

## **Importation of plasma as a vCJD risk reduction measure: reconsideration of “acceptable” source countries**

As agreed by the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) in March 2012, fresh frozen plasma (FFP) is imported for use in the UK for those born after 1<sup>st</sup> January 1996, and for patients with thrombotic thrombocytopenic purpura (TTP). This policy, first introduced in 2006, aims to reduce the potential risk of transmitting variant Creutzfeldt Jakob disease (vCJD) through transfusion. The Spongiform Encephalopathy Advisory Committee (SEAC – dissolved in 2011) issued advice, reviewed by SaBTO in July 2009, about the safe sourcing of such plasma. SaBTO agreed that plasma should be imported from countries with at least 3 logs (ie factor of 1,000) lower estimated prevalence of sub-clinical vCJD compared to the UK; and that for TTP patients, it should be more than 4 logs lower (or that prion-reduced single-donor FFP should be used, subject to satisfactory post-marketing surveillance).

Since then, work has been undertaken to address the mis-match between the predicted number of UK cases of transfusion-transmitted vCJD and the number of such clinical cases actually seen, ie three. A revised risk assessment model was developed by the Health Protection Analytical Team at the Department of Health, based on new evidence on both the prevalence of infection and the infectivity of blood, and on the susceptibility of individuals to infection. This was endorsed by the Advisory Committee on Dangerous Pathogens TSE Risk Assessment Sub-Group, and formed part of SaBTO's review of the importation of fresh frozen plasma (FFP) in March 2012. An updated version of this risk assessment, approved by the Advisory Committee on Dangerous Pathogens on 14 February 2013, is published at <https://www.gov.uk/government/publications/vcjd-and-transfusion-of-blood-components-updated-risk-assessment>.

The Analytical Team has reviewed the advice given in 2009 on sourcing plasma for importation, in light of the revised risk assessment model and any new data available. They found nothing to change their previous assessment of prevalence in other countries relative to that in the UK. However it has proved difficult in practice for UK Blood Services to source sufficient plasma from countries with a 3 log lower prevalence as they are very few in number and tend not to have available capacity to supply the UK. Also the number, complexity and variations in the models used, and the continued uncertainties about some of the data, mean that small distinctions cannot be drawn with confidence. It therefore seems reasonable to consider a minimum of 2.5 logs lower prevalence by all models (3 logs by some) rather than a minimum of 3 logs lower prevalence by all models.

On the basis of the Analytical Team's work, SaBTO advises that imported single donor plasma should be sourced from countries with vCJD prevalence at least 2.5 logs lower than the UK by all assessments, and at least 3 logs lower in some, as set out in the following paper.

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# Importation of plasma as a vCJD risk reduction measure: reconsideration of “acceptable” source countries

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## Introduction

Given that plasma for transfusion is to be imported for some patient groups, in order to reduce any risk of vCJD (variant Creutzfeldt Jakob disease) transmission, there is a need to establish clear criteria as to where such plasma may be imported *from*, in order to achieve an acceptable reduction in risk. This in turn requires some evidence-based judgement as to the likely differentials in sub-clinical vCJD prevalence in different countries, relative to the UK. There are many defensible ways of making such judgements. An obvious initial criterion is to specify source countries that have recorded no indigenous clinical cases of vCJD. Beyond that, one can look for countries with low prevalence of BSE (bovine spongiform encephalopathy) in their domestic cattle herds. However, this is complicated by the existence of widely differing herd sizes (and arguably, dietary patterns), and differences in the reliability of animal surveillance. Data on some countries are in short supply. Although it is possible to factor-in the potential effects of beef imports from the UK, we have not been able to allow for other cross-border flows of beef, cattle or people.

When this question was previously considered (by SEAC – the Spongiform Encephalopathy Advisory Committee - on 4<sup>th</sup> March 2009), we therefore suggested a number of “scoring” methods, giving different weights to various factors. These are summarised in Appendix A. Further investigation has not uncovered any new information that would significantly change the results set out in the table.

There is no conclusive reason for preferring one specific scoring system over all the others. It is therefore important to find a criterion for acceptability of source countries that is *robust* – ie defensible across a variety of possible scoring systems.

In July 2009, and based on the discussion at SEAC, SaBTO made the following recommendations for the sourcing of plasma products for patients born after 1 January 1996 and thrombocytopenic purpura (TTP) patients

- Where possible, at least 3 log less estimated prevalence of subclinical vCJD compared to the UK but in principle the lower the better;
- For pooled product, at least 4 log less estimated prevalence of subclinical vCJD compared to the UK.

Since 2009, the HPA (Health Protection Agency) has reported on a study into the prevalence of abnormal prion protein in samples of appendix tissue taken during

surgery in the UK<sup>1</sup>, which is taken to indicate infection with vCJD. This indicated a central estimate of 1 in 2,000, rather than the 1 in 4,000 from the earlier study by Hilton *et al*<sup>2</sup>. While our estimate of the prevalence of vCJD in the UK has therefore doubled, our understanding of the contributory factors to this, such as prevalence of BSE in the UK cattle herd, has not changed. Similarly, our understanding of these factors in *other* countries during the period of the relevant outbreak has not changed. As a result, we have no cause to revise our assessment of prevalence in other countries *relative to that in the UK*.

Also, Gregori<sup>3</sup> *et al* published research into the vCJD infectivity of blood. In considering this paper, the Advisory Committee on Dangerous Pathogens TSE Risk Assessment subgroup agreed that an estimate of the order of 1 Infectious Dose (ID) per unit was indicated for non-leucodepleted red cells, which would imply “several” ID per unit of whole blood donated<sup>4</sup>. This has led to the adoption of lower-infectivity scenarios, in which infectivity may be of the order of 3 IDs per infected unit of plasma (Page 11 of the updated risk assessment<sup>5</sup> provides more details on how the number of IDs per unit was estimated), significantly fewer than previously assumed.

Using these revised inputs, the DH Health Protection Analytical Team have estimated that with no importation of FFP for any patient groups (or any other safety intervention), of the order of 45 clinical cases (Confidence interval 10-120) of vCJD could result from transfusions of FFP (fresh frozen plasma) taking place after the beginning of 2013. Of these, we estimate that around 18% would have been under 16 at the time of transfusion (taken as a proxy for those born after 1<sup>st</sup> January 1996), and 13% TTP patients. The number of future clinical cases appearing in these *two* patient groups would thus be around 14 (Confidence Interval 3.1- 37.2). These estimates give some indication of the maximum possible effect of importation for these groups on future clinical vCJD case numbers (ie comparing the use of UK-sourced FFP with an alternative carrying zero vCJD risk).

A further consideration is the distinction between pooled and unpooled (single donor) products.

- NHSBT currently imports, and then pathogen-inactivates by methylene blue treatment, single donor FFP from Austria for patients born after 1 January 1996. There are no restrictions on donors’ origins, other than those relating to residence in the UK.
- All UK blood services (with the exception of the Welsh Blood Service, which changed to provision of solvent detergent-treated pooled FFP for children during 2012 following a national policy decision) purchase MB (methylene blue-treated) FFP from NHSBT;

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<sup>1</sup> <http://www.hpa.org.uk/hpr/archives/2012/news3212.htm#bnrmlprn>

<sup>2</sup> Hilton DA, Ghani AC, Conyers L, Edwards P, McCardle L, Ritchie D, *et al*. Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *J Pathol* 2004; **203**: 733-9.

<sup>3</sup> Gregori L Yang H and Anderson S (2011): Estimation of variant CreutzfeldtJakob disease infectivity titers in human blood. *Transfusion* doi: 10.1111/j.15372995.2011.03199.x.

<sup>4</sup> Minutes of this meeting can be found at [http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@ab/documents/digitalassets/dh\\_129920.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalassets/dh_129920.pdf)

<sup>5</sup> The full web references for the main text and the annexes are available at:

<http://www.dh.gov.uk/health/files/2012/06/Updated-Risk-Assessment.pdf>

<http://www.dh.gov.uk/health/files/2012/06/Updated-Risk-Assessment-Annexes.pdf>

- TTP patients currently receive a pooled product, treated using solvent detergent. Independently of NHSBT, some NHS trusts also purchase this for use with children, on the basis of clinical preference<sup>6</sup>.

This paper considers the implications of the new evidence for the original FFP sourcing recommendations. It considers only the reduction in vCJD risk achieved, rather than including the impact of any other risks (some of which may be more significant), such as the reduction in the risks of transfusion-related lung injury from use of a pooled product, residual microbiological risk, or the possibility of any deleterious effects from pathogen inactivation.

### Single Donor Plasma

As noted above, the revised infectivity assumptions imply that an infected donation would contain a substantial infectious dose (several IDs per unit), associated with both plasma and leucocytes. Leucodepletion is taken to remove effectively the infectivity associated with the white cells in the donation, but not that associated with plasma. As a 220-ml-single-unit of FFP contains about 82% of the original volume of plasma in the donation, we make the precautionary assumption that an infected unit would contain all the plasma-associated infectivity in the donation. This is taken to be of the order of 3 IDs per infected unit, sufficient to make transmission of infection virtually certain (95% likelihood using a Poisson dose-response model).

Therefore, the adoption of lower-infectivity scenarios leaves the previous (2009) conclusion regarding single donor FFP unchanged: **receipt of an infected unit would result in virtually certain transmission of infection**. The likelihood of a patient being infected is therefore determined by the prevalence of sub-clinical vCJD among the relevant donor population.

The 2009 recommendation was for a differential in prevalence of at least 3 logs (factor of 1,000) where possible. Given the uncertainties in the scoring mechanisms and problems in securing plasma from countries with this level of reduction, we suggest that it would be appropriate to require a *minimum* of 2.5 logs differential across *all* the methods set out in Appendix A, and at least 3 logs in some. This would provide a clear recommendation for most of the countries listed (though it should be noted that only those countries for which data could be found are listed); but some further consideration is required for Poland and Austria.

The table shows Poland to have a lower estimated prevalence of sub-clinical vCJD than Austria, which is currently regarded as an acceptable source. However, on review, there was a concern that the true picture in Poland might have been obscured by poor BSE surveillance, especially in the years prior to EU accession. Efforts have been made to find further information, with limited success. However:

- The WHO summary of BSE cases detected in a range of countries shows that Poland's numbers are indeed low early on (which would fit with, but by no means prove, poor surveillance). The actual numbers appearing later on are higher than Austria's, but given differences in herd size, the numbers *per million cattle* are broadly similar: see (<http://www.oie.int/animal-health-in-the-world/bse-specific-data/annual-incidence-rate>).

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<sup>6</sup> Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant (2004 The British Society for Haematology, 126, 11–28)

- It should be noted that some of the methods used in the table already add in a factor for possible under-ascertainment of BSE.
- Therefore it is difficult to discern any objective case for treating Poland and Austria differently. If the criteria set out above are deemed to be acceptable, our suggestion is that both Austria and Poland meet them.

As already noted, the expected number of cases from transfusion of unpooled plasma will be proportional to the prevalence of vCJD among the donor population. For example, sourcing of plasma from a country with a 2 log (100x) lower prevalence should avoid 99% of anticipated cases. More generally, we can apply this principle to see the effect of various differentials in prevalence on the number of future cases amongst patients born after 1<sup>st</sup> January 1996, as compared to those that would have been expected from using UK plasma:

**Table 1:** Expected future clinical vCJD cases due to FFP transfusion amongst patients born after 1<sup>st</sup> January 1996

Log reduction(prevalence, compared to UK)	Expected future clinical cases
0 (UK)	8
1	0.8
2	0.08
2.5	0.025
3	0.008

### **Pooled Plasma**

While untreated single donor FFP is categorised as a blood component for the purposes of regulation, pooled solvent detergent FFP is categorised as a medicinal product. It is therefore regulated by the Medicines and Healthcare Regulatory Agency (MHRA) on a different basis, with particular specifications and requirements to be met in order for it to be licensed.

The Committee on Human Medicines within MHRA adopted the following advice concerning the risk of vCJD and other TSEs (transmissible spongiform encephalopathies) relating to medicinal products manufactured from plasma:

- UK plasma should not be used.
- The risk of use of medicinal products obtained from plasma sourced from countries other than the UK with one or more cases of vCJD should be balanced against the benefit-risk profile of the product, the consequences of possible supply shortages should the plasma source not be used, and evaluation of clearance/reduction steps incorporated in the manufacturing process.
- In view of manufacturing facilities processing plasma, in which other plasma that could be contaminated is also processed (shared facility), the risk of contamination of the product with TSE agents should be evaluated by provision of a supportive risk-assessment.

The manufacturers of the medicinal product (pooled plasma – solvent detergent treated) currently used in the UK obtained a variation to their product licence in order

to introduce a ligand in a column format during the manufacturing process. This licence was approved in the UK in 2011.

This product was licensed on the basis that the presence of the prion reduction column may reduce prions were they to be present and the treatment had no deleterious effects on the product. The findings of a SaBTO expert group, attached at Appendix B, suggest that there may be significant benefits. However, the evidence is not definitive. We therefore make the precautionary assumption that no reduction is achieved (so that effective vCJD risk reduction from use of this product will depend entirely on how the plasma is sourced).

Under the relevant licence, plasma used for manufacture of solvent detergent FFP with ligand in a column format may be obtained from collection centres situated in Austria, Estonia, Germany, Slovenia, Sweden, Switzerland, USA, Finland, Latvia, Luxembourg and the Czech Republic, which are all without indigenous cases of vCJD to date. There are no restrictions on donors' origins, other than those relating to residence in the UK.

The relative risk associated with single donor FFP compared with pooled FFP has changed somewhat as a result of the new evidence. Recipients of pooled products have a greater chance of receiving a unit with an infected contribution, but the per-unit dose would be smaller (the infected donation being diluted with uninfected contributions). The results of this "trade-off" in risk are highly-dependent on the level of infectivity present. When previous analyses of the "sourcing" question were carried out, it was assumed that an infected unit of plasma might contain a very large number (hundreds, or even thousands) of infectious doses<sup>7</sup>. Such scenarios provided a strong argument for the avoidance of pooling. For a unit sourced from several donors, the infectivity contained in a single, infected contribution would be sufficient to give the recipient a high dose. The chance of this happening is obviously proportional to the number of donations pooled.

Given the new, lower infectivity inputs, pooling *may* still be disadvantageous, but it is highly dependent on the details of pool size and the (unknown) dose-response relationship. However, it is clear that pooling is much less of a disadvantage than it was under previous "high" infectivity assumptions. (For some dose-response relationships, pooling could even be advantageous, if per-unit infectious dose were to be reduced below some minimum threshold for infection. However, this is speculative, and might be regarded as unlikely.)

We therefore need to reconsider the relative vCJD risk of non-UK-sourced pooled FFP, as compared with UK-sourced single-donor FFP. In particular the balance between lower prevalence and the effect of pooling needs to be considered over a wide range of scenarios. Figure 2 below summarises the results of these calculations, for scenarios involving various differentials in prevalence within the source country, as compared with the UK. To calculate the figures in this table, we have made the following assumptions:

- The probability that a donation from an infected donor causes infection in a susceptible individual is calculated using a Poisson dose-response model;
- The mean residual plasma volume of a transfusion unit is 220 ml for single-donor FFP (the mean total volume is 273 ml, 53 ml being anti-coagulant) and, 200 ml for the pooled product. The probability of infection from the transfusion of a plasma unit is derived from the probability of there being an infectious

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<sup>7</sup> These estimates were based on extrapolation from rodent models. See SEAC position statement on TSE infectivity in blood (July 2006)

donation, multiplied by the probability that the contribution from an infected donor causes infection in a susceptible individual<sup>8</sup>;

- The manufacturing pool size for Solvent Detergent-treated FFP is up to 380 litres, and each pool contains material from between 630 and 1520 donors. The volume of a single donation to the pool batch may be between 250 ml (derived from a whole blood donation) and 800 ml (from an apheresis plasma donor). For the purposes of this risk assessment, the volume donated to the pool from a given donor would be assumed equal to 250 ml for recovered plasma and 800 ml for apheresis plasma;
- The number of transfusion units produced from the pool batch is 1,900 and the end product is filled into 200 ml bags;
- The infectivity of plasma content in a unit of non-UK-sourced solvent detergent-treated FFP depends on the size of infected donations entering the pool. This infectivity is assumed to be 0.002 ID / unit of 250 ml recovered plasma or 0.006 ID / unit of 800 ml plasma from plasmapheresis for donations.

To provide a general comparison for any patient group, the Figures in Table 2 start with a hypothetical number of infections (100) caused by single-donor UK-sourced FFP. We then consider how this number would change if this plasma were to be substituted with imported FFP, either single-donor (Table 2(a)) or pooled (Table 2(b)). The rows show results for differentials in prevalence of 2-, 2.5-, 3- and 5-log as compared with the UK.

**Table 2:** Expected infections from non-UK-sourced FFP, if (hypothetically) 100 result from UK Single-Donor FFP

(a)

<b>Single donor FFP</b>		
Plasma	Log reduction in prevalence	Number of infections
UK-FFP (single donor)	0	100 (baseline)
Non-UK FFP (single donor)	2	1
	<b>2.5</b>	<b>0.3</b>
	3	0.1
	5	0.001

(b)

<b>Pooled Solvent/Detergent-treated FFP</b> (one infected plasma donation per pool)		
Plasma	Log reduction in prevalence	Number of infections
UK-FFP (single donor)	0	100 (baseline)
Non-UK pooled FFP	2	2.9
	<b>2.5</b>	<b>0.9</b>
	3	0.29
	5	0.003

<sup>8</sup> We found that the probability of more than one infectious dose in a pool of non-UK FFP sourced with at least one log reduction had no significant effect on the relative infectivity.



Comparing the figures in this table with those presented to SaBTO in October 2009 (see Appendix C), a 2.5 log prevalence differential for pooled products gives as great a differential in infection risk in the new infectivity scenarios as the previous requirement of >4 log did in the previous “high” infectivity scenario.

For a minimum 2.5 log differential in prevalence for source counties, the infectious risk can be reduced by 99% if the pool contains one or two infected donations (we have found that this figure is not significantly affected by whether the infected donation is from a whole blood or plasmapheresis donor). Requiring a minimum 2.5 log differential in prevalence for source countries therefore appears to provide a differential in risk consistent with the previous SEAC and SaBTO advice.

**APPENDIX A**

**Table 12** below provides a summary of the estimated vCJD prevalence for a number of potential source countries, expressed as a log reduction with respect to the UK for each of the potential risk reduction methodologies discussed in Part III of *A comparison of the relative risk of vCJD transmission via single donor and pooled plasma from the UK and non-UK sources*<sup>9</sup>. These estimates are provided as an illustration of the range of results obtained from the different methods and an indication of the order of magnitude of risk reduction derived from these methodologies.

Country	Estimated log reduction in prevalence relative to UK												
	P <sup>1</sup>	P <sup>2a</sup>	P <sup>2b</sup>	P <sup>2a</sup>	P <sup>2b</sup>	P <sup>2a</sup>	P <sup>2b</sup>	P <sup>2a</sup>	P <sup>2b</sup>	P <sup>2a</sup>	P <sup>2b</sup>	P <sup>2a</sup>	P <sup>2b</sup>
	no UAF			with UAFi		with UAFii		no UAF		with UAFi		with UAFii	
	no BAF							with BAF					
Australia	-	'Infinite'	-	-	-	-	-	4.1	-	-	-	-	-
Austria	-	3.8	3.9	2.8	3.0	4.1	4.2	2.9	2.9	2.6	2.7	2.9	2.9
Belgium	-	2.6	2.4	1.8	1.6	2.8	2.6	2.6	2.4	1.8	1.6	2.8	2.6
Canada*	-	4.6	4.5	-	-	-	-	4.2	4.2	-	-	-	-
Denmark	-	3.3	3.1	2.8	2.5	3.6	3.4	2.0	2.0	1.9	1.9	2.0	2.0
Finland	-	4.1	4.2	4.4	4.5	4.4	4.5	3.5	3.5	3.6	3.6	3.6	3.6
France*	0.9	2.6	2.3	2.0	1.7	2.3	2.0	1.2	1.2	1.1	1.1	1.2	1.1
Germany	-	2.7	4.3	2.4	4.0	3.0	4.6	2.0	2.1	1.9	2.1	2.1	2.1
Ireland	0.8	1.9	0.9	1.5	0.6	1.8	0.9	0.7	0.6	0.7	0.4	0.7	0.5
Italy*	2.2	2.9	3.1	1.9	2.1	3.2	3.4	2.1	2.2	1.7	1.9	2.2	2.2
Netherlands*	1.3	2.9	2.8	2.2	2.1	3.2	3.1	1.6	1.6	1.5	1.5	1.6	1.6
New Zealand	-	'Infinite'	-	-	-	-	-	4.3	-	-	-	-	-
Norway	-	'Infinite'	-	'Infinite'	-	'Infinite'	'Infinite'	3.2	-	3.2	-	3.2	-
Poland	-	3.7	3.5	3.2	3.0	4.0	3.8	3.6	3.4	3.2	2.9	3.8	3.6
Portugal	1.2	1.4	1.5	0.4	0.5	0.9	1.0	1.4	1.5	0.4	0.5	0.9	1.0
Spain*	1.6	2.3	2.3	1.4	1.4	2.3	2.4	2.1	2.1	1.3	1.4	2.1	2.2
Sweden	-	5.2	-	5.5	-	5.5	-	3.2	-	3.2	-	3.2	-
Switzerland	-	1.9	1.7	-	-	-	-	1.9	1.7	-	-	-	-
UK*	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
U.S	-	5.2	6.0	-	-	-	-	4.9	5.1	-	-	-	-

\* P<sup>1</sup> scoring method is based on the number of indigenous cases of vCJD confirmed to April 2008. Since then, cases with clinical symptoms of vCJD have been confirmed in Canada, France, Italy, Netherlands, Spain, Japan, Taiwan and UK - <http://www.cjd.ed.ac.uk/documents/worldfigs.pdf>,

<sup>9</sup> <http://webarchive.nationalarchives.gov.uk/20110316162913/http://www.seac.gov.uk/papers/102-3annex.pdf>

**Table 13:** Summary of the proposed risk assessment methodologies

Methodology	Methodology based on <b>(1) vCJD</b> or <b>(2) BSE</b> incidence	BSE cases defined by <b>(a)</b> cases per million bovine or <b>(b)</b> test positives per human population	Under-ascertainment adjustment factor <b>(UAF)</b> based on <b>(UAFi)</b> OTM test positives or <b>(UAFii)</b> active and passive surveillance test positives	UK beef imports adjustment factor <b>(BAF)</b> used
P <sup>1</sup>	(1) vCJD	-	-	-
P <sup>2a</sup>	(2) BSE	(a)	-	-
P <sup>2b</sup>	(2) BSE	(b)	-	-
P <sup>2a</sup> with UAFi	(2) BSE	(a)	(UAFi)	-
P <sup>2b</sup> with UAFi	(2) BSE	(b)	(UAFi)	-
P <sup>2a</sup> with UAFii	(2) BSE	(a)	(UAFii)	-
P <sup>2b</sup> with UAFii	(2) BSE	(b)	(UAFii)	-
P <sup>2a</sup> with BAF	(2) BSE	(a)	-	(BAF)
P <sup>2b</sup> with BAF	(2) BSE	(b)	-	(BAF)
P <sup>2a</sup> with UAFi and BAF	(2) BSE	(a)	(UAFi)	(BAF)
P <sup>2b</sup> with UAFi and BAF	(2) BSE	(b)	(UAFi)	(BAF)
P <sup>2a</sup> with UAFii and BAF	(2) BSE	(a)	(UAFii)	(BAF)
P <sup>2b</sup> with UAFii and BAF	(2) BSE	(b)	(UAFii)	(BAF)

NOTE; Some countries in Table 12 report 0 positive tests from 0 cattle tested. Though, the active monitoring in these countries reports positively tested animals from many thousand cattle tested.

**ADVISORY COMMITTEE ON THE SAFETY OF BLOOD, TISSUES AND  
ORGANS – PRION REMOVAL DURING PLASMA PROCESSING EXPERT  
GROUP**

**SUMMARY OF MEETING, 18 JUNE 2009**

**Group membership:**

Professor Marc Turner (SaBTO member)  
Dr Mark Head (National CJD Surveillance Unit)  
Dr Peter Foster (ex-Scottish National Blood Transfusion Service)  
Dr Robert Somerville (Roslin Institute)

**Also present:**

Dr Keith Watson (Medicines and Healthcare Products Regulatory Agency)  
Dr Michael Rogers (SaBTO Secretariat)  
Mr Stephen Dobra and Dr Maren Daraktchiev (DH Analytical team)

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The membership of the expert group was chosen to provide advice to SaBTO in the areas of prion biology, experimental protocols for study of prions, and the effect on prions of plasma processing. Regulatory advice was also sought.

The expert group was asked to provide a view to SaBTO regarding the robustness of the claims made by the manufacturer regarding prion removal during (i) the normal processing procedure and (ii) the proposed specific prion removal procedure, based on the available information.

It was noted that the 2.5 log figure for reduction of prions claimed by the manufacturer for the existing processing procedure was obtained from an unrepeatable single experiment. The group were informed that this claim had never been made in a licence application. As there was no evidence of validation or reproducibility of this claim, it was not deemed robust.

The group were reassured that the manufacturer had commissioned independent assessment of the prion removal procedure in the application for the licence variation.

The "X150" study represented a proof of principle study on the abnormal prion protein removal capacity of the ligand used in the manufacturing process. There was some concern that the level of the spike material seemed low. The study was deemed robust although there remained some questions regarding methodology.

The study by Bailey *et al* employed Western Blot (WB) analysis of both the column material and column flow through to investigate the removal of abnormal prion protein from spiked brain preparations during the production of solvent detergent FFP. The group thought it reasonable that the authors described such an approach as "semi-quantitative". The group was reassured that WB had been done on both the column itself and the column flow-through. The binding capacity values of the column were useful. The significance of the PrP competition assay was not clear. While not a major concern, use of a recombinant PrP, which may behave differently

to the actual target, was noted. The WB analyses inferred that 6-8 log PrP can bind to the column. Several limitations of the X150 study were overcome by this work.

The "Hamster" study employed hamster bioassay to investigate the removal of abnormal prion protein on the column flow-through at the end of the manufacturing process. The lack of data breaking down the steps was noted. The data was not always clearly presented. Results from this report did indicate that the claims for passive removal during passive processing were not validated. While it is not clear at what stage the prion is being removed, the group considered that the data showed that the process as a whole removes large amounts of infectivity.

The group considered that:

- Some clarification is needed around several aspects of the data;
- It is unlikely that donations from more than one infected individual would contribute to a pool;
- The infectivity bioassay data was most helpful;
- The 2.5 log passive removal claimed for the process was not seen;
- There is a 3 log removal over process as a whole.

## APPENDIX C

### RISK ASSESMENT SUBMITTED TO SABTO IN 2009

The following table presents the risk assessment for vCJD infection through transfusion of FFP submitted to SaBTO for discussion in 2009.

Table: Risk of infection transmissions from imported FFP (pooled and single-unit<sup>10</sup>) relative to UK single-unit plasma

<b>Relative risk of an infected FFP product for a given volume of plasma</b>					
Fresh Frozen Plasma Products	Log reduction in prevalence	Low Infectivity scenario (the infectivity of residual plasma is 0.07 ID/ml)		High Infectivity scenario (the infectivity of residual plasma is 21 ID/ml)	
<b>Single Unit FFP</b>					
UK-FFP (single unit)	0	100		100	
Non-UK FFP (single unit)	2	1		1	
	3	0.1		0.1	
	5	0.001		0.001	
<b>Solvent/Detergent (SD)-treated FFP</b>					
		One infected donation of 250 ml recovered plasma per pool	One infected donation of 800 ml apheresis plasma per pool	One infected donation of 250 ml recovered plasma per pool	One infected donation of 800 ml apheresis plasma per pool
SD-FFP	2	15	50	1440	1520
	3	1.5	5	144	152
	5	0.015	0.05	1.4	1.5

Assumptions:

- (i) The UK donor prevalence is 1 in 4,000;
- (ii) The volume of infected donation entering the pool from a given donor is 250 ml for recovered plasma and 800 ml for apheresis plasma;
- (iii) The susceptibility to both infection and clinical disease is assumed to be 100%.
- (iv) There is no reduction in infectivity for SD-FFP

<sup>10</sup> 'Single unit FFP' is referred to as 'single donor FFP' in the paper.