed information for consideration by the plasma and fractionation industry, and by member states when addressing the issue of UK plasma safety. It encourages blood authorities and countries striving to increase the global blood and plasma donor base (and thus increase the amount of collected plasma for fractionation) to review and revise their guidelines on the deferral of donors who have lived in, or received a transfusion in, the UK.

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