United Kingdom Plasma Action

"Best Husbandry of the Donors' Gifts. Best Care for Patients"

Draft Memorandum

On

The urgent need to secure more, and more reliable, supplies of Immunoglobulin
and other plasma-derived pharmaceutical products for patients in need,
in the face of growing global shortages of these vital medicines,
via
Discontinuation of the current ban on the pharmaceutical use of
UK donors' plasma and its re-acceptance for medicine manufacture.

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Contents

1 Introduction and Summary

1.1 **UK Plasma Action** (UKPA)

1.1.1. UKPA is an independent not-for-profit organisation founded in June 2019 in response to three important national issues, together seen as a significant and rising threat to UK healthcare services and to the health and welfare of the patients they exist to serve. The issues of concern to the clinicians, patients, blood donors and others that the UKPA team represents are –

a) a growing global shortage of human plasma, causing increasing shortages of immunoglobulin (Ig) and other plasma products upon which thousands of patients depend for their quality of life and often for life itself;

b) an increasing global dependency on the USA for supplies of Ig and other plasma products, classified by the WHO as Essential Medicines in all countries. US exports currently account for over 70% of the total global supply; causing strategic vulnerability for the UK and other countries entirely dependent on imports; and

c) the currently unrealised potential of some 360,000 litres per annum of UK blood donor plasma. This could make a significant contribution to the sufficiency and security of supplies of immunoglobulin and other plasma derived medicines, but is not currently available for this use, due to the UK ban introduced in 1998 as a precaution against Variant Creutzfeldt Jakob Disease (vCJD).

1.2 **UK Donors' Plasma - 2020**

a) Clearly, the UK's ban on the pharmaceutical use of recovered donor plasma has always had unwelcome consequences, in terms of overall cost and plasma product availability, but has been felt to be warranted for safety reasons. Twenty-two years on however, there is now good evidence that the balance of risk factors in this area has shifted significantly and is due for review. A parallel precautionary ban on certain clinical uses of fresh plasma, also instituted in 1998 as a precaution against vCJD, was recently reviewed by the UK's national expert committee on the Safety of Blood, Tissues and Organs (SaBTO). The finding was that the vCJD risks were now much lower than previously thought, that the costs and drawbacks of maintaining the old policy were relatively too great and that the policy should therefore be changed. This was accepted by the UK Government and the old restrictions on the use of UK fresh plasma were lifted in September 2019. However, there has as yet been no equivalent up-date of UK policy with respect to the use of donors' plasma in the manufacture of plasma products.

b) Because of the potential relevance of the SaBTO work to the issues highlighted above, the UKPA team has considered and investigated the possibility that it might be built upon in a follow-up study into the risks attached both to the use and to the non-use of UK recovered plasma, in 2020 and onwards. This is the responsibility of the Medicines and Healthcare products Regulatory Agency (MHRA) and its expert advisory committee, the Commission on Human Medicines (CHM) and falls outside the SaBTO remit.

c) After wide consultation with practicing clinicians, haematologists, other medical specialists and scientists in the field and after consultation with UKPA's Principal Scientific Adviser, Professor Richard Knight (Centre for Clinical Brain Sciences, Edinburgh University), the UKPA team feels it appropriate to respectfully suggest that the MHRA/CHM should now take up the subject, building on SaBTO's findings and also on the significant mass of evidence and experience accumulated over the last 21 years, in the UK, in France and elsewhere. Bearing in mind the current and growing risks of shortages in supply of plasma products, especially Ig, the UKPA team believes that such a follow-up study and risk re-assessment is not only an important priority but also an urgent one.

1.3 **The Need for Action**

1.3.1 On the basis of the evidence and after wide consultation with stakeholders, the UKPA team has reached three provisional conclusions, set out here and expanded upon in Sections 2-10 here below. These are:

a) that SaBTO's recommendations, with which the UK government has agreed in lifting the old restrictions on the use of fresh plasma, are based on reasoning much of which is also relevant to the recovered plasma position;

b) that this, taken together with the mass of other supporting evidence now available and the changed risk situation with regard to imported supplies, suggests the urgent need for a re-assessment of the relevant balance of risks, re-visiting the advisability or otherwise of excluding UK donors' plasma from the medicines supply chain; and

c) that if such a review were to lead to the lifting of the ban on UK donors' recovered plasma that would be a highly desirable outcome – one that would in fact reduce risk overall and would deliver significant benefits for patients, for clinicians, for blood donors and for the NHS as a whole; in terms of patient care, national security of medical supplies and also significant savings in cost.

1.3.2 Therefore, the UKPA team, together with the UK Primary Immunodeficiency Network, the British Society for Immunology, the Immunology and Allergy Nurses Group and our patient representative partners Primary Immune Deficiency UK, on behalf of the many clinicians, patients, and blood donors for whom we speak, have urged the UK Department of Health and Social Care, the MHRA and the CHM to please act promptly to initiate the required review and to implement the resulting recommendations without delay.

1.3.3 This Memorandum has been prepared as a background paper and supporting document in the context of such a review. The UKPA team and those they represent hope that the requested review will soon be initiated and that this Memorandum may be of some assistance as a small part of the review process.

2 Background

2.1 For many years, up to 1998, a significant proportion of the UK's needs for plasma derived medicines ("plasma products") was met using human plasma extracted ("recovered") from the whole blood donated by thousands of UK blood donors. Some 55% of each whole blood donation consists of blood plasma; and over 1,000 litres of plasma are collected in this way in the UK daily. Recovered UK donors' plasma was previously used to produce (and could again produce) a whole range of vital medicines, including - immunoglobulin (Ig) to treat immune deficiency and fight infections - albumin for patients suffering from burns, shock, sepsis, trauma or acute respiratory distress - clotting factors to control bleeding – and many other products. (A list of these is included in Appendix II below (page 16).

2.2 Since 1998 however, UK donors' plasma has not been used to make any therapeutic products. For the last twenty two years the major proportion of it (some 90%) has been discarded or sold off for non-clinical uses. The vital plasma products needed for UK patients are all being imported from overseas. This diversion of UK donors' plasma away from the medicines supply chain is exacerbating the shortages of immunoglobulin (Ig) and other vital plasma-products, for which world-wide demand already exceeds supply and for which demand is rising rapidly. (Estimated, in the case of Ig, to be rising at a rate of some 10% per annum in the developed world and more in developing countries previously less privileged to benefit from this vital medicine.)

2.3 Exports from the United States of America account for over 70% of the World's needs for Ig and other plasma products. These products are classified by The World Health Organisation as Essential Medicines, but many, including Ig, are in short supply globally; leaving many countries, including the UK, strategically vulnerable to shortages and potentially to life-threatening supply discontinuity.

2.4 UK donors' plasma is currently excluded from the plasma product pipeline due to a UK ban, imposed in 1998, as a precaution against possible disease transmission during the Bovine Spongiform Encephalopathy ("Mad Cow Disease") and Variant Creutzfeldt Jakob Disease (vCJD) crisis. The result, as of today, is the diversion of some 360 tonnes of UK donors' plasma annually, to destruction or non-clinical use. For illustrative purposes, in the case of Ig, the production potential of this plasma amounts to 1.6 million grams of immunoglobulin annually – equivalent to approximately 20% of the current total UK demand for patients in need. (Ref. Fig 4 page 11.)

2.5 This exclusion of UK donors' plasma seemed a natural precaution to take in 1998, when relatively little was known about "New Variant CJD" as it was called then. Its tendencies and virulence in potential transmissions via blood and plasma products were not yet at all well understood. However, 21 years on, and now with much more experience and research data available, the UKPA team believe it to be clear that a root and branch re-assessment of the UK's approach to blood donors' plasma is now due. This, for three main reasons –

2.5.1 The first reason is the scientific and medical consensus that vCJD is not nearly as serious a threat to the UK's blood and plasma supplies as was once feared. The much reduced level of perceived vCJD risk since 1998 has adjusted the risk balance towards a more favorable view of the use of UK donors' plasma. Among many other confirmations of this, the most recent are the recommendations of the UK Expert Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) and the resulting DHSC Minister of State's written statement on vCJD (September 2019).

2.5.2 The second major factor that the UKPA team believes is highly relevant is the pharmacovigilance data on the immunoglobulins and other plasma products produced using recovered UK donors' plasma and administered to thousands of patients during the critical years 1983-1999. These UK donor derived plasma products were not involved at the time, and have never been involved since, in any cases of confirmed vCJD transmission (ref: Section 5, page 7 below). This consideration is complementary to but separate from the generally accepted lower vCJD risk status mentioned above (2.5.1). Even with the estimated much higher level of vCJD prevalence in the UK population at the height of the BSE/vCJD crisis and despite there having been known cases of plasma contamination with vCJD at that time (Ref: Appendix I, page 13) the plasma products made then from that "suspect" plasma have been proven to deliver a most reassuringly high level of safety, in both the short and the long term. The potential period available

for any possible vCJD extra-long "incubation" that might be thought possible with the use of these UK plasma products has now reached approximately 37 years at maximum (1983 – 2020) and 21 years at minimum (1999 – 2020). Despite the time spans involved and despite the known presence of vCJD in the donor population and in some plasma batches during the period, there has been no confirmed case of a patient contracting vCJD from a UK-plasma-derived medicine. (Note: The one possible case quoted in the literature remains unconfirmed. See also 2.6 below.)

2.5.3 (Note: Appendix IV, page 19, sets out a draft schema exploring the possible/theoretical picture with respect to potential incubation periods for vCJD, based on the few known facts about cases and dates. There are no recorded cases of any vCJD infection incubating for more than 8 years. This might indicate that, as there were no cases of plasma product infections in the years 1999 – 2007 the first 8 years following the implementation of the UK plasma ban) it would have been safe to resume fractionation of UK donors' plasma in 2008. Some further precautionary margin beyond that might seem sensible, but the UKPA team have as yet found no arguments in support of anything beyond the 22 years that have already passed since the ban was introduced.)

2.5.4 The third and in fact most pressing reason why UKPA and many supporting clinicians, patients, donors and others believe strongly that a policy review is needed relates not to the greatly reduced risks on the UK donor plasma side of the equation, though these are significant, but to the greatly increased level of risk that is now attached to the alternative; in other words, the serious risks of continuing with current policy. In its investigations thus far, the UKPA team has found no clinicians, academic specialists, patients or patient representatives who are content with the current situation with respect to the vulnerability of immunoglobulin (Ig) supplies in this country. That there is a serious and growing shortage of Ig world-wide is an undisputed fact of modern medical life at present. All the signs point to the difficulties and dangers that this shortage causes getting worse in the future rather than better, unless serious steps are taken to alleviate the underlying shortage of human plasma that is the root cause of the problem.

2.5.5 The UKPA team's observation is that the stakeholders (patients, clinicians, immunologists, neurologists, neuropathologists and other relevant interested parties) seem in deep but uncomfortable agreement that the risks attaching to current policy – threats to the sufficiency and continuity of supply of Ig and other important plasma-derived medicines – are high and rising. It is to this aspect of the risk balance that UKPA would suggest that those responsible may wish to focus particular attention during the conduct of the up-coming review of the UK plasma ban.

2.6 Note: In the literature, there is one record of an alleged case of vCJD transmission via a UK-plasma-sourced product, in this case FVIII concentrate. (Peden A, et al. Haemophilia 2010, 16, 296-304). This related to a patient with haemophilia with no symptoms of vCJD who died from other causes. The case involved a positive result for abnormal prion protein in one spleen tissue sample out of 26 tested, post mortem. No trace of this abnormality was found in the other 25 samples from the same patient. The case therefore remains controversial. As noted in a 2016 position statement on the occurrence of vCJD and prevalence of infection in the UK, by the TSE Sub-group of the Advisory Committee on Dangerous Pathogens (ACDP) - "It is challenging to provide a single narrative consistent with all known evidence."

2.7 However, even if that single FVIII case were to be confirmed, it seems safe to say that the existence of only one vCJD transmission after widespread product issue to many thousands of patients, with up to 37 years for symptoms, if any, to develop, would still leave many questions to be answered, in terms of the comparison between the facts that have emerged and the equivalent predicted outcomes based on historic vCJD risk assessments. In this context, the Department of Health paper entitled "Blood-borne transmission of vCJD, re-examination of scenarios" (Bennett and Daraktchiev September 2011) seems even more relevant now than it was then. The paper's closing comments (Section 7, page 35) include the following observation –

"The main current concern, however, is to arrive at a set of working hypotheses on blood-borne transmission risks that are more fully consistent with the evidence now available."

2.8 The UKPA team would respectfully suggest that this dissonance between historical theoretical risk assessments and emerging fact remains a current concern in 2020. For instance, using the most recent ACDP risk model deployed by SaBTO in their 2019 recommendations on fresh plasma, one would arrive at an estimated/expected UK vCJD mortality of 12 over the last 21 years; whereas the actual death rate has been zero. (Ref: Section 6, Page 9).

2.9 In contrast with previous conclusions, based on previous theories, it is the contention of the UKPA team that, on the basis of the accumulated empirical evidence, it seems likely that the use of UK donors' plasma in product manufacture now would be as wise and as safe a policy as can reasonably be expected. Indeed, it may be thought unlikely that there is a safer source of human plasma to be had anywhere in the World. The UKPA team certainly believes that under the circumstances now prevailing, that contention should be thoroughly tested; and that an in-depth review of the position with respect to UK donors' plasma should be conducted as a matter of urgency.

3 The Case for the Restoration of UK Donors' Plasma to the Product Pipeline

3.1 As outlined above, it is the UKPA team's belief that any continuing delay in the implementation of a policy review, with attendant delay to the lifting of the ban on UK donors' recovered plasma, is likely to bring with it significant further increases in risk, including a serious risk of worsening the growing shortages of plasma derived medicines, especially Ig; and exacerbating the risk of discontinuities in supply from possible import pipeline failure.

3.2 Delay also prolongs the undesirable financial implications of having to destroy plasma that has a high intrinsic value. The failure to capitalise on that value, coupled with the additional cost outlay on plasma destruction, adds up to a significant lost opportunity – and an unnecessary extra burden on NHS resources. The safe and sensible pharmaceutical use of UK donors' plasma would create a significant net financial benefit, releasing precious resources for use elsewhere in the UK health and social care system.

3.3 Fully appreciating that these serious matters must and will be dealt with down the proper channels and be subject to rigorous analysis by the relevant expert bodies, it is not UKPA's intention to suggest any short-cuts, nor to offer a shadow risk assessment of our own. This is neither UKPA's legitimate role nor its pretention. This Memorandum is not intended as a full analysis of the merits of the case in favour of UK blood donors' plasma for fractionation. The existing pharmacovigilance data, clinical information, research results and other literature, now added to most helpfully by the excellent work recently completed by the UK expert advisory committee on the Safety of Blood, Tissues and Organs (SaBTO) already covers much of the ground well. The relevant expert committees and responsible bodies will no doubt make the necessary professional judgements in due course. What is intended here is merely a gathering together of some particularly relevant facts as the UKPA team understands them; in the hope that this may assist the proper authorities with their own deliberations.

3.3 The recent Government decision to readmit fresh UK donor plasma for clinical use in areas where that too had been banned since 1998 has been a most encouraging development. The decision was announced on 9th September 2019 in a written statement to the House of Commons by The Minister of State for Care. As the statement confirms "Over the last 15 years, accrued scientific evidence has indicated that the risk of vCJD through the transfusion of UK plasma or platelets is much lower than initially thought; there have been no known transfusion transmissions of vCJD from any blood components since the leucodepletion process was introduced." (Note: The same 100% record of non-infection applies equally to recovered UK donors' plasma, but that did not come within the SaBTO brief and, as far as UKPA enquiries have so far revealed, has not yet been taken into account in any official review of the UK plasma ban to date.)

3.4 Following the SaBTO review and the Government's acceptance of the SaBTO recommendations, it seems clear that a similar review of the position with respect to UK donors' recovered plasma would be advisable and timely. The SaBTO recommendations included a note to the effect that "further work" would be needed to establish a similarly clear re-assessment of the position with respect to recovered plasma and it is precisely to this further work that the UKPA team intends this Memorandum to be directed. These matters are outside of SaBTO's remit, being as they are the responsibility of the Medicines and Healthcare products Regulatory Agency (MHRA) and its expert advisory committee, the Commission on Human Medicines (CHM). It is hoped that the notes in this Memorandum may be of assistance to the UK Department of Health and Social Care and/or to the MHRA/CHM as appropriate, in the context of such a policy review.

3.4 As background to that review, and in the hope that these observations may be helpful to those charged with addressing and updating the position, the UKPA team believes it appropriate to draw particular attention to the following points, expanded upon in the numbered sections below -

- the evidence of the extensive pharmacovigilance data now available - showing the impeccable vCJD safety record of immunoglobulin (2.5 million gms) and other therapeutic components made from UK donors' plasma and administered to patients during the relevant period, even during the worst of the vCJD crisis (Section 5, page 7);
- the parallel safety record of UK donors' whole blood, red cells and other fresh components over the last 21 years and up to the present day - over 60 million units administered to patients without a single confirmed case of vCJD transmission (Section 6, page 8);
- the growing global shortage of plasma products, especially immunoglobulin (Ig) – shortages that could be alleviated by the proper use of UK donors' plasma (Section 8, page 9); and
- the millions of grams of Ig and other valuable plasma products that could be made from UK donors' plasma, if properly recovered and used for the benefit of patients. (Section 9, page 10 and Appendix II, p16.)

4 Immunoglobulin (Ig) and other Plasma Products in Context

4.1 Immunoglobulins, also known as antibodies, are glycoprotein molecules produced by plasma cells (white blood cells). They act as a critical part of the immune response by specifically recognizing and binding to particular antigens, such as bacteria or viruses, and aiding in their destruction. Ig is used to treat various autoimmune, infectious, and idiopathic diseases. It is already one of the top ten highest cost drugs commissioned by the NHS and its use is rising in a wide range of clinical contexts. It is an approved treatment, for instance, for primary immune deficiency, secondary immune deficiency, multifocal motor neuropathy, chronic lymphocytic lymphoma, chronic inflammatory demyelinating polyneuropathy, Kawasaki disease and idiopathic thrombocytopenic purpura (ITP). In 2018/19 NHS England spent £228 million on immunoglobulin and this is expected to rise by approximately 10% each year. (Data from NHS England Immunoglobulin Stakeholder Update July 2019.)

4.2 Ig is an important plasma derivative currently in short supply globally, including in its current main country of origin, the United States of America. It is for this reason that UKPA's focus here is mainly on Ig, responding to the clinical importance and urgency of measures to ameliorate the effects of the global Ig shortage on the large and growing number of UK patients who rely on this vital medicine. This is not however intended to be exclusive. Once the decision is taken to re-admit UK donors' plasma to the production pipeline, all the medicines that will thereby be made available for patients will be of importance. All plasma products are prone to the strategic vulnerability of the UK's undesirable 100% dependence on imports. Some, like C1 inhibitor for instance, are currently very difficult to obtain at all. The UKPA team looks forward to a time when all UK donor recovered plasma will be fully fractionated once again, as it was in the past – benefitting all plasma product supplies, for all relevant categories of patients.

4.3 When the current ban is lifted and when, in due course, appropriate arrangements are in place for the pharmaceutical processing of UK donors' plasma, the DHSC/NHS and their fractionation partners will no doubt wish to make maximum use of all the plasma components and derivative medicines involved - to the financial benefit of the parties - and to the benefit of all patients requiring plasma products of all kinds, both here in the UK and, as appropriate, in other parts of the World. (A potential scenario is illustrated in outline in Appendix II, p16)

5 Pharmacovigilance data on Immunoglobulins (Ig) made from UK Donors' Plasma

5.1 As noted above, the main focus here is on Ig, due to the worrying global shortages. However, as the safety records of other UK-plasma-sourced medicines mirror those of UK Ig, the record shown here also illustrates the high safety level of all the relevant UK plasma fractions and the medicines that could be made from them.

5.2 Before the banning of UK donors' plasma, the two NHS plasma fractionation facilities, at Elstree (The Blood Products Laboratory – BPL) and in Edinburgh (The Plasma Fractionation Centre – PFC) used UK donors' plasma to produce a wide range of licenced plasma products, including Ig. These were administered to many thousands of UK patients during the period thought to be the most potentially dangerous from a vCJD point of view, the critical years in the 1980s and '90s when the vCJD crisis was at its height.

5.3 Fig 1 below summarises the relevant pharmacovigilance data on the Ig products made from UK donors' plasma during the relevant period. More than 2.5 million grams of UK Ig were administered to patients from 1983-'99; and no confirmed cases of their causing vCJD transmission have ever been recorded, neither at the time, nor in the 21 years since the end of the period. (37 years on from their earliest administration to patients during the vCJD era.)

Fig 1: Pharmacovigilance - The Safety Record of Ig made from UK donors' plasma, 1983-1999

1.(i) **Ig Volume** produced - administered to patients -

England & Wales - Blood Products Laboratory (BPL) - 3 yrs ('96-'99)	1,200,000	gms
Scotland & Northern Ireland - Plasma Fractionation Centre -16 years ('83 - '99)	1,326,000	gms
Tot - UK (16 yrs)	2,526,000	gms

1.(ii) **Safety record** of UK immunoglobulins over this critical period

Total UK Ig administered to patients over the 16 yr period	Total Number of Confirmed Cases of vCJD transmission via UK Ig over the period
2,526,000 gms	**0**

1.(iii) **Note**: The Scotland & Northern Ireland figures are from the records. The figures for BPL are estimated.

5.4 This safety record across millions of grams of product and thousands of patients, constitutes a cohort of patient experience covering a total period of 36 years (1983 – 2019) starting with the earliest possible potential date of any vCJD infection by UK Ig and extending to the likely limit of time for the longest reasonably assumable asymptomatic incubation period. This excellent safety record and its implications for current risk management and decision making is further highlighted by the fact that several batches of these products were subsequently identified as having been made from plasma that had been implicated as probably containing vCJD contamination, from donors who later developed the disease. (Listed in Appendix I, p13, from the figures issued by the Health Protection Agency in 2004.)

5.5 There were 124 individual batches of UK-donor-derived plasma products identified as being vCJD suspect, mostly too late for effective product recall. Nevertheless, though administered to many patients in significant quantities, none of these batches of UK-donor-derived plasma products is recorded as having been implicated in any actual vCJD transmission. (The one possible exception of one alleged infection via FVIII is mentioned above, 2.6. It related to a controversial case and was from an era that pre-dated both donor blood leucodepletion and the more modern processing and purification methods now used for human plasma derived Factor VIII production.)

5.6 It is clearly open to argument as to whether this exposure and this length of potential incubation, coupled with a zero result for any signs of infection, is sufficient proof that immunoglobulin and other products made from UK donors' plasma are free from and/or incapable of transmitting vCJD. The UKPA team would of course welcome further comments on this subject from interested parties, particularly with respect to how any such residual risk may compare to the inevitable base-line risk inherent in imported plasma products. However, on the basis of the wide-ranging consultations and discussions the team has conducted to date, it seems clear to UKPA that the data in Fig 1 (above) and Appendix I (page 13) make a very strong case for the safe and efficacious suitability of immunoglobulin and other medicines made from UK donors' plasma, as in the past and as could be again.

5.7 It is of interest to add here that these results are from a period during which donor blood went largely un-filtered (not leucodepleted). While there is some evidence of vCJD transmission by red cells pre-leucodepletion (Ref. section 6 below), it will be noted that the plasma from the unfiltered donations being used at that time for plasma fractionation has not been reported as giving rise to any confirmed cases of transmission via plasma products. Though probably not statistically significant, this observation could nevertheless be taken to imply that UK donors' plasma products were/are more rather than less safe than the red cells from the same donors (which are not of course and never were subject to the ban that has afflicted UK donors' plasma.)

5.8 In their recent paper setting out up-dated recommendations on the use of UK donors' plasma in its fresh frozen form, the UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) reported that –
"In the UK, four people have been known to acquire vCJD infection from blood transfusions with three having died from vCJD (the other died of unrelated causes without any symptoms); the last known case was in 2006. All four had received non-leucodepleted blood before leucodepletion was introduced in 1999. ***There are no known cases of vCJD infection from transfusion of plasma or platelets."*** *(Bold italics by UKPA to highlight SaBTO's point.)*
(Ref: https://www.gov.uk/government/publications/sabto-annual-report-2017-to-2018/sabto-advisory-committee-on-the-safety-of-blood-tissues-and-organs-annual-report-2017-to-2018)

5.9 The UK National CJD Surveillance Centre in Edinburgh is conducting a long-term study into possible vCJD transmission via UK-sourced Ig (https://www.cjd.ed.ac.uk/projects/transfusion-medicine-epidemiology-review-tmer). The National Centre issues regular reports and these are consistently showing a zero vCJD infection return. In the professional opinion of those with whom UKPA has consulted to date, this evidence, further supporting the conclusions of other expert bodies, adds up to an increasingly compelling case for a review of current policy with respect to vCJD risk in the UK, particularly as it relates to the safety of donors' plasma and the plasma products that could be made from it.

5.10 The UKPA team believes that the case is further strengthened by the vCJD safety record of red cell concentrates and other fresh components from the same donor community, post-leucodepletion. This has also been excellent and continues to be excellent to the present day. (Section 6 below refers.) This long safety record of blood and components that are subjected to relatively little pharmaceutical processing or purification must surely provide a further significant source of reassurance with regard to the equivalent units of recovered plasma from the same donors. As recovered plasma units destined for processing into plasma products are put through fractionation and purification steps to which fresh components are not subjected, it seems eminently reasonable to assume that they may in fact constitute an even lower risk of vCJD contamination than their fresh blood-fellows. The pharmacovigilance data summarised above, in respect of UK-plasma-derived Ig from 1983-1999 would certainly not seem inconsistent with that thesis.

6 The Parallel and Continuing Good Safety Record of UK Donors' Red Cells

6.1 In addition to the safety record of UK-plasma-based immunoglobulins and other UK plasma products during the period in question, it is also noteworthy that throughout the 21 years since the vCJD precautionary exclusion of UK plasma became effective, the NHS has continued to administer UK donors' red cells and other fresh blood components to patients up and down the country. Since the introduction of blood filtration measures (leucodepletion) in 1999, no cases of transfusion transmitted vCJD infection have been reported. (There were a total of 4 confirmed cases of vCJD transmission by red cells prior to 1999 but only those 4 and none since. It is notable that UK plasma products did not give rise to any confirmed cases at all, even at the height of the BSE/vCJD crisis.)

Fig. 2 The Clinical Use of UK Donors' Fresh Blood Components - 1999 to 2019

Figures for 1999 - 2018 (courtesy of NHS Blood and Transplant and SNBTS, October 2019)

	Red Cells	Platelets	FFP	SD-FFP	MB-FFP	Cryo	Totals
Unit Totals	44,795,862	5,576,082	6,023,887	729,645	90,606	1,675,789	58,891,871

Estimated approx. total use in 2019	3,000,000
Estimated approx. total 1999-2019	61,891,871

6.2 Fig 2, above, summarises the safety record of the fresh components (red cell concentrate, fresh frozen plasma, platelets, etc) administered to patients over the period 1999 (by which time universal leucodepletion had been introduced) to 2019. Given that none of these many millions of units safely administered to patients gave rise to any cases or suspected cases of vCJD transmission, this must surely highlight the very low level of risk attached to fresh components of UK donors' blood and must surely also have reassuringly positive safety implications for UK plasma products made from the same donors' gifts. A "pool" of over 60 million units without a single vCJD transfusion transmitted infection must surely be a hugely positive sign – particularly when taking into account the fact that any equivalent recovered plasma destined for fractionation would be subjected to significant extra processing and purification – reducing any potential or alleged risk still further.

7 Blood and Blood Components' Risk Factors: theory and experience, in the UK and France

7.1 Pre-leucodepletion, red cell concentrate was identified as the source of 3 confirmed vCJD transmissions. As this compares with a zero return amongst medicines produced from plasma recovered from the same donor population during the same period (Section 5, page 7), it might seem reasonable to speculate that whilst, post-leucodepletion, red cell concentrate is proving to be reassuringly incident free, the parallel plasma product derivatives of the same donations may possibly pose an even lesser vCJD infection risk than do red cells. This conclusion would of course be seriously at odds with all the original vCJD risk assessments made and the predictions made on which the 1998 UK plasma ban was based. However, with the benefit of hindsight, it has to be said that almost all the observed facts now seem to conflict sharply with those original assessments and predictions.

7.2 As shown in section 5 (above, page 6) the many thousands of tonnes of UK donor's plasma that were pooled, fractionated and administered to patients as plasma products, from 1983-1999 , the peak years of BSE/vCJD concern, caused no confirmed vCJD transmissions. In addition, strongly underlining the point, even the batches of suspect vCJD positive batches of plasma products administered to patients during the original crisis (Ref: Appendix I, page 13) also were never implicated in any confirmed cases of infection.

7.3 French experience with their home-grown plasma products over the last 21 years has mirrored the UK experience prior to the UK plasma ban. There have been zero reported cases of vCJD infection via a French plasma product, even during the years when the BSE/vCJD crisis was at its height. With a low but not insignificant incidence of vCJD in the French population and despite the decision to continue to use their own donors' plasma in the product pipeline throughout the relevant period and up to the present day, France has experienced no reported cases of vCJD transmission via a plasma product.

7.4 As noted above (2.7, page 5) Bennett and Daraktchiev, in their paper "Blood-borne transmission of vCJD, re-examination of scenarios" (DoH, September 2011) summed the situation up well - "The main current concern .... is to arrive at a set of working hypotheses on blood-borne transmission risks that are more fully consistent with the evidence now available." With a further eight years of evidence accumulated since then, an in-depth re-assessment of the position would now indeed seem timely. (Further notes on this point are included in Appendix III, page 17.)

8 The Global Shortage of Plasma and Particularly of Immunoglobulins

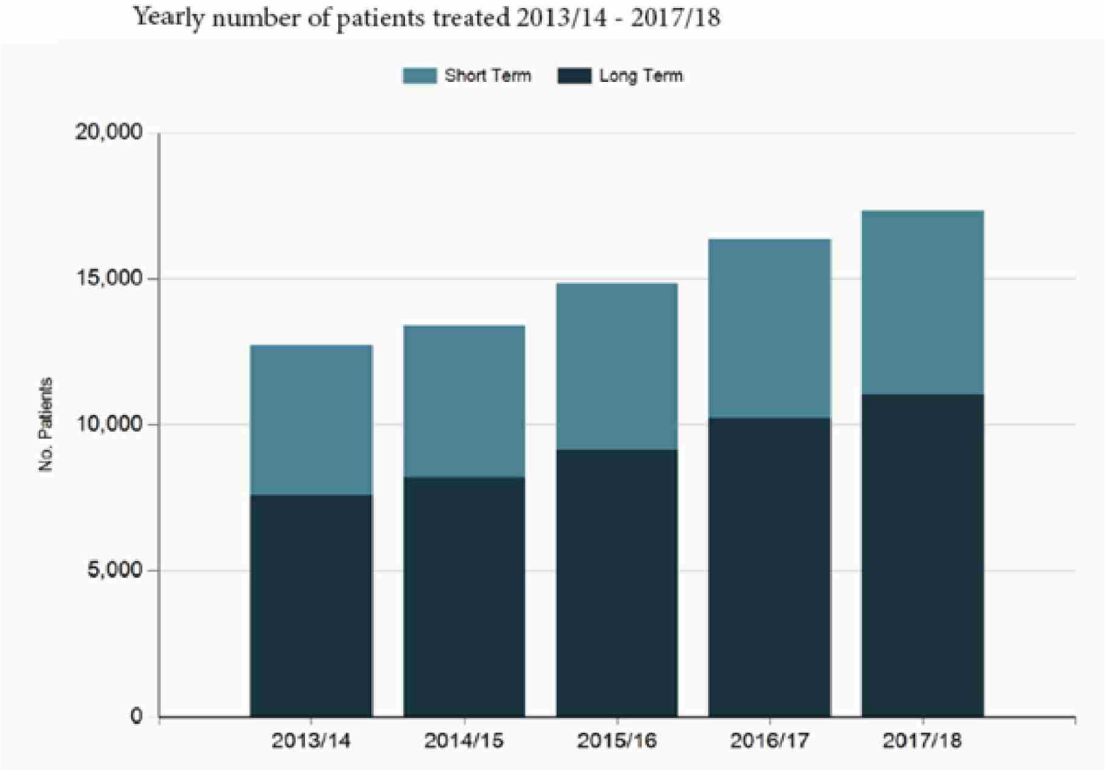
8.1 In recent years the demand for immunoglobulin products has greatly increased, in the UK and globally. It is widely recognized that there is a serious world shortage and that the situation is worsening year by year. The underlying problem is a global shortage of good safe plasma from human donors, currently the only source of large scale polyvalent immunoglobulin supply. Therefore, an increase in the plasma supply, with its corresponding increase in immunoglobulin production, can be seen to be highly desirable. Happily, significant quantities of UK donors' plasma can be made readily available, subject only to a DHSC/MHRA decision to bring an end to the ban on UK donors' plasma and readmit it to the production pipeline.

8.2 The website of the UK National Institute for Health and Care Excellence (NICE) includes the following observation "A global shortage of human immunoglobulin and the rapidly increasing range of clinical indications for treatment with immunoglobulins has resulted in the need for a Demand Management programme in the UK." (https://bnf.nice.org.uk › treatment-summary › immunoglobulins)

This programme of demand management in times of rising demand, global shortage and inevitably restricted supply is achieving remarkable success in minimizing negative impacts on patients. It is however by no means guaranteeing a comfortable and confident life to the clinicians involved, nor to the hard-pressed NHS commissioning teams charged with the job of making the best of an uncomfortable situation. Though the system is undoubtedly as well managed as it could be, the situation is nevertheless recognized as sub-optimal in the short to medium term and unpredictably and dangerously vulnerable in the long term.

8.3 Clinical demand for Ig is growing steadily year by year. Over 15,000 patients are currently affected in one way or another by the current demand management system and that number is expected to grow in the years ahead. Figure 3, below summarises the growth in short and long term usage of Ig over the five years, 2013/14 to 2017/18. (Figures from the most recent MDSAS IG database report). These are of course UK figures. Global demand is reported to be growing at a similar or somewhat faster rate.

Figure 3:



8.3 Given that the UK's plasma product supplies come mainly from the USA, who supply some 70% of the global demand for Ig, the US position is of particular interest. A statement issued by the US Federal Drugs Agency on August 12th 2019 highlights the situation there:

"FDA monitoring confirms that, despite increased supply of immune globulin (IG) products in recent years, the demand for IG product has also increased over that same time and there is an ongoing shortage of Immune Globulin

(Intravenous) (IGIV) and Immune Globulin (Subcutaneous) (IGSC) products in the United States. This shortage could impact patient care."

8.4 John G. Boyle, the President and CEO of the US Immune Deficiency Foundation probably summed the matter up more succinctly than anyone else when, in January 2019, he said -
"Ultimately, the issue is that the world needs more plasma, and the only good way to make that happen is to collect more plasma." (https://www.primaryimmune.org/news/ig-availabilty-issues)
This being so, the UK's daily destruction of some 1,000 litres of the precious fluid must surely be undesirable; both in terms of its direct effect on the total plasma product supply and in terms of national strategic vulnerability to discontinuity in the supply of essential medicines.

9 UK Donor Plasma's potential to enhance supply of Immunoglobulin and other medicines

9.1 Figure 4 below shows the potential effect that UK donor plasma could have on the UK Ig supply, if all recovered plasma were devoted to that end (not destroyed or sold off for non-clinical uses as at present). On the basis of the data provided by NHSBT and SNBTS, the UKPA team estimates that some 360 tonnes of plasma per year is potentially available, offering the possibility of some 1.6 million extra grams of Ig per annum for patients. This would of course also yield other important plasma products, in amounts scaled to the Ig figures, each in its relevant proportion. An outline of the wider potential availability of plasma derived medicines that could be produced from UK donors' recovered plasma is set out in Appendix II below (page 16). Such of these products as are not required for patients in the UK could of course be exportable to other countries in need, if felt appropriate – generating valuable income and benefitting patients in need overseas. (Global shortages of plasma products are not limited to immunoglobulin.)

9.2 Preliminary confidential discussions with commercial fractionators indicate that the re-introduction of UK donors' recovered plasma to the plasma product pipeline would be a welcome development; and that it offers significant financial benefit, both to the NHS as buyers of plasma products and to the manufacturers/suppliers.

Fig 4: Immunoglobulin potentially available from UK donors' recovered plasma – Year 2019/'20

4.(i) UK blood Collection and plasma yield (Figures from NHSBT & SNBTS)	ml per unit donated	Donations Per Annum	Less plasma units used clinically	Available Plasma - units	Available Plasma - litres
Tot. donations & Plasma available UK	470.0	1,775,000	362,518	1,412,482	**365,126.6**
Plasma volume in ml, per donation	258.5				

4.(ii) Immunoglobulin (Ig) potential, if all plasma used

Average Ig yield in gms/litre assumed	**4.50**		
Total Ig potentially available from UK plasma	**1,643,070**	**gms**	
For comparison - total Ig needed/yr UK	**7,789,980**	**gms**	

Proportion of UK Ig needs that could be met by the recovery of current UK Donors' Plasma – as % of the total and of established clinical categories

Of Total Ig needed	**21.09%**
Of Red Indications	**55.6%**
Of Blue Indications	**37.1%**
Of Grey Indications	**407.8%**

4.(iii) Workings: Donations Eng/ Wales 1,600,000

Scot/NI 175,000

UK Total 1,775,000

Plasma Units used clinically

Eng/Wales	338,853
Scot/N.I.	23,665
UK Total	**362,518**

4.(iv) Note

The use of clinical Ig categories has now changed. The red, blue, grey split shown here is for illustrative purposes only.

10 Conclusion

10.1 This Memorandum has been prepared in the hope of helping to address the issues of primary concern to the teams at UKPA, UKPIN, BIS, IANG, PID UK and the many donors, clinicians and patients for whom we speak, namely

a) the growing global shortage of human plasma and the increasing shortages of immunoglobulin (Ig) and other plasma products upon which thousands of patients depend for their quality of life and often for life itself;

b) the UK's increasing dependency on the USA for supplies of plasma products and the dangerous strategic vulnerability that this creates; and

c) the currently unrealised potential of UK blood donor plasma that could and we believe should be recovered to make a significant contribution to the sufficiency and security of supplies of Ig and other medicines;

all pointing to the urgent need for UK authorities to carefully re-assess the current ban on UK donors' plasma.

10.2 The UKPA team believes that the available evidence points towards a conclusion that will almost certainly be supported by the further analysis about to be undertaken by MHRA, CHM and others; namely that global Ig supply shortages and the UK's total strategic reliance on imports of all plasma products will prove now to be a more significant factor in current and future UK plasma discussions than any residual doubts that anyone may still have about UK plasma product safety from a vCJD point of view.

10.3 Therefore, the UKPA team, together with our partners and associates in the clinical and patient representative communities, very much hope that these matters will be addressed promptly by the relevant experts and responsible bodies within the orbit of DHSC, MHRA, CHM and others as appropriate.

10.4 The UKPA team hopes very much that this Memorandum may be of some assistance in that context and is certainly very willingly available for further analysis and discussion of these matters, if asked.

GRO-C

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Chair

United Kingdom Plasma Action

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Appendix I - Variant CJD implicated UK Plasma Product Batches

vCJD and Plasma Products: Implicated batch numbers - 07.09 2004: Health Protection Agency, Colindale

Table 1: Products where the likelihood of a recipient surpassing the threshold dose for public health purposes has been estimated to be HIGH[1,2].

Factor VIII				Factor IX				Antithrombin			
Brand name	Vial Size (iu)	Batch Number	Release date	Brand name	Vial Size [iu]	Batch Number	Release date	Brand name	Vial Size [iu]	Batch Number	Release Date
8Y	500	FHB4116	26.06.92	9A	600	FJA0092	24.05.90	Antithrombin*	500	ATA4535*	20.12.96
8Y	500	FHB4189	14.04.93	9A	600	FJA4239B	09.07.93				
8Y*	500	FHB4419*	31.07.95	9A	600	FJA4308	18.06.94				
8Y*	500	FHB4547*	01.11.96	Replenine	500	FJM4327	10.10.94				
8Y*	500	FHB4596*	06.05.97	Replenine	500	FJM4437	27.11.95				
8Y	250	FHC0289	23.05.90	Replenine*	500	FJM4596*	23.04.97				
8Y	250	FHC0369	18.12.90	Replenine	500	FJM4625	07.07.97				
8Y	250	FHC4237	09.03.94	HT DEFIX (PFC)	276	3502-70210	14.09.87				
Replenate	500	FHE4437	21.09.95								
Replenate*	500	FHE4536*	04.09.96								
Replenate*	500	FHE4548*	17.10.96								
Replenate	1000	FHF4625	29.07.97								
High purity F8	500	FHM3990	17.11.91								
High purity F8	500	FHM4054	06.05.92								
Z8 (PFC)	160	0301-70320	02.08.87								
Z8 (PFC)	190	0304-70510	14.07.87								
Total		16		Total		8		Total		1	

All products manufactured in UK: products from the Protein Fractionation Centre, Scotland are designated 'PFC'. All other products manufactured by Bio Products Laboratory.

Table 2: Products where the likelihood of a recipient surpassing the threshold dose for public health purposes has been estimated to be MEDIUM

Intravenous Immunoglobulin				Albumin 4.5%			
Brand name	Vial Size (g)	Batch Number	Date of release	Brand name	Vial Size (ml)	Batch Number	Date of release
Vigam S	5	VGC018	20.04.94	Albumin 4.5%	500	ADA0232	27/06/1991
Vigam S	5	VGC018 A	12.05.95	Albumin 4.5%	500	ADA0233	28/06/1991
Vigam S*	5	VGC047 *	19.12.96	Albumin 4.5%	500	ADA0234	28/06/1991
Vigam S*	5	VGC048 *	20.01.97	Albumin 4.5%	500	ADA0387	11/08/1993
Vigam S*	5	VGC049 *	30.01.97	Albumin 4.5%	500	ADA 390	15/09/1993
Vigam S	5	VGC085	14.11.97	Albumin 4.5%*	500	ADA0529*	11/07/1995
Vigam S	5	VGC087	21.11.97	Albumin 4.5%	500	ADA0629	14/08/1996

Vigam S	5	VGC110	09.04.98	Albumin 4.5%	500	ADA0631	14/08/1996
Vigam S	5	VGC111	14.05.98	Albumin 4.5%*	500	ADA0680*	08/05/1997
				Albumin 4.5%	500	ADA0763	14/09/1998
Vigam S*	2.5	VGD050*	14.03.97	Albumin 4.5%	250	ADB0163	22/08/1990
				Albumin 4.5%	250	ADB0441	12/05/1994
Vigam L	5	VLC088	05.01.98	Albumin 4.5%*	250	ADB0681*	02/05/1997
				Albumin 4.5%	250	ADB0751	08/04/1998
				Albumin 4.5%	100	ADC0443	18/05/1994
				Albumin 4.5%	50	ADD0632	14/10/1996
				SPPS (PFC)	400	3301-81930	22/03/1988
				SPPS (PFC)	400	3301-81940	11/03/1988
				SPPS (PFC)	400	3301-81990	31/10/1988
				SPPS (PFC)	400	3302-71150	30/04/1987
				SPPS (PFC)	400	3302-71160	08/05/1987
				SPPS (PFC)	400	3302-71170	08/05/1987
				SPPS (PFC)	400	3302-71190	08/05/1987
				SPPS (PFC)	400	3305-71400	19/08/1987
				SPPS (PFC)	400	3305-71410	30/07/1987
				SPPS (PFC)	400	3305-71420	19/08/1987
				SPPS (PFC)	400	3305-71435	21/08/1987
				SPPS (PFC)	400	3312-71920	11/03/1988
Total		11		Total		28	

Table 3: Products where the likelihood of a recipient surpassing the threshold dose for public health purposes has been estimated to be LOW[1,2].

Albumin 20%			Factor VIII (excipient implicated)			Factor VIII (excipient implicated)			Intramuscular Immunoglobulins		
Brand name	Vial Size (ml)	Batch Number	Brand name	Vial Size (iu)	Batch Number	Brand name	Vial Size (iu)	Batch Number	Brand name	Vial Size (mg)	Batch Number
Albumin 20%	100	ABC0065	Replenate	250	FHD4235	High purity Factor 8	500	FHM4200	Normal	750	GGB064
Albumin 20%	100	ABC0111	Replenate	250	FHD4247B	High purity Factor 8	500	FHM4202			
Albumin 20%	100	ABC0157	Replenate	250	FHD4267B	High purity Factor 8	500	FHM4206	Normal	250	GGD077
Albumin 20%	100	ABC0219	Replenate	250	FHD4267C	High purity Factor 8	500	FHM4209	Normal	250	GGD084F
Albumin 20%	100	ABC0229	Replenate*	250	FHD4579*	High purity Factor 8	500	FHM4210	Normal	250	GGD084G
Albumin 20%	100	ABC0233				High purity Factor 8	500	FHM4211	Normal	250	GGD084H
Albumin 20%	100	ABC0237	Replenate	500	FHE4218	High purity Factor 8	500	FHM4212	Normal	250	GGD085
Albumin 20%	100	ABC0246	Replenate	500	FHE4244B	High purity Factor 8	500	FHM4214	Normal	250	GGD086
Albumin 20%*	100	ABC0360*	Replenate	500	FHE4247A	High purity Factor 8	500	FHM4216	Normal	250	GGD130

Albumin 20%	100	ABC0399	Replenate	500	FHE4250	High purity Factor 8	500	FHM4217	Normal	250	GGD131
			Replenate	500	FHE4267A	High purity Factor 8	500	FHM4219			
Albumin 20%	50	ABD0290	Replenate	500	FHE4277A	High purity Factor 8	500	FHM4220	IMIgG (PFC)	745	0709-70190
Albumin 20%	50	ABD0291	Replenate	500	FHE4277B	High purity Factor 8	500	FHM4221			
Albumin 20%	50	ABD0295	Replenate	500	FHE4286	High purity Factor 8	500	FHM4223	Anti-D	500	GDC071
Albumin 20%*	50	ABD0311*	Replenate*	500	FHE4579*	High purity Factor 8	500	FHM4227	Anti-D	250	GDD072
Albumin 20%*	50	ABD0319*	Replenate	500	FHE4653	High purity Factor 8	500	FHM4229			
Albumin 20%*	50	ABD0324*	Replenate	500	FHE4658	High purity Factor 8	500	FHM4246			
Albumin 20%*	50	ABD0325*				High purity Factor 8	500	FHM4249			
Albumin 20%*	50	ABD0332A*	Replenate	1000	FHE4244C	High purity Factor 8	500	FHM4257			
Albumin 20%	50	ABD 389	Replenate	1000	FHF4244C	High purity Factor 8	500	FHM4259			
Albumin 20%	50	ABD0445	Replenate	1000	FHF4252	High purity Factor 8	500	FHM4261			
Albumin 20%	50	ABD0458	Replenate*	1000	FHF4577*	High purity Factor 8	500	FHM4262			
						High purity Factor 8	500	FHM4263			
			High purity Factor 8	500	FHM4127	High purity Factor 8	500	FHM4268			
			High purity Factor 8	500	FHM4136	High purity Factor 8	500	FHM4272			
			High purity Factor 8	500	FHM4136A	High purity Factor 8	500	FHM4275			
			High purity Factor 8	500	FHM4138	High purity Factor 8	500	FHM4278			
			High purity Factor 8	500	FHM4140	High purity Factor 8	500	FHM4281			
			High purity factor 8	500	FHM4142	High purity Factor 8	500	FHM4290			
			High purity Factor 8	500	FHM4144	High purity Factor 8	500	FHM4297			
			High purity Factor 8	500	FHM4148						
			High purity Factor 8	500	FHM4160	High purity Factor 8	1000	FHP4161			
			High purity Factor 8	500	FHM4163	High purity Factor 8	1000	FHP4197			
			High purity Factor 8	500	FHM4164	High purity Factor 8	1000	FHP4213			
			High purity Factor 8	500	FHM4173	High purity Factor 8	1000	FHP4245			
			High purity Factor 8	500	FHM4182	High purity Factor 8	1000	FHP4255			
			High purity Factor 8	500	FHM4183	High purity Factor 8	1000	FHP4265			
			High purity Factor 8	500	FHM4184	High purity Factor 8	1000	FHP4279			
			High purity Factor 8	500	FHM4185	High purity Factor 8	1000	FHP4296			
			High purity Factor 8	500	FHM4186						
			High purity Factor 8	500	FHM4190	High purity Factor 8	250	FHR4175			
Total		21	Total		38	Total		39	Total		12

[1] All products manufactured in UK: products from the Protein Fractionation Centre, Scotland are designated 'PFC'. All other products are from BPL.

Appendix II – Plasma Product Potential from full fractionation

The potential availability of the three major plasma derived medicines - Immunoglobulin (Ig), Albumin and Factor VIII - that could be produced from the current volume of recovered UK donors' plasma (circa 360 tonnes/annum).

1. UK blood Collection and plasma yield	Donations		Less plasma units used clinically	Available	Available
	ml per unit	Units per Annum		Plasma – units	Plasma – litres
Tot. donations & plasma available UK	470.0	1,775,000	362,518	1,412,482	**365,126.6**
Plasma volume in ml, per donation	258.5				

2. Product potential, if all plasma used	
Average Ig yield in gms/litre assumed	**4.50**
Average Albumin yield in gms/litre assumed	**22.00**
Average Factor VIII yield in iu/litre assumed	**150**

3. **Workings**: Donations England/ Wales	1,600,000	Plasma Units used clinically	
		Eng/Wales	338,853
Scotland/Northern IrelandI	175,000		
		Scot/N.I.	23,665
UK Total	1,775,000		
		UK Total	**362,518**

Note 1: Plasma figures provided by the NHSBT and the SNBTS

Note 2: Maximum possible plasma recovery is assumed; and also full fractionation.

Potential - Top 3 Plasma Products		
Potential Ig (gms)	Potential Albumin (gms)	Potential Factor VIII (iu)
1,643,070	**8,032,785**	**54,768,990**

Note 3: Other plasma products potentially available, in proportion (here set out in alphabetical order):

1. ANTI-THROMBIN III
2. FACTOR VIIA
3. FACTOR IX
4. FACTOR X
5. FACTOR XIII
6. FIBRINOGEN
7. FIBRIN SEALANT
8. PROTEIN C
9. PROTHROMBIN COMPLEX
10. THROMBIN

Note 4: The above is for illustrative purposes only. The actual eventual extent of fractionation will of course be a matter for discussion between DHSC/NHS and potential fractionators. It will of course depend, among other things, on UK product needs, global demand and the detailed cost/benefit analysis of the various options available.

It should be noted for instance that global demand for albumin is high and rising, especially in China.

Also, whereas recombinant clotting factors are now the preferred choice for many prescribing clinicians in many countries, there is still significant demand for the human plasma derived equivalents in many other parts of the world. Therefore, it may be envisaged that the FVIII available from UK donors' recovered plasma (as above) could be of great benefit to patients overseas and, through export sales, could also provide welcome financial benefits to the NHS. The extent to which this may also be true of other available plasma fractions will no doubt emerge in due course.

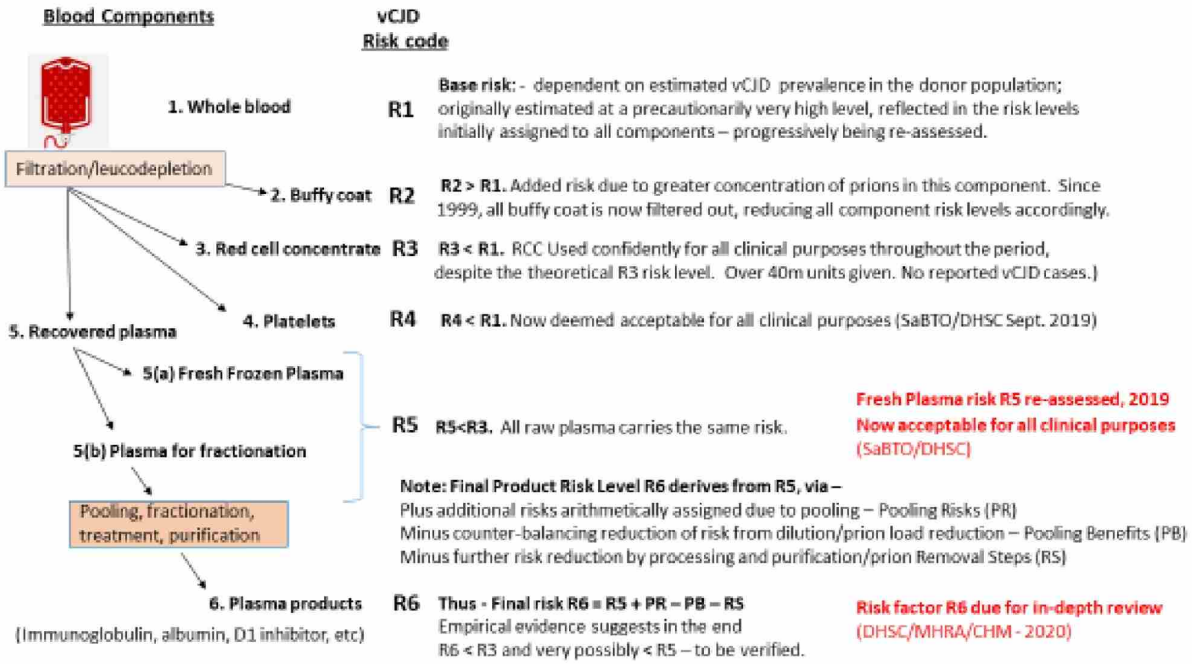
Appendix III – Supplementary Notes on Blood, Blood Components and Recovered Plasma Risk Factors

1. A suggested schema for the concatenation of component risk factors is illustrated below (Figure A.III.1). Due to the extreme uncertainty surrounding many aspects of Variant Creutzfeldt Jacob Disease in the early days of the BSE/vCJD crisis, the base risk (R1) was originally estimated at a high worst-case level on the precautionary principle. This implied of course a very significant risk of numerous fatalities from transfusion transmitted vCJD infection via red cells (risk R3, below) but this simply had to be accepted as an unavoidable hazard, to be faced as events unfolded. Unnecessary administration of red cells was of course (as always) to be kept to a minimum; but where the transfusion of red cell concentrate is a necessary life-saving step there simply is no viable alternative. As there was no other source of sufficient supply of red cells, the risk was therefore taken, as it had to be.

2. Happily however, as events have unfolded, the consistent clinical experience has been that since the introduction of leucodepletion (in 1999) the administration of fresh components gathered from UK donors' blood has not caused any confirmed cases of vCJD transmission, despite the very large number of units involved. (Ref Fig 2, Section 6, above). This does not of course prove zero risk, but with now over 60 million units administered to patients over the last 21 years and not a single reported case of any resultant vCJD infection, it would seem reasonable to assume that in the present era (since leucodepletion was introduced in 1999) UK-sourced red cell concentrate does not in fact pose a significant vCJD risk and that R3 (the base risk level for all filtered blood components) must be very low indeed.

Figure A.III.1.

Blood Donations and vCJD risk– Simplified Component and Risk Flow



3. Bearing in mind that, pre-leucodepletion, red cell concentrate was in fact the source of 3 confirmed vCJD transmissions, compared with zero confirmed cases from fresh plasma or other components of UK blood donations during the same period, it seems reasonable to assume that whilst, post-leucodepletion, red cell concentrate is proving to be reassuringly incident free, the parallel plasma components of the same donations (component 5, Risk level R5, above) may pose even less vCJD infection risk than do red cells. (Hence, R5 < R3).

4. Inevitably, historic risk assessments have placed great emphasis on the risk-multiplier effect of plasma unit pooling. At a simple common sense level, a pool of ten thousand units of individual donors' plasma might be thought to pose ten thousand times the risk to an individual patient, as compared to a single unit infusion. However, this approach has led to risk assessments that turn out to be at odds with the facts. As shown in section 5 (above, page 7) the many thousands of tonnes of UK donor's plasma that were pooled, fractionated and administered to patients as plasma products from 1983-1999 – the peak years of BSE/vCJD concern – caused no confirmed vCJD transmissions.

5. In addition, strongly underlining the point, even the UK plasma products manufactured from batches of plasma that were subsequently found to have been vCJD positive (too late for product withdrawal) that were administered to patients during the original crisis have never been implicated in any reported cases of actual vCJD transmission. (Ref: Appendix I, page 13). It seems reasonable to conclude therefore that, in addition to pooling, one or more other factors must have been at work. This aspect of the up-dating study will of course require further investigation. At this stage, based on the large body of evidence so far at hand, the following four possibilities suggest themselves for further enquiry:

- either the base risk (R1 above) may have been much lower than had originally been estimated; and/or
- pooling may not be as much of a vCJD risk exacerbation as was previously imagined; and/or
- the effects of dilution (the other side of the pooling coin) may have a more positive impact on risk than was previously realised; and/or
- the prion reduction/removal effects inherent in the fractionation process may be more effective than had previously been thought; and/or
- the truth may be a combination of some or all of the above.

6. Note: Of course, one other obvious potential explanation for the widespread and long standing absence of any vCJD infection from UK blood and plasma products might have been that there was in fact no vCJD infection in any of the relevant donors in the first place. Whilst this may be a highly likely explanation of much of the excellent safety record of all the components and medicines in question, it cannot be applied to the plasma products produced from vCJD positive plasma batches (Appendix I, p 13). In those cases (also all non-infective, as far as we know to date) the explanation must surely lie in one of the five bullet points above – or some sixth explanation as yet unformulated.

7. Figure A.III.1 (above) attempts to sketch out the key stages and comparative levels of likely risk in a way that may be useful in a re-assessment of the balance of risks involved in the use/non-use of UK donors' plasma. The UKPA team believe it pertinent to suggest that with previous and current risk assessments having proven, over time, to be an increasingly poor fit with the emerging real-world data, a substantial re-focussing of the risk assessments themselves would seem to be strongly indicated. It is not the intention here to assert anything about what the new risk levels should be set at for the purposes of cost/benefit analysis and the guidance of policy and practice. The formula at the foot of Figure A.III.1 above is offered simply as one possibly helpful approach to the process; one that seems to better fit the facts now available.

8. In this context, there is of course good evidence in the literature with respect to the effect that modern plasma fractionation has on pathogen presence and load, including work done in France, on the basis of which that nation chose not to withdraw its donors' plasma from the product manufacturing pipeline, despite the known presence of vCJD in the French population. These French data may also be helpful in informing UK decisions in 2020.

9. French experience over the last 21 years has certainly tied in very well with the UK experience prior to the UK plasma ban. There were zero reported cases of vCJD infection via any French home grown plasma product(s), even during the years when the BSE/vCJD crisis was at its height. With a low but not insignificant incidence of vCJD in the French population and despite taking no precautions to ban their own donors' plasma from the pharmaceutical product pipeline at any time over the last 21 years, France has experienced no reported cases of vCJD transmission via a plasma product. This fact is of course very welcome from a public health point of view. However, against that background, the plasma product vCJD risk assessments made in the UK at the time and maintained during the 21 years since do seem deeply puzzling.

10. The implications of all of the above may well be that risk level R6 is in fact lower than R5, not higher; taking pooling and processing fully into account. At the very least, this possibility is surely worthy of careful consideration. Given that an up-to-date investigation of R5 has recently been conducted by SaBTO and the resulting recommendations have been accepted by government, it surely goes without saying that R6 should now also be looked at again.

Appendix IV – A Consideration of Potential/Possible vCJD Incubation Periods

Draft Schema - Potential Variant CJD incubation periods - from National Surveillance Centre Statistics

Possible (theoretically conceivable) dates/yrs of original infection shown shaded - assuming no infection pre-'83 or post-'99

Deaths			Possible dates of original infection - at various assumed lengths of incubation period (yrs)													
Year	No.		6	8	10	12	14	16	18	20	22	24	26	28	30	32
1994	0		1988	1986	1984	1982	1980	1978	1976	1974	1972	1970	1968	1966	1964	1962
1995	3		1989	1987	1985	1983	1981	1979	1977	1975	1973	1971	1969	1967	1965	1963
1996	10		1990	1988	1986	1984	1982	1980	1978	1976	1974	1972	1970	1968	1966	1964
1997	10		1991	1989	1987	1985	1983	1981	1979	1977	1975	1973	1971	1969	1967	1965
1998	18		1992	1990	1988	1986	1984	1982	1980	1978	1976	1974	1972	1970	1968	1966
1999	15		1993	1991	1989	1987	1985	1983	1981	1979	1977	1975	1973	1971	1969	1967
2000	28		1994	1992	1990	1988	1986	1984	1982	1980	1978	1976	1974	1972	1970	1968
2001	20		1995	1993	1991	1989	1987	1985	1983	1981	1979	1977	1975	1973	1971	1969
2002	17		1996	1994	1992	1990	1988	1986	1984	1982	1980	1978	1976	1974	1972	1970
2003	18	#	1997	1995	1993	1991	1989	1987	1985	1983	1981	1979	1977	1975	1973	1971
2004	9		1998	1996	1994	1992	1990	1988	1986	1984	1982	1980	1978	1976	1974	1972
2005	5		1999	1997	1995	1993	1991	1989	1987	1985	1983	1981	1979	1977	1975	1973
2006	5	#	2000	1998	1996	1994	1992	1990	1988	1986	1984	1982	1980	1978	1976	1974
2007	5	#	2001	1999	1997	1995	1993	1991	1989	1987	1985	1983	1981	1979	1977	1975
2008	2		2002	2000	1998	1996	1994	1992	1990	1988	1986	1984	1982	1980	1978	1976
2009	3		2003	2001	1999	1997	1995	1993	1991	1989	1987	1985	1983	1981	1979	1977
2010	3		2004	2002	2000	1998	1996	1994	1992	1990	1988	1986	1984	1982	1980	1978
2011	5		2005	2003	2001	1999	1997	1995	1993	1991	1989	1987	1985	1983	1981	1979
2012	0		2006	2004	2002	2000	1998	1996	1994	1992	1990	1988	1986	1984	1982	1980
2013	1		2007	2005	2003	2001	1999	1997	1995	1993	1991	1989	1987	1985	1983	1981
2014	0		2008	2006	2004	2002	2000	1998	1996	1994	1992	1990	1988	1986	1984	1982
2015	0		2009	2007	2005	2003	2001	1999	1997	1995	1993	1991	1989	1987	1985	1983
2016	1		2010	2008	2006	2004	2002	2000	1998	1996	1994	1992	1990	1988	1986	1984
2017	0		2011	2009	2007	2005	2003	2001	1999	1997	1995	1993	1991	1989	1987	1985
2018	0		2012	2010	2008	2006	2004	2002	2000	1998	1996	1994	1992	1990	1988	1986
2019	0		2013	2011	2009	2007	2005	2003	2001	1999	1997	1995	1993	1991	1989	1987
2020	0		2014	2012	2010	2008	2006	2004	2002	2000	1998	1996	1994	1992	1990	1988
Total	178	(deaths)														

Note 1. For cases in any given year, historically or in the future, the extreme range of conceivable incubation periods would be as shown, shaded, assuming no dietary vCJD infections before 1983 or since 1999 (the accepted period of the original BSE-sourced epidemic.)

Note 2: The green cells at years 6 and 8 are highlighted as a reminder that all the known transfusion transmitted infections (all from RCC) had incubation periods within this range. There is no record of any infection known to have incubated for longer than 8 years. The above therefore is intended as an examination of theoretical possibilities only – without comment on the likelihood of any greatly extended incubation periods.

Note 3: The years of the known transfusion transmitted cases (RCC) are highlighted and marked #. All other cases are known or assumed to have been from dietary infection - from eating infected beef. It cannot of course be assumed that incubation periods are the same for these two types of infection (dietary and transfusion transmitted).

Note 4: Given the data on earliest possible dates of infection (during the acknowledged BSE risk period 1983 – 1999) it seems an inescapable conclusion that in the cases reported during the peak years, the disease cannot have incubated for more than 20 years at maximum; in earlier cases, for no more than 12 yrs. Cases reported later could theoretically have incubated for longer; but even then it seems extremely unlikely that one could possibly deduce any conceivable incubation period exceeding 33 years - assuming that the death in 2016 was the result of an infection contracted in 1983 that lay dormant for a very extended period (which seems highly unlikely, but is nevertheless a theoretical possibility).

For comparison, the earliest use of a UK plasma product that could/might have been infected was in 1983 and the latest was in '99, so the range of time with no known infections (so far) is 21yrs - 37yrs.

N.B. It may be helpful to emphasise here that none of the above is intended as the basis for any definitive assertions. It is only proposed as of possible assistance in discussion of the vCJD incubation question. The only known facts in this context are that
a) there has been no known case of a vCJD incubation period exceeding 8 years;
b) the 60m units of fresh components given to patients in the last 21 years have not yet given rise to any reports of vCJD infection;
c) the approximately 2,000 tonnes of UK donors' plasma used to make plasma products during the highest risk vCJD period (1983-1999) have not yet given rise to any confirmed cases of vCJD infection from any of those UK plasma products.