Received: 21 December 2022 | Revised: 16 January 2023 | Accepted: 7 February 2023

DOI: 10.1111/vox.13416

REVIEW

Vox Sanguinis ISBT International Society of Blood Transfusion

Safety profile of plasma for fractionation donated in the United Kingdom, with respect to variant Creutzfeldt–Jakob disease

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Funding information
The authors received no specific funding for this work.

Abstract

Plasma-derived medicinal products (PDMPs) are life-saving and life-improving therapies, but the raw material is in short supply: Europe depends on importation from countries including the United States. Plasma from donors resident in the United Kingdom has not been fractionated since 1999 when a precautionary measure was introduced in response to the outbreak of variant Creutzfeldt–Jakob disease (vCJD). Cases of vCJD have been far fewer than originally predicted in the 1990s. Since the introduction of leucodepletion in 1999, and accounting for the incubation period, more than 40 million UK-derived blood components have been issued with no reports of TT vCJD. In February 2021, the UK Government authorized manufacture of immunoglobulin from UK plasma. Following separate reviews concluding no significant difference in the risk posed, the United States, Australia, Ireland and Hong Kong also lifted their deferrals of blood donors with a history of living in the United Kingdom. Other countries are actively reviewing their position. Demand is rising for PDMPs, and Europe faces a threat of supply shortages. Industry and patient groups are clear that using UK plasma would bring significant immediate benefits to patients and to the resilience of the European supply chain. From this scientific review, we conclude that UK plasma is safe for fractionation and urge blood regulators and operators to take account of this safety profile when considering fractionation of UK plasma, and to revise their guidelines on the deferral of donors who have lived in, or received a transfusion in, the United Kingdom.

Keywords

blood safety, plasma fractionation, prions, vCJD

Highlights

- In 1999, as a precaution against variant Creutzfeldt–Jakob disease (vCJD) transmission, the United Kingdom stopped supplying plasma for fractionation.

- The dietary vCJD outbreak was much smaller than feared, and there have been no transfusion transmissions since 1999. There are numerous and effective risk-reduction steps in the donation and manufacturing process.
- This review concludes that plasma from donors currently or previously resident in the United Kingdom is as safe as any other source of plasma for the manufacture of medicines and concurs with recent reviews in Australia, Ireland, the United States, Hong Kong and by the UK Medicines and Healthcare Products Regulatory Agency.

INTRODUCTION

Europe is dependent on importation from the United States for 38% of the plasma required to meet its patients' needs [1]. Meanwhile, plasma collected from UK donors and from European donors who previously resided in the United Kingdom is not being accepted for fractionation in Europe. This is the result of the precautionary measures implemented in the United Kingdom almost 30 years ago to mitigate the risk of transfusion-transmitted Creutzfeldt–Jakob disease (TT-vCJD). Fortunately, the dietary-related outbreak was much smaller than had been feared and there have been no cases of TT-vCJD since 1999. It is therefore timely to re-assess the current position, and reviews undertaken in the United Kingdom, Australia, United States, Ireland and Hong Kong have concluded that blood and plasma from donors previously resident in the United Kingdom presents no additional risk of vCJD to their respective blood supplies or the manufacture of plasma-derived medicinal products (PDMPs) [2–6].

This paper is an abridged version of a paper reviewing the safety profile of UK plasma, commissioned by the UK Blood Services and written with input from international scientific experts and organizational representatives [7]. The paper considers the epidemiology of vCJD, risk-reduction measures, the latest UK and international decisions, the view of industry and patient groups, ethics and the supply difficulties and demand needs that make reconsideration of these matters so urgently important. The aim of the paper is 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.

Although the original precautionary decision to cease the use of UK plasma for fractionation was taken by the UK Department of Health following a review by the Committee on the Safety of Medicines in 1998, it was then reiterated by other agencies in Europe, resulting in a lack of clarity on the current position [8]. However, the United Kingdom did not prohibit blood donation and the use of blood components. National, European and world bodies introduced a geographical deferral of their blood donors who lived for a certain time or received a transfusion in the United Kingdom during the bovine spongiform encephalopathy (BSE) epidemic; many did not officially prohibit the use of UK plasma for fractionation—this plasma was simply not available. Now, considering the geographic distribution of fractionation plants, some countries have to take a decision on the acceptability for fractionation of UK plasma, despite never having prohibited its use.

The proposed Regulation on standards of quality and safety for substances of human origin (SoHO) intended for human application 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' [9]. Although the European Medicines Agency (EMA) has not issued an official position on UK plasma, there is a CJD position statement from the Committee for Medicinal Products for Human Use (CHMP; agreed by the Biologics Working Party), the third revision of which (2018) is currently pending further review [10]. It includes the text from the first version of the document, issued in 2003, which states '… 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'. Although 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.

In August 2021, the European Centre for Disease Prevention and Control (ECDC) published a risk assessment regarding the potential transmission of vCJD by blood and blood components by donations obtained in the United Kingdom, noting that the absence of a suitable, validated screening test for blood donors makes it difficult to assess the residual risk for transmission in the United Kingdom and Europe [11]. Despite plasma for fractionation being beyond the stated scope of the risk assessment (clarified in July 2022 to be limited to '… the possible transmission of vCJD by blood and blood components from donations obtained in the UK'), it notes the '…risk of… possible transmission… by blood and PDMPs manufactured from donations obtained in the UK'.

The assessment quotes from the MHRA risk assessment, the highly precautionary upper-bound figure of 324 infections per million doses of the highest risk immunoglobulin product if made from non-leucodepleted plasma. The majority of products present a much lower risk, and the use of leucodepletion, which is standard in the United Kingdom and noted to significantly reduce risk, reduces this five-fold to 67 infections per million doses. It is important to note that the MHRA assessment is based on Department of Health and Social Care (DHSC) modelling, which is 'precautionary and uses large input and calibration ranges… [so] will inevitably produce extremely wide estimates with high upper bounds' [12].

The ECDC assessment also notes 'the contrast between the estimated prevalence [as determined from examination of appendix tissue and used in DHSC modelling] … and the reported number of clinical vCJD cases' is such that 'positive' individuals 'may never develop any

symptoms of prion disease, nor may they be capable of transmitting the infection, including through donation of blood and blood products'. This conclusion is supported by findings from a sheep transfusion model which suggest that detectable PrP^{Sc} in lymphoid tissue may be very common following exposure by transfusion, but with no evidence that this leads to detectable PrP^{Sc} in blood, infectiousness or clinical illness, thus supporting the conclusion that the appendix studies do not provide a good estimate for prevalence of an infectious state [13].

Finally, the ECDC assessment comments that the risk of vCJD infection 'is decreased by the safety measures implemented to reduce the risk of donation by exposed donors and during whole blood processing or plasma fractionation'. It presents options for response, suggesting that '…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'.

It is hoped that this paper provides the relevant background information on the above options, including risk-reduction measures applied during donation and processing of blood and evidence on effectiveness of manufacturing processes to remove prions, and will assist and encourage the relevant regulatory agencies when considering their guidance on the fractionation of UK-sourced plasma.

A HISTORY OF TT-vCJD IN THE UNITED KINGDOM

Since 1995, 178 patients with definite and probable vCJD have been reported in the United Kingdom. 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. 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 Factor VIII treatment was considered the probable cause of the vCJD infection; this remains the only case implicating Factor VIII, with the causal connection unproven and no identified case related to any other PDMP [14].

There is a well-established UK CJD surveillance system that employs multiple overlapping case identification methods, with 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 [15–19]. vCJD has not been reported in anyone in the United Kingdom born after 1989 (the year major dietary protection measures were introduced) and there have been no new cases of TT-vCJD since 2007. Transmissions associated with red blood cell transfusions occurred prior to the 1999 introduction of leucodepletion (the removal of the majority of white blood cells from blood components) [20, 21]. Since then, more than 58 million UK-derived blood components have been issued in the country, 40 million of which were issued more than 8 years ago (the approximate incubation period, based on reported TT cases) with no reports of TT-vCJD [22]. There have been no reports of vCJD transmission via plasma or platelet transfusions, and there have been no reported cases of TT-vCJD anywhere else in the world, even though other countries have had cases of vCJD.

France has reported 27 cases of vCJD, the second highest number after the United Kingdom [23], but has continued to collect plasma for the manufacture of PDMPs. The Établissement Français du Sang (EFS) collects around 850,000 L of leucodepleted plasma for fractionation each year, provided to the Laboratoire Français du Fractionnement et des Biotechnologies (LFB). EFS also issues 3 million blood components each year [24]. There have been no reported transmissions of vCJD by LFB-produced PDMPs or EFS-produced blood components.

UK POSITION ON THE SAFETY OF UK PLASMA

Since the first appearance of vCJD, the UK DHSC has periodically carried out a risk assessment on the predicted number of future infections and associated deaths due to TT-vCJD. There was considerable concern regarding the potential length and magnitude of the outbreak, with predictions of 10 cases per year in the 2020s [25], but the reality has been very different (see Figure 1). Since 2011, when there were five cases, there have only been two further (dietary) cases, one in 2013 and one in 2016 [26].

The risk assessment was reviewed in 2018 by the Advisory Committee on Dangerous Pathogens (ACDP), and in 2019 the advisory committee on the Safety of Blood, Tissues and Organs (SaBTO) considered some of the measures in place to mitigate the risk of TT-vCJD in paediatrics. These included importation of fresh frozen plasma (FFP) and use of apheresis platelets for patients born after the beginning of 1996. The risk of TT-vCJD by UK FFP was predicted to be one in every 5.2 million units of plasma transfused [27]. The requirement to import FFP for these patients was removed and UK FFP is now provided.

In 2020, prompted by the increasing supply risks and the diminishing transmission risk, the MHRA reviewed the evidence on the safety of UK plasma for manufacture of immunoglobulins. In October 2020, 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 concluded '…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

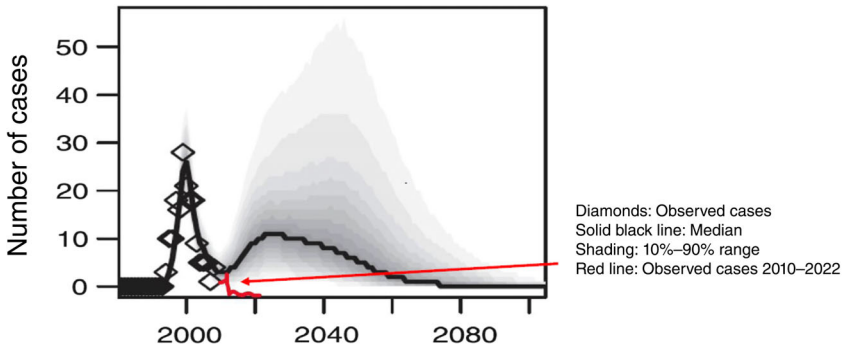

FIGURE 1 Modelling from 2010 predicting a significant second peak of infections. The actual number of cases has been much smaller (adapted from [26]).

products for patients with immunodeficiency and certain autoimmune conditions'. In February 2021, the ban was lifted on the use of UK plasma for manufacture of immunoglobulin for use in the United Kingdom 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 [2]. In October 2022, the CHM approved the use of UK plasma for the manufacture of albumin medicinal products [28] and may consider reviewing other PDMPs depending on its capacity and demand for the products.

INTERNATIONAL PERSPECTIVES ON GEOGRAPHIC DEFERRAL OF DONORS

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

In May 2022, the US Food and Drug Administration (FDA) updated its guidance around the safety of UK plasma, removing '… 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'. [4]. This decision was based on the absence of a significant difference from donors in the United States, where no endogenous cases of vCJD have been reported. 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… 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' [4]. This change has also created a paradox where PDMPs manufactured from US plasma could be used in the United Kingdom or Europe, having been derived from donations from individuals who are currently not allowed to donate in the United Kingdom and EU countries because of previous residency or receipt of a transfusion in the United Kingdom. This makes the current European position inconsistent. If, following this change, US imports are considered to remain acceptable, it would appear reasonable that PDMPs derived from UK plasma should also be considered acceptable.

In April 2022, the Australian Therapeutics Goods Administration overturned its ban on former UK residents donating blood in Australia due to the perceived risk of vCJD. This followed a review concluding that the removal of the deferral would have no negative effect on the safety of the Australian blood supply and would be a safe and effective strategy to increase the donor base [29]. Indeed, Australian Red Cross Lifeblood reported 21,000 new donor registrations in the 10 days following the removal of the ban [30].

In 2019, following a review of vCJD risk by the Irish Blood Transfusion Service, Ireland overturned its deferral of donors who had previously resided in the United Kingdom between 1980 and 1996 or possibly been exposed to vCJD via blood transfusion [5].

Hong Kong announced in December 2022 that it would accept blood donors who had stayed three or more months cumulatively in the United Kingdom between 1980 and 1996, and who had stayed five or more years cumulatively in France or Ireland between 1980 and 2001 [6].

The European Blood Alliance (EBA) has published a statement emphasizing that 'Increasing plasma collection by not-for-profit blood establishments in Europe is a priority… to safeguard the supply of safe PDMPs …for patients in Europe while preserving donor health'. and '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'.

PATIENT AND INDUSTRY PERSPECTIVES

The European Patient Organization for Dysimmune and Inflammatory Neuropathies (EPODIN) and the Platform of Plasma Protein Users (PLUS) represent patients who can suffer major health impacts in the

absence of the appropriate PDMP treatment. Similarly, the International Plasma and Fractionation Association (IPFA) and the Plasma Protein Therapeutics Association (PPTA) are trade organizations that represent, respectively, the not-for-profit organizations engaged in the collection and fractionation of plasma and private sector manufacturers of plasma protein therapies and the collectors of source plasma used for fractionation. CSL Behring is an independent biotechnology company leading in the collection of source plasma and which manufactures a broad range of plasma protein therapies. These organizations concur that a regular and continuous supply of plasma is required as the health independence of Europe is a concern; that initiatives like the MHRA review are welcome as they examine and reassess standards based on accurate scientific reasoning; and that the data presented herein shows that plasma donated by the citizens of the United Kingdom is as safe a raw material for PDMPs as plasma donated anywhere else in Europe.

RISING PATIENT DEMAND FOR PDMPs

The European Union has a shortfall of 3.8 million litres (or 30%) of the plasma needed to manufacture PDMPs for its patients; Europe (including the United Kingdom) depends on US plasma imports for more than 38% of its need; and demand is rising at 6% per year [31, 32]. There are risks associated with this reliance on importation, illustrated by the 2020 fall of 20% in US plasma collection due to the COVID-19 pandemic and the potential for exports to be stopped under the Defence Production Act [33].

The Marketing Research Bureau estimates total immunoglobulin usage in Europe (inclusive of the United Kingdom) to be 64 tons per annum for up to 350,000 patients. To manage the restricted supply, some countries have established usage guidelines and priority lists. Factors such as economic situations, healthcare policies, influence of patient advocacy groups, insurance and other socio-economic factors also vary across EU countries. The UK's National Health Service has implemented prioritization measures to allocate immunoglobulins to patients with the highest clinical need [34]. The United Kingdom needs approximately 1.5 million litres of plasma per year to manufacture sufficient immunoglobulin. The target is to reach 30% self-sufficiency in immunoglobulins by 2025 with a longer term target of 45% self-sufficiency, which would reduce the European plasma demand gap from 38% to 33%. The United Kingdom is currently collecting 240,000 L of recovered plasma per year, which is equivalent to the output of 16 mature and high-performing plasmapheresis centres.

PLASMA RISK REDUCTION METHODS: DONOR SELECTION AND MANUFACTURING PROCESSES

Donor selection criteria in the United Kingdom are stringent and are kept under close review by both the Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) and SaBTO. The criteria currently exclude persons who have been told that they have been put at increased risk from surgery, transfusion or transplant of tissues or organs as well as 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 [35]. People known to have received an allogeneic tissue or blood transfusion since 1980 are also deferred from donation in the United Kingdom although it is likely that this measure will be reviewed given the US decision to now accept donations from people who received transfusions in the United Kingdom.

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 [36, 37]. The United Kingdom has very strong systems in place for donor-to-patient traceability for blood components and this will be applied to collection of plasma for fractionation, through to each manufacturing pool and all resulting products manufactured from that pool.

Leucodepletion of blood components and plasma for fractionation will remain standard practice in the United Kingdom. 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'. [10]. In its review of immunoglobulin manufacture, the MHRA found that 'leucodepletion [of the raw plasma] decreases the risk of infection by a factor of ~5 and the risk of clinical case by a factor of ~3.5' [2].

Regulatory authorities require PDMP manufacturers 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 [10]. Although the physical and biochemical characteristics of prion agents suggest that they could be removed by separation technologies used in the preparation of PDMPs, suitable experimental data are required to determine the extent to which this is achieved in practice [38].

Nanofiltration with 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 in spike models with in vitro and in vivo read-outs [39, 40]. 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-outs [39, 41, 42]. Other purification steps such as chemical precipitation steps, low pH depth filtration and chromatography further contribute to the prion reduction capacity of PDMP manufacturing [39, 43, 44].

The PRFs claimed by one manufacturer ranged from 4.8 log to >11 log for a range of PDMPs; another reported 12.9 log reduction for an immunoglobulin preparation, and manufacturer responses

quoted in the MHRA risk assessment for immunoglobulin range from 4.8 log to 10.5 log and from 7.3 to 9.4 for hyperimmune immunoglobulin [2, 40, 45]. Comprehensive reviews of processes and PRFs have been published [39, 46].

Based on currently available experimental studies from manufacturers, it is estimated that PDMPs have >4 log manufacturing process reduction of the vCJD agent [39, 47].

There is a theoretical risk that, should prions causing vCJD be present in a pool of plasma, they may contaminate the manufacturing equipment. Sanitization of manufacturing equipment is a regulatory requirement for inclusion between batches, and the use of sodium hydroxide or other reagents has been shown to be effective for stainless steel decontamination and regeneration of chromatography resins. Manufacturers of PDMPs perform small-scale studies to demonstrate the effective reduction of experimental prion agents by the cleaning regimen of manufacturing lines [43, 48–50]. No additional cleaning or sanitization methods are necessary when processing UK plasma.

CONSIDERATION OF THE RELATIVE RISK OF UK PLASMA

As part of the analysis to support the 2018 SaBTO review of vCJD risk-reduction measures for labile blood components, it was 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 [27].

The risks per unit of plasma used to derive PDMPs will be different from this for two main reasons: pooling of multiple units of plasma and prion reduction during fractionation. The calculations, which may be found in the full paper, show that the risk from each unit of donated plasma that is fractionated, using a process with a 4 log PRF, is over 7000 times less likely to lead to a vCJD transmission than if that unit was used for transfusion [7]. This suggests that there would be less than one death from vCJD for every 36.4 billion units of plasma that are fractionated. It is predicted that approximately 1.1 million units of plasma will be collected each year in the United Kingdom, meaning that there may be one death from vCJD transmission every 33,000 years. 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 vCJD transmission through the use of UK plasma for fractionation is extremely low.

ETHICAL CONSIDERATIONS OF THE USE OF UK PLASMA FOR PDMP MANUFACTURE

Manufactured medical products such as PDMPs are rightly expected to meet high safety standards, but there can be valid ethical arguments not to apply every safety measure that would further reduce small residual risks [51]. 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.

Although arguably it was appropriate, on a precautionary basis, to decide in 1994 to cease fractionation of UK plasma, maintaining this policy under current circumstances cannot be justified by appealing to the precautionary principle. Application of the principle must be consistent and proportionate [52, 53], which implies that it cannot be used to justify retaining the ban on UK-sourced PDMPs: retaining this ban would, in any scenario that is credible today, cause more serious harm than it would prevent. Over the last two decades, it has been found that the risk is much smaller than had been feared, although 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 and strongly suggests that retaining the ban will have worse consequences for patients relying on PDMPs than lifting it. Retaining adequate haemovigilance with respect to vCJD to ensure that any unforeseen adverse effects would be identified promptly is arguably still a proportionate precautionary measure.

When considering removing a safety measure, one may ask whether such a policy would be implemented given the latest evidence. Removing safety measures may be more politically sensitive than deciding not to implement them, but it is doubtful that there is any ethical difference [54]. It is unlikely that a ban on UK plasma would be implemented today, knowing that this would not improve safety tangibly but would exacerbate shortages of PDMPs, and removing the ban thus seems ethically warranted.

CONCLUSION

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. There have been no documented cases of vCJD in the UK population previously treated with UK-sourced immunoglobulin, and no transmissions reported in France, where there were dietary transmissions of BSE/vCJD yet leucodepleted domestic plasma continued to be used for the manufacture of PDMPs.

In countries that have conducted a review of the risk of vCJD transmission, there has been found to be no significant difference in risk posed by the receipt of blood or blood products from UK donors, than from any other donors. The United Kingdom now permits the use of domestic plasma for transfusion to all recipients and for the manufacture of immunoglobulin.

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

It is important to review these precautionary safety measures considering 23 years of epidemiological evidence, which suggests 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. The same principle applies to other donor-deferral criteria, which should be kept under regular review to ensure an appropriate balance between safety and sufficiency of supply.

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 the current European dependency on importation of US plasma, improving strategic independence and benefiting patients who depend on life-saving treatment with PDMPs, which currently be restricted based on supply.

ACKNOWLEDGEMENTS

The authors would like to thank all participants in the working group who produced the full paper [7]: Peter O'Leary (Executive Director, EBA), Leni von Bonsdorff (Executive Director, IPFA), Benoît Flan (Chair, Biological Safety Working Group, IPFA), Bob Perry (Senior Advisor, IPFA), Gerry Gogarty (Director, Plasma for Medicines, NHSBT), Rachel Meeke (Lead Quality Specialist, NHSBT), Mette Mikkelsen (Governance Lead, NHSBT), Hetty Wood (Secretariat, NHSBT), Marc Turner (Director, SNBTS), Johan Prevot (Steering Group Member, PLUS), Brian O'Mahony (Steering Group Member, PLUS), Frank Willersinn (Steering Group Member, PLUS), Thomas R. Kreil (Vice President Global Pathogen Safety, Takeda; Chair PPTA Global Pathogen Safety Working Group; GPSWG), John More (Director of R&D, BioProducts Laboratory Ltd; PPTA GPSWG), Elisa Moretti (Pathogen Safety Director, Kedrion Sp.A, PPTA GPSWG), Martyn Paddick (Head of Biosafety, BioProducts Laboratory Ltd; PPTA GPSWG) and Peter Richardson (Head of Quality Assurance, Welsh Blood Service). The expert advice of Peter Foster (retired), Gary Mallinson (NHSBT), Michael Jones (SNBTS) and David McIntosh (UK Plasma Action) is also gratefully acknowledged.

G.M., L.K., J.B. and L.M. conceived and commissioned the paper; S.T. led the writing group with significant contributions from B.R., D.D., K.K., D.K., S.S., D.M., J-P.P., F.R., D.M. and R.K. All authors reviewed and approved the manuscript.

CONFLICT OF INTEREST STATEMENT

Stephen Thomas, Barnaby Roberts, Dragoslav Domanović, Koen Kramer, Jean-Philippe Plançon, Lauren Kirkpatrick, Gail Miflin, Janet Birchall, Lorna McLintock and Richard Knight have no conflicts of interest to declare.

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How to cite this article: Thomas S, Roberts B, Domanović D, Kramer K, Klochkov D, Sivasubramaniyam S, et al. Safety profile of plasma for fractionation donated in the United Kingdom, with respect to variant Creutzfeldt–Jakob disease. Vox Sang. 2023.