



Variant Creutzfeldt-Jakob Disease and Haemophilia A Risk Assessment of Plasma-derived Products

**Prepared by Albert Farrugia, BSc, PhD, on behalf of the
WFH Task Force on TSEs**

Revised November 15, 2001

The usual forms of Creutzfeldt-Jakob disease (CJD) are extremely rare, rapidly progressive and fatal neurologic diseases thought to be caused by a new form of infectious agent called a prion. Concerns were raised in the mid-1990s that blood obtained from donors incubating the disease might be able to transmit the disease to persons receiving blood or blood products, such as clotting factor concentrates, which are made from the donor blood. Extensive studies over the past five to six years have failed to identify any episodes of transmission of these usual forms of CJD to blood recipients or users of plasma products, and public health workers are more confident that the risk of transmission by these products is minimal, if it exists, for these forms of CJD.

In 1985, a number of dairy cows in Britain developed a new, fatal illness characterized by symptoms of abnormal and aggressive behaviour and ataxia (loss of muscle coordination). Autopsies on these cows showed findings resembling scrapie in sheep, and the disease was named bovine spongiform encephalopathy (BSE). The epidemic that followed affected more than 180,000 cattle in Britain. The evidence pointed to a common source cause for the outbreak, a food supplement made from meat and bone meal produced by commercial rendering plants.

Beginning in 1995, a new human form of CJD (called variant CJD or vCJD) appeared among people in Britain. These patients developed early psychiatric and behavioural changes, and had persistent paresthesia (prickling or tingling of the skin) and dysesthesia (impairment of sensitivity of touch), followed by ataxia⁽¹⁾. All had eaten meat prior to 1991, and it was suggested that the disease was the result of cross-species transmission of BSE. Evidence continues to accumulate to support this hypothesis.

Worrisome for public health workers have been the subsequent studies on endogenous mouse⁽²⁾ and exogenous sheep⁽³⁾ models of bovine spongiform encephalopathy (BSE) that suggest that the disease can be transmissible by blood. Recently, a mouse model of vCJD has also shown infectivity in the blood and basic cellular and plasma components^(3a). As a result, vCJD has now assumed a predominant role in considerations of blood safety worldwide. Variant CJD may be viewed as the human "model" for BSE. The purpose of this document is to provide information on the risk of vCJD to recipients of concentrates of coagulation factors VIII and IX derived from biological sources, in particular, the risk of blood donors from continental European countries contributing to plasma pools for haemophilia products.

There are two factors which will affect the potential of coagulation factor concentrates contaminated with the vCJD agent to transmit the disease to people with haemophilia:

1. The amount (“load”) of infectivity in the starting plasma raw material. This will depend on the epidemiology of vCJD in the blood donor population and the extent to which the infectivity in blood is partitioned into the plasma.
2. The extent to which starting plasma infectivity is partitioned into product during the course of concentrate manufacture.

Both factors are subject to significant uncertainties, principally because of:

- (i) The extent to which BSE and vCJD have established themselves outside Britain is unknown.
- (ii) The behaviour of the BSE/vCJD agent in plasma fractionation schemes is also unknown.

Potential Infectivity in European Donor Plasma

Variant CJD in Europe may arise from the consumption of beef products from two sources:

- Imported meat products from Britain.
- Meat products from BSE-infected cattle in Europe.

According to the World Organisation for Animal Health (OIE) ⁽⁴⁾, 11 European countries had reported internal (non-imported) BSE as of 3 January 2001. The Scientific Steering Committee (SSC) to the European Commission, in its Opinion of 6 July 2000⁽⁵⁾, classified all the countries of the European Union at a level of II and above in its Global BSE Risk Scale, i.e., the likelihood of BSE could not be excluded for any member states.

The following table includes European countries that contribute plasma to products available for the treatment of haemophilia A and von Willebrand disease on the export market ⁽⁶⁾. Products manufactured by national fractionators solely for domestic use are not considered at this stage. It is felt that any donor deferral measures emanating from the U.S. Food and Drug Administration (FDA) are more likely to impact on the supply export-directed products in the first instance, given the worldwide influence of the FDA. In January, an Advisory Committee of the FDA met to discuss whether the FDA should reconsider its policies on the suitability of blood donors who lived or travelled in countries where BSE has been identified, and the risks of CJD and vCJD transmission by human cells, tissues, and cellular and tissue-based products. The Advisory Committee recommended tightening restrictions on blood donors and donations from France, Portugal, and Ireland. The Committee decided that the number of BSE cases elsewhere in Europe was too small to justify adding other countries to the blood donation ban.

EUROPEAN COUNTRIES THAT CONTRIBUTE PLASMA TO PRODUCTS AVAILABLE FOR THE TREATMENT OF
HAEMOPHILIA A AND VON WILLEBRAND DISEASE ON THE EXPORT MARKET

Country	Global BSE Risk	Comments	Products	Fractionation method	
Austria	Unlikely but not excluded	The likelihood of BSE in Austria is considered to be low because of good practice in cattle husbandry and a specific surveillance system over the low numbers of cattle imported from countries with BSE.	Biotest <ul style="list-style-type: none"> FVIII (Haemoctin) 	Anion exchange chromatography	
			Baxter Immuno <ul style="list-style-type: none"> FVIII (Immunate) PCC (Prothromplex-T) FIX (Immunine) 	FVIII	Anion exchange chromatography
				PCC	Ion-exchange
				FIX	Ion-exchange & hydrophobic chromatography
Octapharma <ul style="list-style-type: none"> FVIII (Octanate) FIX (Octanyne) 	FVIII	Ion exchange chromatography			
	FIX	Ion-exchange & affinity chromatography			
Sweden	Unlikely but not excluded	Although animal husbandry practices and meat rendering techniques were not satisfactory in Sweden in the early 1980s, the level of bovine material entering the system from BSE countries was low to negligible.	Pharmacia-Upjohn <ul style="list-style-type: none"> FVIII (Octonativ-M) FIX (Nanotiv) 	FVIII	Monoclonal Ab chromatography
				FIX	Ion-exchange & heparin ligand chromatography
			Baxter Immuno – see under Austria		

Belgium	Confirmed at a low level	BSE is confirmed in Belgium. The poor husbandry methods and the high level of importation of at risk bovines makes it likely that the incidence will increase for the next few years. The EU's active surveillance system introduced in late 2000 has confirmed that the rate of BSE in Belgium is higher than the currently reported clinical figures.	Biotest – see under Austria			
France	Confirmed at a low level	France has BSE and the incidence increased strongly in 2000. (France has also had three cases of vCJD). Effective enforcement of feed bans and high imports of at risk bovines was delayed until the mid-1990s. The incidence is expected to continue to increase over the next few years. Preliminary results from the active surveillance program also suggest a higher incidence than is evident from the clinical case rate.	LFB <ul style="list-style-type: none"> • FVIII (Facteur VIII LFB) • PCC (Kaskadil) • FIX (Facteur IX LFB) 	FVIII	Chromatography	
				PCC	DEAE sephadex adsorption, anion exchange chromatography	
				FIX	DEAE sephadex, anion exchange, affinity chromatography	
Germany	Confirmed at a low level	Since the publication of the SSC's assessment, Germany has reported BSE. This was predicted by the SSC on the basis of inadequate husbandry and a high importation of at risk bovines, some of which developed BSE from Britain. The recently introduced active surveillance system is expected to find more cases.	Biotest – see under Austria			
			Baxter Immuno – see under Austria			
			Octapharma – see under Austria			
			Aventis <ul style="list-style-type: none"> • FVIII (Haemate-P, Beriate-P) • PCC (Beriplex P/N, Faktor IX HS) • FIX (Berinin-P = Berinin-HS) 	FVIII	Haemate-P Beriate-P	Multiple precipitation Ion-exchange
				PCC		DEAE-sephadex
FIX		DEAE-sephadex, affinity heparin chromatography				
Italy	Confirmed at a low level	Although indigenous BSE has not been detected in Italy as of mid-January 2001, the SSC considers it very probable that BSE is present in Italy and this is confirmed by the recent detection of a case through active surveillance. A high level of importation of at risk bovines – demonstrated by two cases in imported cattle in 1994 – combined with delayed introduction of satisfactory husbandry practices, leads to this expectation.	ISI <ul style="list-style-type: none"> • FVIII (Emoclot) • FIX (Aimafix D.I.) 	FVIII	Ion-exchange chromatography	
				FIX	Ion-exchange chromatography	

It is assumed that the potential vCJD infectivity in European plasma is a function of the incidence of vCJD in the donor population; it is also assumed that vCJD incidence is a function of BSE incidence in the country. These assumptions may both be challenged, but should provide a basis for assessment. In particular, this approach will assume that, relative to consumption of BSE-tainted meat products from the country of origin, consumption of contaminated meat products imported from the United Kingdom will contribute a minor component to any vCJD outbreak. It is felt that this assumption is tenable with the exception of France, as a French expert group reports that France was the principal importer of bovine products from the U.K. during the period in question⁽⁷⁾. The case of France will be assessed separately.

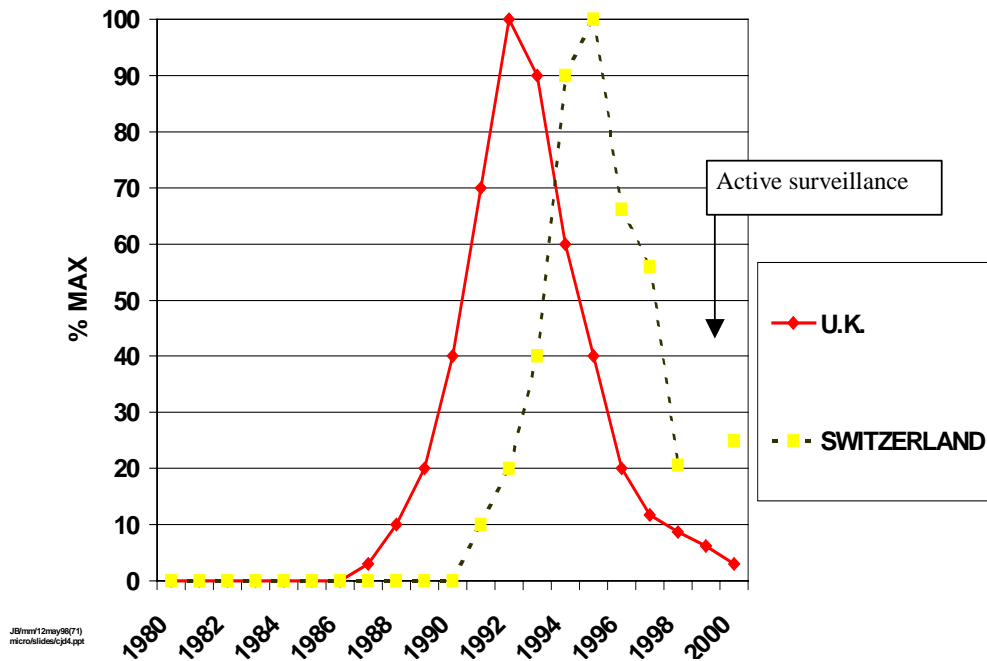
Therefore, a crucial component of this assessment is a prediction of the potential size of the BSE epidemic in the countries whose plasma goes into products that are exported, which at this stage comprise:

- Belgium
- France
- Germany
- Italy

As indicated in the table, Belgium, France, and Germany are all now confirmed as countries with confirmed cases of BSE. Cases of BSE have also been confirmed in Ireland and Portugal, but no products are exported from these countries so they have not been included in this assessment. Belgium and France have had significant increases in the level of BSE in 2000. With the introduction of active surveillance systems whereby bovine carcasses are tested for BSE prior to processing into meat products, the number of cases detected is expected to increase in both countries. It is expected that this will be the case for the next few years.

In attempting to predict the size of the BSE epidemic in these countries, it is worth examining the case of Switzerland. Although an increase of cases has been noted in recent years, this is probably due to the introduction of active surveillance and the number of clinical cases detected has continued to decline. The epidemic peaked in 1995, six years after the detection of the first clinical case. This pattern was similar to that observed in the U.K. (see figure). A similar pattern is also discernible in Portugal. If this pattern is repeated in the countries identified above, cases of BSE in Belgium can be expected to peak in 2002, and in Germany in 2005. As only one case of indigenous BSE, detected through active surveillance, has been found in Italy, predictions for this country would be premature at this stage.

BSE IN U.K. & SWITZERLAND



The French situation is more complex, as the data indicates that France is already in its eleventh year. However, a significant increase from the previous year's figures was only observed in 1998. On this basis, it is assumed that the BSE epidemic in France will peak around 2003-04. It may be confidently predicted that France's status will be changed from Category III to Category IV by the SSC in the near future.

The limitations of these assumptions will be obvious. However, the indications so far are supportive of the expectation that BSE in Europe will peak in the countries identified in this document in 2002-05, and that the epidemic will be considerably smaller than that experienced in the U.K. This latter expectation is based upon the rate at which the epidemic has progressed in the years observed so far. On this basis, France is expected to have the largest epidemic. France may also be expected to have the largest incidence, relative to the other countries of interest, of vCJD, as French consumption of British beef products was the highest in Europe. France therefore has the highest risk of having vCJD infectivity in its donor pool. The potential infectivity in Germany, Belgium, and Italy is expected to be considerably lower as both risk factors – vCJD from imported British beef and indigenous BSE leading to vCJD – are smaller in these countries.

Summary

- *The BSE epidemic in European countries contributing plasma to the world supply of coagulation factor products will not peak until 2002 – 05.*
- *This epidemic is expected to lead to a BSE incidence measured in the hundreds to the low thousands of cattle, as opposed to the hundreds of thousands experienced in the U.K.*

- *Active surveillance should allow more precise quantification of the BSE risk in Europe over the next year.*
- *In the interim, it may be assumed that the highest risk of plasma donor infectivity for vCJD comes from France. The more significant German donor pool, which contributes to a wide range of products, is much less affected.*

Elimination of vCJD Agent during Manufacture of Concentrates

In small animal models of scrapie⁽⁸⁾, the human TSE Gerstmann-Sträussler-Scheinker Syndrome (GSSS)⁽⁹⁾, and in the indigenous mouse⁽²⁾ and exogenous sheep⁽³⁾ model for BSE, infectivity has been demonstrated in the blood before the relevant animals became sick. It must be assumed that a similar infectivity is present in the blood of donors in the pre-clinical phase of vCJD. A crucial aspect of the safety of coagulation factor concentrates is therefore the capability of the manufacturing process to eliminate any infectivity.* No experiments have been reported thus far on the ability of plasma fractionation processes to eliminate the BSE/vCJD agent, but a growing literature has addressed the potential elimination of other TSEs.

Factor VIII Concentrates

The first step in the manufacture of plasma-derived FVIII concentrates is cryoprecipitation. Three studies⁽⁹⁻¹¹⁾ demonstrate that 1-2 logs of scrapie are removed by this step in spiking experiments of human plasma fractionation and small animal models of endogenous TSE. It is worth noting that the higher levels of removal – 2 logs – were observed when tracking with the bioassay which is more sensitive than the immunological-based Western blot. Similar results were found for exogenously introduced scrapie and endogenously induced GSSS, suggesting that different strains of TSE will behave similarly in plasma fractionation. This has been confirmed recently when cryoprecipitation resulted in similar clearance factors for vCJD and classical CJD when these TSE strains were used in spiking experiments for a FVIII concentrate purification^(11a).

Further purification of the FVIII concentrates from the countries identified above involves ion-exchange chromatography, with the exception of one product which is purified using precipitation. Two studies reporting on ion-exchange purification steps in FVIII purification⁽¹¹⁻¹²⁾ demonstrate 3 and 6 logs of clearance of exogenous scrapie. The capacity of chromatography to clear TSEs is also demonstrated in other biological purifications (reviewed by Foster)⁽¹¹⁾. In addition, Foster reports 1 log of removal through sterile (0.22 µm) filtration.

Assurance on the capacity of the process used to purify the German product Haemate-P is less easy to acquire. The scant literature available on the manufacturing process for this product⁽¹³⁾ indicates that it is purified by a glycine precipitation which removes fibrinogen in

* Estimating the level of infectivity: Most scientists develop estimates based on variations of the following process. Serial dilutions (usually by tenfold) of infectious samples are made and the dilutions are examined for infectious activity—for example in an assay animal. The dilution at which half the animals become infected is the infectious titre. For example, if 5 tenfold dilutions are required, the sample might be defined as having 5 logs of infectivity. After treating or manipulating the sample, the process is repeated. If, as expected, the treatment or manipulated sample has fewer logs of activity, the scientist assumes that this difference is produced by removal or inactivation of the infectious agent.

the precipitate followed by a sodium chloride precipitation on the glycine supernatant which concentrates the FVIII. Broadly speaking, precipitation steps may be expected to clear TSEs into the precipitate, and precipitation of cryoprecipitate using polyethylene glycol (PEG) has been shown to clear 2 to 3 logs of infectivity of spiked scrapie into the waste (fibrinogen) precipitate⁽¹⁴⁾. The analogous step in Haemate-P's manufacture is glycine-precipitation, which removes fibrinogen in the precipitate, and may also be expected to contribute to TSE removal. This has indeed been demonstrated for vCJD and classical CJD strains in experiments modelling this product's manufacture^(14a).

Summary

- ***Most current methodologies for the purification of plasma derived FVIII concentrates may be expected to clear 3 to 6 logs of vCJD infectivity present in a plasma pool.***
- ***This capacity should be adequate to assure the safety of FVIII manufactured from plasma from the European countries of interest.***
- ***This assessment depends on whether the vCJD strain of TSE is similar in its biochemical properties – charge, solubility etc – to other TSEs which are cleared to a high extent during FVIII purification. So far, every indication is that this is the case^(11a,14a).***

Factor IX Concentrates

The treatment of choice for haemophilia B is infusion of concentrates specifically enriched in factor IX. Some treatment centres still use prothrombin complex concentrates (PCCs) to treat haemophilia B because of lack of access to high purity FIX products. The technology for FIX concentrates is much more uniform than for FVIII.

For PCCs, DEAE-anion exchange chromatography is the basic purification method. A spiking study with scrapie⁽¹¹⁾ shows that this step eliminates 3 logs of TSE from the product.

FIX concentrates from plasma from the countries identified above are manufactured using two types of techniques:

- Anion-exchange plus heparin affinity chromatography. This has been shown⁽¹¹⁾ to contribute a further 4.4 logs of TSE clearance to the elimination provided by the purification of PCC (a necessary preliminary step to FIX purification). Therefore, the available evidence suggests a potential elimination of TSE of the order of 7 logs.
- Immuno-affinity chromatography. The one product of interest to this assessment is produced in the Netherlands. There is no data available for potential TSE clearance for the immuno-affinity step; a similar step for FVIII is claimed to clear endogenous scrapie by 4.4 logs. In addition to the minimum of 6 logs contributed to the process by the pre-affinity chromatography steps, it is possible that significant amounts of TSE are removed by the nanofiltration at 15 nm which is used to enhance the product's viral safety^(15,16).

Summary

- *Current methodologies for the purification of FIX concentrates may be expected to eliminate about 7 logs of vCJD infectivity present in a plasma pool.*
- *This capacity should be adequate to assure the safety of FIX manufactured from plasma from the European countries listed above.*
- *Since the potential safety from vCJD of PCCs .can be expected to be less than for purified FIX, treaters should accelerate their efforts to ensure all haemophilia B patients are treated with pure FIX products.*
- *Since the safety of concentrates may be significantly enhanced through nanofiltration at 15 nm, this process step should be incorporated in all FIX purification methods. (Note – biochemical factors make this measure less feasible for FVIII.*
- *This assessment depends on whether the vCJD strain of TSE is similar in its biochemical properties – charge, solubility, etc. – to other TSEs which are cleared to a high extent during FIX purification.*

Questions have arisen about recombinant clotting factors that contain human albumin made from donors who may be at risk for vCJD. Currently, none of these products are made from plasma obtained from donors in countries that have identified cases of vCJD.

Conclusions

An epidemic of BSE is expected in several countries in Europe which currently contribute plasma for manufacture into haemophilia treatment products. The following are considerations for these countries:

1. **This epidemic is expected to peak over the next four to six years, and to result in a BSE incidence one to two orders of magnitude lower (10 to 100 times lower, for example) than the BSE epidemic in the U.K.**
2. **This epidemic may be associated with a low incidence of vCJD, particularly in France where the consumption of contaminated meat products from the UK make this donor population more susceptible than in other countries.**
3. **The expected incidence of vCJD may lead to a low titre of infectivity for this disease in plasma pools for fractionation.**
4. **Current knowledge on the behaviour of TSE agents suggests that manufacturing of FVIII and FIX concentrates should lead to the elimination of infectivity, assuming the infectivity is low in blood.**
5. **However, certain measures may currently enhance the capacity for elimination or carry a lower risk:**
 - **Use of factor VIII concentrates which are highly purified through multiple chromatographic techniques.**
 - **Use of FIX concentrates that have been nanofiltered as a final processing step.**
 - **Use of FIX concentrates in preference to PCCs in routine treatment.**
6. **The ability of plasma fractionation processes, including the techniques used to manufacture FVIII and FIX, to eliminate the agents associated with TSEs has been acknowledged by the FDA's current draft guidance which exempts European source plasma donors (with the exception of the U.K. and France) from deferral measures**

(16a)

Glossary of Terms

CJD	Creutzfeldt-Jakob disease
BSE	bovine spongiform encephalopathy
vCJD	variant Creutzfeldt-Jakob disease
OIE	World Organisation for Animal Health
SSC	Scientific Steering Committee to the European Commission
FDA	Food and Drug Administration
GSSS	Gerstmann-Sträussler-Scheinker Syndrome
TSEs	transmissible spongiform encephalopathies

References

1. Cousens SN, Zeidler M, Esmonde TF, De Silva R, Wilesmith JW, Smith PG, Will RG. Sporadic Creutzfeldt-Jakob disease in the United Kingdom: analysis of epidemiological surveillance data for 1970-96. *BMJ*. 1997;315(7105):389-395
2. Taylor DM, Fernie K, Reichl HE, Somerville RA (2000). Infectivity in the blood of mice with a BSE-derived agent. *J Hosp Infect* 46:78-79
3. Houston F, Foster JD, Ching A, Hunter N, Bostock CJ (2000) Transmission of BSE by blood transfusion in sheep. *Lancet* 356:999-1000
- 3a. Cervenakova L (2001) vCJD infectivity in blood of experimental mice. Presented at "The policies and science of prions and plasma workshop" Washington DC 23-24 October 2001
4. World Organisation for animal health (2000) Number of reported cases of BSE worldwide. Available at http://www.oie.int/eng/info/en_esbmonde.htm
5. European Commission (2000) Final opinion of the Scientific Steering Committee on the geographical risk of bovine spongiform encephalopathy (GBR) Adopted on 6/July/2000. Available on http://europa.eu.int/comm/food/fs/sc/ssc/out113_en.pdf
6. Kasper CK & Costa e Silva M (2000) World Federation of Haemophilia Registry of coagulation factor concentrates. Available at <http://www.wfh.org>
7. Agence Francaise de Securite Sanitaire des Produits de Sante (2000) Report – Revision of measures to minimising the risk of TSE transmission via blood products
8. Rohwer RG (1998) Experimental studies of blood infected with TSE agents. In: Proceedings of the fourth meeting of the FDA advisory committee on Transmissible Spongiform Encephalopathies: 18 Dec 1998. Available at <http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3484t1.pdf>
9. Brown P, Rohwer RG, Dunstan BC, MacAuley C, Gajdusek DC, Drohan WN (1998) The distribution of infectivity in blood components and plasma derivatives in experimental models of transmissible spongiform encephalopathy. *Transfusion* 38:810-6
10. Lee DC, Stenland CJ, Hartwell RC, Ford EK, Cai K, Miller JLC et al (2000) Monitoring plasma processing steps with a sensitive Western blot assay for the detection of prion protein. *J Virol Methods* 84:77-89
11. Foster PR, Welch AG, McLean C, Griffin BD, Hardy JC, Bartley A et al (2000) Studies on the removal of abnormal prion protein by processes used in the manufacture of human plasma products. *Vox Sang* 78: 86-95
- 11a. Petteway S (2001) Partitioning of transmissible spongiform encephalopathy (TSE) by plasma or biotechnology manufacturing processes. Presented at "The policies and science of prions and plasma workshop" Washington DC 23-24 October 2001

12. Drohan WN (1999) Removal of scrapie infectivity during the purification of factor VIII. In : Proceedings of Cambridge Healthtech Institute's fifth annual conference on "Blood safety and screening"
13. Heimburger VN, Schwinn H, Gratz P, Luben G, Kumpe G, Herchenhan B (1981) Factor VIII concentrate, highly purified and heated in solution (German) *Arzneimittel-Forschung* 31:619-22
14. Lee DC, Stenland CJ, Miller JLC, Cai K, Ford EK, Gilligan KJ, Hartwell RC et al. (2001) A direct relationship between partitioning of the pathogenic prion protein and transmissible spongiform encephalopathy infectivity during the purification of plasma proteins. *Transfusion* in press
- 14a. Baron H (2001) Plasma, prions, and production of therapies. Presented at "The policies and science of prions and plasma workshop" Washington DC 23-24 October 2001
15. Mertens K, Schotanus DC, Sprengels A, Tissing M, et al (1999) A novel immunopurified factor IX concentrate (Nonafact) prepared employing a monoclonal antibody that distinguishes between intact and cleaved factor IX. Presentation at the *Plasma Product Biotechnology Meeting, Daydream Island, Australia*. Available at <http://www.bo-conf.com/ppb99/abstracts/145.htm>
16. Tateishi J, Kitamoto T, Ishikawaw G, Manabe S (1993) Removal of causative agent of Creutzfeldt – Jakob disease (CJD) through membrane filtration method. *Membrane* 18:357-362
- 16a. Centre for Biologics Evaluation and Research (2001) Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob disease (vCJD) by Blood and Blood Products – draft guidance. Available on <http://www.fda.gov/cber/gdlns/cjdvcjd.pdf>

Acknowledgments

I thank Dr Dorothy Scott of the Office of Blood Research and Review of the Food and Drug Administration for invaluable discussion and advice. Dr. Bruce Evatt of the Centers for Disease Control, Atlanta, USA, and Dr. Paul Giangrande of the Oxford Haemophilia Centre, Oxford, U.K., kindly reviewed, edited, and enhanced the manuscript. Any misinterpretations of the available data on this difficult field are my own.

This document is intended to provide information only. The World Federation of Hemophilia does not engage in the practice of medicine and under no circumstances recommends particular treatment for specific individuals. In the case of vCJD and individual medical inquiries, the WFH suggests that further details should be sought from personal doctors or hemophilia centre staff.

World Federation of Hemophilia, 2001

World Federation of Hemophilia
 1425 René Lévesque Blvd West, Suite 1010, Montréal, QC, H3G 1T7, CANADA
 Tel: (514) 875-7944 • Fax: (514) 875-8916
 E-mail: wfh@wfh.org • Internet site: <http://www.wfh.org>