

**Draft Risk Assessment:  
Potential Exposure to the vCJD agent in United States  
recipients of Factor XI coagulation product  
manufactured in the United Kingdom**

**Center for Biologics Evaluation and Research  
U.S. Food and Drug Administration**

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## EXECUTIVE SUMMARY

In December 2003 the U.K. government announced that vCJD had likely been transmitted via blood transfusion to a 69 year-old patient that had died. This was followed by the announcement in July 2004 of a second presumptive case of transfusion-transmitted vCJD that had occurred in a patient that had displayed no symptoms of the disease and had died of other causes. Cases of variant Creutzfeldt-Jakob disease (vCJD) were first reported in humans in the U.K. in 1996 – and as of January 2005 over 170 cases have been reported worldwide. Variant CJD is a fatal neurodegenerative disease attributed to human infection with the agent of Bovine Spongiform Encephalopathy (BSE), most often transmitted by the consumption of beef products from infected cattle.

The probable transmission of vCJD via whole blood or blood components raised a similar possibility that plasma derivatives might also pose a risk of vCJD transmission. Accordingly, U.K. authorities recently notified some recipients of plasma derivatives that they might be at increased risk of vCJD. These products included coagulation factors VIII, IX, and XI, as well as antithrombin III, and intravenous immunoglobulins. The derivatives of concern were manufactured from plasma of U.K. donors between 1980 and late in 1999, when--consistent with a decision announced in 1998—U.K. manufacturers stopped using U.K. plasma. The last expiry date for any of the U.K. products was in 2001.

**Problem:** Some Factor XI made from U.K. plasma was used between 1989 and 1997 to treat relatively small number of patients participating in several Investigational New Drug (IND) studies in the U.S. No Factor XI product used in the U.S. was manufactured from a pool containing plasma from a donor diagnosed with variant CJD (that is, there were no known "implicated" lots). However, U.K. plasma donors are at a significantly higher risk for vCJD.

**Question addressed by risk assessment:** *Given the probable recent transmission of vCJD via transfusion of whole blood and component products, what is the risk to US recipients that received human plasma derived Factor XI product manufactured in the U.K.?*

### Results from the Model

The prevalence of vCJD in the U.K. population is estimated as 1 in 4,225 based on a surveillance study by Hilton, *et al* (2004). Therefore, the model assumes that there is nearly 100% likelihood that a plasma pool containing 20,000 donations will contain at least one donation from a vCJD-infected individual. Results from the model are presented in Table I. The intravenous (i.v.) ID<sub>50</sub> per single unit and per vial of Factor XI was estimated by the model. A single ID<sub>50</sub> is defined as exposure to an amount of infective material that causes infection in 50% of the population. Three scenarios were modeled to depict various plausible levels of utilization of FXI. Scenario 1 involves the treatment of a 60 kg individual prior to surgery with 50 units/kg, or a total of 3,000 units given to restore FXI levels to normal. FXI doses in the literature typically range from 20 – 50 u/kg, but doses as high as 15,000 u/patient have been administered in the postoperative setting, over a period of days. Scenario 2 and Scenario 3 assume a treatment

regimen consisting of 9,000 units, and 15,000 units of FXI, respectively. Clinical treatment under the three scenarios suggests patients may be exposed to vCJD i.v. ID<sub>50</sub> during the course of treatment that may pose a risk of causing infection. It is not possible to estimate the precise magnitude of risk faced by patients that received U.K.-manufactured FXI product.

**Table I – Potential exposure to vCJD agent i.v. ID<sub>50</sub> via Factor XI.** Results are expressed as per unit or vial of FXI. Hypothetical scenarios provide an estimate of the magnitude of exposure to vCJD agent i.v. ID<sub>50</sub> that might occur per surgery incident. A surgical incident includes prophylactic treatment prior to surgery and possibly several post-operative treatments with FXI.

Scenario	Quantity* Factor XI Utilized	Mean vCJD <sup>(1)</sup> i.v. ID <sub>50</sub>	5 <sup>th</sup> (1) percentile	95 <sup>th</sup> (1) percentile
<b>A single unit FXI</b>	1 u	$2 \times 10^{-5}$	$6.8 \times 10^{-7}$	$7.0 \times 10^{-5}$
<b>One vial FXI</b>	1,000 u	$2 \times 10^{-2}$	$6.8 \times 10^{-4}$	$7.0 \times 10^{-2}$
<b>Scenario 1:</b> Treatment 3,000 u	3,000 u	$6 \times 10^{-2}$	$2.1 \times 10^{-3}$	0.21
<b>Scenario 2:</b> Treatment 9,000 u	9,000 u	0.17	$6.2 \times 10^{-3}$	0.6
<b>Scenario 3:</b> Treatment 15,000 u	15,000 u	0.28	$1.0 \times 10^{-2}$	1.0

\*u - represents international units of Factor XI  
 (1) Estimates may have been rounded

## Conclusions

No U.K.-manufactured FXI product distributed in the US from 1989 to 1997 is known to have been manufactured from “implicated” plasma pools that were known to have contained plasma from a donor later diagnosed with vCJD. If the prevalence of vCJD in the U.K. is assumed to be 1/4,225, it is likely that most plasma pools used to manufacture FXI until 1998 could have contained a plasma donation from a person infected with vCJD. Although results of the model suggest that exposure may have occurred, it is not possible to provide a *precise* estimate of the vCJD risk to patients that may have used Factor XI manufactured in the U.K. in the 1990s.

## Background

### Factor XI

Factor XI is a clotting factor present in blood plasma that plays a role in the very early stages of the blood coagulation pathway. It is a precursor to plasma thromboplastin, which is one of the proteins that alters the shape of blood platelets and facilitates clotting. Factor XI is normally present at concentrations of 50-70 u/dl in human plasma.

Factor XI (FXI) deficiency is a rare bleeding disorder that was first described in the 1950s. Unlike other hemophilias, it is an autosomal bleeding disorder that affects both genders equally. Generally, bleeding with FXI deficiency is less severe than with hemophilias A and B and does not usually involve joints or muscles or spontaneous bleeding in those areas. ([http://www.hemophilia.org/bdi/bdi\\_types9.htm](http://www.hemophilia.org/bdi/bdi_types9.htm)). Factor XI deficiency is usually categorized as (1) severe or (2) partial. Those with severe deficiency have FXI levels below 15 u/dl and are at high risk of excessive bleeding if injured, or after surgery or dental extractions. Medical intervention that brings FXI levels to the 50 u/dl to 70 u/dl range is recommended prior to surgical procedures on severely deficient patients. Therapy can include infusion with fresh plasma, antifibrinolytic agents, or FXI preparations.

Factor XI manufactured in the U.K. between 1989 and 1997 was used by a small group of patients in several IND studies in the U.S. and this risk assessment estimates the potential exposure to vCJD agent via that product. Currently, there is no Factor XI product commercially licensed in the United States.

### I. Hazard Identification

The hazard identification portion of the risk assessment provides an in-depth overview and analysis of information from laboratory studies, epidemiological studies, the scientific literature, government reports and other credible or peer-reviewed sources of data that establish a causal relationship between the hazard and adverse effects on humans. To date, no epidemiological evidence suggests that vCJD has been transmitted by plasma derivative products.

A new human variant Creutzfeldt-Jakob disease (vCJD) was first described in the U.K. in 1996. As of January 2005, 171 cases have been reported including 157 in the U.K., 9 (not U.K.-acquired) in France, and single non-U.K. acquired cases in Ireland and Italy. In addition, single cases of vCJD in former long-time residents of the U.K. have occurred in Ireland, Canada, and the U.S.

Both vCJD and BSE belong to a class of diseases known as transmissible spongiform encephalopathies (TSEs). The leading theory is that the transmissible infectious agent is a proteinaceous infectious agent, or "prion," that originates in the misfolding of a ubiquitous protein (Prp) normally expressed in many cells. The altered PrP, known as PrP<sup>res</sup>, is highly stable and resistant to degradation by high heat and many chemical treatments commonly used to denature proteins. The incubation period for TSEs is long. For example, the mean incubation period for BSE in cattle (interval between first exposure to contaminated feed and onset of

illness) has been estimated at about 5 years, and that for blood-borne vCJD to exceed 10 years. Individuals become symptomatic with most forms of CJD only in the last few months of life, making early detection very difficult. Diagnostic tools can usually detect BSE in the later stages, usually in cattle more than 24 months old. Confirmation of vCJD requires postmortem examination of brain tissue to confirm diagnosis, but abnormal prion protein has been detected in antemortem tonsil biopsies early in clinical illness and archived appendices of two asymptomatic individuals one and two years prior to the onset of symptoms. There are currently no rapid tests available to detect the vCJD in its early stages or to detect the presence of TSE agents in blood.

### **I.A. Transmission of TSEs through transfusion of blood products in animal models**

Transmission of TSEs through the transfusion of blood or blood products has been demonstrated in animal models on multiple occasions. At least four studies reported transmission via blood transfusion in the same animal species: sheep experimentally infected with BSE (Houston *et al* 2000) and naturally infected with scrapie (Hunter *et al* 2002), and experimentally infected rodents (hamsters with scrapie and mice with a human TSE (Rohwer *et al* 2004, Brown *et al* 1999).

Brown, Rohwer, Taylor and others have attempted to estimate the amounts of infectivity present in blood, which generally fell between two and 20 icLD<sub>50</sub>/ml. A recent study of scrapie-infected hamsters concluded that more than 40% of the infectivity present in whole blood was associated with plasma (approximately 58% [Gregori L, *et al.* 2004].) The model uses the more conservative of the two outcomes and assumes that 58% of infectivity is associated with plasma.

### **I. B. Transfusion transmission of vCJD in the U.K.**

In December 2003 the U.K. government announced that vCJD had likely been transmitted via blood transfusion to a 69 year-old patient. The patient had received a transfusion of non-leucoreduced red blood cells in 1996 from a donor that died three years later of vCJD. This first case was followed by the announcement in July 2004 of yet another probable case of transfusion-transmitted vCJD that died of ruptured aortic aneurysm without signs of vCJD, but postmortem testing detected PrP<sup>Sc</sup> in spleen tissue and cervical lymph node.

It is possible that dietary exposure may have been responsible for the cases, however the probabilities for either or both of these two events are small. As Llewelyn *et al* (2004) pointed out in their publication discussing the first presumed transfusion-transmitted case “the age of the patient was well beyond that of most vCJD cases, and the chance of observing a case of vCJD in a recipient in the absence of transfusion transmitted infection is about 1 in 15,000 to 1 in 30,000.” The combined probability that two elderly patients in a small cohort of transfusion recipients—in an age group underrepresented among vCJD cases—both acquired infection from food, is remote.

The presumptive transmission of vCJD via by labile blood components raises the possibility that plasma derivatives may pose a risk. The U.K. authorities recently notified some recipients of plasma derivatives that they might be at increased risk of vCJD. These products included coagulation factors, as well as antithrombin III, and intravenous immunoglobulins. The derivatives of concern were manufactured from plasma of U.K. donors between 1980 and late in 1999, when--consistent with a decision announced in 1998—U.K. manufacturers stopped using U.K. plasma. The last expiry date for any of the U.K. products was in 2001. To date, no cases of vCJD have been detected in patients that have received human plasma-derived coagulation products from implicated lots made in the U.K.

The focus of this risk assessment is on the risk of vCJD for patients in the U.S. that received Factor XI manufactured in the U.K. in the 1990s.

## II. Hazard Characterization

The hazard characterization component (also known as dose-response) relates the information in the exposure assessment, which determines the dose, to the adverse consequence(s) such as infection, illness, etc., at the individual, subpopulation, or population level. Determining dose-response relationships are extremely complex and often difficult to accomplish because data are limited, especially exposure and outcome data for humans. Other factors such as characteristics of the hazard (e.g. strain, chemical make-up, etc.), route of introduction, genetics of exposed individuals, influence the dose-response relationship but are often difficult to characterize. Often in lieu of human data, animal data are used and appropriately extrapolated to estimate the dose-response relationship for humans. Another challenge is estimating the probability of infection when the exposure to TSEs is small and/or occurs repeatedly over a period of time. It is unknown whether there is a minimal amount of the agent, or threshold, that is needed to initiate infection in an individual. Furthermore, it is not known whether the effects of small multiple exposures over a period of time are cumulative and may result in infection and disease. Some risk assessments have made assumptions concerning the exposure and dose for TSE agent that leads to infection. For instance, the Det Norske Veritas (Feb 2004) blood products risk assessment assumes that exposure to infectivity, quantified in ID<sub>50</sub> units, is cumulative over the period of one year. The ID<sub>50</sub> is the common metric used to quantify the infectivity of transmissible spongiform encephalopathies (TSEs). One ID<sub>50</sub> is defined as the amount of infectious material or tissue that is necessary to initiate infection in 50% of the population. The route of exposure to TSE infectious material influences the efficiency of transmission of the disease and it has been shown that the intracerebral (i.c.) route (injection directly into the brain) is the most efficient mode, the intravenous (i.v.) route is approximately 5 to 10 times less efficient than the i.c. route.

In estimating the dose-response relationship for TSEs one could use a strict interpretation of the ID<sub>50</sub> and assume a linear relationship between exposure and infection. In such a case exposure to 1 ID<sub>50</sub> would suggest a 50% probability of infection, exposure to 0.1 ID<sub>50</sub> would suggest a 5% probability of infection, and so on. However, given the lack of information and high degree of uncertainty on the dose-response relationship for TSE agents it is plausible that low level exposures, even on a chronic basis, may not attain the threshold necessary to initiate infection in

humans. The conservative assumption is that low-level exposure to a TSE agent could potentially lead to infection.

### **III. Exposure Assessment**

Exposure assessment evaluates the routes of exposure to a hazard, the probability that exposure occurs and the amount of a hazardous agent to which a person or population may be exposed. This exposure assessment specifically addresses exposure to the vCJD agent that may have been present in Factor XI manufactured in the U.K. and administered to U.S. patients during a clinical study under an IND application. The administration of Factor XI, and thus the route of exposure, is intravenous and used in the clinical treatment of individuals prophylactically prior to surgery and after surgery to control bleeding.

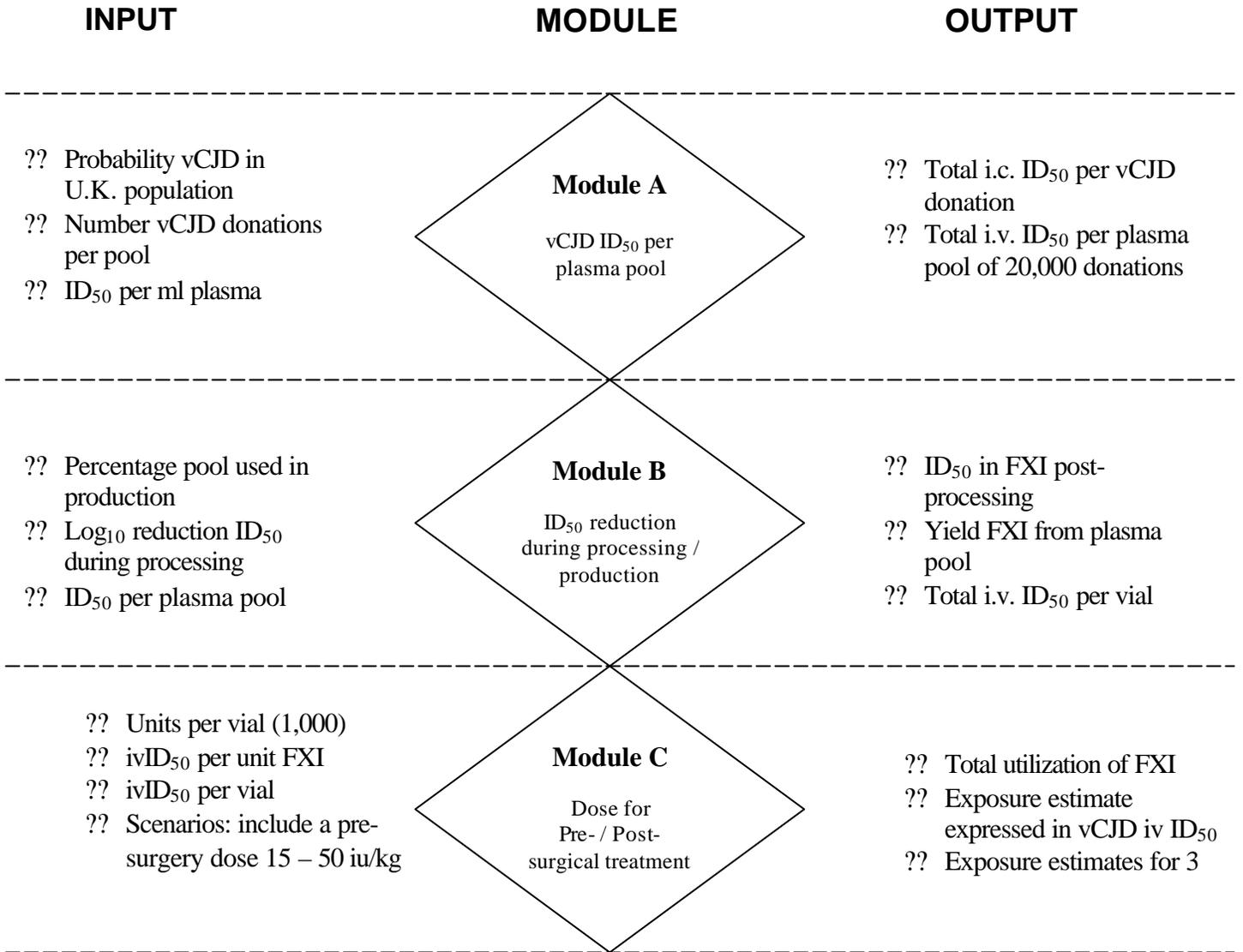
Pools consisting of 20,000 or more plasma donations collected from U.K. plasma donors were used as the starting material from which FXI was purified. Because of the relatively large number of donations per plasma pool and the prevalence of vCJD in the U.K. population it is possible that at least one or more plasma donations per pool may have been collected from asymptomatic individuals unknowingly infected with vCJD. The worst-case assumption is also that TSE infectivity is present in the blood of an incubating donor at any stage of incubation.

Assumption used in the model: The probability of at least one donation from a vCJD-infected individual being present in a plasma pool used to manufacture Factor XI in the U.K. in the 1990s is nearly 100%.

#### **Overview of Model**

Module A (vCJD ID<sub>50</sub> per plasma pool) uses estimates of vCJD prevalence in the U.K. population of 1 in 4,225 (Hilton *et al* 2004) to estimate the number of vCJD donations that could be present in a plasma pool of 20,000 donations. The output of this module is an estimate of the vCJD ivID<sub>50</sub> per plasma pool. Module B approximates the reduction of vCJD agent during manufacturing. The model estimates a reduction of between 0 and 4 log<sub>10</sub> reduction (10,000 fold) in the amount of agent with a most likely level of reduction of 2 log<sub>10</sub> reduction (100 fold). The output of this module is an estimate of the ID<sub>50</sub> per vial of Factor XI. Module C (Dose for Pre- / Post- surgical treatment) estimates utilization of FXI by patients. The outcomes are expressed in i.v. ID<sub>50</sub> per single unit FXI, per vial (1,000 units) and for three possible clinical treatment scenarios.

## Model of Exposure Assessment



### III. A. Total intravenous vCJD infectivity ( i.v. ID<sub>50</sub> ) per plasma pool

#### III. A.1. P<sub>vCJD</sub> - Probability of vCJD-infected individual in U.K. population

In the scientific literature estimates of the rate of incubating vCJD cases in the U.K. have been derived from two potential sources – (1) mathematical modeling and (2) surveillance testing of tissues such as tonsil and appendix. For this risk assessment we used the estimates derived from the tonsil and appendix studies since they are surveillance studies and would be expected to provide a more representative estimate of the potential rate of vCJD in the population. In vCJD patients the distribution of infectivity in tissues throughout the body is different than for other forms of CJD. Infectivity has been observed in the tonsil and spleen (Bruce *et al* 2001) as well as in the lymph nodes (Wadsworth *et al* 2001) of vCJD patients at the time of death. PrP<sup>Sc</sup> has also been observed in appendices of two asymptomatic vCJD individuals one and two years (but not 10 years) prior to the onset of symptoms (Hilton *et al* 1998).

The most recent surveillance results for the U.K. by Hilton *et al* (2004) indicated three appendectomy samples from different patients showed accumulation of prion protein in tonsil and/or appendix samples examined from a total of 12,674 individuals. For the risk assessment model we converted this 3 in 12,674 individuals sampled to an average rate of vCJD in the U.K. population of 1 in 4,225 ( 1 / 20,300 to 1 / 1,450 at 95% CI ). The data from tissue studies were then used to generate variables and parameters representing the potential number of vCJD donations that may be present in a batch of 20,000 recovered plasma donations used to manufacture Factor XI product in the U.K. in the 1990s. Assuming an average prevalence of 1 in 4,225 ( 1 / 20,300 to 1 / 1,450 at 95% CI ) there would be an estimated 4.7 (95% CI 0.98 - 13.8) potential vCJD donations per plasma pool of 20,000 donations (20,000 donations x 1 / 4,225 = 4.7).

Although the potential rate of vCJD is derived from surveillance studies there may be some limitations on the data because the number of samples tested is still relatively small (about 12,000) and even in the U.K. population, vCJD is a rare illness. Therefore, many caveats are given with these estimates. For instance, the survey may underestimate the number of cases in the population if PrP<sup>Sc</sup> is not detected in the tissues of vCJD-infected individuals until later in the disease process. It is also possible that the estimates derived from the tissue testing surveillance programs may in some way overestimate the risk. For example, the population surveyed for the tonsil and appendix studies may not be identical, e.g. in terms of age, to the plasma donor population. However, this estimate is selected as the most conservative estimate.

Assumption used in the model: An average prevalence of vCJD in the U.K. population was assumed to be 1 in 4,225 ( 1 / 20,300 to 1 / 1,450 - 95% CI ).

**Table II. Summary of surveillance testing of tissues including tonsil and appendix in the UK.**

Reference	Ages of population examined	Type tissue examined	Years tissue taken	Number of positives	Total samples examined	Rate per million (95% CI)

DRAFT

Ironside JW, et al. 2000	10–50 yr	Tonsils and appendices	1995-1999 (?2000)	0	>3,000	0
Hilton DA, et al. 2002	10–50 yr	Tonsils and appendices	1995-1999	1 appendix	8,318	
Hilton DA, et al. 2004	20 – 29 yrs	Tonsils and appendices	1995 - 1999	3 appendices	12,674 appendices	237/million (49–692 per million)

**III. A.2.  $D_{T_{pool}}$  - Total number of donations per pool**

Assumption used in the model: Factor XI was manufactured from a pool of approximately 20,000 recovered plasma donations.

**III. A.3.  $D_{vCJD}$  - Total number of vCJD donations per pool**

The estimate in the model of the total number of donations from individuals incubating vCJD that may be present in a pool of 20,000 plasma donations used to manufacture Factor XI was estimated from surveillance studies that tested lymphoreticular tissue from patients in the U.K. for the presence of vCJD agent. Surveillance studies testing for the presence of prion protein in tonsil and appendectomy samples from U.K. health clinics identified a total of 3 prion protein positive appendix samples from a total of 12,674 individuals tested (Hilton *et al* 2004). These testing results for appendices and tonsils suggest a potential prevalence of 1 positive vCJD case per 4,225 individuals in the U.K. Hilton *et al* (2004) suggest that an average of 237 vCJD infections per million individuals with a 95% CI of 49 to 692 vCJD cases per million.

Given the potential vCJD prevalence of 1 case per 4,225 individuals in the U.K. from Hilton *et al.* (2004) it is likely that there is nearly a 100% probability that one or more donations from vCJD infected individuals will be present in each pool. The model represents the uncertainty of the estimated number of vCJD donations per plasma pool using a statistical distribution.

Assuming an average prevalence of 1 in 4,225 ( 1 / 20,300 to 1 / 1,450 at 95% CI ) there would be an estimated 4.7 (95% CI 0.98 - 13.9) potential vCJD donations per plasma pool of 20,000 donations (20,000 donations x 1 / 4,225 = 4.7). The model assumed all donations were comparable in volume and there were no partial donations; all partial donations were rounded to the nearest whole number.

Assumption used in the model: The number of vCJD donations per pool is represented by a triangular distribution that assumes a minimum of 0 donations from vCJD individual will be present, it is most likely that as many as 2 donations (or an average of approximately 5 donations) from vCJD cases could be present, and a there is a small probability that a maximum

of 14 donations from vCJD individuals may be present in a plasma pool consisting of 20,000 donations.

### **III. A.4. $I_D$ - Estimated Total Infectivity (or i.c. $ID_{50}$ ) per vCJD donation**

The model estimates the total infectivity or i.c.  $ID_{50}$  per vCJD donation as a function of the volume of plasma per donation multiplied by the infectivity associated with plasma. The i.c.  $ID_{50}$  in plasma are calculated from the percentage of infectivity that is estimated to be present in plasma. The model expresses intracerebral (i.c.) vCJD infectivity in terms of the i.c.  $ID_{50}$  as the amount of tissue material, in this case blood or plasma, that when injected into the brain causes infection in 50% of the population. More details on the variables and parameters for this portion of the model are described below.

#### **III. A.4.a. $D_V$ - Amount of recovered plasma per donation**

**$D_V$**  - The amount of plasma recovered from a unit of whole blood is represented in the model by a single value point estimate of 200 milliliters

A unit of whole blood has a volume of approximately 450 milliliters. Recovered plasma is the plasma portion separated from the cellular portion of a unit of whole blood within hours of its collection.

Assumption used in the model: The model assumes that approximately 200 milliliters (mls) of plasma can be separated away from the blood cells.

#### **III. A.4.b. $I_{bl}$ - Infectivity of vCJD (or i.c. $ID_{50}$ ) present in infected blood per ml**

**$I_{bl}$**  - The potential amount of vCJD agent present in whole blood collected from a vCJD infected individual is represented in the model by a triangular statistical distribution of (0.1, 10,1000) i.c.  $ID_{50}/ml$  (minimum, most likely, and maximum).

Conclusions from two research groups arrive at somewhat similar estimates for the quantity of infectivity that might be present in the whole blood of mice and hamsters. Using a murine model and human CJD Brown *et al* (1999) found that infectivity in the blood of mice rose to as high as 100 infectious units (iu) per ml of buffy coat. Furthermore, Brown *et al* (1998, 1999) conducted experiments to determine the infectivity of buffy coat material and plasma but not red blood cells. Assuming that red blood cells retain approximately 25% of the infectivity of whole blood, then the infectivity present in whole blood could be estimated to be in the range of approximately 10 i.c.  $ID_{50}$  and 20 i.c.  $ID_{50}$  per ml. Cervenakova *et al* (2003) found levels of 20 – 30 infectious doses per ml ( 10-15 i.c.  $ID_{50}$  per ml) associated with buffy coat and plasma during incubating and symptomatic stages of the disease. Red blood cells were not found to be infectious. Transfusion of blood products using the hamster scrapie model by Rohwer suggests that addition of infectivity levels derived for individual blood components would generate a titer for whole blood of approximately 2 to 20 i.c.  $ID_{50}/ml$ .

Assumption used in the model: Whole blood collected from a vCJD-infected individual potentially carries a minimum of 0.1 i.c. ID<sub>50</sub> per ml, a most likely of amount of 10 i.c. ID<sub>50</sub> per ml, and a maximum of 1,000 i.c. ID<sub>50</sub> per ml. Attempts to identify vCJD infectivity titers in human blood have not been successful, but the assay sensitivity for vCJD in vitro and in animal models is limited (Bruce *et al* 2001 and Wadsworth *et al* 2001). Wadsworth *et al* estimated a limit of sensitivity of about 1,000 ID<sub>50</sub>/ml by their assay (Wadsworth, 2001).

**III. A.4.c. I<sub>PI-perc</sub>** - *Percentage infectivity associated with plasma (i.c.ID<sub>50</sub>/ml)*

**I<sub>PI-perc</sub>** - *The percentage of vCJD agent associated with the plasma portion of whole blood is represented in the model by a single value point estimate of 58%.*

Studies have shown that greater than 50% of transmissible spongiform encephalopathy agent present in whole blood is associated with plasma. Two sets of experiments (Gregori *et al.* 2004) using a hamster – sheep scrapie model showed that approximately 58% of infectivity in whole blood is associated with plasma.

Assumption used in the model: The model uses the more conservative of the two outcomes and assumes that 58% of infectivity is associated with plasma.

**III. A.4.d. I<sub>D</sub>** - *Total infectivity (or i.c.ID<sub>50</sub>) per vCJD recovered plasma donation*

Total i.c.ID<sub>50</sub> per vCJD donation is represented by the equation:

$$I_D = D_V \times I_{bl} \times I_{PI-perc}$$

In this case **I<sub>D</sub>** or total infectivity or i.c. ID<sub>50</sub> per vCJD donation equal to the volume of plasma per donation (**D<sub>V</sub>**) multiplied by the infectivity associated with plasma which is derived from the ID<sub>50</sub>s present in blood (**I<sub>bl</sub>**) times the percentage of infectivity present in plasma (**I<sub>PI-perc</sub>**). Total vCJD infectivity is expressed in terms of the ID<sub>50</sub> or the infectious dose needed to cause infection in 50% of the population.

Assumption used in the model: One ID<sub>50</sub> is the amount of material containing infectious agent that has a 50% probability of causing infection in an individual or population.

**III. A.4.e. A<sub>ic-iv</sub>** - *Adjustment for intravenous route of infection*

**A<sub>ic-iv</sub>** - *is represented in the model by a uniform distribution between 5 and 10. This variable provides an adjustment for the difference in efficiency between the intravenous and intracerebral routes of introduction in initiating infection.*

Studies with mouse-adapted scrapie agent suggest that the i.v. route of administration is approximately 10 times less efficient in causing infection than the intracerebral route (Kimberlin *et al* 1996). Brown *et al* (1999) used a mouse-adapted human TSE agent to show that i.v. injection of plasma was about seven times less efficient and i.v. injection of buffy coat approximately 5 times less efficient than were i.c. inoculations of the same materials in transmitting infection.

Assumption used in the model: Exposure to infectivity by the i.v. route is between 5 and 10 times less efficient at causing infection than introduction via the intracerebral route.

**III. A.5.  $I_{iv-pool}$  - Total intravenous infectivity or i.v.ID<sub>50</sub> per plasma pool of 20,000 donors**

The output of this component of the model, total i.v. ID<sub>50</sub> per plasma pool, is represented by the equation:

$$I_{iv-pool} = \frac{D_{vCJD} \times I_D}{A_{ic-iv}}$$

Total intravenous vCJD infectivity per plasma pool ( $I_{iv-pool}$ ) was calculated in the model by multiplying the total vCJD donations per pool,  $D_{vCJD}$ , by the total quantity of infectivity,  $I_D$ , (ID<sub>50</sub>) per donation and dividing the product by the adjustment for intravenous route of introduction,  $A_{ic-iv}$ .

**III.B. Total i.v. ID<sub>50</sub> per vial after processing / production of Factor XI**

This component of the model estimates the total i.v. ID<sub>50</sub> of vCJD infectivity that may be present in a vial of Factor XI that was manufactured in the U.K. and used in the U.S. under IND. Production of Factor XI in the U.K. involved the pooling of recovered plasma from a pool of approximately 20,000 donations. Some steps during production may be expected to remove vCJD infectivity, thereby reducing the amount in the finished product. There were two steps that reduced the amount of infectivity. First, the original starting plasma material was approximately 5,000 kg of plasma from which approximately 800 kg was removed and used to produce the Factor XI product. This means that only approximately 16% (800/5,000) of infectivity from the large pool of 20,000 donations remained. Finally, because of the processing steps used in the manufacture of Factor XI we assumed a most likely reduction in infectivity of 2 log<sub>10</sub> (or 99%). These two steps would result in a significant reduction in the amount of vCJD present in the Factor XI product from the U.K. However, the model assumes that infectivity would only be reduced and not eliminated. Therefore, some vCJD infectivity is predicted by the risk assessment model to have been present in vials of Factor XI produced in the U.K. and may have posed a risk of transmitting vCJD to patients that received the product.

**III.B.1.  $R_W\%$  - Percentage of pool used to manufacture Factor XI**

The initial starting amount of material from 20,000 recovered plasma donations in the U.K. was estimated to weigh 5,000 kg of which 800 kg (or 16%) of the material was removed and used to produce Factor XI. As stated earlier this step represents an 84% reduction in infectivity from the pool of 20,000 plasma donations.

Assumption used in the model: Approximately 16% of starting plasma material from 20,000 donations was used in the manufacture of FXI.

**III.B.1.a.  $W_{st}$  - Weight of starting product**

Assumption used in the model: Weight of starting product is represented in the model by a single value point estimate of 5,000 kg.

**III.B.1.b.  $W_m$  - 800kg portion removed and used to extract Factor XI**

$W_m$  - Portion of total product used in manufacturing is represented in the model by a single value point estimate of 800 kg.

Assumption used in the model: 800 kg of material was removed and used to produce Factor XI.

Portion used is represented by the equation and calculations:

$$R_W = W_m / W_{st}$$

$$R_W = 800 / 5,000$$

$$R_{W\%} = 0.16$$

The removal of 800 kg or 16% of the pooled product from the original starting material of 5,000 kg represents an 84% reduction in the amount of i.v. ID<sub>50</sub>s present in the original pool of 20,000 donations.

**III.B.2.  $R_{Log}$  - Log reduction in ID<sub>50</sub> during processing**

*Represented in the model by a triangular statistical distribution representing a reduction in ID<sub>50</sub> during processing of (0, 2,4) Log<sub>10</sub> i.v. ID<sub>50</sub>/ml (minimum, most likely, and maximum).*

TSE agents are highly resistant to conventional inactivation methods such as alcohol, other solvents, and heat denaturation. At least one step during the production of Factor XI has potential to reduce the amount of agent present by physical separation (partitioning). CBER has estimated by internal expert opinion that the level of removal of agent during processing corresponds to a reduction of a minimum of 0, a most likely reduction of 2 Log<sub>10</sub> ID<sub>50</sub>, and a maximum possible reduction of 4 Log<sub>10</sub> ID<sub>50</sub> per ml. Empirical verification of these estimated levels of reduction has not been done to our knowledge.

Assumption used in the model: Processing reduction is represented by a triangular statistical distribution representing a reduction in ID<sub>50</sub> during processing of (0, 2, 4) Log<sub>10</sub> i.v. ID<sub>50</sub>/ml (minimum, most likely, and maximum).

Assumption used in the model: The model assumes that infectivity is reduced but not entirely eliminated from plasma and the product during processing. Therefore, although the amount of ID<sub>50</sub> vCJD agent may be reduced the percentage of pools and vials containing the agent still remains the same.

**III.B.3.  $I_{pp}$**  - Total i.v.  $ID_{50}$  present per pool of Factor XI post-processing

$$I_{pp} = I_{iv-pool} \times R_W \times 1/R_{Log}$$

The total i.v. infectivity (i.v.  $ID_{50}$ s) present in processed product ( $I_{pp}$ ) is a function of the total infectivity present in the pool ( $I_{iv-pool}$ ) prior to processing steps that might reduce the amount of infectivity present in the final Factor XI product. The infectivity in the pool ( $I_{iv-pool}$ ) is multiplied by  $R_W$  because only 800kg out of the original 5,000 kg (or 16%) of starting plasma pool is used and multiplied by processing reduction steps ( $R_{Log}$ ), which are expected to reduce the infectivity in the final Factor XI product by a most likely of  $Log_{10} 2$  (or 99%), or by a maximum level of  $Log_{10} 4$  (or 99.99%).

**III.B.4.  $Y_{FT}$**  - Total yield of Factor XI from plasma pool

Factor XI is present in trace amounts in human plasma.

Assumption used in the model: The estimated the yield of FXI per kg plasma was approximately 150 to 180 units, subsequently the model estimates the total yield of Factor XI as 120,000 to 144,000 units per batch of 800 kg starting material. FXI was distributed in vials containing 1,000 units each. The term unit (u) is equivalent to the term international unit (i.u.).

The yield of Factor XI from the starting material was represented in the model by the equation:

$$Y_{FT} = W_M \times Y_{f-kg}$$

**III.B.4.a.  $Y_{f-kg}$**  - Yield of Factor XI per kg of plasma

Yield in the model was estimated to be between 150 to 180 units of FXI per kg plasma. This variable was represented in the model using a uniform distribution with a minimum yield of 150 units and a maximum yield of 180 units per kg of starting plasma material.

**III.B.5.  $V_{iu}$**  - Vial size or number of units per vial

It was assumed that each vial contained 1,000 units of factor XI.

**III.B.6.  $V_T$**  - Total number vials produced

The Factor XI product was aliquoted into vials with approximately 1,000 units each, and the total number of vials produced was estimated in the model by the simple equation:

$$V_T = Y_{FT} / V_{iu}$$

**III.B.7.  $I_{vial}$**  - Total i.v.  $ID_{50}$  per vial

The total i.v.  $ID_{50}$  present in each vial of Factor XI was estimated by dividing the total estimated i.v.  $ID_{50}$  per pool ( $I_{pp}$ ) of starting material by the total number of vials produced. Calculations used in the model are represented by the equation:

$$I_{\text{vial}} = I_{\text{pp}} / V_{\text{T}}$$

or including all component variables by the equation:

$$I_{\text{vial}} = \left[ \frac{D_{\text{vCJD}} \times D_{\text{V}} \times I_{\text{bl}} \times I_{\text{pl-perc}}}{A_{\text{ic-iv}}} \right] \times R_{\text{W}\%} \times 1/R_{\text{L}\log} / (W_{\text{m}} \times Y_{\text{f-kg}} / V_{\text{iu}})$$

Summary of variable names used above are:

$D_{\text{vCJD}}$  - Total number of vCJD donations per pool

$D_{\text{V}}$  - Amount of recovered plasma per donation

$I_{\text{bl}}$  - Infectivity of vCJD (or i.c.ID<sub>50</sub>) present in infected blood per ml

$I_{\text{pl-perc}}$  - Percentage infectivity associated with plasma (i.c.ID<sub>50</sub>/ml)

$A_{\text{ic-iv}}$  - Adjustment for intravenous route of infection

$R_{\text{W}\%}$  - Percentage of pool used to manufacture Factor XI

$R_{\text{L}\log}$  - Log reduction in ID<sub>50</sub>s during processing

$W_{\text{m}}$  - Portion of total product used in manufacturing(800 kg).

$Y_{\text{f-kg}}$  - Yield of Factor XI per kg of plasma

$V_{\text{iu}}$  - number FXI units per vial

### III.C. Utilization by patients with Factor XI deficiency undergoing Surgery

Factor XI normally circulates in the human bloodstream at a concentration of approximately 50 u/dl and has been observed by some researchers to be present at concentrations as high as 70 u/dl. Those with very severe Factor XI deficiency have < 15 unit per deciliter (u/dl) of blood. The commonly used treatment dose is 50 units per kg body weight. Individuals at risk for excessive bleed prior to surgery can receive prophylactic treatment at the recommended dose in anticipation of surgery. Because the half-life of FXI is approximately 52 hrs (Mannucci *et al* 1994), patients may need additional post-surgical maintenance treatments every 2 to 3 days to maintain therapeutic levels.

#### III.C.1. Total Dose for Pre- and Post-surgical treatment with Factor XI

Published data are available on the per surgical event utilization of Factor XI (Mannucci *et al* 1994, Aledort *et al* 1997) manufactured in the U.K. so that potential exposure to the vCJD agent can be estimated more accurately. It is difficult to determine the exact dose given to each patient without the patient medical record because only the dose per body weight of 50 u/kg is provided. The scenarios described below approximate the amount of factor XI given per patient to provide insight into the possible magnitude of risk. In this portion of the model we lay out three possible scenarios:

**Scenario 1** – Treatment of a 60kg individual with Factor XI (50 u/kg) once during or after surgery for a total patient dose of approximately 3,000 units.

**Scenario 2** - Treatment of a 60kg individual both pre- and post-surgery with a total of approximately 9,000 units of Factor XI.

**Scenario 3** - Treatment of a 60kg individual both pre- and post-surgery with a total of approximately 15,000 units of Factor XI. .

**III.C.1.a.  $D_{Pre}$  - Prior to major Surgery - doses of 50 u/kg given**

Assumption used in the model: The dosage prior to surgery is approximately 50 u/kg body weight. This dosage scheme is represented in the model with a point estimate.

$$D_{Pre} = \text{Dose (50 u/kg)} \times \text{Patient weight (kg)} \times \text{Number treatments}$$

**III.C.1.b.  $D_{Post}$  - Post-surgical maintenance of 50 u/kg every 2 - 3 days**

Assumption used in the model: The post-surgery maintenance dosage is assumed to be 50 u/kg given every two to three days. This dosing scheme is represented in the model with a point estimate.

$$D_{Post} = \text{Dose (50 u/kg)} \times \text{Patient weight (kg)} \times \text{Number treatments}$$

**III.C.1.c.  $D_T$  - Total Factor XI doses given per patient per surgical procedure**

The output is a sum of all doses of Factor XI given pre- and post-surgery to prevent or minimize bleeding by Factor XI deficient patients. The sum of doses is represented by the equation:

$$D_{Tu} = D_{Pre} + D_{Post}$$

**III.C.2. Scenario 1: Treatment 60 Kg individual**

A 60 Kg person receives one dose factor XI to minimize potential bleeding episodes at a concentration of 50u/kg would receive a total of approximately 3,000 units. Output is the estimated total units Factor XI received and estimated vCJD ID<sub>50</sub> received. This dosing regimen for one IND using U.K. manufactured factor XI in the United States is described in Aledort *et al* (1997). It should be noted that 12 of the patients in the study received 50 u /kg but one patient in the study received only 20 u / kg.

**III.C.3. Scenario 2: Treatment with 9,000 units Factor XI**

Assumption used in the model: During preparation and recovery from surgery the model assumes that a patient receives a total dose of 9,000 units Factor XI to minimize potential bleeding episodes. Output is the estimated total units Factor XI received and estimated vCJD ID<sub>50</sub> received.

Scenario 2 is similar to amounts of Factor XI given in three dosing regimens given at 50 units per kg body weight -one treatment given prior to surgery and two treatments given during post-operative recovery (Mannucci *et al* 1994).

**III.C.4. Scenario 3: Treatment with 15,000 units Factor XI**

Assumption used in the model: During preparation and recovery from surgery the model assumes that a patient receives a total dose of 15,000 units Factor XI to minimize potential bleeding episodes. This scenario may involve a 60 kg individual that receives approximately five treatments both prior to and following surgery at a dose of 50 u/kg.

Output Scenario 3: Estimated Total units Factor XI received and estimated vCJD ID<sub>50</sub> received.

## **IV. Risk Characterization**

The risk characterization section of the risk assessment integrates the hazard identification, hazard characterization and the exposure assessment components to arrive at estimates of the risks posed by a hazard.

In this risk assessment data for hazard characterization are lacking, so we could not develop a human vCJD dose-response. The dose-response relationship provides information needed to use the exposure (dose) assessment results to estimate the probability of adverse responses including infection, illness or mortality – based on assessment of exposure (dose) to the hazard. Many TSE models and risk assessments, including our model, use the ID<sub>50</sub>, or amount of material that leads to infection in 50% of the population, as a semi-quantitative estimate of the amount of TSE agent. It is possible to interpret the ID<sub>50</sub> as representing a linear dose-response relationship or linear relationship between exposure and the probability of infection. In such a case exposure to 1 ID<sub>50</sub> would suggest a 50% probability of infection, exposure to 0.1 ID<sub>50</sub> would suggest a 5% probability of infection, and so on. Given the limited data available, any extrapolation or interpretation has limited utility in actually estimating clinical outcomes such as infection and illness. Therefore, any estimate of the risk based on estimates of exposure to the vCJD agent through use of Factor XI will be imprecise and extremely uncertain.

### **IV.A. The Model**

This risk assessment and model link the available scientific and epidemiological data together to mathematically approximate the processes (predicted presence of vCJD in U.K. population, manufacturing, reduction of vCJD agent, and patient utilization) leading to exposure of US patients to vCJD agent present in U.K.-manufactured Factor XI. A summary of the variables, parameters and equations used in the model were described in Section III. Exposure Assessment and a summary of the variables and equations are provided in Appendix A. Where data were not available, simplifying assumptions were used in the model and are detailed in the preceding documentation. Assumptions used in the model are presented in tabular form in Appendix B.

The model was run using @Risk software package (Palisades Corp, NY) to conduct the Monte Carlo analysis. Simulations of 10,000 iterations were run.

The model provided predictions of estimated exposure to the vCJD agent in the form of intravenous (i.v.) ID<sub>50</sub> in patients treated with U.K.-manufactured Factor XI. Because an accurate dose-response relationship (or hazard characterization) for vCJD exposure and the probability of human illness has not been developed it is not possible to predict with any accuracy the probability of vCJD infection and illness in an individual exposed to the agent.

#### **IV. B. Results from the Model**

Results from the model are presented below in Table 4.1. The intravenous (i.v.) ID<sub>50</sub> per single unit and per vial (of 1,000 units) of Factor XI was estimated by the model. Additionally, results that predict exposure for 3 scenarios depicting various levels of utilization that approximate clinical treatment with FXI are presented.

**Table I – Potential exposure to vCJD agent i.v. ID<sub>50</sub> via Factor XI.** Results are expressed as per unit or vial of FXI. Hypothetical scenarios provide an estimate of the magnitude of exposure to vCJD agent i.v. ID<sub>50</sub> that might occur per surgery incident. A surgical incident includes prophylactic treatment prior to surgery and possibly several post-operative treatments with FXI.

Scenario	Quantity* Factor XI Utilized	Mean vCJD <sup>(1)</sup> i.v. ID <sub>50</sub>	5 <sup>th</sup> (1) percentile	95 <sup>th</sup> (1) percentile
<b>A single unit FXI</b>	1 u	$2 \times 10^{-5}$	$6.8 \times 10^{-7}$	$7.0 \times 10^{-5}$
<b>One vial FXI</b>	1,000 u	$2 \times 10^{-2}$	$6.8 \times 10^{-4}$	$7.0 \times 10^{-2}$
<b>Scenario 1:</b> Treatment 3,000 u	3,000 u	$6 \times 10^{-2}$	$2.1 \times 10^{-3}$	0.21
<b>Scenario 2:</b> Treatment 9,000 u	9,000 u	0.17	$6.2 \times 10^{-3}$	0.6
<b>Scenario 3:</b> Treatment 15,000 u	15,000 u	0.28	$1.0 \times 10^{-2}$	1.0

\*u - represents international units of Factor XI

(1) Estimates may have been rounded

#### IV. C. Sensitivity Analysis

Sensitivity (or importance) analysis is a process of varying the value of variables in the model to identify those with the greatest influence on the estimated risk outcome(s). A simple sensitivity analysis of the Factor XI model suggests that the estimated number of vCJD donations per plasma pool ( $D_{vCJD}$ ) had the greatest influence on the final risk estimate. In the model  $D_{vCJD}$  was bounded by a minimum value of 0 vCJD donation per pool, a most likely estimate of 2 (average of approximately 5) vCJD donations per pool and a maximum value of 14 vCJD donations per pool. The second most influential factor in the model was the log reduction of vCJD agent ( $R_{Log}$ ) during processing and manufacture of Factor XI product. For  $R_{Log}$  it was assumed that the minimum level of reduction was 0, the most likely level of reduction was  $2 \log_{10}$  and the maximum level of reduction in agent that could occur was  $4 \log_{10}$ .

#### IV. D. Uncertainty and Data Gaps

Uncertainty arises from the absence of information or availability of limited information. In our probabilistic model statistical distributions are used to represent the uncertainty of the information used in the model. We express the uncertainty of the final risk estimates generated from the model using a mathematical mean (average) of exposure in  $ID_{50}$  units and the 5% and 95% confidence intervals for each estimate. The uncertainty for the risk estimates generated from by this FXI risk assessment model is significant and decision makers should use the results with caution. In the future, additional research and information may be substituted for assumptions or used to improve estimates for the individual parameters and ultimately improve the precision of the final risk estimates generated by the model.

Even considering the associated uncertainty of estimated risks, risk assessment provides a best estimate of risk based on the current and known information. It is still a useful tool that informs the science-based decision making process. It can identify data gaps and research priorities where additional research and information would have the greatest impact on enhancing the final risk estimates. Results from the sensitivity analysis in Section IV.C. indicated that the risk assessment results are highly dependent upon

- ?? Estimation of the prevalence of vCJD in the U.K., and in turn, the parameter for vCJD donations per plasma pool ( $D_{vCJD}$ ), and
- ?? Log reduction of vCJD agent ( $R_{Log}$ ) during the manufacturing process

Improved data and surveillance studies on the estimated vCJD prevalence in the U.K. would enhance the precision of the estimated number of incubating donors that would contribute to a plasma pool. Data from laboratory studies could improve the estimate of the reduction of vCJD during manufacturing. The modeled estimates were based upon levels of reduction seen for a manufacturing step that was similar in some but not all respects to that used for FXI.

No data are available on the level of infectious units or  $ID_{50}$  units present in the bloodstream of vCJD infected individuals at the time of blood donation. The model extrapolates an estimate of the level of vCJD agent that might be present in human blood based on data from several animal models. However, the presence and level of agent present in an infected individual at the time of blood donation could differ from our assumption and this adds to the uncertainty of the risk assessment outcomes.

The model estimates exposure to the vCJD agent in the form of intravenous  $ID_{50}$  units. Data are not available to estimate the probability of various clinical outcomes, such as infection or illness that might be predicted to arise from exposure to a particular level of agent. Therefore, we did not estimate a probability of infection or illness in our model. However, a meaningful dose-response model will need to be generated for vCJD exposure in humans to estimate the probability of adverse clinical outcomes for humans. Until then, estimates of the probability of vCJD infection or illness arising from exposure to the agent are extremely uncertain and should be viewed with caution.

## IV. E. Conclusions

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Potential exposure to vCJD agent present in Factor XI manufactured in the U.K. and used during investigational studies in the U.S. from 1989 to 1997 was estimated in this probabilistic risk assessment.

Although no U.K.-manufactured FXI product distributed in the U.S. during the 1990s is known to have been manufactured from “implicated” batches that contained donations from an individual(s) later diagnosed with vCJD, it is possible that FXI product manufactured from U.K. plasma in the 1990s may have been manufactured from plasma pools that contained a plasma donation(s) from an individual that was incubating vCJD. To date, no recipients of plasma derivatives in the U.K. or elsewhere have been diagnosed with vCJD. However, given the potentially prolonged incubation times for human TSEs, it is still theoretically possible that such transmissions occurred are yet to be identified.

## Appendix A

### Summary of Model Components

Variable name		Input	Numerical input / output
<b>A. Total intravenous vCJD infectivity ( i.v. ID<sub>50</sub> ) per plasma pool</b>			
<b>Inputs</b>			
A.1.	<i>Probability individual has vCJD in U.K. population</i>	<b>P<sub>vCJD</sub></b>	1 / 4,225 (5% CI = 1 / 1,452) (95% CI = 1 / 20,280)
A.2.	<i>Total number of donations per pool</i>	<b>D<sub>T</sub></b>	20,000 donations
A.3.	<i>Total number of vCJD donations per pool</i>	<b>D<sub>vCJD</sub></b>	<u>Triangular distribution</u> Minimum = 0 donations Most likely = 2 donations (Mean ~5) Maximum = 14 donations
A.4.a.	<i>Amount of recovered plasma per donation</i>	<b>D<sub>V</sub></b>	200 mls
A.4.b.	<i>Infectivity of vCJD in infected blood per ml</i>	<b>I<sub>bl</sub></b>	<u>Triangular distribution</u> Minimum = 0.1 ID <sub>50</sub> Most likely = 10 ID <sub>50</sub> Maximum = 1,000 ID <sub>50</sub>
A.4.c.	<i>Percentage infectivity in plasma (ID<sub>50</sub>/ml)</i>	<b>I<sub>pl-perc</sub></b>	58%
A.4.e.	<i>Adjustment for intravenous route of infection</i>	<b>A<sub>ic-iv</sub></b>	<u>Uniform distribution</u> Minimum = 5 Maximum = 10
<b>Outputs</b>			
A.4.d.	<i>Total infectivity (or i.c.ID<sub>50</sub>) per vCJD donation</i>	<b>I<sub>D</sub> = D<sub>V</sub> × I<sub>bl</sub> × I<sub>pl-perc</sub></b>	
A.5.	<i>Total i.v. ID<sub>50</sub> per plasma pool of 20,000 donors</i>	<b>T<sub>iv-pool</sub> = <math>\frac{D_{vCJD} \times I_D}{A_{ic-iv}}</math></b>	
Summary of output at this point in the model:			
$T_{iv-pool} = \frac{D_{vCJD} \times D_V \times I_{bl} \times I_{pl-perc}}{A_{ic-iv}}$			

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<b>B. Total i.v. ID<sub>50</sub> per vial after processing / production of Factor XI</b>			
<b>Inputs</b>			
B.1.a.	<i>Weight of starting product</i>	$W_{st}$	5,000 kg
B.1.b.	<i>Portion removed and used to extract Factor XI</i>	$W_m$	800kg
B.1.	<i>Percentage of pool in manufacture Factor XI</i>	$R_{W\%} = W_m / W_{st}$	0.16
B.2.	<i>Log reduction in ID<sub>50</sub>s during processing</i>	$R_{Log}$	<u>Triangular distribution</u> Minimum = 0 log <sub>10</sub> Most likely = 2 log <sub>10</sub> Maximum = 4 log <sub>10</sub>
B.4.a.	<i>Yield of Factor XI per kg of plasma</i>	$Y_{f-kg}$	<u>Uniform distribution</u> Minimum = 150 iu/kg Maximum = 180 iu/kg
B.5.	<i>Vial size or # iu per vial</i>	$V_{iu}$	1,000 iu
<b>Outputs</b>			
B.3.	<i>Total ID<sub>50</sub> in Factor XI post-processing</i>	$I_{pp} = I_{iv-pool} \times R_W \times 1/R_{Log}$	
B.4.	<i>Total yield of Factor XI from plasma pool</i>	$Y_{FT} = W_m \times Y_{f-kg}$	
B.6.	<i>Total number vials and vial size produced</i>	$V_T = Y_{FT} / V_{iu}$	
B.7.	<i>Total ID<sub>50</sub> per vial</i>	$I_{vial} = I_{pp} / V_T$	
Summary of output at this point in the model:			
$I_{vial} = \left[ \frac{D_{vCJD} \times D_v \times I_{bl} \times I_{pl-perc}}{A_{ic-iv}} \right] \times R_W \times 1/R_{Log} \quad / \quad (W_m \times Y_{f-kg} / V_{iu})$			

<b>B. Total Utilization of Factor XI</b>			
<b>Inputs</b>			
C.1.a.	<i>Prior to major Surgery - dose 50 iu/kg given</i>	$D_{Pre}$	50 u/kg
C.1.b.	<i>Post-surgical maintenance of dose 50 iu/kg given every 2 - 3 days</i>	$D_{Post}$	50 u/kg
<b>Output</b>			
C.1.c.	<i>Total Utilization of Factor XI</i>	$D_{Tu} = D_{Pre} + D_{Post}$	

## Appendix B

### Summary of Model Assumptions

Section	Variable and description	Assumptions used in the model
III.	Not applicable	The probability of at least one donation from a vCJD-infected individual being present in a plasma pool used to manufacture Factor XI in the U.K. is nearly 100%.
III. A.1.	$P_{vCJD}$ - Probability individual has vCJD in U.K. population	An average prevalence of vCJD in the U.K. population was assumed to be 1 in 4,225.
III. A.2.	$D_{Tpool}$ - Total number of vCJD donations per pool	Production of Factor XI included the pooling of plasma donations recovered from whole blood from approximately 20,000 donations
III. A.3.a.	$D_V$ - Amount of recovered plasma per donation	The model assumes that approximately 200 milliliters (mls) of plasma can be separated away from the blood cells.
III. A.3.b.	$I_{bl}$ - Infectivity of vCJD (or i.c.ID <sub>50s</sub> ) present in infected blood per ml	Whole blood collected from a vCJD-infected individual potentially carries a minimum of 0.1 i.c. ID <sub>50</sub> per ml, a most likely of amount of 10 i.c. ID <sub>50</sub> per ml, and a maximum of 1,000 i.c. ID <sub>50</sub> per ml.
III. A.3.c.	$I_{pl-perc}$ - Percentage infectivity associated with plasma (i.c.ID <sub>50/ml</sub> )	The model uses the more conservative of the two outcomes and assumes that 58% of infectivity is associated with plasma.
III. A.3.d.	$I_D$ - Total infectivity (or i.c.ID <sub>50</sub> ) per vCJD recovered plasma donation	One ID <sub>50</sub> is the amount of material containing infectious agent that has a 50% probability of causing infection in an individual or population.
III. A.3.e.	$A_{ic-iv}$ - Adjustment for intravenous route of infection	Exposure to infectivity by the i.v. route is between 5 and 10 times less efficient at causing infection than introduction via the intracerebral route.
III.B.1.	$R_{W\%}$ - Percentage of pool used to manufacture Factor XI	Approximately 16% of starting plasma material from 20,000 donations was used in the manufacture of FXI.
III.B.1.a.	$W_{st}$ - Weight of starting product	Weight of starting product is represented in the model by a single value point estimate of 5,000 kg.
III.B.1.b.	$W_m$ - 800kg portion removed and used to extract Factor XI	800 kg of material was removed and used to produce Factor XI.
III.B.2.	$R_{Log}$ - Log reduction in ID <sub>50s</sub> during processing	Processing reduction is represented by a triangular statistical distribution representing a reduction in ID <sub>50s</sub> during processing of (0, 2,4) Log <sub>10</sub> i.v. ID <sub>50/ml</sub> (minimum, most likely, and maximum).
		The model assumes that infectivity is reduced but not entirely eliminated from plasma and the product during processing. Therefore, although the amount of ID <sub>50</sub> vCJD agent may be reduced the percentage of pools and vials containing the agent still remains the same.
III.B.4.	$Y_{FI}$ - Total yield of Factor XI from plasma pool	The yield of FXI per kg plasma was approximately 150 to 180 units, subsequently the model estimates the total yield of Factor XI as 120,000 to 144,000 units per batch of 800 kg starting material. FXI was distributed in vials of 1,000 units each.

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