Hampson Hilary

From: MIME :terry.snape GRO-C
Sent: 30 January 2001 16:35
To: Hampson Hilary
Subject: RE: vCJD briefing


vCJD briefing paper.doc

Hilary:
try the attached file. I just forwarded Sue's file to you - it may be she saved it using Word 2000 with the Word97 option switched off. Ring me straight away if you have trouble.
Terry

-----Original Message-----
From: hilary.hampson GRO-C
Sent: Tuesday, January 30, 2001 3:03 PM
To: terry.snape GRO-C
Subject: RE: vCJD briefing

Terry

I have tried to open and print the attachment but it starts to churn out hundreds of pages of hieroglyphics!

Help!

Hilary

-----Original Message-----
From: MIME :terry.snape GRO-C Sent: 30 January 2001 15:41
To: Robinson Angela (Medical Director)
Subject: FW: vCJD briefing

Angela/Hilary:

The attached file is the one that will go to Liam Donaldson this afternoon.

Hilary: please print a good paper copy for Angela - let me know if you have any problems.

Angela: there are quite a few changes since version 9 that you have. Mostly emphasis and expression, but worth re-reading the lot if you have time.
If you need a short-cut, the most significant changes are in:
section 1 - emphasis on shelf-life as discriminating between blood components and plasma products in respect of recall;
section 3 - clarification of dates of notification to BPL (3.1.1); bit more detail on logic for leucodepletion (3.3.2);
section 5 - TMER section (5.1.2) updated; FFP section (5.4) modified to take account of Jan MSBT (Charles confirmed your comments except he recorded a clear preference for single donor FFP still)

May I offer a copy to BPL? Steve saw an earlier draft for confirmation of BPL information but I'd like to be able to give BPL an approved copy.

Charles also has an early draft (briefing for the clinical incidents panel meetings); Lorna and Pat saw that same early draft for checking their own areas of interest. You may wish me to recover those copies and supply final

copy. What do you think?

>From my perspective at least (and with today's news in mind) my remarks in the penultimate paragraph of section 3.1.2 are the most inflammatory. I'm sure it needed emphasis here though.

Let me know what more I can do to help. It's been a challenging but satisfying assignment and I'm really grateful to you for involving me. At least the back is broken if material has to be pulled together for legal purposes.

Best regards,

Terry

vCJD, Blood Components and Plasma Products

A Briefing Paper Including a Review of:

- Risk Factors Involved
- Risk Assessments Undertaken
- Immediate Responses to Perceived Risk
- Ethical Considerations
- Implications for UK Blood Transfusion Practice
- Attitudes to CJD and vCJD in Other Countries
- UK Research Initiatives

Prepared by:

Dr Susan Shepherd
Dr Terry Snape (Independent Consultant, previously Technical Director BPL)

30 January 2001

TABLE OF CONTENTS

1 INTRODUCTION AND BACKGROUND

Summary

- *Classical* or *familial Creutzfeldt-Jakob disease (CJD)* and *variant Creutzfeldt-Jakob disease (vCJD)* are potentially transmissible neurodegenerative disorders caused by abnormal forms of prion protein
- There is no research evidence that the classical or familial forms of CJD have ever been transmitted between humans as a result of treatment with blood components or plasma products
- Whilst there is equally no evidence of transmission of vCJD by blood components or plasma products, risk of transmission cannot be excluded since:
  - vCJD is a new emerging disease – it is too soon to conclude absence of risk
  - transmission of BSE has been demonstrated by blood transfusion in sheep
  - there is evidence of involvement of the lymphatic system in the vCJD disease process (if not in disease transmission)
- The characteristics of blood components and plasma products that have been important in the transmission of blood-borne viruses also have relevance to the potential for transmission of prion disease by these same treatments

This paper sets out action taken and the current situation with respect to variant Creutzfeldt-Jakob disease (vCJD) and components and fractionated plasma products derived from blood.

1.1 Prion Diseases – Transmissible spongiform encaphalopathies (TSEs)

Prion diseases, or transmissible spongiform encaphalopathies, are rapidly progressive, invariably fatal, neurodegenerative disorders. Characterised by a progressive spongiform encephalopathy and loss of brain function, TSEs are thought to be caused by an abnormal isoform of a cellular glycoprotein known as prion protein.

1.1.1 Evidence for transmission of TSEs by blood transfusion

There is experimental evidence of transmission of BSE by blood transfusion in sheep[1]. Blood (not leucodepleted) from a BSE-infected sheep was transfused into 19 healthy, scrapie-free, sheep. After 610 days there was evidence of BSE infection in 1 out of 19 of the transfused sheep. The study continues.

1.1.2 Distinction between vCJD and other CJD risks in man

On a worldwide basis, there is general agreement that individuals who have received blood components or fractionated plasma products from donors who later develop either classical or familial CJD are not themselves at increased risk of developing the disease[2,3,4], though there are several reports that have reasonably been dismissed as not reflecting a causal relationship between treatment and disease[5,6].

1.2 Blood components and fractionated plasma products

Blood components and fractionated plasma products carry risks associated with blood-borne, transmissible agents of infection. Typically, concern has focused on transmission of viruses as a risk factor – enveloped viruses like the hepatitis B, hepatitis C and HIV, as well as non-enveloped viruses like hepatitis A and parvovirus B19.

With identification of vCJD[7], and with recognition of lymphatic system involvement, at least in disease progression, if not in transmission[8], it became necessary to extend surveillance and preventive measures to address this new risk.

1.2.1 Definition of terms

Blood component is a generic term used to describe any component derived from a *single* blood donation or by plasmapheresis on a *single* occasion. It includes all the components defined in Section 1, chapter 6 of 'Guidelines for the Blood Transfusion Services in the United Kingdom, 4th Edition[9], as follows:

- whole blood,
- red cells,
- platelets,
- granulocytes
- fresh frozen plasma,
- cryoprecipitate.

The definition includes platelets prepared by secondary pooling and processing of buffy coats (a fraction containing platelets and white cells, making up about 3% of blood volume). Typically, buffy coats from four donations are pooled.

All blood components inevitably contain small amounts of plasma that itself contains white blood cells. White blood cells (leucocytes) comprise approximately 0.1% of the blood volume. Leucocytes are mostly phagocytic (engulfing and destroying bacteria and foreign bodies), with an important exception in lymphocytes, which make up 20-40% of the leucocyte population. Lymphocytes originate from the bone marrow but reproduce in lymphoid tissue and are able to circulate between the blood and lymphoid tissues. Lymphocytes are an important part of the immune system, with B cells (25% of lymphocytes) providing antibody-mediated response to antigens and T cells (75% of lymphocytes) providing cell-mediated response.

The potential involvement of B cells in vCJD, and, therefore, the potential benefits of leucodepletion (removal of leucocytes), is discussed in section 3.3.2.

Since November 1999, with the exception of granulocytes, all blood components produced in the UK have been leucodepleted.

Fractionated plasma product (shortened in this report to plasma product) is used as a generic term for any therapeutic preparation manufactured from *pooled* human plasma and subjected to further purification and formulation to make it suitable for injection or infusion.

These include coagulation factors (especially Factors VIII and IX), immunoglobulin preparations for intravenous and intramuscular injection, and albumin preparations. The range of products and their characteristics are described in Section 2 of "Guidelines for the Blood Transfusion Services in the United Kingdom", 4th Edition 2000.

The term ***plasma fraction*** is reserved for any intermediate fraction recovered from plasma and used in the manufacture of a fractionated plasma product.

Plasma products have shelf-lives ranging from one to three years; in each case the shelf-life is measured from a date defined during product manufacture (typically the date of sterilising filtration). When stocks of plasma and frozen intermediates are high (and this was typically so in the early 1990s), the start of the in-date period for a plasma product may post-date blood donation by several years, resulting in products with end of in-date period perhaps 5 years after the date of blood donation.

In contrast, the in-date period for blood components starts at the time of blood donation, and can never post-date blood donation by more than 12 months, making it much less likely that blood components will be in-date at the time of confirmation of a diagnosis of vCJD in a donor.

Recall is, therefore, an important issue for plasma products, but will hardly ever be relevant to blood components. The issue of product recall, and policy governing this, are taken up in later sections.

Excipients are pharmaceutically non-active substances such as amino acids (an end product of protein breakdown), albumin (a constituent of blood) and gelatin used in the manufacture of many medicinal products, including plasma products and vaccines. Excipients are included to achieve a product formulation that will be stable during the end stages of processing (e.g. virus inactivation, sterilising filtration or freeze drying), during storage prior to administration (which can be many months and years after manufacture) and that will be well tolerated on administration.

2 FACTORS WITH RISK IMPLICATIONS

Summary

- Since risk of transmission of prion disease cannot be excluded, it is important to recognise significant differences between blood components and plasma products in factors which condition risk:
  - Blood components from *one* donation are usually given to no more than *two or three* recipients;
  - plasma products are prepared from pools of *many* donations; therefore, products from a single plasma pool will be used to treat *thousands* of individual recipients
  - For albumin, in particular, this effect may be amplified by its use as an excipient
  - Pooling (for plasma products) has a multifactorial effect – dilution of one donation in a pool with many others may reduce the infection risk in any one dose, but greatly increases the numbers exposed to risk
  - Fractionation processes include many steps that contribute to elimination of prion by separation and partitioning, but it is difficult to prove that all infective prion will be eliminated

2.1 Single donor components vs pooled plasma products

Two or three different blood components (say, red cells, platelets and fresh frozen plasma) will normally be prepared from a single blood donation, and each will usually be administered to a different recipient.

In comparison, fractionated plasma products are prepared not from single plasma donations but from pools of many such donations. The number of donations pooled for processing varies, but is normally in excess of 1,000 donations (a requirement if preparation of normal immunoglobulin is intended, in order to achieve an acceptable antibody profile in the product) and is more usually in excess of 10,000 donations.

The distinction between *fresh frozen plasma* (FFP) for clinical use and *plasma for fractionation* is primarily one of application though, as indicated in section 5.4, there are also important differences in regulatory definition and control. Most importantly, however, FFP is a blood component and is, therefore, supplied from single donations or as single doses prepared from a comparatively small number of donations that have been pooled and subjected to virus inactivation.

The term *plasma for fractionation* describes plasma (often collected by plasmapheresis, but sometimes recovered from whole blood) prepared in accordance with EU or FDA requirements specifically for inclusion in large pools for the manufacture of fractionated plasma products.

The impact, on risk of iatrogenic transmission, of pooling plasma donations, is multifactorial. Treatment of a patient with a single unit of blood containing vCJD

prion ensures that the patient receives the whole of the (potentially) infective dose. If the plasma from that same blood donation is included in a 10,000-donor fractionation pool, the prion is distributed through the whole pool, potentially compromising every dose of Factor VIII, Factor IX, albumin and immunoglobulin made from the pool. Inclusion of albumin from that same pool, as excipient in a batch of high purity or recombinant Factor VIII, in a radiolabelled lung scan reagent, or as excipient in a vaccine, further amplifies potential exposure to the prion.

The outcome in terms of infection risk will be determined by:

- The *concentration* of prion in the plasma pool
- The extent to which processing at each stage *eliminates* or *inactivates* the prion
- Any *minimum infective dose* for transmission
- *Susceptibility* of the individual recipient to infection
- *Repeated treatment* of a patient with product from the same batch and any potential for *cumulative dose effects*

These considerations are very different from those applying in consideration of assessment of risk from direct one-off exposure, such as in the case of neurosurgery involving instruments previously used on a patient subsequently diagnosed as suffering from vCJD.

The risks involved in use of blood and blood products were reviewed in some detail in a report prepared for DH by Det Norske Veritas (DNV)[10], and although scientific understanding has advanced since that report was written, the fundamental considerations remain the same. Figures 1 through 3, abstracted from that report, underline the assumptions made on potential spread of risk associated with blood components and plasma products.

Figure 1 summarises the best estimates at the time, of the numbers of doses of each type of product manufactured from the 2,215 million whole blood donations collected each year.

Figure 2 indicates the number of patients, in representative patient groups, treated with those blood components and fractionated plasma products. Whilst comparable *numbers* of patients are involved (460,000 treated with blood components; 281,088 treated with fractionated plasma products) the *spread of exposure* is much greater for plasma products. Every dose of a plasma product represents exposure to the 10,000 or so donations included in each plasma pool. Furthermore, repeated treatment for diseases such as haemophilia (treated with Factor VIII) and primary immune deficiency (treated with Intravenous Immunoglobulin, IV IgG), mean that each patient is probably exposed to five or more different product batches each year. Spread of exposure is greatly extended if albumin made from infected plasma pools is used as excipient in other blood products and in vaccines.

However, for a variety of reasons explored in sections 2.2 and 2.3, exposure to plasma product does not necessarily mean exposure to vCJD risk.

Figure 3 includes a generic risk calculation flowchart and the application of that generic approach to one plasma product, IV IgG. It must be recognised that the assumptions underpinning this risk model, including those on minimum dose of vCJD prion for infection and the amount of infective prion likely to be included in each product dose, remain as uncertain now as they were two years ago when the report was prepared. An equally important assumption, that vCJD prion introduced by IV injection is capable of transmitting vCJD, is given some support by BSE transmission studies in sheep[1].

2.2 Prion Distribution in Blood Components and Plasma Fractions

A simplified outline fractionation schematic, illustrating the production of plasma fractions from pooled plasma, is included as Figure 4. The details of these arrangements are less important than a few fundamental features of the process:

- that many donations of plasma are included in each starting plasma pool – typically >10,000 – diluting vCJD prion present in any one donation, but extending risk exposure to many doses of each derived product
- that a range of products is made from each pool – extending risk exposure to different patient groups
- that each product is the outcome of multiple processing steps (including many separation and purification activities not shown in Figure 4) – probably eliminating most, if not all, vCJD prion present in the starting plasma pool

Studies on prion distribution through blood components and plasma fractions were undertaken in two different animal (mouse and hamster) models. The first studies reported were those undertaken by Paul Brown and co-workers[11,12], using blood taken from symptomatic mice infected with a strain of human CJD (Fukuoka-1 strain, GSS syndrome). More recent work by Rohwer[13] involved hamster-adapted scrapie (strain 263K), allowing larger volumes of blood to be made available for modelling studies. In both studies, prion activity in derived fractions was monitored by inoculation into infection-free animals of the same species. The results of these studies are summarised in Table 1 (adapted from Foster[14]).

The greatest infectivity, detectable in buffy coat, was approximately 5 logs lower than the concentration in brain extract, with lower (but still measurable) titres in plasma, cryoprecipitate and ethanol fractions of plasma.

The findings in respect of buffy coat, together with the observations on the role of B cells in neuroinvasion by prion in scrapie[8], contributed significantly to the arguments for leucodepletion of blood components.

Although very influential in forming preliminary thinking on practical measures that might be implemented to reduce risk (the results of the Brown study were made known in 1996, two years in advance of eventual publication), these studies have significant limitations:

- the small scale of the studies (determined by the volume of blood recoverable)
- concerns for accuracy of representation of complex fractionation processes
- the relatively low levels of prion recovered into blood and plasma limits useful study to the earlier steps of fractionation

2.3 Risk Reduction by Separation or Removal of Prion

Notes to the outline flowsheet in Figure 4 make reference to "further purification steps" for each product type. In practice, all fractionated products are subjected to multiple generic and specific purification procedures before final formulation for therapeutic use. With the exception of the virus inactivation procedures included in each process, these treatments are designed to separate and purify whilst conserving the structure and activity of the protein(s) involved. It is unlikely therefore that they could be expected to contribute in any significant way to inactivation of prion – characterised as highly resistant to inactivation by chemical or physical methods. On the other hand each of these steps will contribute (in some instances – as for purification by highly selective adsorption and subsequent elution – very effectively indeed) to elimination of prion by separative partitioning.

A number of studies have been undertaken to establish the effectiveness of this serendipitous elimination of prion[11,15]. This work, summarised in Table 2, indicates 3 to 5 logs clearance for ethanol precipitation and affinity or ion exchange chromatography steps. In view of the fact that the manufacturing processes for most products incorporate several such steps, significant clearance of prion is achieved. Unfortunately, the clearance of prion achieved in this way cannot be validated using the rigorous approaches that are mandated for removal of, for example, viruses. The difficulties to be overcome include:

i. achieving a concentration of prion "spike" that would be sufficient to be measured before and after the step being characterised for removal;

ii. providing convincing evidence that removal by any "partitioning" step (where any fraction less than 100% is removed) can be considered to have been rigorously validated.

3 Risk Assessment and The Immediate Responses to Perceived Risks

Summary

- UK, European and US policies coincide in respect of the need to recall plasma products derived from plasma pools containing a vCJD-affected donation (definite or probable)
- Identification of 7 such donations from 3 UK donors resulted in 2 recalls of plasma products in October and November 1997
- Identification, in December 2000, of 2 donations from one vCJD-affected donor did not lead to a recall (there were no in-date products) but consignees were notified
- More than 100,000 individuals would have been treated with plasma products from batches implicated by the donors identified in 1997
- In the UK, recipients of affected batches of plasma products have not been informed – in other countries, some or all recipients of these products are informed
- Risk assessments undertaken during 1998 identified two immediate actions:
  - Debarment of UK plasma as unsuitable for fractionation
  - Implementation of leucodepletion to enhance the safety of blood components
- Consideration was given to several other risk-reduction measures, including optimising usage of whole blood and blood components

3.1 Risk assessment carried out by the National Blood Authority (NBA) and Bio Products Laboratory (BPL) (in discussion with the Medicines Control Agency and DH)

3.1.1 Identification of "vCJD risk" donors (October 1997 and December 2000)

On 6 October 1997 Sir Kenneth Calman, the then Chief Medical Officer, issued a statement on CJD[16]. The statement included notification that "... *one suspected and three confirmed nvCJD patients have given blood and the Surveillance Unit are following this up.*"

In October and November 1997, BPL was notified on three separate occasions of 7 donations of plasma, donated by the 3 donors who had been confirmed as having died from vCJD. BPL's records showed that six of the seven donations had been included in separate fractionation pools. The actions taken by BPL in response to these notifications are summarised in section 3.1.2.

A report on products implicated by these incidents is attached as Annex 1.

On 8th December 2000, BPL was notified of another two donations of plasma donated by one further donor with confirmed vCJD. The actions taken by BPL in response to these notifications are summarised in section 3.1.4.

To date there have been no further reports of plasma supplied to BPL from donors with definite or probable vCJD.

3.1.2 Recall by BPL of plasma products manufactured from plasma pools compromised by vCJD donor plasma (October/November 1997)

At the time of the first notification to BPL on 24th October 1997, the UK/EU position on the appropriate response to such a notification was under active review. The extant BPL procedure on review of post-donation information, which was also under review at the time, did not require recall of affected product. After exhaustive discussion with the MCA, and based on MCA advice that the Committee on Proprietary Medicinal Products (CPMP) position was hardening in favour of recall of any vCJD-implicated plasma product, a decision was taken to recall affected products. By the time of the second and third notifications on 31st October 1997 the commitment to recall was clear (this was subsequently reflected in a CPMP position statement published in February 1998[17]).

The principles for recall, established and agreed at that time with MCA, NBA and DH, were:

- Only in-date product should be recalled.
- Recall should be made to consignee level (hospitals and pharmacies) only.
- Individual recipients of product should not be contacted.
- Consignees were advised that the policy on notification of recipients was that the interests of individual recipients were best served if they were not notified.

A copy of the position statement, issued in December 1997, on notification of recipients is appended at Annex 2.

The recall, initiated on 30th October 1997, involved:

- one batch of in date Factor VIII
- one batch of in date albumin

- Outdated albumin, Human Normal Immunoglobulin and Anti-D Immunoglobulin was not recalled and consignees were not contacted about these products.

- An unfinished ethanol fraction (designated "fraction IV paste") had been exported and was also recalled.

All statements on the recall, from BPL, NBA and DH emphasised the precautionary nature of the recall and the uncertainty in respect of the nature and magnitude of the risks involved.

Within days of the first recall, BPL received its second and third notifications. The principles of recall having been established, a second recall was initiated on 4th November 1997. This second recall also implicated multiple batches of a range of products (Factor VIII, Factor IX, albumin and human normal immunoglobulin). Once again, only in-date product was recalled (Factor VIII and albumin).

The number of final product containers implicated in the October and November 1997 recalls (as an indicator of the potential clinical impact) exceeds 388,000, including 123,024 vials of Human Normal Immunoglobulin (supplied primarily for pre-travel prophylaxis).

Allowing for use of multiple doses in haemophiliacs and primary immune deficient patients, and for unused and recovered product, numbers suggest that affected product was administered to more than 100,000 individuals in the UK alone.

Since most of the high purity Factor VIII issued by BPL over a two-year period included excipient albumin from one of the vCJD-affected batches, it must be assumed that the product was administered to about 1,800 of the 3,000 haemophiliacs receiving regular treatment in the UK each year for those two years. These high rates of exposure through plasma products contrast sharply with much lower exposure due to blood components. (See section 5.1.2) and were a powerful factor in the argument for excluding UK plasma for fractionation. This is taken up again in section 3.2.1.

Subsequently, notification was made to the Health Ministries of all countries to which affected product had been supplied, irrespective of the in-date status of the product. This was undertaken on explicit instruction from DH[18] in order that the appropriate authorities should have all of the information necessary to make appropriate public health decisions.

3.1.3 Recall of Nycomed Amerscan Pulmonate II lung scan reagent

Twenty bottles of albumin from one of the batches affected by the 4th November 1997 recall had been supplied to Amersham Laboratories, for use in the manufacture of a radio-labelled diagnostic (Pulmonate II). On 17th November 1997, on the basis of advice from MCA, Nycomed Amersham implemented a world-wide recall of 4 batches of Pulmonate II prepared using the affected BPL albumin. In some instances, notably Eire and New Zealand, national authorities took the view that individual recipients of product should be contacted. At least one such notification (in Eire) is now the subject of a litigation claim in respect of the distress and anxiety caused by that notification.

3.1.4 Notification by BPL of plasma products manufactured from plasma pools compromised by vCJD donor plasma (December 2000)

Ongoing surveillance identified no further vCJD-implicated plasma supplied to BPL until 8th December 2000, when BPL was notified of two donations of plasma donated by a donor with confirmed vCJD. BPL's records showed that the donations had been included in separate fractionation pools in 1996 and 1997 respectively. Products affected were Factor VIII, Factor IX, antithrombin, albumin and Human Normal Immunoglobulin (IV).

All affected batches had date-expired, so that product recall was unnecessary.

In discussion with MCA, and in the light of the CPMP Position Paper on CJD[17] published in February 1998, which specifies that " *... the supply chain should be informed of all batches of product and intermediate implicated whether or not supplies of the batch are exhausted",* all consignees of affected batches were notified. Actions in respect of this notification are ongoing.

3.1.5 Revised criteria in respect of "vCJD risk" donors

On 26th February 1998 simultaneous statements from DH[19,20] and from CPMP[17] set out further precautionary measures in respect of vCJD risk from blood, including:

- Confirmation that "precautionary withdrawal" is appropriate for plasma products manufactured from a plasma pool which includes plasma from a vCJD-donor

- Notification to fractionator if donor "strongly suspected" – in order to eliminate the time delay that inevitably arises if post mortem confirmation is held as the criterion

- Albumin for use as an excipient should not be sourced from plasma from countries where a number of vCJD cases have occurred

This last condition made the ultimate debarment of UK plasma practically inevitable – albumin declared unfit for excipient use would be considered unfit for any clinical use; if albumin is declared unfit, then any product manufactured from the same plasma would be considered unfit. This was reflected in the statement from the DCMO, Dr Metters, CEM/CMO/98/5[19] that stated:

> "*The CSM advice effectively signals a review of the use of UK-sourced plasma, a component of blood used in the manufacture of a variety of blood products. The CSM will accordingly be looking at all products individually to ensure a safe supply of blood products to the NHS."*

3.2 Risk Assessment by the Committee on Safety of Medicines (CSM), May 1998

In accordance with the DH statements of 26th February 1998, the UK fractionators BPL and PFC (Protein Fractionation Centre, Edinburgh) were invited to make submissions to the MCA, for review by CSM. These submissions were required to include:

- *Details of the products supplied by both manufacturers, including amounts supplied annually and comments on any national dependency*

- *Such evidence as might be available on the potential for processes to eliminate prion*

3.2.1 Review of the safety of UK plasma as source material for fractionated plasma products

UK fractionators' submissions to CSM were considered on 1st April 1998, at a meeting of a special subcommittee of CSM (to which BPL and PFC representatives were invited). In recommendations[21] from a meeting of CSM on 13th May 1998, it was concluded that:

- *Manufactured blood products should not be sourced from UK plasma*
- *BPL and PFC should be asked to commit to dates by which non-UK products would be available*
- *A date after which UK blood products would not be released should be agreed – it was not intended that UK blood products should be recalled*
- *All CTXs (i.e. all clinical trials) for UK blood products should be suspended*
- *Research should be undertaken on identification/removal of nvCJD agents*
- *Clinicians should be educated in minimising the use of blood products*

Addressing a recognised concern in respect of virus safety of plasma products manufactured from non-UK plasma (and especially US paid donor plasma) the Press Release[22] issued by DH in respect of the CSM Recommendations noted:

> *"Only when quality inspectors are assured that the stringent safety standards applied to the new sources of plasma are equivalent to those currently available in the UK will plasma be imported."*

All proposed plasma suppliers were audited by the UK fractionators (BPL or PFC), and by the MCA, before derived plasma products were released. (US paid donor plasma is not subjected to leucodepletion – see section 3.3.2. This is unimportant if the arguments in respect of population risk for vCJD are sound.)

CSM recommendations[21] did not exclude the possibility of a return to UK plasma:

> *"In the future when a test is available to identify the agent of nvCJD in blood donors or when a validated inactivation process is developed it is hoped that there will be a return to the use of UK donor plasma."*

The DH Press Release[22] identified a third criterion for evaluation of the reasonableness of a return to the use of UK donor plasma:

> *" ... or it is proven that nvCJD cannot be transmitted through blood products".*

The timetable for switching from UK plasma to non-UK plasma for fractionated plasma products is set out in section 3.3.1.

3.3 Risk Assessment by Det Norske Veritas (DNV) on behalf of UK Health Departments (February 1999)

A final version of the DNV report (Revision 4) was published in February 1999. This report made two firm recommendations on risk reduction and drew attention to several other potential risk reduction measures. These may be summarised as follows.

- Firm recommendations assumed most likely to reduce the risk of transmitting vCJD:
  - Discontinue use of UK plasma for fractionation – to reduce the risk of vCJD infection by treatment with plasma products (section 3.3.1)
  - Establish leucodepletion – to reduce the risk of vCJD infection by transfusion of blood components (section 3.3.2)

- Measures with some potential to reduce the risk of transmitting vCJD:
  - Optimise (reduce) the use of blood components
  - Permanently defer donors who have received blood transfusion(s)
  - Use whole blood rather than components (to minimise donor exposure)
  - Extend the opportunities for autologous transfusion
  - Use imported (pooled) plasma instead of fresh frozen plasma from UK donors
  - Discontinue use of intermediate purity Factor VIII (for which prion removal by the manufacturing process appears least effective)
  - Consider pentosan sulphate prophylaxis in those at risk of vCJD infection

3.3.1 Switch from UK to non-UK plasma for fractionated plasma products

Arrangements undertaken for the conversion to non-UK plasma may be summarised as:

- Securing an alternative supply of plasma (including supplier audit)
- Stock build-up of each product type (made from UK plasma) to cover shutdown
- Decommissioning and decontamination of plant (for BPL alone, the associated costs of replacing components that could not be decontaminated exceeded £600,000)
- Process validation for each product using the proposed source plasma
- Preparation of consistency batches for each product type
- Preparation and submission of a Product Licence Variation (PLV) for each product
- Inspection and approval of plant and cleaning validation by the MCA
- Manufacturing from new plasma source to create inventory for launch
- Introduction of product from non-UK plasma, with "recover and replace" arrangements as appropriate

Key dates in this programme for manufacture of mainstream products (Factor VIII, Factor IX, albumins, intravenous immunoglobulins) at BPL were:

- Decommissioning and decontamination of plant begun May 1998

- First batches of US plasma processed September1998
- US plasma-derived products released December1998/January1999

Manufacture of Hyperimmune Specific Immunoglobulins (Anti-D, Tetanus, Hepatitis B, Varicella-zoster, Rabies) utilises a separate area of the manufacturing facility. The switch from UK plasma to non-UK plasma for these products was deferred by approximately four months. US plasma-derived products became available between May and December 1999.

3.3.2 Leucodepletion

There is some evidence of B cell involvement in the development of experimental scrapie[8,23]. This work suggests that B lymphocytes are essential to development of neurological disease (in scrapie at least), providing a locus for expansion of variant prion and facilitating neuroinvasion. If this is true in the development of vCJD in man, it would be reasonable to assume that the extent of infectivity of a blood component would be proportional to the number of B cells present in that component. The evidence was reviewed as part of the risk assessment reported in Section 3.3. It was suggested that removal of white cells from blood by filtration could reduce such risk of vCJD transmission as might exist. The process of removing leucocytes from whole blood in this way is known as leucodepletion.

In July 1998[24], acting on advice from SEAC, the then Secretary of State for Health, Frank Dobson, announced that all blood components produced by UK Blood Centres would undergo leucodepletion. This was to be achieved without endangering the national blood supply. It was recognised that there would need to be a phasing in period, therefore an end date of 1st November 1999 was agreed, by which date all blood components prepared and issued by UK Transfusion Centres would be depleted of leucocytes. This target was achieved. Previously issued components were not initially withdrawn. Labile components (shelf-life up to 35 days) prepared without leucodepletion would, therefore, have been used up to 35 days after 1st November. Fresh frozen plasma (with a shelf-life of 12 months from preparation) prepared without leucodepletion was withdrawn in March 2000. (This date was chosen in order not to jeopardise supplies over the Millennium period; in fact very little remained.)

Leucodepleted blood components are prepared to meet a national standard of $<5 \times 10^6$ leucocytes per unit, compared with 4×10^9 leucocytes per donation in blood at collection. An optimistic estimate would be that risk of vCJD transmission might be reduced by the same Factor (1,000-fold) – optimistic in that the count is of intact cells and does not take account of cell fragments, which might also carry prion. Leucocyte counting is performed on a random sample of prepared units, and the data is managed by statistical process control (SPC) techniques. Quality control is good, with processes meeting defined specifications. Wastage of blood is minimal, at less than 1%.

4 ETHICAL CONSIDERATIONS

Summary

- It is the view of experts, in the UK and elsewhere, that individuals who have received blood components or plasma products from donors who later develop classical or familial CJD are not themselves at increased risk of developing CJD.
- In respect of vCJD:
  - there is no evidence of transmission of vCJD by blood components or plasma products. However, since vCJD is a new emerging disease, it is too early to conclude on the absence of risk;
  - there is currently no confirmatory test of product infectivity, no data on magnitude of infection risk, no diagnostic test to detect infection in a recipient, no prophylactic, palliative or corrective treatment.
- Against this background, it is UK policy that:
  - recipients of blood components and plasma products are not informed that they have received blood from individuals who develop vCJD;
  - strategies have been developed to deal with the situation should the recipient of an implicated blood component apply to become a blood donor;
  - there is currently no policy to identify the recipients of implicated plasma products should they apply to become blood donors;
  - there is currently no policy to exclude the recipients of implicated plasma products from becoming blood donors (other than for reasons of an underlying disqualifying medical condition).
- UK policy on notification is considered in section 5.

4.1 Notification of recipients of affected products

On a worldwide basis, there is general agreement that individuals who have received blood components or fractionated plasma products from donors who later develop either classical or familial CJD are not themselves at increased risk of developing the disease[2, 3,4]. This perception is reflected in the assessment of risk by the European Medicines Evaluation Agency (EMEA), in successive reviews[25].

It is not current UK policy to inform recipients of the facts[26] (indeed, it is not policy to advise recipients of donations given by individuals found to have been suffering from any disease, including for example HIV or hepatitis infection).

The ethical situation with respect to informing recipients of blood components and plasma products, when the donor subsequently goes on to develop vCJD, has been discussed at a number of meetings, including meetings of the "Expert Group on the Management of CJD Incidents"[27]. Although there is no documented case of transmission of vCJD by blood transfusion in humans (there is one transmission study with BSE in sheep[1]), vCJD is a new and emerging disease and there is insufficient evidence to give absolute reassurance on *lack of risk*.

In these circumstances, there is no unequivocally agreed position. Many experts have expressed concern at informing recipients of blood components and plasma

products from donors who later develop vCJD, when there is no method of evaluating the risk to which they have been exposed and when there is no treatment. This opinion is enhanced by the fact that the disease has a long incubation period and would impose a long period of uncertainty and anxiety on the individual. It has been suggested that in these instances it would be unethical to impose such knowledge on individuals. Other experts believe that distress will be caused if individuals are not informed and later discover that information regarding their health has been withheld.

It has been argued that all individuals have the right to know, but an equal view that others have the right not to know. There is some evidence that in comparable situations (for example, Huntington's chorea) the majority of the population would prefer not to be informed. The knowledge of a risk to health of this magnitude could have incalculable implications on life decisions – such as the decision to have children – and would also affect life insurance premiums.

The assumption cannot be made that adults are incompetent to receive information about their health. It would be dangerous to assume that adults in this situation are not competent to understand and accept the risk of vCJD. However, it is not yet possible to give an indication of the magnitude of the risk involved, or whether there is any risk at all. The current ethical view must also be considered in the light of the fact that the whole population of the UK has been potentially exposed to the risk of vCJD via exposure to BSE in one form or another.

In an attempt to resolve this issue, the 'flagging' approach, described in paragraph 5.1.1 is generally approved[28]. This system also provides an option to inform individuals in the future should a diagnostic test be developed.

In the US, the position on notification of recipients of CJD- and vCJD-affected blood components and plasma products has been incorporated in a "Guidance to Industry" advice note issued on 23rd November 1999[29]. The guidance requires a search of records to identify prior collections from an affected donor extending back at least five years (indefinitely where computer records exist). The guidance requires provision of information to consignees (for example, transfusion centres) of previously distributed blood components from the donor, in order to:

> *"... enable the consignee to inform the physician or other qualified personnel responsible for the care of the recipient so that recipient tracing and medically appropriate notification and counselling may be performed at the discretion of care providers."*

The guidance specifies that:

> *"In cases of donors diagnosed with nvCJD or donors under investigation for nvCJD, FDA recommends that Establishments inform consignees of affected plasma derivatives as well as blood components."*

In respect of donors identified as being in an nvCJD risk group (including donors domiciled in the UK for 6 months from 1980 through 1996) the FDA recommends consignee notification to allow quarantine and destruction of in-date blood components, but does not recommend consignee notification for the purpose of tracing and notifying prior recipients.

4.2 Notification of donors

The current UK position on notification of donors is considered in sections 5.1 and 5.2 of this note.

5 OUTCOMES AND EFFECTS ON BLOOD TRANSFUSION PRACTICE IN THE UK

Summary

- UK residence criteria apart, UK policies on donor exclusion in respect of CJD risk are in line with North America and mainland Europe (se also section 4)
- A CJD surveillance programme is in place which:
  - Identifies all CJD patients who donated blood before onset of disease
  - Identifies previous blood transfusions in all CJD patients
- vCJD has been diagnosed in 13 UK individuals who donated blood at some time
- so far 20 individuals have been identified as having received blood components donated by UK individuals who subsequently developed definite vCJD
- Recipients of blood components linked to vCJD-affected individuals are identified and deferred as donors
- There is no equivalent mechanism for identifying recipients of implicated plasma products

5.1 Surveillance programmes

A CJD surveillance programme exists, managed between the UK Blood Transfusion Services (UKBTS) and the UK CJD Surveillance Unit (CJDSU). The outcome of this surveillance is reported annually (with interim updates) in the form of a Transfusion Medicine Epidemiology Review (TMER). Surveillance is undertaken in two modes:

- **TMER**: review of all CJD patients (and matched controls) who donated blood before disease onset.

- **R-TMER**: a reverse arm of the study to determine any association between diagnosis of all types of CJD and previous blood transfusion

The surveillance involves notification by the CJDSU to the UKBTS of all individuals with probable[30] or definite[31] vCJD.

The TMER report for 31st October 2000 (the latest available), summarised in section 5.1.2, confirms diagnosis of vCJD in 13 individuals in the UK who had at some time donated blood.

5.1.1 Surveillance in the UK using TMER

UKBTS use the TMER programme to trace donations originating from donors who later develop vCJD, and to identify the recipients of *blood components* prepared from such donations.

The total number of *recipients* of blood components traced from UK-only cases is 20. No donation of blood originating from such a recipient is permitted to enter the national blood supply. The strategy used in such cases is as follows:

- the recipient is pre-registered on the UKBTS blood donor record system in case this person attends as a future potential donor;
- the pre-registered information is not visible to donor clinic staff;
- the recipient's record is, therefore, flagged so that no donation originating from that individual can enter the blood supply;
- the donated blood is quarantined and discarded;
- the recipient is then contacted and informed of the situation

A decision was taken not to inform recipients before they volunteered to donate blood because:

- the individual recipient may never become a blood donor
- it is not possible to provide the necessary counselling in a busy blood donor clinic

UKBTS also use the TMER programme to provide notification, to national fractionators, of plasma for fractionation previously supplied from individuals who later developed vCJD. In date product is withdrawn, but recipients are not informed.

5.1.2 Data at 30th January 2001

- Total number of vCJD notifications from CJDSU to UKBTS is 78 cases:
    - This includes one confidential notification of a case from Eire reported to have donated in England. However, this case is not in the UK figures compiled by CJDSU. This case registered as a donor in England, but no donations were made.
    - For UK cases only, therefore, the total figure is 77.
- Total number reported by CJDSU to have been donors is 14 (including the Irish case).
    - For UK-only cases the number is 13.
- Tracing takes time and information reported by relatives to CJDSU is not always confirmed; of these 13 the total number of cases traced so far by UKBTS is 10 (including the Irish case).
    - For UK-only cases the figure is 9.
- Total number of recipients of blood components traced from the 9 UK-only cases, and whose details are known and on the TMER database, is 20.
    - The current UK figure is, therefore, 20 recipients of blood components from the 9 UK donors diagnosed as suffering from vCJD-affected donors.

- This is a much smaller number than those potentially exposed to risk from vCJD-affected fractionated plasma products – section 3.1.2

5.2 Policy on donor selection and exclusion – (blood)

In the UK, a number of categories of individuals are excluded from donating blood. The exclusion categories are as follows:

- those treated with human pituitary-derived hormones (growth hormone and gonadotrophins prepared from cadaver pituitary glands were available up to 1985; subsequent treatment was with synthetically-derived products)
- the recipients of corneal transplants;
- those with a family history of CJD;
- those who have had brain surgery or an operation for a spinal tumour or spinal cyst before August 1992, because of the risk of exposure to infected *dura mater*.

All potential donors, falling into the excluded categories, are informed at the blood donor clinic that they cannot be accepted as donors and a brief explanation of the reasons is given. A follow-up letter from the Blood Centre, confirms the advice and emphasises the small risk of CJD in these situations.

Only a very small proportion request further advice or reassurance – statistics from the North London centre place the percentage at ~3%, based on 3 out of 105 in 1998 and 2 out of 77 in 1999[32].

A further exclusion category was added in October 1999[33]:

- those who have received a blood transfusion in the past, subsequently identified as originating from a donor who later developed vCJD.

5.3 Policy on donor selection and exclusion – tissues (not blood)

The policy for tissues, other than blood, is set out in the agreed text on "Revised Guidance on the Microbiological Safety of Human Tissues and Organs Used in Transplantation"[34]. The policy on selection and exclusion broadly reflects that for blood, except that, in the case of identified risk Factors for classical CJD, the exclusion policy for implicated tissues/organs is qualified: " ... contraindication to donation *except in life saving situations after full discussion with organ recipient or those close to the patient*".

In respect of probable or definite vCJD, implicated tissues are excluded without qualification.

5.4 Policy on fresh frozen plasma for clinical use (TSE risk, virus risk, availability, clinical practice)

The suitability of plasma for any clinical application is determined by:

- country of origin (affecting vCJD risk)
- the characteristics of the donor population (affecting virus risk).

Fresh frozen plasma (FFP) is a blood component (see definitions in section 1.2.1), as opposed to a fractionated plasma product – with all the attendant implications of risk of transmission of vCJD associated with single compared to pooled products. There are currently no restrictions on the sourcing of FFP (in the same was as there are no restrictions on the sourcing of blood components). Considerations for FFP for clinical use are different from those for plasma for fractionation:

- In EU member states, requirements for plasma for fractionation are mandated through the CPMP; requirements for FFP are determined nationally.

- The English national fractionator (BPL) has so far taken the view that plasma for fractionation sourced from any European member state presents a greater theoretical risk of vCJD than US plasma, and is therefore a potential commercial risk.

- The established risk of transmission of blood-borne viruses, which may be significantly enhanced for plasma derived from certain donor populations, may outweigh the theoretical risk of vCJD transmission. Unless some means is available for reliable inactivation of blood-borne viruses, it is argued that FFP from UK donors is preferable to FFP from, for example, US paid donors (such as is used as plasma for fractionation).

- Alternative approaches to the provision of virus-safe FFP from plasma from non-UK donors include:

  - Virus inactivation of pooled plasma donations (using established, licensed, virus inactivation technology – a solvent-detergent mix)
  - Virus inactivation of single plasma donations (using methylene blue – not licensed in the UK; application for licensing declined in Germany because of toxicology concerns in respect of methylene blue)

Options for the provision of FFP, taking into account vCJD and virus risks, were discussed at the January meeting of the advisory committee on "Microbiological Safety of Blood and Tissues for Transplantation" (MSBT).

Following this meeting it was agreed that the National Blood Service will determine the feasibility of switching to non-UK plasma (addressing concerns for vCJD risk). In these circumstances, virus safety concerns are paramount and virus inactivation is an absolute requirement. FFP from single plasma donations would be the

preferred approach. FFP prepared from pooled plasma would be the second option.

Because of the limited shelf life of FFP, it is unlikely (but not impossible) that the identification of a vCJD donor, subsequently linked to this product, would result in its withdrawal. However, the recipient of an implicated dose of FFP would be considered in the same way as recipients of other implicated blood components (section 5.1.1)

6 THE RESPONSE TO CJD AND vCJD RISK IN OTHER COUNTRIES

6.1 US actions on classical CJD risk – impact on plasma product availability

On 11th December1996 the FDA's Center for Biologics Evaluation and Research (CBER) issued "Revised precautionary measures to reduce the possible risk of transmission of Creutzfeldt-Jakob disease (CJD) by blood and blood products"[35]. This document included a requirement for donor exclusion and withdrawal of blood products (that is both blood components and plasma products) in respect of:

> " *... potential donors who have been told that their families are at risk of CJD, or who have two or more family members with CJD*".

With respect to this, the FDA listing of Recalls/Withdrawals (http://www.fda.gov/cber/recalls.htm) shows 41 separate withdrawals "*because of donors at increased risk for CJD*" in the two years following publication. Many of these were multiple derivative withdrawals such as the example at Annex 3 to this report.

This approach was one of two factors contributing to a significant shortfall of plasma products worldwide between 1997 and 2000. The other factor was closure or restricted operation by several US manufacturers consequent on poor plant inspection reports. During the same period the price of intravenous immunoglobulin increased from $28 to $45 per gram[36]

Revised FDA guidance[29] issued in draft in August 1999 and confirmed on 23rd November 1999 identified a requirement for withdrawal in respect of plasma products implicated by a vCJD-affected donor but rescinded the requirement for withdrawal in respect of plasma products affected by donors "*at increased risk for CJD*".

The US position on the notification of recipients of affected products is set out in Section 4.

6.2 Initiatives of non-UK governments in excluding donors on basis of UK residence

In August 1999, US and Canadian regulatory authorities announced permanent donor deferral in respect of donors domiciled in the UK for more than 6 months since 1980. American Red Cross (ARC) sources suggested a 10.7% reduction in blood supplies as a consequence[37]. Canadian Blood Services (CBS) estimate a 3% reduction in the donor base[38].

6.3 Incidence of vCJD in other countries

vCJD has been identified in France (3 definite cases) and Eire (1 definite case). A reported case of vCJD in Germany remains unconfirmed.

Fractionators and regulators in France continue to monitor the incidence of vCJD, with understandable concern. The requirement for plasma to meet French national requirements is of the order of 600 tonnes per annum.

In spring 1998, when BPL needed to source 450 tonnes plasma per annum to replace UK plasma, there was a surplus of plasma in the world market resulting from closures of US fractionation facilities to undertake remedial actions in response to FDA "Team Biologics" inspections. Those conditions no longer exist – indeed it has been possible to secure BPL's plasma requirements only by long-term contracts. It is hard to see that an additional 600 tonnes of plasma could be obtained from existing US sources.

Such a consideration must have a significant impact on any decision to abandon plasma for fractionation collected in France.

7 RESEARCH

7.1 Overview of TSE research initiatives

In 1996 the Department of Health published 'Strategy for research and development relating to the human health aspects of Transmissible Spongiform Encephalopathies'. This document covered a wide range of issues including whether medical practices such as blood transfusion and transplantation can transmit infectivity between humans. The Department of Health has a substantial TSE research programme in place.

Where there is direct National Blood Service involvement, research projects are reviewed on a regular basis by a Steering Group (the *NBS vCJD Research and Development Strategy Group*) chaired by Dr Tim Wallington, Consultant Immunologist, based at National Blood Service, Bristol. The steering group has members from the NBS, SNBTS, the National Institute for Biological Standards and Control (NIBSC) and the Department of Health.

Funding for these studies comes from DH, the NBS, SNBTS and from the Medical Research Council.

More information on all the research studies listed may be obtained from John Stephenson in the Department of Health Research Division.

7.1.1 Investigation into transmissibility of TSEs via blood

Professor Bostock	Start April 1998	End March 2005

The research aims to assess the risk of transmissibility of TSEs by transfusion of blood, using two sheep models. The first model uses sheep with natural scrapie, the second employs oral infection of sheep with BSE. Early results were published recently in the Lancet.

Results show that the blood of sheep orally infected with BSE can contain prions and that these prions can transmit disease to other sheep by transfusion. However, data suggest that levels of infectivity are low and infection is rare.

7.1.2 Bioassay of infectivity from patients with CJD

Dr Moira Bruce	Start December 1997	End March 2001

This research aims to determine whether blood and blood fractions from clinical cases of vCJD and sporadic CJD contain TSE infectivity and thence pose a transfusion risk.

So far this research has failed to detect any infectivity in whole blood, in plasma or in white cells. However, the sensitivity of these experiments is not good.

7.1.3 A "cost consequence" study of leucocyte-depleted blood in prevention of post-operative infection following elective surgical procedures

Drs L Williamson/W Murphy	Start December 1998	End mid 2001

The UK has implemented universal leucodepletion at an estimated cost of £70-80 million a year. This project will determine the financial consequences of leucodepletion in large patient populations, other than reducing the theoretical risk of transmission of vCJD.

There is considerable, but not complete, evidence, that leucodepletion reduces the negative effects of transfusion on the recipient's immune response. These negative effects might be manifest as an increased risk of infection or as an increased risk of cancer recurrence.

Two cohorts, each of 2,000 patients, are under study, undergoing elective orthopaedic and cardiac procedures in 11 UK hospitals. One study cohort will have received leucodepleted blood, the other not. Two untransfused groups are included to account for other variables.

7.1.4 Studies of the effect of leukocyte depletion on prions

Drs Turner, Anstee, Pamphilon, Williamson et al	Start 1998	End Spring 2001

These research studies are taking place in four centres (Bristol, Brentwood, Cambridge and Edinburgh) and are related to the implementation of leucocyte depletion. They include development work relating to enumeration of leucocytes and their subsets; virus removal; and a project to examine generation and removal of cellular microparticles and normal PrP^C during leucocyte depletion procedures.

7.1.5 Investigation of pentosan polysulphate as a potential prophylactic agent against the transmission of vCJD by blood products

Ms C Farquhar	Start May 1999	End April 2003

Through the use of hamster and mouse models, this research aims to establish whether pentosan polysulphate can be used as a prophylactic against infection from vCJD in humans following blood transfusion. If this is the case, the research will also aim to establish the mode of action of pentosan polysulphate, required dose and most effective route of application.

Preliminary results indicate that pentosan polysulphate is capable of lengthening the incubation of vCJD, but not of effecting a cure in affected animals. Results also show that to have any effect at all, pentosan polysulphate must be given at

the time of, or near the start of, infection – long before any clinical symptoms appear.

7.1.6 TSE spiking study in blood fractionation

Dr Chris Prowse	Start July 1999	End June 2000

The research will determine whether clearance of TSE infectivity at each step in the preparation of blood products is additive or not. This, in turn, will give better information on the likely risks of TSE transmission through the use of blood products.

Prion protein has a natural tendency to stickiness and to 'clumping'. Extrapolating from these characteristics it is reasonable to assume that prion protein will behave in this way during the process of plasma fractionation, such that some blood products resulting from the fractionation process will be free of prions, even though the plasma pool from which these products are derived contains infectious material.

This assumption is being tested by 'spiking' plasma with model prions, passing it through the steps of fractionation and then testing the resulting plasma products for the presence of prion protein. This is being done both by analysis in the laboratory and by infectivity testing, by injecting fractionated material directly into susceptible mice.

The results of laboratory analysis are published and support the above hypothesis. Infectivity work in mice is current but not published. It is too early to draw any firm conclusions from this work.

7.1.7 Research into the development of a diagnostic tool

DH is currently discussing with five research groups additional research projects to develop and evaluate new diagnostic tests in humans. Researchers believe that there will be a valid test within the next two years.

A meeting of academics and industry representatives is being arranged to take place in Cambridge in February 2001 to take this area of research forward.

Figure 1: **Numbers of treatments with products from blood donations in England and Wales**

[Taken from the Report "Assessment of the Risk of Exposure to vCJD Infectivity in Blood and Blood Products", Final Report for the Spongiform Encephalopathy Advisory Committee (SEAC) and the Department of Health, Revision 4, February 1999, Det Norske Veritas]

Figure 4.1 Products from Blood Donations in England & Wales

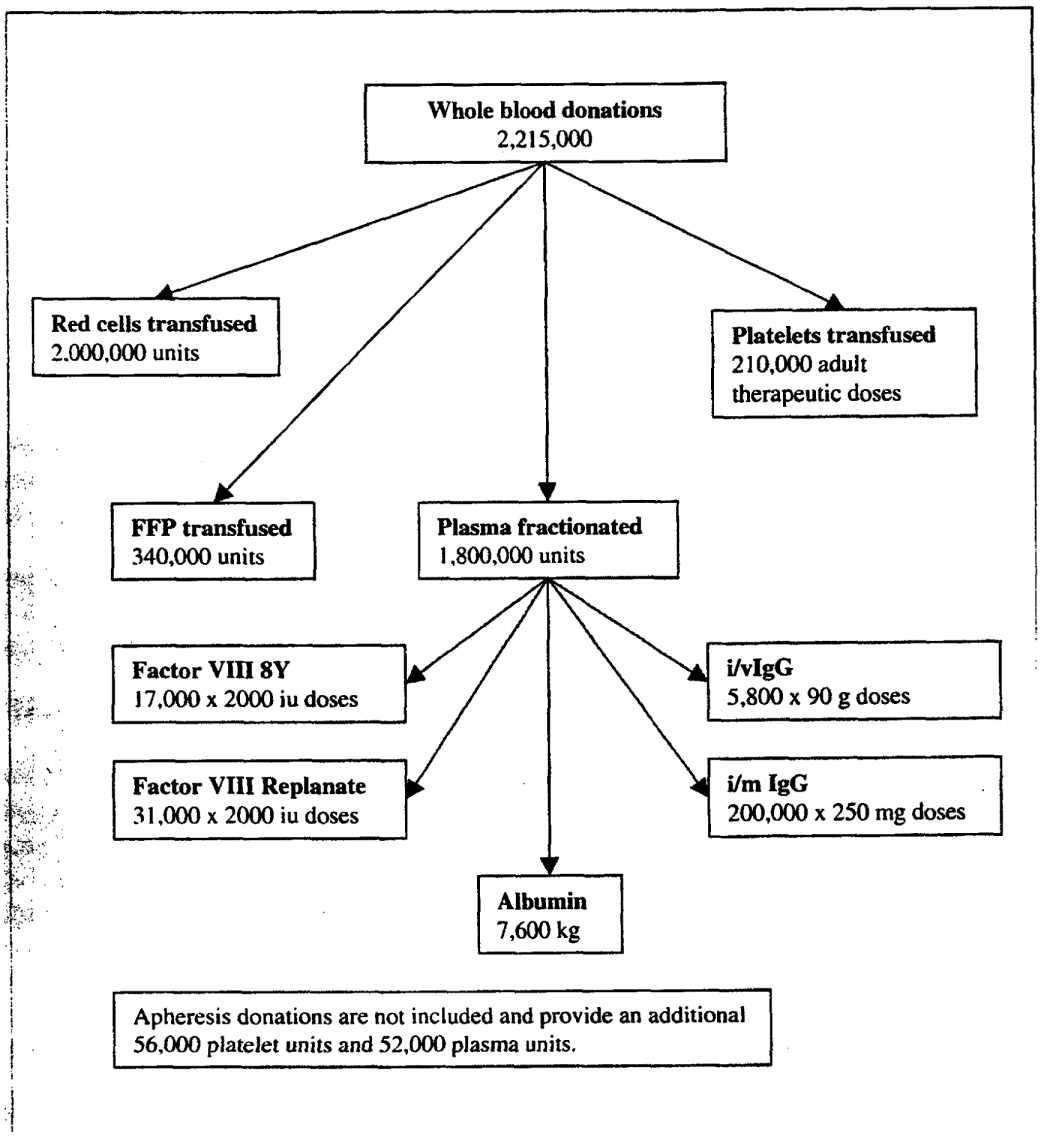


Figure 2: Exposure of representative patient groups to blood components and fractionated plasma products

[Taken from the Report "Assessment of the Risk of Exposure to vCJD Infectivity in Blood and Blood Products", Final Report for the Spongiform Encephalopathy Advisory Committee (SEAC) and the Department of Health, Revision 4, February 1999, Det Norske Veritas]

Table I.7.1 Exposure of Patient Groups to Blood Components

PATIENT GROUP	PATIENTS (per year)	NEXT YEAR	BLOOD PRODUCT	DOSE (units/year)	LIFE EXPECTANCY (years) or SURVIVAL PROBABILITY
Acute blood loss (inc surgery)	72,000	New	Red cells	2	90% survival
Acute blood loss with complications	80,000	New	Red cells Plasma	5 2	50% survival
Massive blood transfusion	8,000	New	Red cells Platelets Plasma	15 3 5	20% survival
Chronic acquired anaemia	144,000	Ongoing	Red cells	4	15
Bone marrow failure	60,000	Ongoing	Red cells Platelets	10 3	5
Anaemia/coagulopathy	24,000	Ongoing	Red cells Plasma	10 5	5
Congenital anaemia	12,000	Ongoing	Red cells	5	25
Anaemia of prematurity	6,000	New	Red cells	1	50% survival
HDN babies	920	New	Red cells	1	95% survival

Table I.7.2 Exposure of Patient Groups to UK Plasma Derivatives

PRODUCT	REPRESENTATIVE PATIENT GROUP	UK ISSUES (per year)	PATIENTS (per year)	TYPICAL DOSE	DOSE RATE (dose/year)
Factor VIII	Haemophilia A	100 m iu	1800	2000 iu	27
Factor IX	Haemophilia B	16 m iu	250	1250 iu	52
Anti Thrombin	Sepsis	1.2 m iu	34	7000 iu	5
Factor VII	Warfarin overdose	0.75 m iu	30	4000 iu	6
Factor XI	Factor XI deficiency	0.13 m iu	40	1000 iu	3
Factor XIII	Factor XIII deficiency	0.32 m iu	6	4000 iu	12
Albumin 4.5%	Shock	120,000 l	59,000	1 litre	2
Albumin 20%	Intensive care	11,000 l	27,500	100 ml	4
i/v IgG	ITP + PIA	526,000 g	1450	90 g	4
NIgG (i/m)	HAV prophylaxis	27,500 g	90,000	250 mg	1.2
Anti D IgG	HDN prophylaxis	33,000 g	88,000	250 mg	1.5
Tetanus IgG	Tetanus prophylaxis	2,000 g	8,000	250 mg	1
Hepatitis B IgG	HBV prophylaxis	750 g	3000	250 mg	1
Var zoster IgG	Var zoster prophylaxis	1,350 g	1800	250 mg	3
Rabies IgG	Rabies prophylaxis	130 g	178	250 mg	3

Figure 3: **A risk calculation flowchart – illustrated using the example of treatment with intravenous immunoglobulin**

[Taken from the Report "Assessment of the Risk of Exposure to vCJD Infectivity in Blood and Blood Products", Final Report for the Spongiform Encephalopathy Advisory Committee (SEAC) and the Department of Health, Revision 4, February 1999, Det Norske Veritas]

Figure 4.5 Risk Calculation Flowchart

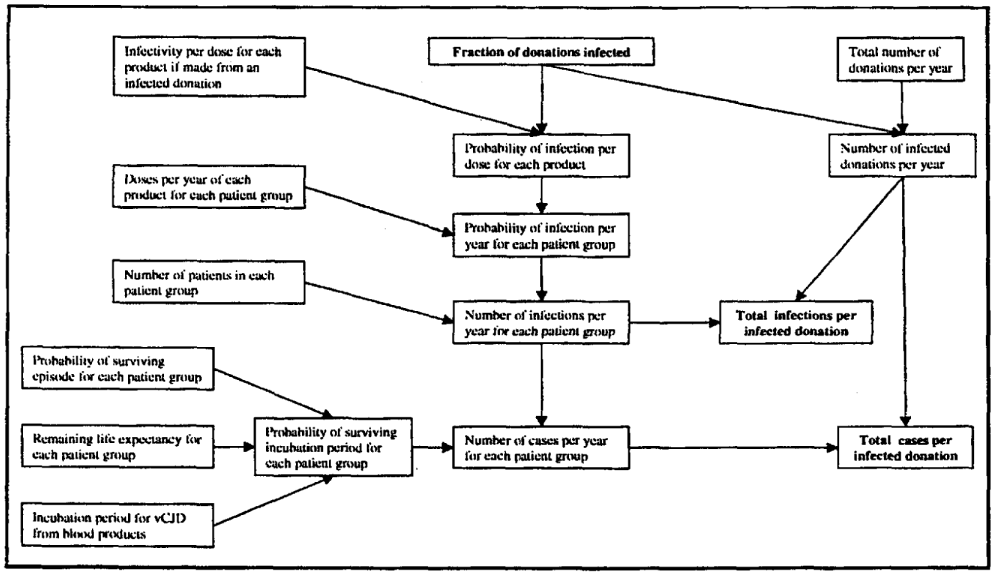


Figure 4.6 Example Calculation for i/v IgG Patients

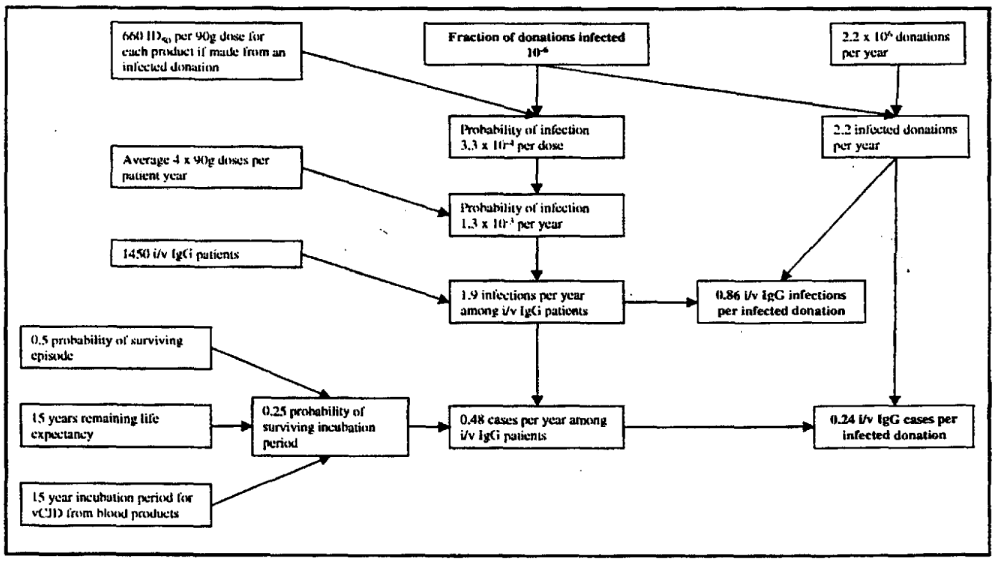
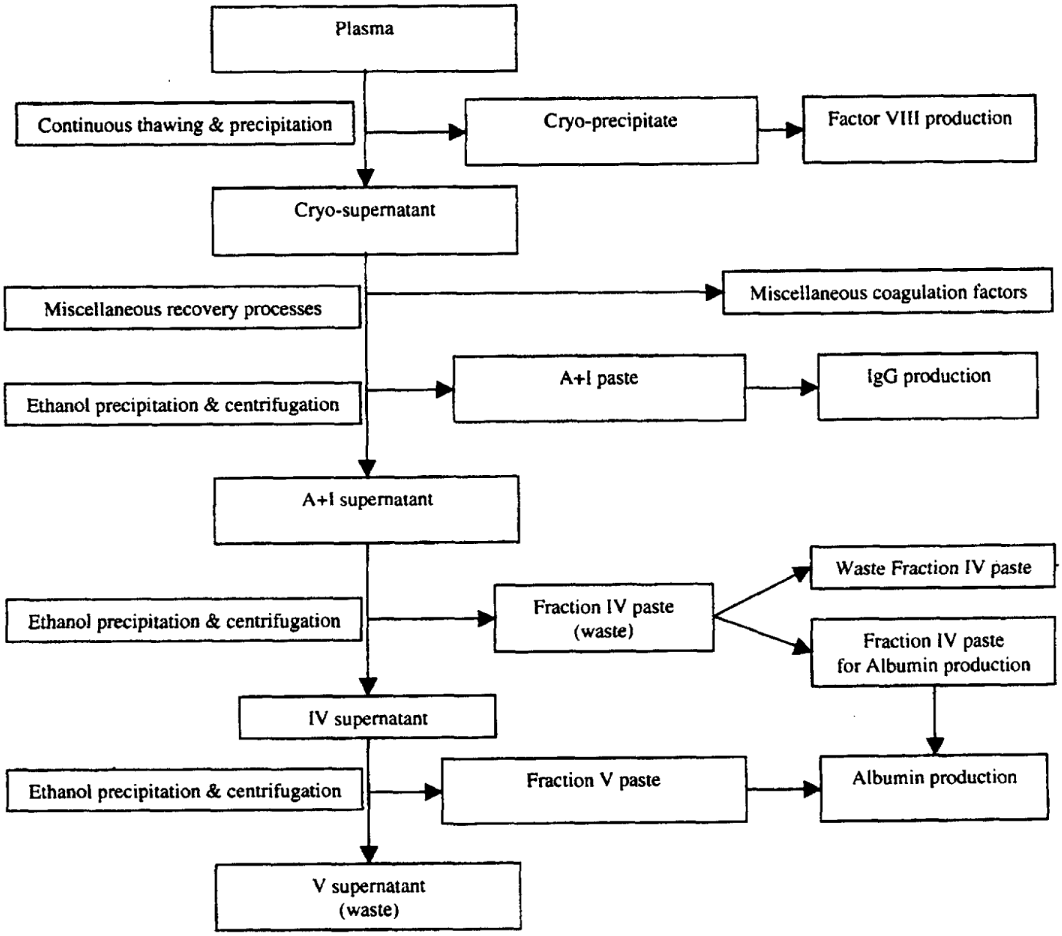


Figure 4: Outline Schematic of the Plasma Fractionation Process (BPL)

Figure I.5.1 Outline of Plasma Fractionation at BPL



Notes:

1. This schematic is greatly simplified. Preparation of each therapeutic product from the relevant plasma fraction (Factor VIII from cryoprecipitate, Immunoglobulin – IgG from A+I paste, Albumin from fraction V paste) involves a considerable number of further purification steps. Some of these are generic steps (centrifugation, filtration, ultrafiltration, gel permeation chromatography). Others are specific to the protein being purified – or to an impurity being removed – including ion-exchange and affinity chromatography. Each of these steps makes a contribution to removal of prion protein. The contribution to prion removal of some of these steps is summarised in Table 2.

The reference in the figure to use of fraction IV paste for Albumin production applies uniquely to surplus fraction IV supplied by BPL to a fractionator outside the UK. BPL manufacture Albumin exclusively from fraction V paste.

Table 1: **Distribution of TSE infectivity across blood components and plasma fractions** [Adapted from Foster[14]]

Component/fraction	TSE infectivity, iu/ml (ic[1]), using prion from mouse-adapted GSS[2] syndrome	TSE infectivity, iu/ml (ic[1]), using prion from hamster-adapted Scrapie 263K
Brain	$10^6 - 10^7$	5×10^7
Blood	Not detectable	4 – 24
Buffy coat	44.4 – 106.0	
Plasma	10.3 – 34.4	3.9
Cryoprecipitate[3]	1.2 – 2.6	0.6
Fraction I+II+III	0.8	0.3
Fraction IV	0.0 – 0.5	
Fraction II (intermediate fraction used to prepare IgG)		Not detectable
Fraction V (intermediate fraction used to prepare Albumin)	0.0 – 0.3	Not detectable

Table 2: **A summary of results from studies on prion elimination by plasma fractionation processes** [Adapted from Foster[14]]

Product	Process step	Scrapie[4] log reduction (bioassay)	Scrapie[4] log reduction (Western blot)
Factor VIII	Cryoprecipitation	2.1	<1.0 – 1.0
	Affinity chromatography	4.4	
	Ion-exchange chromatography	6.3	
Factor IX	Ion-exchange chromatography		3.0
Albumin	Cryoprecipitation		<1.0 – 1.0
	Fraction A+I precipitation	2.1 – 5	1.3 – 5
	Fraction IV precipitation	3.0 – 5	3.0 – 5
	Filtration of fraction V solution		2.3 – 4.9
IgG	Cryoprecipitation		<1.0 – 1.0
	Fraction I+III precipitation	3.4 – 5	4 – 5
	Filtration of fraction II solution		>2.8

[1] Infectivity is measured as ID_{50} by intracerebral inoculation into mice or hamsters
[2] Gerstmann-Strausler-Scheinker syndrome
[3] Cryoprecipitate is used both as blood component in its own right and as the intermediate from which Factor VIII concentrates are derived
[4] Reduction measured using Scrapie 263K

Annex 1: Report on Products Implicated By vCJD Donor Notifications in October 1997

BPL

Introduction

This report summarises notifications to BPL of delivered plasma donations subsequently implicated due to information relating to an episode or risk of C-JD. The report is divided into 2 sections, reports and trace results on nvCJD, numbers of donations implicated by familial / classical C-JD affected donors. The total number of donations notified to BPL is reported for each section, in the case of classical / familial C-JD the traces have only been undertaken for donations received after September 1991(a convenient cut-off date since the implementation of HCV-Ab screening at that time ensures that no products from earlier donations will still be in use).

New Variant C-JD Notifications

Up to the end of December 1997 BPL has been notified of 7 donations obtained from 3 donors who subsequently developed nvC-JD. One of these was donated in January 1990; insufficient information is available to trace the plasma start pool.

The following products were manufactured from the 6 other start pools, or incorporated implicated albumin as an excipient, and released for sale or for clinical trial use.

Table 1. Batches produced from nvC-JD implicated pools

Dose/ strength	Batch number	Expiry date	Number released	Dose/ strength	Batch number	Expiry date	Number released
Human Albumin Solution, Zenalb 20%							
100ml	ABC0065	1/4/95	2971	50ml	ABD0295	11/9/97	8805
100ml	ABC0111	5/1/95	4314	50ml	ABD0319[1]	6/8/98	9043
100ml	ABC0219	18/11/96	4220	50ml	ABD0324[1]	4/9/98	9203
100ml	ABC0229	7/12/96	4269	50ml	ABD0325[1]	5/9/98	8654
50ml	ABD0290	13/8/97	8625	50ml	ABD0332A[1]	5/8/98	8174
50ml	ABD0291	14/8/97	8837				
Human Albumin Solution, Zenalb 4.5%							
500ml	ADA0387	30/6/96	4022	500ml	ADA0529[1]	14/11/97	3826
500ml	ADA0390	26/7/96	3323	250ml	ADB0163	30/5/93	3167
Human Normal Immunoglobulin, intramuscular							
750mg	GGB064	19/11/93	4229	250mg	GGD085	9/12/94	17205
250mg	GGD077	14/1/95	19106	250mg	GGD086	18/12/94	16585
250mg	GGD084F	9/11/94	5421	250mg	GGD130	21/5/96	18323
250mg	GGD084G	9/11/94	17903	250mg	GGD131	18/6/96	19252
250mg	GGD084H	9/11/94	5000				
Human Anti-D Immunoglobulin, intramuscular							
500iu	GDC071	2/11/96	19685	500iu	GDC072	26/1/97	8931
Factor VIII, Type 8Y							
500iu	FHB4116	9/4/95	1476	250iu	FHC0289	1/3/93	2481
500iu	FHB4419[1]	6/6/98	1988	250iu	FHC4237	4/10/96	4982
500iu	FHB4547[1]	19/9/97	1789				

Table 1 continued

Dose/ strength	Batch number	Expiry date	Number released	Dose/ strength	Batch number	Expiry date	Number released
Factor VIII, Replenate							
250iu	FHD4235 (2)	24/8/96	3363	500iu	FHE4267A (2)	30/8/96	1060
250iu	FHD4247B (2)	5/9/96	3445	500iu	FHE4277A (2)	14/12/95	2202
250iu	FHD4267B (2)	1/3/96	2380	500iu	FHE4277B (2)	21/12/95	1309
250iu	FHD4267C (2)	25/4/96	1491	500iu	FHE4286 (2)	16/12/95	4041
500iu	FHE4218	17/6/94	1634	500iu	FHE4548 (1)	2/9/98	3321
500iu	FHE4244B (2)	4/10/94	1106	1000iu	FHF4244C (2)	4/10/94	608
500iu	FHE4247A (2)	18/8/96	1829	1000iu	FHF4252 (2)	5/9/96	1684
500iu	FHE4250 (2)	5/9/96	3173				
Factor VIII, 8SM (2)							
250iu	FHR4175	16/11/95	3360	500iu	FHM4217	17/5/96	1623
500iu	FHM4127	4/6/95	1698	500iu	FHM4219	22/6/96	1637
500iu	FHM4136	8/6/95	2112	500iu	FHM4220	28/6/96	3035
500iu	FHM4136A	11/6/95	1603	500iu	FHM4221	5/7/96	2966
500iu	FHM4138	17/8/95	1601	500iu	FHM4223	30/6/96	1412
500iu	FHM4140	20/8/95	1865	500iu	FHM4227	9/9/96	1626
500iu	FHM4142	21/9/95	1844	500iu	FHM4229	16/8/96	1695
500iu	FHM4144	24/9/95	1930	500iu	FHM4246	28/9/96	1428
500iu	FHM4148	14/9/95	1751	500iu	FHM4249	3/10/96	1400
500iu	FHM4160	28/9/95	1989	500iu	FHM4257	21/10/96	1347
500iu	FHM4163	21/10/95	1750	500iu	FHM4259	24/10/96	1568
500iu	FHM4164	26/10/95	2003	500iu	FHM4261	26/10/96	1461
500iu	FHM4173	21/11/95	1776	500iu	FHM4262	2/11/96	1454
500iu	FHM4182	7/2/96	2109	500iu	FHM4263	16/11/96	1386
500iu	FHM4183	7/12/95	1946	500iu	FHM4268	14/11/96	1395
500iu	FHM4184	31/12/95	1687	500iu	FHM4272	5/12/96	2909
500iu	FHM4185	1/2/96	2039	500iu	FHM4275	16/12/96	1400
500iu	FHM4186	4/2/96	1970	500iu	FHM4278	20/1/97	1579
500iu	FHM4190	31/12/95	1681	500iu	FHM4281	3/2/97	1582
500iu	FHM4200	31/12/95	1771	500iu	FHM4290	13/2/97	681
500iu	FHM4202	31/12/95	1799	500iu	FHM4297	24/2/97	5692
500iu	FHM4206	31/12/95	1666	1000iu	FHP4161	29/10/95	879
500iu	FHM4209	31/12/95	2030	1000iu	FHP4197	11/3/96	931
500iu	FHM4210	31/12/95	1604	1000iu	FHP4213	6/5/96	862
500iu	FHM4211	31/12/95	1743	1000iu	FHP4245	14/9/96	697
500iu	FHM4212	4/5/96	1777	1000iu	FHP4255	31/10/96	687
500iu	FHM4214	31/12/95	1672	1000iu	FHP4265	2/12/96	689
500iu	FHM4216	9/9/96	1637	1000iu	FHP4279	1/2/97	791
				1000iu	FHP4296	15/2/97	1158
Factor IX, Type 9A							
600iu	FJA0092	16/4/91	798	600iu	FJA4239B	12/7/96	473

(1) = product recalled. (2) = ABC0065 used as excipient. Total units released = 388,109.

Annex 2: Position Statement on "Notification of Recipients" Adopted in December 1997 by BPL and NBA

Position Statement:

on "the nature of advice to be given to patients who have been treated with plasma products manufactured from a plasma pool which includes plasma from a donor suffering from nvCJD"

1 **SCOPE**

Too little is known about nvCJD to allow a position to be defined which can be assumed to be indefinitely valid. The position outlined is defensible in the context of the stated premises. In the event that one or more of these premises is disproved or modified, the position must be assumed to be invalid (or, at best, unreliable pending urgent review).

2 **PREMISES**

2.1 There is no evidence that nvCJD has ever been transmitted by blood or blood products.

2.2 There is no available test to determine whether a given batch of product contains the infective agent for nvCJD.

2.3 There is no available test for pre-clinical infection with nvCJD.

2.4 There is no available prophylaxis against the development of clinical nvCJD.

2.5 There is no available treatment for clinical nvCJD.

3 **POSITION**

In the event that post-donation advice indicates that an individual subsequently identified as suffering from nvCJD has contributed to a plasma pool:

3.1 derived products should be withdrawn in accordance with current BPL procedures and in consultation with MCA;

3.2 no attempt should be made to advise individual recipients that they may have been treated with product from an affected batch;

3.3 this position, and its basis, should be explained to consignees as part of the withdrawal action;

3.4 consignees seeking advice on patient follow-up should be reminded that:

3.4.1 a confidential permanent record of any human recipients, date of transfusion event, product and batch number of material transfused needs to be kept for future reference if necessary;

3.4.2 for any patient transfused/treated with blood, blood components or plasma products (including albumin, immunoglobulins, vaccines, coagulation factor concentrates), record in the patient's medical record - *(i) the product, (ii) date given, (iii) unit/batch number.*

4 **BASIS FOR THE POSITION**

4.1 The Lothian Ethics Committee, which reviewed the ethical basis of decision making in respect of the follow-up study being undertaken by the national CJD Surveillance Unit, determined that no attempt should be made to trace recipients, or to tell them they had received CJD-implicated donations.

4.2 The Ethics Committee was subsequently asked to advise on policy in respect of recipients of fractionated products from pooled plasma containing an nvCJD donor, and reiterated its earlier advice.

4.3 It is possible that the very act of advising a recipient in these circumstances would itself be construed as an injury, given the mental suffering that would undoubtedly result and given the probable impact on the recipient's status with respect to life/healthcare insurance.

5 **COROLLARY**

It follows from the above that there is no basis for assuming that individuals in receipt of therapeutic material from an implicated batch of plasma product should be considered to be in an "at risk" category with respect to blood donation, provided in all other respects they meet our current donor selection criteria.

6 **REVIEW**

This position will be reviewed at least annually by the National Medical Director of the NBA, and on any other occasion if the underlying premises change.

National Blood Authority Page 1 of 1 Final: Revision 1.0
File reference C:\Documents and Settings\tjs\Desktop\vCJD, BPL & NBS position on notification.DOC December 16, 1997

Annex 3: **Example of CBER Recall "Because Donor at Increased Risk for CJD" – page 1**

FDA CBER CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Withdrawal of Nine Derivative Products Because Donor at Increased Risk for CJD

WITHDRAWAL DATE: July 29, 1997

PRODUCTS / LOT NUMBERS / ***EXPIRATION DATES*****:**

Baxter Healthcare Corporation:

Immune Globulin Intravenous (Human), Solvent Detergent Treated, Polygam:
26205095AA, *09/27/1997*
26205098AA, *10/16/1997*
26205103AA, *10/27/1997*
26205109AA, *11/20/1997*
26205110AA, *11/22/1997*
26205112AA, *11/27/1997*
26205096AA, *10/11/1997*
26206003AA, *01/15/1998*

Plasma Protein Fraction (Human), 5%, Plasmarc:
28365421AA, *02/18/2000*
28365422AA, *02/19/2000*
28365423AA, *02/19/2000*
28365527AA, *10/13/2000*
28365528AA, *10/13/2000*

Albumin (Human), 25%, Albumarc:
28376242AB, *04/10/1999*
28376266AA, *06/22/1999*
28376272AA, *06/29/1999*
28375218AA, *02/19/1998*
28375306AA, *10/08/1998*
28374301AA, *09/04/1997*
28375308AA, *10/13/1998*
28374298AA, *09/02/1997*
28376313AA, *10/19/1999*
28375219AA, *02/21/1998*

Albumin (Human), 5%, Albumarc:
29246173AA, *04/03/1999*
29246173AB, *04/03/1999*
29245145AA, *02/25/1998*
29245146AA, *02/26/1998*
29245147AA, *02/26/1998*
29245284AA, *10/13/1998*
29244237AA, *09/01/1997*
29244238AA, *09/02/1997*
29244239AA, *09/01/1997*

Annex 3: Example of CBER Recall "Because Donor at Increased Risk for CJD" – page 2 (page 3 omitted deliberately)

Antihemophilic Factor (Human), Method M, Monoclonal Purified:
29356040AA, *06/13/1998*
29356001AA, *01/05/1998*
29356002AA, *01/06/1998*

Fraction IV-1 Paste:
26286079AA, 26286080AA, 26286081AA, 26286082AA
26286083AA, 26285026AA, 26285027AA, 26285028AA
26285029AA, 26285030AA, 26285031AA, 26285232AA
26285233AA, 26285234AA, 26285235AA, 26285236AA
26284214AA, 26284215AA, 26284216AA, 26284217AA
26284218AA, 26284219AA

Fraction IV-4 Paste:
27965045AA, 27965046AA, 27965047AA, 27965244AA
27965245AA, 27964364AA, 27964365AA, 27964366AA
27964367AA, 27964368AA, 27964369AA, 27962403AA
27962404AA, 27962405AA, 27962406AA, 27962407AA
27962408AA

Fraction I+II+III Paste:
05316043AA, 05316044AA, 05316045AA, 05316046AA
05316047AA, 05316023AA

Central Laboratory Blood Transfusion Service Swiss Red Cross

Albumin (Human), 25%:
5.270.046.0, *06/23/1998*
5.280.004.0, *01/20/1998*
5.280.047.0, *06/07/1998*
5.280.073.0, *08/31/1998*
6.280.001.0, *01/08/1999*

MANUFACTURERS:

Hyland Division of Baxter Healthcare Corporation
Glendale, CA

Central Laboratory Blood Transfusion Service Swiss Red Cross
Bern, Switzerland

DISTRIBUTOR:

Plasma collected by, and product distributed by, the American Red Cross

REASON:

The Hyland Division of Baxter Healthcare Corporation and the Central Laboratory Blood Transfusion Service Swiss Red Cross were notified that one of the plasma donors is considered to be at increased risk for CJD. This donor was confirmed to have received a dura mater transplant on October 14, 1985 during surgery for the repair of a congenital malformation of the brain stem.

The information in this listing reflects CBER's best efforts to communicate information

Chronology of Events and Significant Announcements

Date	Event
25 Nov 87	FDA Office of Biologics Memorandum "*Deferral of donors who have received human pituitary-derived growth hormone*"
13 Mar 95	CPMP/BWP/269/95 "*Note for Guidance on plasma-derived medicinal products*" revised guidance, including donor deferral for individuals treated with human pituitary extracts or with family history of CJD.
20 Mar 96	CEM/CMO/96/1 "Message from Sir Kenneth Calman, Chief Medical Officer" confirming recognition of a new variant of CJD, possibly linked to BSE.
6 Apr 96	Publication of landmark Lancet article "A New Variant of Creutzfeldt-Jakob Disease in the UK" by Bob Will and co-workers
11 Dec 96	FDA CBER Memorandum "*Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) by Blood and Blood Products*" – provides the agency's current thinking on donors considered to be CJD risk; requirements on recall and advice to consignees
1 Jul 97	DH (97/153) report advice from SEAC on research into the link between nvCJD and BSE which concluded "*... the most likely explanation for the cases of the new variant CJD was exposure to BSE before the introduction of the Spongiform Bovine Offals (SBO) ban in 1989.*"
Oct 97	Three UK (English) plasma donors confirmed as having died from nvCJD (total number of definite vCJD cases at the time = 22)
30 Oct 97	BPL recall (PR97/205) Factor VIII and albumin from pool with definite vCJD donor (1st)
31 Oct 97	Advice to BPL of 2nd definite vCJD donor (K97/347) – no in-date product, no recall (in this regard note later advice of CPMP/201/98)
Nov 97	BBC Panorama programme, "The British Disease"
4 Nov 97	BPL recall (PR97/208) Factor VIII and albumin from pool with definite vCJD donor (3rd)
5 Nov 97	EMEA statement on vCJD for BBC "Newsnight" (recall inappropriate for classical CJD; position on vCJD under review)
6 Nov 97	SEAC Meeting Public Summary (97/333) confirms advice to DH on safety of blood and blood products in respect of vCJD
6 Nov 97	DH (97\335) accept SEAC advice to commission risk assessment on blood and blood products
18 Nov 97	Recall (by Nycomed Amersham) of Pulmonate II prepared using vCJD-affected BPL albumin
20 Nov 97	CPMP press release (CPMP/1056/97) including a statement on nvCJD and blood products advises "... as a *precautionary measure ... prudent to withdraw batches of plasma derived medicinal products ...donor ... confirmed diagnosis of nvCJD ... consequences for essential medicinal products where alternatives may be unavailable will need careful consideration.*"
25 Nov 97	First CBER notification of product recall (IV IgG, Sandoglobulin) resulting from use of albumin excipient implicated by inclusion of CJD-risk donation
27 Nov 97	UKHCDO press release recommending use of recombinant Factor VIII[39]

Dec 97	UKHCDO statement on preferred concentrates makes UK-derived f.VIII product of last resort
3 Dec 97	UK "Beef on the Bone" ban
11 Dec 97	FDA "Dear Biologic Product Manufacturer" letter, advising manufacturers of CJD-implicated plasma product batches and requiring notification within 30 days of any batch used at any stage during manufacture of a licensed product.
16 Dec 97	NBA/BPL Position Statement on "*the nature of advice to be given to patients who have been treated with plasma products manufactured from a plasma pool which includes plasma from a donor suffering from nvCJD*"
6 Feb 98	PL (CO) (98) 1: DH provided "general" advice on patient notification "New Variant CJD – Patients who have received implicated blood products" – recipients need not be notified – but clinician i/c free to exercise judgement
26 Feb 98	DH (98/076) BPL to be allowed to import plasma; NBA to prepare leucodepletion strategy
26 Feb 98	CEM/CMO/98/5 reports CSM advice: product to be recalled if donor strongly suspected of vCJD; vaccines used in UK don't contain UK albumin
26 Feb 98	CPMP/201/98: no evidence of transmission of classical CJD by blood/plasma; vCJD recognisably different, therefore precautionary recall of plasma products, this to include informing "supply chain" even if products exhausted; excipient albumin not to be sourced from countries with vCJD
Apr 98	France, Ireland and Portugal mandate total leucodepletion
1 Apr 98	BPL and PFC make presentations to a Special Subcommittee of CSM on vCJD risk from products manufactured from UK plasma
5 May 98	Meeting involving DH, Scottish Office, CJDSU, SNBTS and NBA/BPL to review basis and mechanisms of advice of vCJD infection – CJDSU to notify blood services only when vCJD confirmed or "strongly suspected" (i.e. probable)
13 May 98	CSM/98/8th Meeting – considered manufactured blood products should not be sourced from UK plasma (accepted that the processes may separate prions but this could not be validated, therefore theoretical risk of vCJD remains)
13 May 98	DH Press Release (R0965-01) reporting CSM advice: UK fractionators to source plasma from outside UK
Apr 98	BPL begin quality audits of potential US plasma suppliers
May-Jun 98	UK fractionators shutdown manufacture from UK plasma; cleaning & decontamination of plant; submit PLVs for all products
17 Jul 98	DH Press Release 98/295 confirming acceptance of SEAC advice on leucodepletion
Jun-Aug 98	UK fractionators manufacture commissioning batches from US plasma collected pre-MCA audit of suppliers; MCA inspection of decontaminated UK facilities; US plasma suppliers satisfy MCA
27 Aug 98	DH Press Release (98/351) reporting the finding of vCJD prion protein in the appendix of a patient who went on to develop the disease

Aug 98 - Jan 99	UK fractionators manufacture fractionated plasma products from US plasma to create inventory
Dec 98 - Jan 99	UK fractionators release and issue fractionated plasma products from US plasma
Jan 99	World Federation of Hemophilia monograph "*Creutzfeldt-Jakob Disease and Haemophilia: Assessment of Risk*" – pragmatic review by Bruce Evatt, concludes "*... doctors and patients must weigh the unknown, but likely small, risk of CJD against the unavoidable, known, dangers of not receiving treatment. In most cases the answer is obvious.*"
Feb 99	Publication of the DNV Report "Assessment of the Risk of Exposure to vCJD Infectivity in Blood and Blood Products" (Final – Rev. 4)
Feb 99	"Recover and replace" activity to ensure UK plasma-derived product does not remain in indefinite use (not a formal recall)
May 99	Release and issue of anti-D immunoglobulin (IgG) derived from US plasma
Jul 99	Release and issue of HBs IgG and V-Z IgG from US plasma
Aug 99	Release and issue of tetanus IgG derived from US plasma
1 Nov 99	Only leucodepleted components manufactured by UK Transfusion Centres from this date
23 Nov 99	CBER "Guidance for Industry" on "*Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products*" – provides the agency's current thinking; distinguishes between CJD (no recall of plasma products) and vCJD (recall); requires advice to consignees – recipient notification subject to clinical judgement
Dec 99	Release and issue of rabies IgG derived from US plasma
12 Jan 00	Letter DH to NBA (copied to territorial offices) confirming advice of PL(CO)(98)1 on recipient notification still effective but under active review
25 Jan 00	First meeting of the DH "Expert Group on the Management of CJD Incidents", under the chairmanship of Prof Don Jeffries
28 Apr 00	DH Press Release 2000/0250 reporting first (negative) findings from the survey of human tissues
17 Jul 00	DH Press Release following SEAC Meeting of 17 July 2000: with 76 "definite" and 7 "probable" cases of vCJD, the Committee concluded a significant rising trend (20%-30% p.a.)
8 Dec 00	BPL incident reference 11723/3: notification to consignees (UK and overseas) of plasma products affected by a definite vCJD donor
3 Jan 01	Monthly CJD statistics reflect 81 "definite" and 7 "probable" cases of vCJD

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[1] EMEA/CPMP/BWP/3293/99: "CPMP Report of the Expert Working Group on New Variant CJD and Donor Exclusion Criteria for Plasma-Derived Medicinal Products"; EMEA, London; 16 Dec 99
[1] Executive Letter PL(CO)(98)1, 6 Feb 98; status quo confirmed to NBA in letter dated 12 Jan 00, from MMcG to EAER
[1] The DH "Expert Group on the Management of CJD Incidents", under the chairmanship of Prof Don Jeffries, met first on 25 Jan 00. The group has wide representation including representatives from CJDSU, SEAC, NBA, PHLS, DH CJD/BSE Policy Unit and MDA, as well as user and lay representatives. It was established to provide a mechanism for the development of a consistent approach to the handling of different situations in which patients may have been exposed to the potential risk of secondary vCJD infection.
[1] The DH "Clinical Incidents Panel" succeeded the DH "Expert Group on the Management of CJD Incidents"
[1] FDA (CBER): "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products"; 23 Nov 1999
[1] "Probable" vCJD cases are those that fulfil the diagnostic criteria for vCJD but are either still alive, or have died and await post mortem pathological confirmation (if post mortem does not take place, such cases remain in the "probable" category)
[1] A diagnosis of "definite" vCJD requires recognition of progressive neuropsychiatric disorder and neuropathological confirmation of vCJD
[1] Letter dated 22 May 00, from Dr Patricia Hewitt (NBS London & SE) to Dr Ailsa White (DH CJD/BSE Policy Unit)
[1] Agreed on 6 Oct 99 in discussions between NHSE, DH and NBA; reviewed and affirmed by MSBT at its meeting on 28 Oct 99; confirmed in letter dated 12 Jan 00, from MMcG to EAER
[1] Paper produced by the "Guidance Review Working Group" under chairmanship of Dr Tim Wyatt (Consultant Clinical Scientist, Belfast) and presented to MSBT for review at its meeting on 26 Jun 00.
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