FDA DRAFT Risk Assessment: Potential Exposure to the variant Creutzfeldt-Jakob Disease Agent in United States Recipients of Factor XI Coagulation Product Manufactured in the United Kingdom

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EXECUTIVE SUMMARY

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal neurodegenerative disease attributed to human infection with the agent of bovine spongiform encephalopathy (BSE) and is most often transmitted by the consumption of beef products from infected cattle. Cases of vCJD were first reported in humans in the UK in 1996, and as of August 2006, 195 cases have been reported worldwide, with 162 cases in the UK. Since December 2003, there have also been three reports in the United Kingdom (UK) of probable vCJD transmission by red blood cell transfusions. The donors were healthy at the time of donation, but later developed vCJD. Of the three red blood cell recipients who probably became infected with the vCJD agent after transfusion, two developed vCJD and died from the disease. The third died of an unrelated illness

The probable transmission of vCJD via red blood cell transfusions raised the possibility that plasma derivatives might also pose a risk of vCJD transmission, although there have as of yet been no reported cases of vCJD in any recipients of plasma derivatives in the UK, where the risk is considered greatest, or elsewhere. UK authorities have notified physicians in the UK and their patients who received plasma derivatives made from plasma from UK donors, about the potential for risk of vCJD from these products. These products included coagulation factors VIII, IX, and XI, as well as antithrombin III, and intravenous immune globulins. The derivatives of concern were manufactured from plasma collected from UK donors from 1980 through 1997. In 1998 UK manufacturers stopped using UK plasma. The last expiry date for any of the UK products was in 2001.

Problem: Some Factor XI (FXI) made from UK plasma was used between 1989 and 2000 to treat a small number of patients, estimated to be 50 or fewer, who participated in several Investigational New Drug (IND) studies at various sites in the US. No FXI product used in the US was manufactured from a pool containing plasma from a donor diagnosed with vCJD (that is, there were no known "implicated" lots). However, the UK population, including UK plasma donors, is at a considerably higher risk for vCJD than the US population due to food chain exposure to BSE, although the estimates of risk vary widely.

Question addressed by risk assessment: *Given the probable recent transmission of vCJD via transfusion of red blood cells, what is the estimated range of potential risk to US recipients who received a human plasma derived FXI product manufactured from UK plasma?*

FDA presented the “Draft Risk Assessment: Potential Exposure to the vCJD Agent in United States Recipients of Factor XI Coagulation Product Manufactured in the United Kingdom” at the February 8, 2005 meeting of the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) for review and comment. The risk assessment computer model predicted that recipients of UK manufactured FXI may have potentially been exposed to the vCJD agent, and although the risk of possible vCJD infection could potentially be significant, the actual risk is highly uncertain and could be low. On October 31, 2005 FDA sought advice and discussion on several risk assessment model inputs for plasma derivatives and potential vCJD risks. FDA has incorporated comments and advice provided by the TSEAC at the February 8, 2005 and October 31, 2005 meetings, and by FDA staff and Special Government Employee peer reviewers to develop this revised risk assessment (revisions summarized in Table 1 of the Risk Assessment) of potential vCJD risks for US recipients of FXI manufactured from UK donor plasma.

Results from the Model

While the risk assessment suggests that the possibility of exposure to vCJD in FXI could be potentially significant the actual risk is highly uncertain. One important, highly uncertain parameter in driving the risk assessment results is what estimate is used for vCJD prevalence in the UK. The prevalence of vCJD in the UK population was estimated in the model using two different approaches. The first approach to estimating vCJD prevalence in the UK was from a study based on epidemiological modeling that was derived using actual reported vCJD cases in the UK and an estimate, based on the epidemic, of future vCJD cases (Clarke and Ghani, 2005). Several factors used in epidemiologic modeling approaches are difficult to quantify and add uncertainty to the final estimated number of future vCJD cases. These factors include: the intensity of human exposure to the BSE agent, incubation period, time of infection, and whether illness will develop in individuals who are not homozygous for methionine at codon 129 of PrP. All cases of vCJD to date have occurred in individuals who are homozygous for methionine at this location. Our calculations, based on results from Clarke and Ghani (2005), yielded an estimate of approximately 4 vCJD cases per million. Running the model with this vCJD case prevalence estimate of 4 per million produces an estimate suggesting that, on average, there is a 1.6% likelihood that a plasma pool of 20,000 donations will contain at least one donation from a vCJD-infected individual. Therefore, on average, 98.4% of the time the model predicts the product as administered will contain no vCJD agent and this is reflected in the (0 – 0) values for the 5^{th} and 95^{th} percentiles shown for the lower prevalence estimate results in Table I (below).

However, it is possible that the prevalence of vCJD in the UK is higher than the estimate based on the epidemiological model-based approach noted above. This could happen if there are people infected who never develop the disease (but can still spread the infection) or if some individuals take extremely long to become ill. Therefore, a second approach to estimating vCJD infection prevalence was used based on a relatively small tissue surveillance study by Hilton, *et al* (2004), which tested stored tonsil and appendix tissues from the UK for accumulation of prion protein. It yielded a much higher estimate of 1 in 4,225 (237 infections per million). This study was not controlled using tissues from a non-BSE exposed population, and false positive findings or interpretations from the tissue samples are possible. It is also not known whether the staining of appendicial tissues used in this study is a reliable marker for vCJD pre-clinical infection or for an individual's capability to transmit the infection through blood donation. However, while unconfirmed, the findings from this study provide a higher prevalence estimate and therefore should also be considered. Use of these data as the basis for a vCJD infection prevalence estimate which is then used in the model produces a significantly higher estimate suggesting that, on average, if it were correct, there could be a 50% likelihood that a plasma pool containing 20,000 donations will contain at least one donation from an individual whose blood contains the vCJD agent. (see Sections III. A.1.a.iii and III. A. 1. b. below for a more complete discussion of some of the uncertainties in these prevalence estimates).

Table I – Mean Potential vCJD Risk per Person per FXI Treatment Scenario

		MODEL OUTPUT USING LOWER PREVALENCE ESTIMATE *vCJD Case Prevalence from epidemiological modeling ~4 per million (Clark and Ghani, 2005)*	***MODEL OUTPUT USING HIGHER PREVALENCE ESTIMATE*** *vCJD Infection estimate from tissue surveillance study 1 in 4,225 (Hilton et al 2004)*
Scenario	**Quantity* FXI Utilized**	**Mean potential vCJD risk per person **** (5^{th}, 95^{th} perc)	**Mean potential vCJD risk** per person** (5^{th}, 95^{th} perc)
Scenario 1: Treatment 3,000u	3,000 u	1 in 643 **(**0 - 0**)**	1 in 17 **(**0 – 1 in 3.5**)**
Scenario 2: Treatment 9,000 u	9,000 u	1 in 214 **(**0 - 0**)**	1 in 5.6 **(**0 – 1 in 1.2**)**
Scenario 3: Treatment 15,000 u	15,000 u	1 in 129 **(**0 - 0**)**	1 in 3.4 **(**0 – 1 in 1**)**

*u - represents units of FXI
**Mean potential vCJD risk per treatment scenario – the risk of potential vCJD infection based on animal model dose-response information.

Results from the model are presented in **Table I**. The mean potential vCJD risk per person per treatment scenario is based on data derived from rodent animal models. Although we assume that results from the animal model are similar for humans, it is uncertain whether this is the case.

Three scenarios were modeled to depict various plausible levels of utilization of FXI. FXI doses in the literature typically range from 20 – 50 u/kg, and total doses as high as 15,000 u/patient have been administered as the sum of several doses during the postoperative setting, over a period of days. Therefore, Scenario 1 involves the treatment of a 60 kg individual with 20 – 50 u/kg, or a total of 3,000 units given to restore FXI levels to normal. Scenario 2 and Scenario 3 assume a treatment regimen consisting of 9,000 units, and 15,000 units of FXI, respectively.

The model estimates risk ranges from a high in Scenario 3, using the high prevalence estimate, with a mean estimated per person (per treatment course) risk of vCJD infection of 1 in 3.4. The lower end of the range of risk is illustrated in Scenario 1, at the lower prevalence estimate which is based on the current epidemic of disease, with a mean estimated per person (per treatment course) risk of vCJD infection of 1 in 643. It can be seen that in this model that the prevalence estimate may determine whether anyone receiving this product may or may not have been likely to be

exposed to a vCJD risk. It is simply not known at present which prevalence estimate may more accurately reflect the true prevalence of vCJD in the UK.

Readers may notice that the 5^{th} and 95^{th} percentile intervals for all of the model outputs using the lower prevalence estimate are from 0 to 0 meaning that the chance of an infected donor donating to a plasma pool would be an infrequent event. This means that at least ninety five percent of the time the model estimates the risk to be zero because vCJD agent was not present in FXI product vials used during treatment. However, the model predicts that 1.6% of the time the exposure to vCJD may be greater than zero. Although the model suggests that exposure of FXI recipients may have occurred, it is not possible at this time to determine if exposure did in fact occur because of the large variability and uncertainties in the data used in the model.

Conclusions

No UK-manufactured FXI product used in the US under IND from 1989 to 2000 was manufactured from "implicated" plasma pools that were known to have contained plasma from a donor later diagnosed with vCJD. With use of the lower, case-based, prevalence estimate for vCJD of ~ 4 vCJD cases per million, the model predicts that only about 1.6% of plasma pools, on average, might contain the vCJD agent. However, if the higher prevalence estimate, based on a single tissue study, for vCJD in the UK of 1/4,225 is used as a possible higher estimate of the actual vCJD prevalence, the model predicts that most (50%) 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 there may have been exposure to the vCJD agent, and there could be a potential risk of infection, it is not possible to provide a truly meaningful or accurate estimate of the vCJD risk to individual patients who used FXI manufactured from UK plasma through 2000. Assuming that the UK vCJD prevalence estimate generated from epidemiological modeling is correct, the possibility of exposure and the risk of infection would be considerably lower. Again, although the risk may be low, it is difficult to actually estimate the risk with confidence given the multiple unknowns and uncertainties of the available data used in the model (see sections III.A.1. and IV.D. for discussion). In considering which prevalence estimate is more likely to be correct and in considering in general the risk estimates from the model, it is important to note that to date we are not aware of any cases of vCJD having been reported worldwide in patients receiving plasma-derived products. This includes patients receiving this product as well as patients receiving large amounts of other products manufactured from UK plasma donations over a long period of time. Although the actual risk is highly uncertain, the risk assessment model indicates that the most important factors affecting risk are the clearance of the vCJD agent though manufacturing steps, how much product individuals used, efficiency of the i.v. versus the i.c. route of exposure, and the vCJD prevalence in the UK donor population.

RISK ASSESSMENT

BACKGROUND

FXI

FXI is a clotting factor present in blood plasma that plays a role in the very early stages of the blood coagulation pathway. FXI is normally present in human plasma at concentrations of 50-70 u/dl.

FXI deficiency is a rare bleeding disorder first described in the 1950s. Unlike hemophilia A or B, it is an autosomal bleeding disorder that affects both genders equally. Generally, bleeding in patients with FXI deficiency is less severe than with hemophilia A or B and does not usually involve joints or muscles, or spontaneous bleeding in those areas (http://www.hemophilia.org/bdi/bdi_types9.htm). FXI deficiency is usually categorized as severe or 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 (BPL, 2001) prior to surgical procedures on severely deficient patients.

FXI, manufactured from UK donor plasma collected through 1997, was used by a small group of patients in several IND studies in the US between 1989 and 2000, and this risk assessment estimates the potential exposure to vCJD agent via that product. Currently, in the United States where there is no commercially licensed FXI product; clinicians typically utilize Fresh Frozen Plasma from US donors, and/or antifibrinolytic agents for therapy.

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 of Creutzfeldt-Jakob disease (vCJD) was first described in the UK in 1996. As of August 2006, 195 cases worldwide have been reported including 162 in the UK (United Kingdom National CJD Surveillance Unit, August 2006).

Both vCJD and BSE belong to a class of diseases known as transmissible spongiform encephalopathies (TSEs). The leading theory concerning the agent responsible for infection is that of a proteinaceous infectious agent, or "prion," that originates in the misfolding of a ubiquitous prion protein (PrP) normally expressed in many cells. The altered PrP, which is now suggested to be designated as PrP^{TSE}, (World Health Organization Guidelines, 2006, also known as PrP^{res}, or PrP^{Sc}) is highly stable and resistant to degradation by high heat and many chemical treatments commonly used to denature proteins. The incubation from the time of exposure to TSEs to the

development of symptoms of disease 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 food-borne vCJD is estimated to exceed 10 years. Individuals become symptomatic with vCJD only in the last few months of life, making early detection very difficult. Confirmatory diagnosis of vCJD requires postmortem examination of brain tissue. However abnormal prion protein has been detected in some antemortem tonsil biopsies early in clinical illness, and in an archived appendix sample from an asymptomatic individuals several months prior to the onset of symptoms (Hilton *et al* 1998). There are currently no validated tests available to detect the vCJD infectious agent in early stages of infection 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 different TSE agents 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 2004, Brown *et al* 1999).

Brown, Rohwer, Taylor (Taylor *et al* 2000) and others have attempted to estimate the amounts of intracerebral (i.c.) infectivity present in blood, which generally fell between 2 and 20 i.c. ID_{50}/ml. A recent study of scrapie-infected hamsters concluded that approximately 58% of the infectivity present in whole blood was associated with plasma (Gregori *et al* 2004). The model uses this more conservative estimate in the published literature and assumes that 58% of infectivity is associated with plasma.

I. B. Transfusion transmission of vCJD in the UK

In December 2003 the UK government announced that vCJD had likely been transmitted to a 69 year-old patient via blood transfusion. The patient had received non-leukoreduced red blood cells in 1996 from a donor who died three years later of vCJD. This first report was followed by the announcement in July 2004 of another probable case of transfusion-transmitted vCJD. The patient died of a ruptured aortic aneurysm without clinical evidence of vCJD, but postmortem testing detected PrP^{TSE} in spleen tissue and cervical lymph node. In February 2006 a third case of probable transfusion transmitted vCJD was reported in the UK in a 31 year-old male; the patient had received a transfusion eight years earlier from a donor who died of vCJD 20 months after donation. None of the donors were known to have had vCJD at the time of donation.

It is possible that dietary exposure may have been responsible for some or all of the three cases that were reported after red blood cell transfusions. However, the probabilities for occurrence of either a single, or, particularly, two or three such 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 the first two transfusion cases both acquired infection

from food, identified in two elderly patients in a small cohort of transfusion recipients in an age group underrepresented among vCJD cases, is remote.

The presumptive transmission of vCJD via red blood cell transfusion in the UK raises the possibility that plasma derivatives may pose a risk, based on the finding in animal models that plasma contains the infectious agent when blood is infectious. The UK authorities have notified physicians in the UK and their patients who received plasma derivatives made from plasma from UK donors about the potential for risk of vCJD from these products. These plasma derivative products included coagulation factors, as well as antithrombin III, and intravenous immune globulins. The derivatives of concern were manufactured from plasma of UK donors between 1980 and late in 1999, when--consistent with a decision announced in 1998—UK manufacturers stopped using UK plasma. The last expiry date for any of the UK products was in 2001. To date, no cases of vCJD have been reported in any recipients of plasma derivatives, either in the UK, where the risk is considered greatest, or elsewhere, including in patients who have received human plasma-derived coagulation products from implicated lots (i.e. lots that were later found to contain donations from people who later developed vCJD) made in the UK.

This risk assessment examines the possible exposure to vCJD agent and the risk of vCJD infection for FXI manufactured from UK plasma between 1989 and 1997 and used by a small group of patients in several IND studies in the US between 1989 and 2000.

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 can be 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, and 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 as best as is possible to estimate the dose-response relationship for humans.

The rodent animal models drawn on for this risk assessment on vCJD risks use other TSE agents such as the scrapie agent – hamster model used by Rohwer (2004) and the CJD agent-mouse model used by Brown (1998, 1999). Brown (1998, 1999) and Rohwer (2004) use the metric of infectious unit (IU), which is the minimal amount of any inoculum required to initiate an infection in 100% of the rodent population using the intracerebral (i.c.) route of introduction. The FDA model assumes that this infectious unit is equivalent to two ID_{50}s which assumes the two metrics are linearly related, further adding to the uncertainty of the model.

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, for TSE diseases there is a minimal amount of the agent (presumably the prion protein PrP^{TSE}), or threshold that is needed to initiate infection in an individual, such as is seen with many other pathogens such as viruses or bacteria, for which infection requires exposure to at least one, and often more, units of the infectious agent. Furthermore, it is not known whether the effects of small multiple exposures

over a period of time are cumulative and may result in the possibility of infection and disease equivalent to a single, larger exposure (e.g., via intracerebral injection in laboratory animals). Some risk assessments have made assumptions concerning the exposure and dose for TSE agent that lead to infection. For instance, the Det Norske Veritas (Feb 2003) blood products risk assessment assumes that exposure to infectivity, quantified in ID_{50} units, is cumulative over the period of one year. Based on advice from the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) (2005), and consistent with suggestive data from studies of TSE agents in animal models (Diringer *et al* 1998, Jacquemot *et al* 2005), FDA also assumes that exposure to vCJD ID_{50} is cumulative over a one year period. The ID_{50} is the common metric used to quantify the infectivity of TSEs. One ID_{50} is defined as the amount of infectious material or tissue that is necessary to initiate infection in 50% of the treated population. The route of exposure to TSE infectious material influences the efficiency of transmission of the disease. Based on advice provided to FDA by the TSEAC (October 31, 2005) the model assumes that transmission via the intravenous (i.v.) route is between 1 and 10 times less efficient than the transmission via intracranial (i.c.) route.

In estimating the dose-response relationship for TSEs one could use a strict interpretation of the ID_{50} and assume a linear relationship between exposure and infection. In the FXI model FDA assumed there was a linear relationship between the exposure dose of vCJD agent and the probability of infection. The ID_{50} relationship used in the model was based on infectious TSE units estimated from rodent model studies (Brown 1998, 1999; Rowher 2004). We further assumed there was no threshold or minimum dose necessary to initiate infection, that is, exposure to even low quantities of vCJD agent have a probability of initiating infection in an individual, albeit the probability of infection would likely be low at low levels of exposure. The model further assumes that in such a case exposure to 1 ID_{50} would suggest a 50% probability of infection, exposure to 0.1 ID_{50} 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 because of the limited data available for TSE agents it is plausible that low level exposures, even on a chronic basis, may not attain a threshold or minimum quantity of agent necessary to initiate infection in humans. Again, FDA makes a conservative assumption that low-level exposure(s) over the period of one year to any quantity of vCJD agent could potentially lead to infection and that there is not a minimum dose necessary to initiate infection.

There are considerable uncertainties in determining the correct form for the vCJD-human dose-response model. For instance, the nature of the dose-response line, its slope, or whether it is more accurately described using a dose-response curve is uncertain because animal data are so limited and human data are not available. The FDA risk assessment estimates the potential individual risk of infection and assumes that a linear interpretation of the rodent model accurately reflects the pathology and progression of vCJD infection and disease in humans, but it may not. Furthermore, exposure to the vCJD agent may not necessarily lead to infection, and vCJD infection may not necessarily produce symptomatic vCJD disease or illness in an individual or population.

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 FXI manufactured in the UK and administered to US patients during clinical studies under several IND applications. The administration of FXI, and thus the route of exposure, is intravenous and used in the clinical prophylactic treatment of individuals prior to surgery and after surgery to control bleeding.

Pools consisting of 20,000 or more plasma donations collected from UK plasma donors were used as the starting material from which FXI was purified. Because of the number of donations per plasma pool and the prevalence of vCJD in the UK population, it is possible that some plasma pools may have contained one or more plasma donations from asymptomatic donors unknowingly infected with vCJD.

Overview of Model

Figure 1 depicts the major elements and some of the types of input data and information used in the FDA FXI – vCJD risk assessment. Module A (vCJD ID_{50} per plasma pool) uses two different estimates of UK vCJD prevalence. The first is a vCJD case prevalence based on epidemiological modeling of actual reported cases in the UK and an estimate of future vCJD cases (Clarke and Ghani, 2005), which yielded an estimate of approximately 4 vCJD cases per million. Limitations associated with estimates of future vCJD cases and vCJD incidence in the UK generated by epidemiological modeling based on the current reported vCJD cases are described in section A.1.a. The second is a vCJD infection prevalence based on a tissue surveillance study by Hilton *et al* (2004), which yielded an estimate of 1 in 4,225 (237 infections per million) which represents a possible higher prevalence scenario. However, there are limitations to using the Hilton et al tissue surveillance study in estimating vCJD prevalence and those are described in section A.1.b.

After accounting for the age distribution and/or incubation period of possible vCJD cases, these prevalence estimates are used to predict the number of vCJD donations that could be present in a plasma pool of 20,000 donations. After adjusting for the relative efficiency of intravenous and intracerebral administration, the output of this module is an estimate of the vCJD i.v. ID_{50} per plasma pool. Module B approximates the reduction of vCJD agent during manufacturing. The model estimates a reduction of between 0 and 4 $\log_{10}$ (10,000 fold) in the amount of agent with a most likely level of reduction of 2 $\log_{10}$ (100 fold). The output of this module is an estimate of the ID_{50} per vial of FXI. Module C (Dose for Pre- / Post- surgical treatment) estimates utilization of FXI by patients. Estimates for potential exposure and potential vCJD infection risk were generated by the model for three possible clinical treatment scenarios.

Revisions of the February 8, 2005 FDA DRAFT Factor XI – vCJD risk assessment and model

FDA presented the first version of the risk assessment: "Draft Risk Assessment: Potential Exposure to the vCJD agent in United States recipients of Factor XI coagulation product manufactured in the United Kingdom" at the February 8, 2005 meeting of the TSEAC for review and comment. The risk assessment model predicted that recipients of UK manufactured FXI may have potentially been exposed to the vCJD agent. On October 31, 2005 FDA sought advice from the TSEAC and discussion on several risk assessment model inputs for plasma derivatives and potential vCJD risks. This newly updated, second iteration of the FDA Draft FXI vCJD risk assessment incorporates many of the comments and much of the advice provided by the TSEAC at the February 8, 2005 and October 31, 2005 meetings, and more recently by FDA staff and peer reviewers (revisions summarized in Table 1).

Figure 1. Model of Exposure Assessment

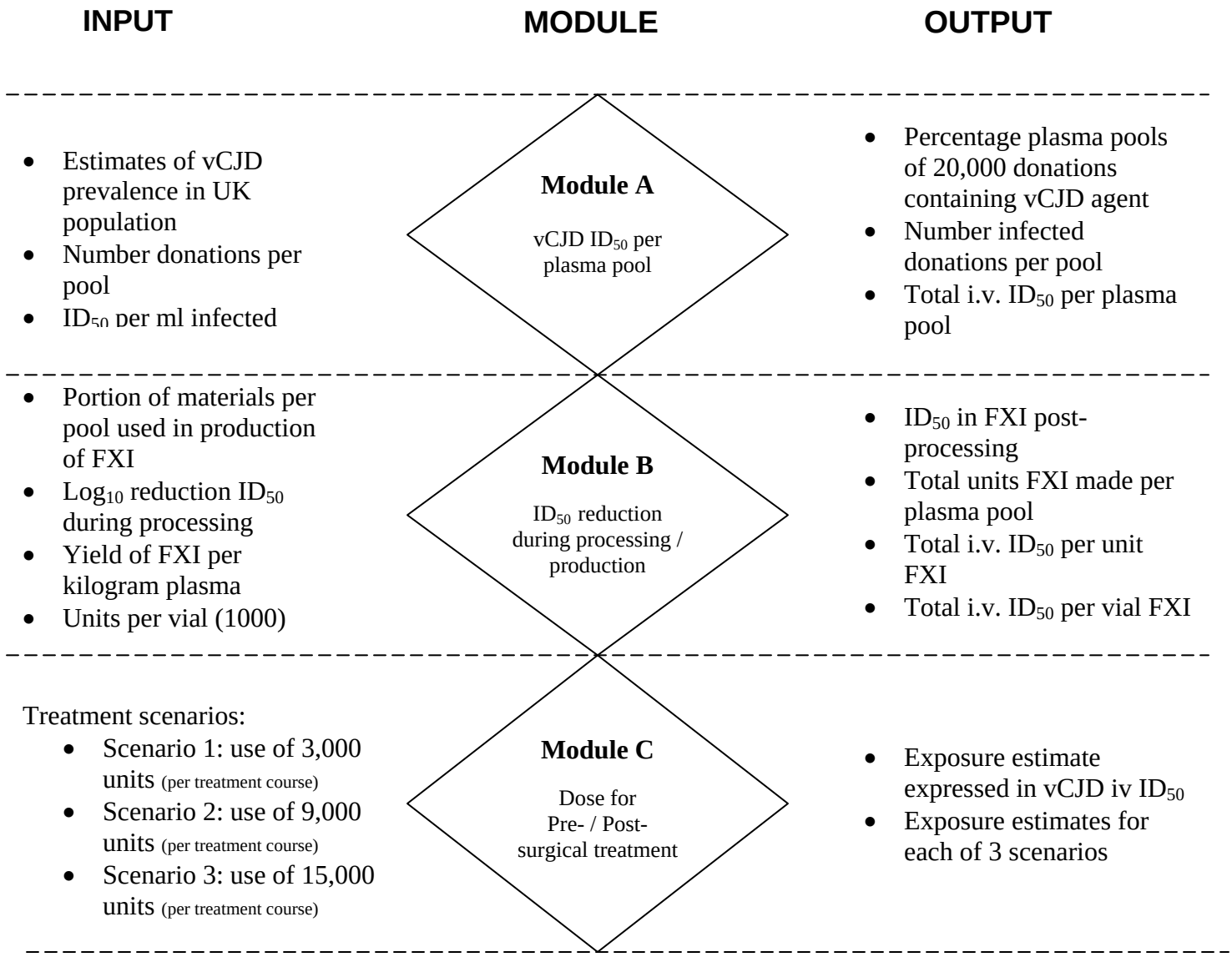


Table 1. FXI Model Input Changes from February 2005 to September 2006

	Model: Presented before TSEAC February 8, 2005 **Document:** Draft Risk Assessment: Potential Exposure to the vCJD Agent in United States Recipients of FXI Coagulation Product Manufactured in the United Kingdom	**Model: Revised September 2006** **Document:** FDA Draft Risk Assessment: Potential Exposure to the variant Creutzfeldt-Jakob Disease Agent in United States Recipients of FXI Coagulation Product Manufactured in the United Kingdom
Input Parameter Name and description	**Data and Parameters**	**Data and Parameters** TSEAC provided advice on vCJD and plasma derivatives at the October 31, 2005 meeting
UK vCJD Prevalence	Prevalence: **1 in 4,225** The UK vCJD Infection prevalence based on Surveillance study of tonsils /appendices samples from patients mostly 20 – 30 yrs of age *(Hilton et al 2004)*	Use two separate prevalence estimates: 1) HIGHER prevalence estimate – of UK vCJD Infection prevalence was based on Surveillance study tonsils/appendices of **1 in 4,225** *(Hilton et al 2004)* 2) LOWER prevalence estimate – vCJD Case prevalence estimate based on predictive modeling estimates - implies prevalence of **~4 vCJD infections per million** *(based on Clark and Ghani, 2005)*
Tissue surveillance or vCJD Infection prevalence: adjustment for donor age	No age adjustment was made. Prevalence based on surveillance study of tonsils /appendices samples from patients mostly 20 – 30 yrs of age was used.	Prevalence adjusted based on: 1) Age of donor population 2) Age information of reported vCJD cases
Time during incubation period when infectivity is present in blood	Infectivity assumed to be present **throughout the entire incubation period**	Infectivity assumed to be present only during **last half of incubation period**
Quantity of infectivity present in blood	Distribution: Triangular Minimum: **0.1** Most likely: **10** Maximum: **1,000** i.c ID50/ml	Distribution: LogNormal Minimum: **0.1** 5th percentile: **2** Median (50th perc): **12** 95th percentile: **30** Maximum: **1,000** i.c ID_{50}/ml
Adjustment for efficiency of transmission via intravenous (i.v.) versus intracerebral (i.c.) exposure	**0.5 -1**	**0.1 - 1**

III. A. Probability of donation containing vCJD infectivity and the total quantity of intravenous vCJD infectivity (i.v. ID_{50}) per plasma pool

Potential exposure to vCJD infectivity via UK manufactured FXI is a function of the probability that a plasma pool contains a donation with vCJD agent and the quantity of agent present in the donation and the larger assembled plasma pool. Prevalence of vCJD in the UK population directly influences the probability that a donation with vCJD agent will be present in a plasma pool.

III. A.1. Estimation of UK vCJD prevalence via two methods

The potential prevalence of vCJD in the UK was and continues to be dynamic and changes over time as people are exposed to the BSE agent, potentially infected with vCJD, develop the disease and eventually die. Variant CJD exposure and infections in the UK population likely occurred in proportion to the UK BSE epidemic which peaked in 1992. The first human vCJD cases were referred to UK public health authorities in 1994. To date, the number of cases in the UK reached a maximum of 28 in the year 2000, and since then has been declining annually with a total of 5 deaths in 2005. During the manufacture of FXI in the UK from plasma collected as late as 1997, the prevalence of human vCJD was likely higher than it is today in 2006 since exposure to BSE agent has ebbed and deaths of infected individuals lower the total number of infected persons. As of August, 2006 the UK recorded a total of 162 cases of definite or probable vCJD (CJD Surveillance Unit, 2006). However, the disease is likely to still be present in at least some members of the population as pre-clinical and asymptomatic infections. Most known infections and deaths have occurred in individuals who are homozygous methionine, or MM, at codon 129 of the PrP gene product. Prion positive tissue has been observed in individuals who are heterozygous methionine and valine (or MV) or homozygous valine (VV) at codon 129 (also called non-MM individuals) but to date none have developed symptoms and died of vCJD. Whether non-MM individuals will become symptomatic with vCJD or are capable of transmitting the disease is unknown.

In the scientific literature estimates of the rate of incubating vCJD cases in the UK have been derived from two potential sources: (1) epidemiological modeling studies based on the actual number of reported vCJD cases, and (2) a single study of surveillance testing for possible vCJD related protein accumulation, in tissues such as tonsil and appendix, which may or may not indicate a vCJD infectivity risk. This risk assessment used prevalence estimates derived both from the results of the appendix surveillance study, which yielded a vCJD prevalence estimate that may be representative of a possible higher prevalence scenario for potential vCJD infection, and from the epidemiological model, which yielded a lower vCJD prevalence estimate of potential vCJD cases based on a number of assumptions.

These estimates were used independently to generate two distinct estimates for UK vCJD prevalence for use in the model. Prevalence estimates derived from each data source are dramatically different. The mean vCJD case prevalence estimated using an epidemiological approach based on actual cases and projected case numbers, 4 infections per million people, is approximately 60 times lower than the mean infection prevalence estimated based on the study of tissue surveillance, 1 in 4,225. The data used to generate each prevalence estimate have limitations and uncertainties that contribute to the pronounced difference and uncertainty between the prevalence estimates, as noted above and cited below.

Two versions of the model were separately run using the two different estimates. Other parameters remained identical for each version. Results for each of the two different prevalence estimates were generated and are shown in the results tables for the model.

III. A.1.a. $\mathbf{P_{vCJD\text{-}Epi}}$ - *Probability of vCJD-infected individual in UK population who will develop symptoms – determined by epidemiologic modeling-based prevalence estimate.*

$$\mathbf{P_{vCJD\text{-}Epi}} = \mathbf{N_{vCJD\text{-}CE}} / \mathbf{N_{pop\text{-}UK1997}}$$

The probability of a vCJD-infected individual in UK population who will eventually develop symptoms is represented by the variable, $\mathbf{P_{vCJD\text{-}Epi}}$ *. It is derived by calculating the predicted number of vCJD cases that will progress to symptoms and be reported as a vCJD case to public health authorities divided by the size of the total population ,* $\mathbf{N_{pop\text{-}UK1997}}$*, in the UK in the year 1997.*

$\mathbf{N_{pop\text{-}UK1997}}$ - this represents the estimated size of the UK population in 1997 which was 58 million (United Kingdom Office for National Statistics, 1997).

III. A.1.a.i. $\mathbf{N_{vCJD\text{-}CE}}$ - *Estimated Number of vCJD-infected individuals in UK population using recorded vCJD cases (1997 – 2004) and epidemiological modeling based prevalence estimate*

Estimation of the UK vCJD prevalence during the period of interest during the manufacture of FXI from 1989 – 1997 was calculated by combining the number of reported vCJD cases during the time period from 1997 through 2004 with the future predicted cases of vCJD estimated by Clarke and Ghani (2005) for the period from 2005 to 2080. Although the total period spans from 1997 – 2080 (more than 80 years) and some of the future cases may not have been infected until after 1997, the calculations provide a conservative estimate that may slightly overestimate the number of cases as predicted in current epidemiological models. According to the United Kingdom National CJD Surveillance Unit (2006) (Table 2 below), there were 138 diagnosed vCJD cases through 2004. The variable, $\mathbf{N_{vCJD\text{-}CE}}$, is the sum of 138 diagnosed vCJD cases, $\mathbf{N_{vCJD\text{-}Case}}$, and the cases estimated by epidemiological modeling, $\mathbf{N_{vCJD\text{-}Epi}}$, or an estimated 70 future cases. The sum of the expression is a total mean of 208 cases vCJD (95% CI: 148 – 328) and represented by the equation:

$$\mathbf{N_{vCJD\text{-}CE}} = \mathbf{N_{vCJD\text{-}Case}} + \mathbf{N_{vCJD\text{-}Epi}}$$

III. A.1.a.ii. $\mathbf{N_{vCJD\text{-}Case}}$ - *Number of reported vCJD cases in UK population 1997(and before) – 2004.*

Table 2. Number of Diagnosed vCJD Cases in the UK (Health Protection Agency, 2006)

Year	**1997 and prior years**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**Total**
Diagnosed vCJD cases	12	17	17	28	25	16	16	8	138

III. A.1.a.iii. $\mathbf{N_{vCJD\text{-}Epi}}$ - *Number of future vCJD-infected individuals in the UK population based on epidemiological modeling prevalence estimate*

Epidemiological modeling based prevalence estimates. Estimations of the future number of possible vCJD cases have narrowed considerably in the last decade and many recent estimates now predict a similar range for the number of possible future cases. Below (Table 3) are representative references of predicted future cases of vCJD that can be used to estimate the prevalence of vCJD in the UK. Our model uses the Clarke and Ghani (2005) estimate of 70 future cases of vCJD with a 95% confidence interval of 10 – 190 cases for the years 2004 – 2080. Assuming the population of the UK in 1997 is approximately 58 million, the prevalence of vCJD (United Kingdom Office for National Statistics, 1997) would be a mean of approximately 4 vCJD infections per million((138+70) cases / 58 million) population.

There are some limitations associated with estimates of future vCJD cases and vCJD incidence in the UK generated by epidemiological modeling based on the current reported vCJD cases. Many of the published models of future vCJD cases or vCJD incidence in the UK, including Clarke and Ghani (2005) and Cooper and Bird (2003), use simplifying assumptions in generating their predictions. Although these simplifying assumptions are a necessary part of vCJD case estimation efforts, they contribute considerable uncertainty to the final case estimates. Generally, the types of assumptions used to estimate vCJD cases fall into four general areas. First, the models must estimate the number of clinical and pre-clinical BSE-infected cattle slaughtered in the UK to estimate the intensity of human exposure to the BSE agent. Second, they assume a level of effectiveness of the 1989 Specified Ban on Offals which was assumed to reduce the quantity of infectious BSE agent in the food supply, thereby reducing human exposure in the UK. Third, the models generate an appropriate mathematical representation (or statistical distribution) for the incubation period, which is represented by many using a unimodal statistical distribution. There may be constraints on the incubation period (e.g. less than 40 years, etc.). Fourth, many of the modeling approaches incorporate age-specific dependencies that influence exposure, susceptibility to the disease, and incubation period. Depending on the assumptions used, estimates of future cases of vCJD have varied considerably. Past estimates of vCJD cases from epidemiological models predicted from 250 to 440 future cases under certain assumptions (d'Aignaux *et al* 2001). As actual reported vCJD cases peaked in 2000 and have since been declining, predicted estimates of future cases have decreased (Boelle *et al* 2003, Clarke and Ghani 2005, Cooper and Bird, 2003).

There are additional uncertainties in predicting future vCJD cases that might arise from individuals with different genetic backgrounds and susceptibilities in the UK population. To date, all known cases of vCJD have occurred in individuals that were methionine homozygous (MM genotype) at the PRNP codon 129. Recent research has identified two individuals who were valine

homozygous (VV genotype, also called non-MM genotype) at PRNP codon 129 (Ironside *et al* 2006) among the three prion protein positive samples identified by Hilton *et al* (2004). Clarke and Ghani (2005) did incorporate the possibility of wider genetic susceptibilities in some of their estimates of future vCJD cases. However, because no cases of clinical vCJD have been identified yet in individuals with a non-MM genotype, it is uncertain whether such individuals will in fact develop clinical disease or be capable of transmitting the disease. Therefore, any estimation of the incubation period for potential cases with the non-MM genotype would rely heavily on assumptions, which adds considerable uncertainty to any estimate of the size or number of cases in a possible secondary wave of vCJD cases that might occur in non-MM individuals.

Table 3. Recent Representative Epidemiological Model-based Estimates of vCJD in the UK.

Reference	Years	vCJD cases (95% CI)	Comments
Clark and Ghani (2005)*	2004 - 2080	70 (10 – 190) (additional future cases)	Considers: Only MM cases (non-MM susceptibility*)
Cooper and Bird (2003)	2001 – 2005 2006 - 2010	164 (127 – 219) 88 (62 – 121) (additional future cases)	Considers: Only MM cases

* Clarke and Ghani 2005 provide estimates for two scenarios of wider susceptibility (in a non-MM population) using non-constrained assumptions but those estimates were not used in our model.

Assumption used in the model: The variable, $\mathbf{N_{vCJD\text{-}CE}}$, is the sum of 138 vCJD cases diagnosed between 1997 and 2004, $\mathbf{N_{vCJD\text{-}Case}}$, and the 70 future cases since 2004 estimated by epidemiological modeling, $\mathbf{N_{vCJD\text{-}Epi}}$; the sum of the expression is a total mean of 208 cases vCJD (95% CI: 148 – 328) assuming the population of the UK in 1997 is approximately 58 million the prevalence of vCJD would be a mean of approximately 4 cases per million (208 cases / 58 million) population.

III. A.1.b. $\mathbf{P_{vCJD\text{-}Surv}}$ - *Probability of vCJD-infected individual in UK population using the surveillance prevalence estimate*

Surveillance prevalence estimate. 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^{TSE} has also been observed in an appendix sample of one asymptomatic vCJD individual several months prior to the onset of symptoms (Hilton *et al* 1998) and in the appendix sample of a symptomatic individual (Joiner *et al* 2004). Results from an ongoing surveillance study have been published in the literature on three separate occasions (Ironside *et al* 2000, Hilton *et al* 2003, 2004). The most recent report by Hilton *et al* (2004)

summarizes the results from the surveillance study, which included a total of 12,674 patients (results summarized in Table 4). Appendectomy samples from three of these 12,674 patients showed accumulation of prion protein. No tonsil biopsies showed such accumulation. Limitations to this study that contribute to uncertainty include the fact that this study was not controlled using a non-BSE exposed population and that a false positive interpretation could not be excluded. It is also not known whether this look at prions in tissues is a reliable marker for vCJD pre-clinical infection or for an individual's capability to transmit the infection through blood donation.

For the risk assessment model we assumed the sensitivity and specificity of the testing method for the accumulation of prion protein in tissues was 100%. The results of 3 positive samples in a total of 12,674 tissues tested (Hilton *et al* 2004) equates to an average rate of vCJD in the UK population of 1 in 4,225 or a mean of 237 infections per million (95% CI: 49 – 692 cases per million) for all age groups in the study. The authors (Hilton *et al* 2004) indicated that approximately 60% of the samples tested (from approximately 7,600 patients) came from patients 20-29 years of age. Furthermore, demographic information of reported vCJD cases (Table 5) indicated that the younger population that was deliberately oversampled in this study may have been more susceptible to the disease. The vCJD prevalence among UK donors might, therefore, be over-represented by the prevalence of 20-29 years age group derived from the surveillance study. To account for the age-specific bias in the sampling of tissues we calculated the age-specific prevalence for the 20-29 year old group and used that information to estimate the age-specific UK vCJD prevalences for the other age groups. To account for the age of individuals and populations in the model we assumed that there were 3 positive samples among the 7,600 20-29 year old patients in the Hilton *et al* study (2004). This yields an approximate UK vCJD prevalence of 1 infection in 2,500 individuals aged 20-29 years. This estimate is equal to approximately 400 infections per million for which we assumed a 95% CI of 100-1200 cases per million. We then derived the prevalences for the remainder of the UK donor population by determining the proportional difference between the vCJD prevalence from the tissue study group and the number of actual reported vCJD cases for donors in the 20-29 years age group. This proportion was then applied to the remaining age groups in the distribution of reported vCJD cases to determine the prevalence for each age group. By multiplying our extrapolated vCJD prevalence for incubating cases times the total donor population we were able to estimate the number of possible incubating vCJD cases in each UK donor age group. We assumed that a plasma pool used to manufacture Factor XI product in the UK in the 1990s consisted of 20,000 donations, and all donations came from different donors. The estimated prevalence was then used to generate variables and parameters representing the potential number of vCJD donors or donations that might be present in a plasma pool.

However, there are some possible limitations of using the Hilton *et al* tissue surveillance study in estimating vCJD prevalence. In their tissue survey, Hilton *et al*. stressed that there were uncertainties and suggested caution in attempting a prevalence estimate for infection or a prediction of future vCJD cases in the UK based on detection by immunohistochemical staining of abnormal prion protein in three of 12,674 adequate appendix samples studied. First, because the stage of vCJD infection during which the appendix first accumulates detectable amounts of abnormal prion protein is not known and because the accumulations might not be uniformly distributed throughout the tissue, the prevalence of infection might have been underestimated. Second, because the study design (lacking examination of a large number of similar appendices from a non-BSE-epidemic country) did not permit an estimate of specificity of the method or an independent confirmation of results, it is possible that the results might have been false positives

leading to an overestimation of prevalence. In their paper the authors stated: "Although immunohistochemical accumulation of PrP in lymphoreticular tissues has not been demonstrated in any disease other than vCJD, the significance of the positive samples in this study is not certain. In one case, the immunohistochemical pattern of immunoreactivity resembled that seen in appendix tissue from pre-clinical and autopsied cases of vCJD, but in the other two cases, a more finely granular pattern of staining was present in relation to follicular dendritic cells, raising the possibility that these may be false positives. However, we have been unable to demonstrate PrP immunoreactivity in a range of other disorders including other human prion diseases, neoplastic disease, or a range of inflammatory conditions."

Assumption used in the model: The higher prevalence estimate of vCJD infection in the UK population was based on surveillance studies of tonsils and appendices (Hilton *et al* 2004) and assumed to be a mean of 1 in 4,225 (1/20,300 to 1/1,450 - 95% CI).

Table 4. Summary of Surveillance Testing of Tissues including Tonsil and Appendix in the UK.

Reference	Ages of population examined	Years tissue taken	Number of positives	Total samples examined	Rate per million (95% CI)
Hilton *et al* 2004	10 – 60+ yrs (60% of patients were 20-29 yrs)	1995 - 1999	3 Appendices	14,964 Appendices 1,739 Tonsils 4,029 excluded	237/million (49–692 per million)

Table 5. Reported vCJD Cases (Hilton *et al* 2004).

Age group	**<10**	**10-14**	**15-19**	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-69**	**>70**
Reported vCJD cases (through 2003)	0	5	27	32	30	22	13	5	3	5	0	5		

III. A.2. Estimation of probability that infectivity will be present in blood (prionemia) in vCJD infected individuals at time of donation

Animal studies suggest that TSE infectivity is likely not present in the blood during the early stages of infection but rather manifests in blood during the later stages of the disease [reviewed in Brown (2005)]. Humans infected with vCJD are assumed in the model to display a similar pattern of infectivity in the blood (here termed "prionemia"). Accordingly, the model assumes that infectivity is present in the blood or plasma of donations from vCJD infected donors during the last

half of the incubation period. This means donations of blood or plasma from these individuals, especially in the early stages of the disease, may not contain vCJD agent and thus, at times, may not be capable of transmitting infection to recipients of whole blood, plasma, or plasma derivatives.

Calculation of the occurrence of infectious agent in blood of infected donors requires specific information or assumptions about the time or year of exposure to BSE and subsequent vCJD infection, and incubation time of the disease to determine the timing and occurrence of the last half of the incubation period, when infectivity is assumed to be most likely present in the blood of a vCJD infected donor. Because FXI was manufactured in the UK from the plasma of UK donors it was assumed that dietary exposure to the BSE agent led to subsequent vCJD infection. It was further assumed that the number of human infections in a specific year from 1980 to 1996 was proportional to the magnitude of the BSE epidemic in the specific year. Food chain control was in place in the UK in 1996. Therefore, we assume that the risk of exposure to BSE agent through dietary exposure after 1996 in the UK was negligible. Since the UK product, used under IND in the US, was manufactured from 1989 through 1998 – the model does not consider possible human exposure to the BSE agent after 1997. It was assumed that there is a lag of 6 months to one year from the time plasma is collected until it was manufactured/distributed as final product; therefore, plasma collected in 1997 was assumed manufactured into product in 1998.

III. A.2. a. BSE_y-*BSE cases reported in year y*

To estimate the relative magnitude of possible human exposure to the BSE agent in the UK, data on number of cases of BSE reported in cattle in the UK from prior to 1987 through 1996 were used as a relative metric of annual human exposure to BSE infectivity. We assumed that the amount of BSE agent that entered the UK food supply after 1996 was negligible. The number of human vCJD infections in any given year was assumed to be proportional to the number of BSE cases in cattle in a given year compared to the total number of cases that occurred through 1996. For example, out of a total of 169,473 BSE cases observed (data shown in Table 6) through1996, 37,280 cases or 22% of all cases (37,280/169,473 = 0.22) were observed in 1992. Proportionally, it would be predicted that approximately 22% of all human vCJD infections that occurred through 1996, would have occurred in 1992.

Data used in the model*:* Data from the World Organization for Animal Health (OIE, 2006), shown in Table 6, was used to determine the number of cases of BSE reported in the UK

Table 6. Number of BSE Cases (Cattle) Reported in the UK from 1980 through 1996 (OIE, 2006)**.**

Year	1987 and before	1988	1989	1990	1991	1992	1993	1994	1995	1996	**TOTAL**
Number cases of BSE reported in the UK	446	2514	7228	14407	25359	37280	35090	24438	14562	8149	169,473

Assumption used in the model: There is a six month to one year (or longer) lag from the time plasma was collected from UK donors until it was manufactured into FXI for distribution. For

example, the model assumes that FXI distributed in 1998 was manufactured from UK plasma collected in 1997 or earlier.

III. A.2. b. $P_{infect\text{-}y}$-*Probability an infection occurring in year y - calculated by the equation:*

$$P_{\inf ect-y} = BSE_y \,/\, \sum_{y=1980}^{1996} BSE_y$$

That is, the probability of infection with vCJD in a given year ($P_{infect\text{-}y}$) is a proportion equal to the number of reported BSE cases in the given year divided by the total reported number of BSE cases from 1980 through 1996. The summation in this section covers years 1980 through 1996 and does not address human exposure to the BSE agent in the UK after 1996 because the human exposure risk to the BSE agent thereafter was assumed to have dropped precipitously. After the announcement of 10 human vCJD cases in the spring of 1996, the UK implemented strict measures to prevent BSE infected cattle from entering the human food supply. Although cases of BSE were reported in the UK after the measures were imposed in 1996, the likelihood that BSE containing tissue entered the human food supply was low. Therefore, the model assumes that food-borne exposure to the BSE agent in the UK after 1996 was negligible.

Assumption used in the model: The probability of a vCJD infection occurring in a specific year is a function of exposure in that specific year, which is proportional to the number of BSE cases reported in that specific year (more BSE cases higher probability of getting infected) compared to the total BSE cases for all years through 1996.

III. A.2.c. $P_{LH\text{-}y}$ – *Probability that the blood of an individual infected in year y will contain vCJD agent in the year 1997*

The models considered the possibility that although patients may be infected with vCJD, infectivity may not actually be present in the blood or plasma at the time the donation is collected. This phenomenon lowers the apparent prevalence of prionemia in infected donors meaning that many of the donations from infected individuals will not contain vCJD agent and would presumably pose little risk of transmitting vCJD. As discussed earlier, animal studies demonstrate that TSE agents appear in the blood during later stages of the disease. Accordingly, the FDA model assumes that vCJD agent was present in the blood of vCJD infected individuals during the last half of the incubation period and products derived from donations with infectivity may lead to exposure to vCJD (see below).

Assumption used in the model: FXI was made from UK donor plasma collected through 1997. For modeling purposes, we made a conservative assumption that the vCJD risk for all plasma collected for the manufacture of FXI used in the US was equal to the vCJD risk for plasma collected in the year 1997. We assumed that the vCJD risk for 1997 was likely the highest among all years that UK plasma was collected and used to make FXI used in the US because the total number of vCJD infections in the UK population (and the vCJD prevalence) were likely at or near their peak. Presumably vCJD prevalence would begin to decrease in 1997 and in subsequent years as the number of new vCJD infections declined due to the implementation of the stringent UK food chain controls of 1996. In addition to the decline in new vCJD infections, the vCJD prevalence and risk for the UK population likely started to decrease around 1997 and in subsequent years as patients died from the disease.

Assumption used in the model: The variability and uncertainty of the incubation period of vCJD (IP_{vCJD}) is represented mathematically by a gamma distribution, specifically Gamma (4.7, 3.6). A gamma distribution is usually used to represent intervals between events, in this case, the time from infection to the emergence of symptomatic disease. The distribution is defined by two parameters, one that produces the shape of the curve and a second that generates the scale between events which for vCJD is the mean incubation period of 14 years. Similar statistical methods and estimates for the vCJD incubation time have been used by others (Ghani *et al* 2004, Clarke and Ghani 2005).

IP_{vCJD} = The incubation period of vCJD was calculated in the model using a gamma distribution represented by the expression Gamma (4.7, 3.6) and expressed as:

IP_{vCJD} = Gamma (4.7, 3.6)

Assumption used in the model: The vCJD agent is present in the blood of infected individuals only during the last half of the incubation period. This assumption was expressed mathematically in the model as the probability that the incubation period of the disease was less than or equal to twice the elapsed period (1997-y). The period (1997 – y) is the number of elapsed years from the time of initial infection of an individual (in year *y*) until plasma was collected in the year 1997. For example, if an individual was infected in year y (for instance in 1987), and their blood or plasma was collected in 1997, the time since infection would have been (1997-y) years (1997 – 1987 or 10 years). In our example if we assume that the vCJD incubation period is 15 years, which is less than twice the elapsed period of 20 years (i.e., two times 10 years) the model would predict that the donor had vCJD agent in their blood in 1997.

The probability that an individual had the vCJD agent in their blood in year 1997 was represented in the model using the expression:

$P_{LH\text{-}y}$ = Cumulative frequency of Gamma (4.7, 3.6), at $x=2\times(1997\text{-}y)$

III. A.2. d. P_{LH}- *Probability of an infected individual having vCJD agent present in their blood (prionemic) in year 1997.*

The probability that an individual infected in year *y* had the vCJD agent in their blood in the year 1997 was estimated in the model by determining if the incubation period of the disease was equal to or shorter than twice the elapsed period (1997-y). The period (1997 – y) is the number of elapsed years from the time of initial infection of an individual (in year *y*) until plasma was collected in the year 1997. Overall the probability that an individual was infected during the whole period between 1980 and 1996 is the sum of the product of $P_{infect\text{-}y}$ and $P_{LH\text{-}y}$, for y equal to each year from 1980 through 1996. An individual potentially could be exposed to the BSE agent and acquire vCJD infection in any year between 1980 and 1997. Therefore, the probability that an individual was infected during the period 1980-1997 and was prionemic in year 1997 was calculated by the equation:

$$P_{LH} = \sum_{y=1980}^{1996} (P_{\inf ect-y} \times P_{LH-y})$$

III. A.2. e. $P_{vCJD-LH}$-The prevalence of prionemia among the UK donors in year 1997 is represented by the equation:

$$P_{vCJD-LH} = P_{vCJD} \times P_{LH}$$

The prevalence of prionemia among the UK population for the year 1997, $P_{vCJD-LH}$, shown in the equation above is a product of the probability a person will have vCJD (P_{vCJD}) times the probability they were prionemic, P_{LH-y}. The probability of vCJD occurring in the UK population was estimated for two distinctly different vCJD prevalences as described previously in section III. A. 1. The first prevalence estimate of 1 in 4,225 was based on an surveillance study of lymphoreticular tissues conducted in the early to mid-1990s in the UK (Hilton *et al* 2004) and may represent potential vCJD infections. The second prevalence estimate of 4 vCJD infections per million was based on epidemiological modeling of reported UK vCJD cases and is more reflective of known and potential vCJD cases (Clarke and Ghani 2005). However, given the uncertainty and disparity between each of these prevalence estimates it is difficult to say with any precision which, if either, is the best estimate for the potential infectivity of donors.

III. A. 3. Estimation of probabilities that a plasma pool contains a vCJD donation and probable number of vCJD donations per plasma pool

Estimation of the probability and number of vCJD donation(s) in a plasma pool in the model is a function of two factors:

- The prevalence of prionemia among the UK donors
- Number of donors per pool

Two versions of the model were used to generate two separate sets of results: one version of the model used the higher vCJD prevalence estimate and a second version of the model used the lower vCJD prevalence estimate; the prevalence estimates are described above. Results from each of the two versions of the model are shown in the risk characterization section (Section IV) of this document.

III. A.3. a. $\mathbf{D_{Tpool}}$ **-** *Total number of donors per pool*

Assumption used in the model: FXI was manufactured from a pool of approximately 20,000 plasma donations. Each donation was presumed to come from different donors. Therefore,

D_{Tpool} *= 20,000 donors*

III. A.3. b. D_{vCJD} *-Probable number of vCJD donors or donations present per plasma pool*

Assumption used in the model: The number of vCJD donors per plasma pool is represented by a binomial distribution defined by two arguments alpha (α) and beta (β) (represented in the model by the expression Riskbinomial (α, β)). Alpha represents the total number of donors per plasma pool (D_{Tpool}), which is 20,000 in this case. Beta is the probability of a donor to have prionemia when donating, which is the prevalence of prionemia among the UK population in year 1997 ($P_{vCJD\text{-}LH}$ calculated in III.A.2.e). D_{vCJD} is represented by the expression:

D_{vCJD} = Riskbinomial (α, β) = Riskbinomial (D_{Tpool}, $P_{vCJD\text{-}LH}$,) or Riskbinomial (20000, $P_{vCJD\text{-}LH}$)

The probable number of vCJD donors (donations) present in a single plasma pool was estimated for the two UK vCJD prevalences discussed in section III. A. 1 (based on the tissue surveillance study and epidemiological modeling-based methods).

III. A.3. c. $P_{\mathbf{vCJD\text{-}pool}}$-*Probability of a plasma pool containing a vCJD donor (donation)*

The probability of a plasma pool containing a vCJD donor (donation) depends on number of donors who contribute to a pool and vCJD prevalence among the UK donor population.

Assumption used in the model: The number of vCJD donors per plasma pool is represented by a binomial distribution defined by two arguments alpha (α) and beta (β) (represented in the model by the expression Riskbinomial (α, β)). Alpha represents the total number of donors per plasma pool (D_{Tpool}), which is 20,000 in this case. Beta is the probability of a donor to have prionemia when donating, which is the prevalence of prionemia among the UK population in year 1997 ($P_{vCJD\text{-}LH}$ calculated in III.A.2.e). Cumulative frequency of binomial distribution (D_{Tpool}, $P_{vCJD\text{-}LH}$) at X=0 represents the probability of a plasma pool not to contain any infected donor (donation); therefore, the probability a plasma pool containing a vCJD donor (donation) was calculated by:

$P_{\mathbf{vCJD\text{-}pool}}$**= 1-** Cumulative frequency of Binomial(D_{Tpool}, $P_{vCJD\text{-}LH}$), at x=0

III. A.4. Estimation of Quantity of vCJD agent per donation and in plasma pools used in manufacturing UK FXI

III. A.4.a. $\mathbf{I_D}$ - *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 is 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. i. **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. The plasma portion is 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.a. ii. **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 vCJD infected individuals is represented in the model by a log normal statistical distribution of (*2, 12, 30*)* i.c. ID_{50}/ml *(5th percentile, most likely, and 95th percentile) with minimum and maximum of 0.1 and 1,000, respectively.*

Based on limited available data (see below), FDA believes that the quantity of infectivity present in blood from a vCJD infected individual in i.v. ID_{50} is likely represented by a distribution with the following characteristics: Minimum value = 0.1, 5th percentile = 2, Most likely value = 10, 95th percentile = 30, and Maximum value= 1,000 i.v. ID_{50}. Given the possible parameters, statistical distributions were fitted to the selected parameters using Best Fit part of the @Risk Professional software package (Palisade Corporation, New York). Using the software we determined that a log normal statistical distribution (of (2, 12, 30) i.c. ID_{50}/ml (5th percentile, most likely, and 95th percentile) with minimum and maximum of 0.1 and 1,000, respectively) provided the best fit.

Conclusions from several 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 mouse model and human CJD Brown *et al* (1999) found a range from 0.5 to 15 mouse i.c. infectious units (IU) per ml which we assumed to be roughly equivalent to 1 to 30 i.c. ID_{50} (assuming a linear dose-response for infectivity). One IU is the quantity of infectivity associated with a 100% probability of infection in recipients and roughly equates to two ID_{50} units (1 IU = 2 ID_{50}). 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 as high as 20 – 30 infectious doses per ml (40-60 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. Summarizing the above literature it seems that the range of reported values for infectivity ranged from 0.5 to as high as 30 i.c. ID50 with the possibility that at times the infectivity present in blood may exceed this range.

Assumption used in the model: Whole blood collected from a vCJD-infected individual can vary from person to person in the quantity of infectivity it contains. The model used a log normal statistical distribution to represent the variability and uncertainty of the quantity of infectivity in

blood. It was assumed that whole blood from an infected person potentially carries a minimum of 0.1 i.c. ID_{50} per ml, a 5^{th} percentile of 2 i.c. ID_{50} per ml, a median of 12 i.c. ID_{50} per ml, a 95^{th} percentile of 30 i.c. ID_{50} per ml and a maximum of 1,000 i.c. ID_{50} 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_{50}/ml by their assay meaning that infected blood containing less than 1,000 ID_{50} would not have elicited infection or disease in their animal model, hence infectivity would not have been detected (Wadsworth, 2001).

III. A.4.a**.** iii. **$I_{Pl\text{-}perc}$** - *Percentage infectivity associated with plasma (i.c. ID_{50}/ml)*

$I_{Pl\text{-}perc}$ - *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 in animal models have shown that greater than 50% of transmissible spongiform encephalopathy agent present in whole blood is associated with plasma. Experiments by 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 assumes that 58% of infectivity is associated with plasma.

III. A.4.a**.** iv. **I_D** - *Total infectivity (or i.c.ID_{50}) per vCJD recovered plasma donation*

Total i.c.ID_{50} per vCJD donation is represented by the equation:

$$\mathbf{I_D = D_V \times I_{bl} \times I_{Pl\text{-}perc}}$$

In this case **I_D** or total infectivity or i.c. ID_{50} per vCJD donation equal to the volume of plasma per donation (**D_V**) multiplied by the infectivity associated with plasma which is derived from the ID_{50}s present in blood (**I_{bl}**) times the percentage of infectivity present in plasma (**$I_{Pl\text{-}perc}$**). Total vCJD infectivity is expressed in terms of the ID_{50} or the infectious dose needed to cause infection in 50% of the population.

Assumption used in the model: One ID_{50} is the amount of material containing infectious agent that has a 50% probability of causing infection in an individual or population.

III. A.4.a**.** v. **$A_{ic\text{-}iv}$** - *Adjustment for intravenous route of infection*

$A_{ic\text{-}iv}$ - *is represented in the model by a uniform distribution between 1 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. Based on discussion and advice from the FDA Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) (Oct 31, 2005) the range of efficiency of i.v. route (versus the i.c. route) was assumed in the model to range between the values of 1 and 10.

Assumption used in the model: Exposure to infectivity by the i.v. route is between 1 and 10 times less efficient at causing infection than introduction via the intracerebral route. Using a value of 1 for the ratio of the lower bound of the efficiency is a conservative estimate and assumes that theoretically there would be no difference between the efficiency in initiating infection between the i.c. and i.v. routes.

III. A.4.b. $\mathbf{I_{iv\text{-}pool}}$ - *Total intravenous infectivity or i.v.ID_{50} per plasma pool of 20,000 donors*

The output of this component of the model, total i.v. ID_{50} per plasma pool, is represented by the equation:

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

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

III.B. Total i.v. ID_{50} per vial after processing / production of FXI

This component of the model estimates the total i.v. ID_{50} of vCJD infectivity that may be present in a vial of FXI that was manufactured in the UK and used in the US under IND. Production of FXI in the UK 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 FXI 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 types of processing steps used in the manufacture of FXI we assumed a most likely reduction in infectivity of 2 $\log_{10}$ (or 99%). These two steps would result in a significant reduction in the amount of vCJD present in the FXI product from the UK. However, the model assumes that infectivity would only be reduced and not eliminated. Therefore, if present in the original donations, some vCJD infectivity is predicted by the risk assessment model to persist, following manufacturing, in some FXI final product produced in the UK and may have then posed a risk of transmitting vCJD to patients that received the product.

III.B.1. $R_{W\%}$ - *Percentage of pool used to manufacture FXI*

The initial starting amount of material from 20,000 recovered plasma donations in the UK was estimated to weigh 5,000 kg of which 800 kg (or 16%) of the material was removed and used to produce FXI. As stated earlier this step represents an 84% reduction in the quantity of starting materials; consequently any infectivity that may be present would also be removed 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 FXI*

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 FXI.

Portion used is represented by the equation and calculations:

$$R_W = W_m / W_{st}$$
$$R_W = 800 / 5{,}000$$
$$R_W = 0.16$$
$$R_{W\%} = 16\%$$

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_{50}s present in the original pool of 20,000 donations.

III.B.2. R_{Log} - *Log reduction in ID_{50} during processing*

Represented in the model by a triangular statistical distribution representing a reduction in ID_{50} during processing of (0, 2,4) Log_{10} i.v. ID_{50}/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 FXI has the potential to reduce the amount of vCJD agent present by physical separation (partitioning). Based on available

scientific data for similar processes, as well as studies of prior reduction during manufacturing of different plasma products, CBER has estimated by internal expert opinion that the level of removal of the vCJD agent during processing corresponds to a reduction of a minimum of 0, a most likely reduction of 2 Log_{10} ID_{50}, and a maximum possible reduction of 4 Log_{10} ID_{50} 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_{50} during processing of (0, 2, 4) Log_{10} i.v. ID_{50}/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_{50}* vCJD agent may be reduced, the percentage of pools and vials containing the vCJD agent still remains the same.

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

$$\mathbf{I_{pp} = I_{iv\text{-}pool} \times R_W \times 1/10^{Rlog}}$$

The total i.v. infectivity (i.v. ID_{50}s) present in processed product ($\mathbf{I_{pp}}$) is a function of the total infectivity present in the pool ($\mathbf{I_{iv\text{-}pool}}$) prior to processing steps that might reduce the amount of infectivity present in the final FXI product. The infectivity in the pool ($\mathbf{I_{iv\text{-}pool}}$) is multiplied by $\mathbf{R_W}$ because only 800kg out of the original 5,000 kg (or 16%) of starting plasma pool is used and multiplied by processing reduction steps ($\mathbf{R_{Log}}$), which are expected to reduce the infectivity in the final FXI 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. $\mathbf{Y_{fT}}$ - *Total yield of FXI from plasma pool*

FXI is present in trace amounts in human plasma.

Assumption used in the model: The estimated yield of FXI per kg plasma was approximately 150 to 180 units, subsequently the model estimates the total yield of FXI as 120,000 to 144,000 units per batch of 800 kg starting material. FXI was distributed in vials containing 1,000 units each (BPL, 2001).

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

$$\mathbf{Y_{fT} = W_M \times Y_{f\text{-}kg}}$$

III.B.4.a. $\mathbf{Y_{f\text{-}kg}}$ - *Yield of FXI 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_u - *Vial size or number of units per vial*

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

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

The FXI 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:

$$V_T = Y_{fT} / V_u$$

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

The total i.v. ID_{50} present in each vial of FXI 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:

$$I_{vial} = I_{pp} / V_T$$

or including all component variables by the equation:

$$I_{vial} = \left[\frac{D_{vCJD} \times D_V \times I_{bl} \times I_{pl}}{A_{ic\text{-}iv}} \right] \times R_W \times 1/10^{RLog} \Big/ (W_m \times Y_{f\text{-}kg} / V_u)$$

Summary of variable names used above are:
D_{vCJD} - *Total number of vCJD donations per pool*
D_V - *Amount of recovered plasma per donation*
I_{bl} - *Infectivity of vCJD (or i.c.ID_{50}) present in infected blood per ml*
I_{pl} - *Proportion infectivity associated with plasma (i.c.ID_{50}/ml)*
$A_{ic\text{-}iv}$ - *Adjustment for intravenous route of infection*
R_W - *Portion of pool used to manufacture FXI*
R_{Log} - *Log reduction in ID_{50}s during processing*
W_m - *Portion of total product used in manufacturing(800 kg).*
$Y_{f\text{-}kg}$ - *Yield of FXI per kg of plasma*
V_u - *number FXI units per vial*

III.C. Utilization by patients with FXI deficiency undergoing surgery

FXI normally circulates in the human bloodstream at a concentration of approximately 50 u/dl (5ug/ml) and has been observed by some researchers to be present at concentrations as high as 70 u/dl. Those with very severe FXI deficiency have < 1 unit per deciliter (u/dl) of blood (BPL, 2001). The commonly used target treatment dose ranged from 20 – 50 u/ kg body weight. Individuals at risk for excessive bleeding 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 FXI

Published data are available on the per surgical event utilization of FXI (Mannucci *et al* 1994, Aledort *et al* 1997) manufactured in the UK 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 20 – 50 u/kg is provided. The scenarios described below approximate the amount of FXI 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 60 kg individual with FXI (20 – 50 u/ kg) once during or after surgery for a total patient dose of approximately 3,000 units.

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

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

III.C.1.a. D_{Pre} - *Prior to major Surgery - doses of 20 – 50 u/ kg given*

Assumption used in the model: The dosage prior to surgery is approximately 20 – 50 u/kg body weight. This dosage scheme is represented in the model with a point estimate.

D_{Pre} = **Dose** (*20 – 50 u/kg)* x **Patient weight (kg) x Number treatments**

III.C.1.b. D_{Post} - *Post-surgical maintenance of 20 – 50 u/kg every 2 - 3 days*

Assumption used in the model: The post-surgery maintenance dosage is assumed to be *20* – 50 u/kg given every two to three days. This dosing scheme is represented in the model with a point estimate.

$\mathbf{D_{Post}}$ = **Dose** (*20 – 50 u/kg)* x **Patient weight (kg) x Number treatments**

III.C.1.c. D_T - Total FXI doses given per patient per surgical procedure

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

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

III.C.2. Scenario 1: Treatment 60 Kg individual with 3,000 units FXI

A 60 Kg person receives one dose FXI to minimize potential bleeding episodes at a concentration of *20* – 50 u/kg would receive a total of approximately 3,000 units. Output is the estimated total units FXI received and estimated vCJD ID_{50} received. At this time, the actual dosing that patients received is not known.

III.C.3. Scenario 2: Treatment with 9,000 units FXI

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 FXI to minimize potential bleeding episodes. Output is the estimated total units FXI received and estimated vCJD ID_{50} received.

Scenario 2 is similar to amounts of FXI given in three dosing regimens given at 20 – 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 FXI

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 FXI 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 20 – 50 u/kg.

Output Scenario 3: Estimated Total units FXI received and estimated vCJD ID_{50} 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_{50}, 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_{50} 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_{50} would suggest a 50% probability of infection, exposure to 0.1 ID_{50} would suggest a 5% probability of infection, and so on.

In assuming a linear dose-response relationship we have chosen a conservative approach with respect to the risk that may be present at decreasing exposure levels below an ID_{50}. However, it is possible that exposure to less than 1 ID_{50} may not result in infection. 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 FXI will be imprecise and extremely uncertain.

IV.A. The Model

This risk assessment and simulation model links the available scientific and epidemiological data together to mathematically approximate the processes (predicted presence of vCJD in UK population, manufacturing, reduction of vCJD agent, and patient utilization) leading to potential exposure of US patients to vCJD agent present in UK-manufactured FXI. 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 risk assessment uses Monte Carlo simulation to randomly draw values from probability input distributions (which are statistical representations of input data) once per iteration; thousands of iterations are used to generate the model outputs as risk estimates. This simulation method is often used in situations when a model is complex, non-linear, or involves several uncertain parameters. The output generated is usually an aggregate distribution whose shape can be summarized using measures of central tendency (mean, median, mode) or with boundaries such as the 95% confidence interval (CI), the 5^{th} and 95^{th} percentiles (representing the 90% CI) or the range, bounded by the minimum and maximum values generated as part of the output. The strength of Monte Carlo analysis is that it generates resulting risk estimates as statistical distributions which reflect the underlying uncertainty and variability of the original input data and parameters.

The model provided predictions of estimated exposure to the vCJD agent in the form of intravenous (i.v.) ID_{50} in patients treated with UK-manufactured FXI. **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 in Table 7 show the estimates of potential probabilities that a plasma pool used to manufacture FXI from UK donor plasma may potentially contain a vCJD donation and predicts the number of possible vCJD donations per pool. Using the epidemiological case based prevalence estimate (4 infections per million population) the modeling estimates that a mean of 1.6% of pools may contain a vCJD agent. Using the higher tissue sample surveillance– based prevalence estimate (1 in 4,225) as a possible higher prevalence scenario the model estimates that an average of 50% of pools may possibly contain vCJD agent. A more detailed version of Table 7 is provided in Appendix C (Table C.I.) and in addition displays the median estimates of the potential probabilities of a vCJD donation and number of vCJD donations per plasma pool.

Table 7. Potential Probabilities and Number of vCJD donations per Plasma Pool

	MODEL OUTPUT USING LOWER PREVALENCE ESTIMATE *vCJD Case Prevalence from epidemiological modeling ~4 per million (Clark and Ghani, 2005)*		***MODEL OUTPUT USING HIGHER PREVALENCE ESTIMATE*** *vCJD Infection estimate from tissue surveillance study 1 in 4,225 (Hilton et al 2004)*	
	Mean	**5th- 95th percentiles[(a)]**	**Mean**	**5th- 95th percentiles[(a)]**
Probability pool contains vCJD donation	**1.6%**	1.1% - 2.1%	**50%**	18% - 77%
Number vCJD donations per pool	**0.02**	0 – 0[b]	**0.75**	0 - 3

[a] The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.

[b] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FXI recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FXI plasma pool would be rare and more than 90% of FXI product lots (of vials) would not be predicted to contain vCJD agent.

Table 8 displays results from the model of estimates of risk for 3 different treatment scenarios. FDA recently reviewed the original IND protocols and patient treatment regimens – the three scenarios reflect representative treatment scenarios and the range of FXI quantities used in the original IND studies. The model indicates risk ranges from a low in Scenario 1, at the lower prevalence estimate, with a mean exposure of 3.11×10^{-3} i.v. ID_{50} and a mean estimated per person

(per treatment course) risk of vCJD infection of 1 in 643. The higher end of the range of risk is illustrated in Scenario 3, using the higher estimate of prevalence, the model estimated a mean exposure of 0.59 i.v. ID_{50} and a mean estimated per person (per treatment course) risk of vCJD infection of 1 in 3.4.

Readers may notice that the results for "mean potential vCJD risk per person" generated by the model using the low vCJD case prevalence estimate have 5^{th} and 95^{th} percentile values of 0 and 0, respectively (Table 8). Because at low vCJD prevalence the model results indicate that the chance of an infected donor (with infectious vCJD agent in their blood at the time of donation) donating to a plasma pool would be an infrequent event. The zero values for the 5^{th} and 95^{th} percentiles indicate that at least 95 percent of the time the model predicted the risk of possible vCJD infection was zero for FXI recipients because the vCJD agent was not present in FXI product as administered during treatment. However, 1.6% of the time FXI lots may contain the vCJD agent and this results in an average per person exposure that is greater than zero as shown for the low vCJD case prevalence under the column "Mean vCJD i.v. ID_{50}" in Table 8. Although the model suggests that exposure of FXI recipients may have occurred, particularly when the higher estimate of prevalence based on tissue samples is used, the large variability and uncertainties in the data used in the model, and in assumptions used in the model itself do not allow us at this time to determine if exposure to the vCJD agent, in fact, did or did not occur in FXI recipients and it is not possible to estimate the precise magnitude of risk faced by recipients of UK-manufactured FXI product. Also, the possibility of vCJD exposure and infection does not necessarily mean that an individual will go on to develop symptoms of vCJD or vCJD disease. A more detailed version of Table 8 is available in Appendix D (Table D.I.), which also displays the median estimates of the potential probabilities of a vCJD donation and number of vCJD donations per plasma pool.

Table 8. Mean Potential Exposure and Mean Potential Risk per Person per FXI Treatment Scenario.

		MODEL OUTPUT USING LOWER PREVALENCE ESTIMATE *vCJD Case Prevalence from epidemiological modeling ~4 per million (Clark and Ghani, 2005)*		***MODEL OUTPUT USING HIGHER PREVALENCE ESTIMATE*** *vCJD Infection estimate from tissue surveillance study 1 in 4,225 (Hilton et al 2004)*	
Scenario	**Quantity* Factor XI Utilized** (u*)	**Mean potential exposure to vCJD i.v. ID_{50}**** (5^{th} - 95^{th} perc)[a]	**Mean potential vCJD risk*** per person** (5^{th} - 95^{th} perc)[a]	**Mean potential exposure to vCJD i.v. ID_{50}**** (5^{th} - 95^{th} perc)[a]	**Mean potential vCJD risk*** per person** (5^{th} - 95^{th} perc)[a]
Scenario 1: Treatment 3,000 u	3,000 u	**3.11×10^{-3}** (0 - 0)[b]	1 in 643 (0 - 0)[b]	**0.12** (0 – 0.57)	1 in 17 (0 – 1 in 3.5)
Scenario 2: Treatment 9,000 u	9,000 u	**9.33×10^{-2}** (0 - 0)[b]	1 in 214 (0 - 0)[b]	**0.36** (0 – 1.70)	1 in 5.6 (0 – 1 in 1.2)
Scenario 3: Treatment 15,000 u	15,000 u	**1.55×10^{-2}** (0 - 0)[b]	1 in 130 (0 - 0)[b]	**0.59** (0 – 2.86)	1 in 3.4 (0 – 1 in 1)

*u - represents units of Factor XI – and is equivalent to the term "unit" or "units" used in this document
** Mean vCJD i.v. ID_{50} (per treatment course) - the average predicted quantity of vCJD agent an individual in a specific treatment group is predicted to receive based on the model.
***Mean potential vCJD risk per person – the per person risk of potential vCJD infection based on animal model dose-response information. Mean potential vCJD risk per person = Total mean quantity i.v. ID_{50} (per treatment course/per person) x 0.5 (50 % chance infection - ID_{50})
[a] The 5^{th}- 95^{th} perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model are expected to fall within this defined interval at least 90% of the time.
[b] For a 5^{th} and 95^{th} percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FXI recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FXI plasma pool would be rare and more than 90% of FXI product vials would not be predicted to contain vCJD agent.

IV. C. Sensitivity Analysis

Sensitivity analysis is used to identify the input parameter or parameters that have the greatest impact on the risk estimates generated by the model. Our goal in doing the analysis was to identify the key input parameters that have the greatest influence on annual exposure to the vCJD agent. Generally, sensitivity analysis is conducted by varying the values of key input parameters about a range of values and then evaluating the effects on the final risk estimate. The model was examined and candidate variables for the sensitivity analysis were chosen from the model that exhibited the largest potential for variability and/or uncertainty and those values are listed in Table 9. We conducted a type of sensitivity analysis called importance analysis which evaluates the impact of a minimum and a maximum value on the risk estimate and ranks the factors in the model based on their importance (or influence) on the risk estimate. Our analysis used two values, one at the 5^{th}

percentile (or minimum) value and one at the 95th percentile (or maximum) value to provide a reasonable estimate of impact across the range tested. Results from the analysis are displayed as tornado graphs (Figures 2.A. and 2.B.), which graphically shows the relative influence of each input parameter evaluated on the final model estimates. For the FXI risk assessment the output being monitored in the sensitivity and importance analyses was the predicted annual exposure (I_{yr}) to vCJD agent, quantified in i.v. ID_{50} units, to recipients of FXI.

The sensitivity analysis was run separately each time using one of the two surveillance estimates. The first analyses used the higher vCJD Infection prevalence estimate of 1 in 4,225 (or 237 per million) derived from a tissue surveillance study (Hilton *et al* 2004) For the purposes of this analysis we first adjusted the prevalence for donor age and the presence of infectivity in the blood during the last half of the incubation period, which generated a range about the adjusted HIGHER vCJD Infection prevalence ($P_{vCJD\text{-}AdjSurv}$) based on the tissue surveillance study with a 5th percentile value of 3 per million and a 95th percentile value of 135 per million. The second set of analyses used the lower vCJD Case prevalence estimate of ~1.8 per million based on epidemiological modeling from actual vCJD occurrence conducted by Clarke and Ghani (2005). As for the first analyses, prevalence was adjusted by donor age and the presence of infectivity in the blood during the last half of the incubation period which generated a range about the adjusted LOWER vCJD Case prevalence ($P_{vCJD\text{-}AdjEpi}$) based on epidemiologic modeling with a 5th percentile value of 0.5 per million and a 95th percentile value of 1 per million.

Table 9. Input Variables included in Importance Analysis

Name of input variable	Description of variables	Range for importance analysis
$P_{vCJD\text{-}AdjSurv}$	Adjusted Tissue surveillance-based prevalence (HIGH prevalence estimate): vCJD Infection prevalence (at last half incubation period) in UK donor (cases/million)	5th perc: 3 95th perc: 135
$P_{vCJD\text{-}AdjEpi}$	Adjusted Epidemiological modeling based prevalence(LOW prevalence estimate): vCJD prevalence (at last half incubation period) in UK donor (cases/million)	5th perc: 0.5 95th perc: 1
$A_{ic\text{-}iv}$	Adjustment factor for i.v. infectivity vs i.c. infectivity	Minimum: 0.1 Maximum: 1
I_{bl}	i.c. infectivity of infected human blood	Minimum: 2 Maximum: 30
Y_{VIII}	FXI Yield (u/L plasma)	Minimum: 150 Maximum: 180
R_{Log}	Reduction of infectivity during manufacturing	Minimum: 0 Maximum: 4
D_T	Annual usage of FXI (u/year)	Minimum: 3,000 Maximum: 15,000

The analysis was performed for each variable by doing two sets of simulations, each with 5,000 iterations. For each set of simulations the value of one testing variable was set at the minimum or 5th percentile value for the input distribution and the simulation run; for the second run the variable was set at the maximum or 95th percentile value and the simulation run. The results of all simulations and the ranking of input parameters by their importance are graphically depicted using

a tornado plot or graph as shown in Figures 2.A. and 2.B. The tornado plot displays the correlations between key inputs in the model and the model output of exposure. A tornado plot prioritizes the various input factors with the most influential factors at the top and those that are least influential or those with negative influence on the risk are at the bottom of the plot.

Figure 2. A. FXI Importance Analysis Ranking Influential Factors for Predicted Annual vCJD Exposure (I_{yr}) Using an Adjusted Tissue Surveillance-Based (HIGH) Prevalence Estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of FXI recipients.

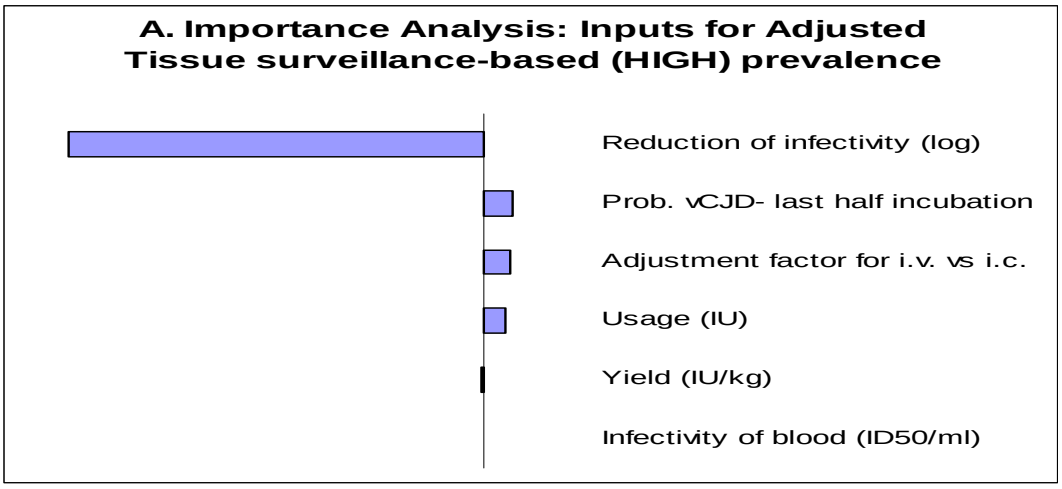
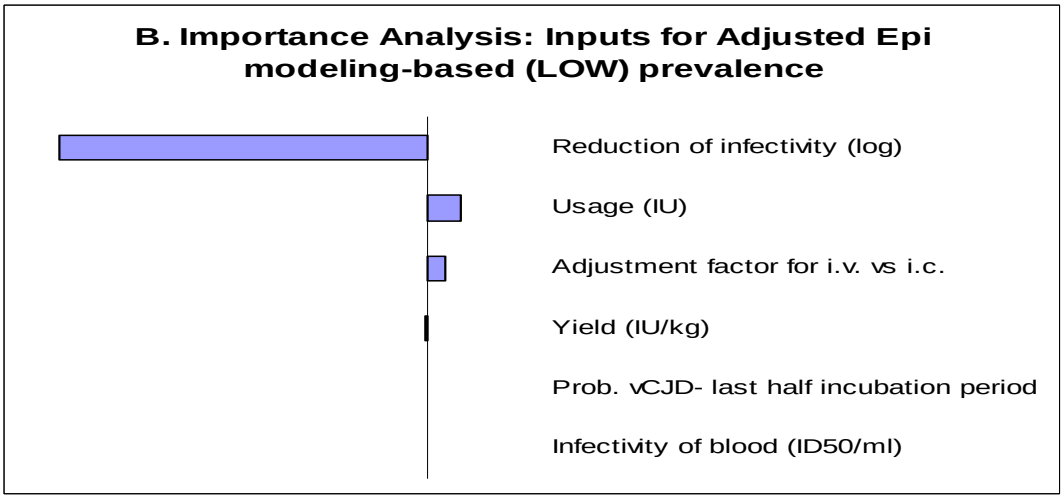


Figure 2. B. FXI Importance Analysis Ranking Influential Factors for Predicted Annual vCJD Exposure (I_{yr}) Using an Adjusted Epidemiological Modeling-Based (LOW) Prevalence Estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of FXI recipients.



The order of the influence of the specific input factors varies slightly when the importance analysis is conducted using the two difference prevalence estimates. The tornado plots in Figures 2 A and B both show that clearance or Log reduction of vCJD agent ($\mathbf{R_{Log}}$) during the manufacturing

process is the dominant factor that influences the annual exposure or risk for a FXI recipient. The importance analysis suggests that changes in the input values for prevalence used in the analysis can cause some moderate yet visible changes in the rank order of the influence of the various input factors. For instance, using the HIGH prevalence estimate ranks the probability of vCJD agent in the blood during the last half of the incubation period as the second most influential factor in the model (Figure 2 A), while using the LOW prevalence it ranks fifth (Figure 2 B). The four variables – the presence (or not) of vCJD agent in blood during the last half of incubation period ($\mathbf{P_{LH}}$), adjustment for route of administration ($\mathbf{A_{ic\text{-}iv}}$), FXI usage ($\mathbf{D_{Tu}}$) (u), and FXI yield ($\mathbf{Y_{fT}}$) (u/kg), do reassort and change rank when the two different prevalence estimates were used. Overall, however, they were somewhat similar in asserting their influence on the estimated risk outcome(s), but had significantly less influence when compared to that of reduction of infectivity during processing and manufacture. Although these types of sensitivity analysis and tornado plots are often used to identify influential factors of risk, their use has some limitations. Factors are examined singly or in isolation so interaction among various factors that may influence the risk estimate are not addressed.

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, where possible, to represent the uncertainty of much of the information used in the model. There are uncertainties in the information and the model that we were unable to quantify and that are not represented in the final risk estimates. Some of the difficult to quantify uncertainties are associated with the extrapolation of a human dose-response relationship based on animal data, an assumed linear dose response with no uncertainty or variability bounds, and assumption of infectivity in the last 50% of the incubation period. 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^{th} and 95^{th} percentiles, which represent the 90% confidence interval for each estimate. The uncertainty for the risk estimates generated by this FXI risk assessment model is significant and decision makers should use the results with caution. Similarly, patients and physicians should understand that the uncertainties are too great at this time to determine the presence, absence or degree of actual risk. 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 an estimate of risk based on the current and known information. It is still a useful tool that can inform 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. The sensitivity analysis results in Section IV.C. indicated that the risk assessment results are highly dependent upon log reduction of vCJD agent ($\mathbf{R_{Log}}$) during the manufacturing process. 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. More high quality data on the levels of vCJD agent clearance achieved during the FXI manufacturing would likely improve the final risk estimate generated by the FDA model. Given the lack of data on vCJD agent clearance for FXI uncertainty is considerable.

Better information on when infectivity is present in human blood during the incubation period is a critical factor in the model, especially if the HIGHER vCJD infection prevalence estimate (of 1 in 4,225) is in the range of the actual vCJD prevalence, and would improve predictions generated by the model. There are no data 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. Although we did estimate a probability of infection in our model, the uncertainty associated with the estimate is considerable. However, a meaningful dose-response model would need to be generated for vCJD exposure in humans to improve estimates of the probability of adverse clinical outcomes for humans. The type of data needed to generate a dose-response model that would improve the quality of TSE risk assessment predictions would necessitate injection of groups of animals at several different concentrations of ID_{50}, including low doses below 1 ID_{50} using a protocol that mimics transfusion transmission of vCJD in humans. Both infection and duration of the incubation periods at several different i.v. ID_{50} concentrations would be useful endpoints for developing informative dose-response relationships. Given the state of the current TSE science, estimates of the probability of vCJD infection or illness arising from exposure to the vCJD agent are still extremely uncertain. Nevertheless risk assessment is a tool that provides insight into important factors where additional research is needed into production processes, tools, or strategies that may further reduce vCJD risks and advance product safety for patients.

IV. E. Conclusions

Potential exposure to the vCJD agent present in FXI manufactured in the UK and used during investigational studies in the US from 1989 to 2000 was estimated in this probabilistic risk assessment.

Although no UK-manufactured FXI product used in the US under IND from 1989 to 2000 was manufactured from “implicated” plasma pools that contained donations from an individual(s) later diagnosed with known vCJD, it is possible that FXI product manufactured from UK plasma in the 1990s may have been manufactured from plasma pools that contained a plasma donation(s) from an individual who was unknowingly incubating vCJD. The results of the computer modeling suggest that, if so, there could have been exposure to the vCJD agent and a potential risk of infection to some recipients of FXI, particularly if the incidence of unsuspected infection with vCJD in the UK is higher than scientists generally believe based on the occurrence to date of vCJD cases. Unfortunately, there are so many uncertainties that it is not possible based on available scientific information to provide an actual or precise estimate of any potential risk. Although the actual risk, if any, remains unknown, the computer model indicates that the most important factors affecting the potential for risk are the clearance of the vCJD agent though manufacturing steps, how much product individuals used, efficiency of the i.v. versus the i.c. route of exposure, and the vCJD prevalence in the UK donor population.

In considering the results of the risk assessment it is important to note that to date we are not aware of any cases of vCJD having been reported worldwide in patients receiving plasma-derived products, including pdFXI.. This includes patients receiving large amounts of other products manufactured from UK plasma donations over a long period of time. This observation suggests that the actual risk of vCJD infection from pdFXI is likely to be low. The absence of cases does not rule out the possibility of exposure that could potentially result in illness in some recipients at some future point in time.

Appendix A

Table A. Summary of Model Components and Inputs

Input Data and Information in the FXI – vCJD Risk Assessment			
III. A. Probability of donation containing vCJD infectivity and the total quantity of intravenous vCJD infectivity (i.v. ID_{50}) per plasma pool			
	Variable description	**Variable name**	**Numerical input / output**
A.1.	*Estimation of UK vCJD prevalence via two methods*		
A.1.a.	*Probability of vCJD-infected individual in UK population who will develop symptoms – determined by epidemiologic modeling-based prevalence estimate.*	$\mathbf{P_{vCJD\text{-}Epi}}$	4 infections per million (95% CI: 3-6 cases per million)
A.1.a.i.	*Estimated Number of vCJD-infected individuals in UK population using recorded vCJD cases (1997and before) – 2004*) and epidemiological modeling based prevalence estimate*	$\mathbf{N_{vCJD\text{-}CE}}$	$\mathbf{N_{vCJD\text{-}CE}}$, is the sum of 138 reported vCJD cases, $\mathbf{N_{vCJD\text{-}Case}}$, and the cases estimated by epidemiological modeling, $\mathbf{N_{vCJD\text{-}Epi}}$, or an estimated 70 future cases; the sum of the expression is a total mean of 208 cases vCJD (95% CI: 148 – 328)
A.1.a.ii.	*Number of reported vCJD cases in UK population 1997 – 2004.*	$\mathbf{N_{vCJD\text{-}Case}}$	138 cases
A.1.a.iii.	*Number of future vCJD-infected individuals in UK population based on epidemiological modeling prevalence estimate*	$\mathbf{N_{vCJD\text{-}Epi}}$	The cases estimated by epidemiological modeling, $\mathbf{N_{vCJD\text{-}Epi}}$, is an estimated 70 future cases
A.1.b.	*Probability of vCJD-infected individual in UK population using the surveillance prevalence estimate*	$\mathbf{P_{vCJD\text{-}Surv}}$	237 infections per million (95%CI: 49-692) Or (1 / 4,225) (95% CI = 1 / 20,280)
A.2.	*Estimation of probability that infectivity will be present in blood (prionemia) in vCJD infected individuals at time of donation*		The vCJD agent is present in blood during the last half of the incubation period in vCJD infected individuals.
A.2 a.	*BSE cases reported in year y*	$\mathbf{BSE_y}$	BSE case numbers shown in table 6.
A.2 b.	*Probability an infection occurring in year y*	$\mathbf{P_{infect\text{-}y}}$	Based on equation: $P_{\inf ect-y} = BSE_y \,/\, \sum_{y=1980}^{1996} BSE_y$
A.2 c.	*The incubation period of vCJD was calculated in the model using a gamma distribution represented by the expression Gamma (4.7, 3.6)*	$\mathbf{IP_{vCJD}}$	IP_{vCJD} = *Gamma (4.7, 3.6)*

	Probability that the blood of an individual infected in year y will contain vCJD agent in the year 1997	**P_{LH-y}**	P_{LH-y} = Cumulative frequency of Gamma (4.7, 3.6), at x=2×(1997-y)
A.2 d.	*Probability of an infected individual having vCJD agent present in their blood (prionemic) in year 1997.*	**P_{LH}**	Based on equation: $P_{LH} = \sum_{y=1980}^{1996} P_{\inf ect-y} \times P_{LH-y}$
A.2 e.	The prevalence of prionemia among the UK population in year 1997	**$P_{vCJD-LH}$**	The prevalence of prionemia among the UK population for the year 1997, $P_{vCJD-LH}$, shown in the equation above is a product of the probability a person will have vCJD (P_{vCJD}) times the probability they will be prionemic, P_{LH}. The probability of vCJD occurring in the UK population was estimated for two distinctly different vCJD prevalences as described previously in section III. A. 1.
A. 3.	*Estimation of probabilities that a plasma pool contains a vCJD donation and probable number of vCJD donation per plasma pool*		
A. 3.a.	*Total number of donors per pool*	**D_{Tpool}**	20,000 donors or donations
A. 3. b.	*Probable number of vCJD donors or donations present per plasma pool*	**D_{vCJD}**	D_{vCJD} = Riskbinomial (α, β) = Riskbinomial (D_{Tpool}, $P_{vCJD-LH}$) or Riskbinomial (20000, $P_{vCJD-LH}$)
A. 3. c	*Probability a plasma pool containing any infected donor (donation)*	**$P_{vCJD-pool}$**	$P_{vCJD-pool}$= 1- Cumulative frequency of Binomial(D_{Tpool}, $P_{vCJD-LH}$), at x=0
A.4.	Estimation of Quantity of vCJD agent per donation and in plasma pools used in manufacturing UK FXI		
A.4.a.	*Estimated Total Infectivity (or i.c.ID_{50}) per vCJD donation*	**I_D**	(Also see outputs below)
A.4.a.i.	*Amount of recovered plasma per donation*	**D_V**	200 mls
A.4.a.ii.	*Infectivity of vCJD in infected blood per ml*	**I_{bl}**	<u>Lognormal distribution</u> Minimum = 0.1 ID_{50} 5th perc = 2 ID_{50} Median = 12 ID_{50} 95th perc = 30 ID_{50} Maximum = 1,000 ID_{50}
A.4.a.iii.	*Percentage of infectivity in plasma (ID_{50}/ml)*	**I_{pl}**	58%
A.4.a.**i**v.	*Total infectivity (or i.c.ID_{50}) per vCJD recovered plasma donation*	**I_D**	Total i.c.ID_{50} per vCJD donation is represented by the equation: **I_D = D_V x I_{bl} x $I_{Pl-perc}$**
A.4.a.v.	*Adjustment for intravenous route of*	**A_{ic-iv}**	<u>Uniform distribution</u>

	infection		Minimum = 1 Maximum = 10
Outputs			
A.4.a.	*Total infectivity (or i.c.ID_{50}) per vCJD donation*	$\mathbf{I_D = D_V \times I_{bl} \times I_{pl}}$	
A.4.b.	*Total i.v. ID_{50} per plasma pool of 20,000 donors*	$\mathbf{T_{iv\text{-}pool} = \frac{D_{vCJD} \times I_D}{A_{ic\text{-}iv}}}$	
Summary of output at this point in the model: $\mathbf{T_{iv\text{-}pool} = \frac{D_{vCJD} \times D_V \times I_{bl} \times I_{pl\text{-}perc}}{A_{ic\text{-}iv}}}$			

B. Total i.v. ID_{50} per vial after processing / production of FXI			
Inputs			
B.1.	*Percentage of pool used to manufacture FXI*	$\mathbf{R_{W\%}} = W_m / W_{st} \times 100\%$	16%
B.1.a.	*Weight of starting product*	$\mathbf{W_{st}}$	5,000 kg
B.1.b.	*Portion removed and used to extract FXI*	$\mathbf{W_m}$	800kg
B.2.	*Log reduction in ID_{50}s during processing*	$\mathbf{R_{Log}}$	Triangular distribution Minimum = 0 $\log_{10}$ Most likely = 2 $\log_{10}$ Maximum = 4 $\log_{10}$
B.4.a.	*Yield of FXI per kg of plasma*	$\mathbf{Y_{f\text{-}kg}}$	Uniform distribution Minimum = 150 u/kg Maximum = 180 u/kg
B.5.	*Vial size or # u per vial*	$\mathbf{V_u}$	1,000 u
Outputs			
B.3.	*Total ID_{50} in FXI post-processing*	$\mathbf{I_{pp}}$	$\mathbf{I_{pp} = I_{iv\text{-}pool} \times R_W \times 1 / 10^{RLog}}$
B.4.	*Total yield of FXI from plasma pool*	$\mathbf{Y_{fT}}$	$\mathbf{Y_{fT} = W_m \times Y_{f\text{-}kg}}$
B.6.	*Total number vials and vial size produced*	$\mathbf{V_T}$	$\mathbf{V_T = Y_{fT} / V_u}$
B.7.	*Total ID_{50} per vial*	$\mathbf{I_{vial}}$	$\mathbf{I_{vial} = I_{pp} / V_T}$
Summary of output at this point in the model: $\mathbf{I_{vial} = \left(\frac{D_{vCJD} \times D_V \times I_{bl} \times I_{pl}}{A_{ic\text{-}iv}} \right) \times R_W \times 1/10^{RLog} \Big/ (W_m \times Y_{f\text{-}kg} / V_u)}$			

C. Total Utilization of FXI			
Inputs			
C.1.	*Total Dose for Pre- and Post-surgical treatment with FXI*		
C.1.a.	*Prior to major Surgery - dose 20 – 50 u/kg given*	$\mathbf{D_{Pre}}$	20 – 50 u/kg
C.1.b.	*Post-surgical maintenance of dose 20 – 50 u/kg given every 2 - 3 days*	$\mathbf{D_{Post}}$	20 – 50 u/kg
Output			
C.1.c.	*Total Utilization of FXI*	$\mathbf{D_T = D_{Pre} + D_{Post}}$	
C.2.	*Scenario 1: Treatment 60 Kg individual with 3,000 u FXI*		Shown in Table 8
C.3.	*Scenario 2: Treatment with 9,000 u FXI*		Shown in Table 8
C.4.	*Scenario 3: Treatment with 15,000 u FXI*		Shown in Table 8

Appendix B

Table B. Summary of Model Assumptions

Section	Variable and description	Assumptions used in the model
III.	Not applicable	
III. A.1. a.	$\mathbf{P_{vCJD\text{-}Epi}}$ - *Probability of vCJD-infected individual in UK population who will develop symptoms – determined by epidemiologic modeling-based prevalence estimate.*	The lower prevalence estimate of vCJD in the UK population was based on Epidemiologica Modeling of predicted future cases 2004 – 2080 (Clark and Ghani, 2005) and reported vCJD cases in the UK from 1997 through 2004. Prevalence was estimated to be a mean of 4 per million.
III. A.1.a.i.	$\mathbf{N_{vCJD\text{-}CE}}$ - *Estimated Number of vCJD-infected individuals in UK population using recorded vCJD cases (1997 – 2004*) and epidemiological modeling based prevalence estimate*	The variable, $\mathbf{N_{vCJD\text{-}CE}}$, is the sum of 138 reported vCJD cases, $\mathbf{N_{vCJD\text{-}Case}}$, and the cases estimated by epidemiological modeling, $\mathbf{N_{vCJD\text{-}Epi}}$, or an estimated 70 future cases; the sum of the expression is a total mean of 208 cases vCJD (95% CI: 148 – 328)
III. A.1.a.ii.	$\mathbf{N_{vCJD\text{-}Case}}$ - *Number of reported vCJD cases in UK population 1997 – 2004.*	Based on reported cases of vCJD from 1997 through 2004 of 138 cases (see Table 3).
III. A.1.a.iii.	$\mathbf{N_{vCJD\text{-}Epi}}$ - *Number of future vCJD-infected individual in UK population based on epidemiological modeling prevalence estimate*	Our model uses the Clarke and Ghani (2005) estimate of 70 future cases of vCJD with a 95% confidence interval of 10 – 190 cases for the years 2005 – 2080. Assuming the population of the UK in 1997 is approximately 58 million.
III. A.1.b.	$\mathbf{P_{vCJD\text{-}Surv}}$ - *Probability of vCJD-infected individual in UK population using the surveillance prevalence estimate*	The higher prevalence estimate of vCJD in the UK population was based on surveillance studies of tonsils and appendices (Hilton et al 2004) and assumed to be a mean of 1 in 4,225 (95% CI: 1 / 20,300 to 1 / 1,450) or 237 per million (95% CI: 49-692 per million).
III. A.2.	**Estimation of probability that infectivity will be present in blood (prionemia) in vCJD infected individuals at time of donation**	
III. A.2 a.	$\mathbf{BSE_y}$-*BSE cases reported in year y*	**Data used in the model***:* World Organization for Animal Health (OIE, 2006), shown in **Table 5**, was used to determine the number of cases of BSE reported in the UK. [[http://www.oie.int/eng/info/en_esbru.htm#4 (Accessed on May 30, 2006)]
III. A.2 b.	$\mathbf{P_{infect\text{-}y}}$-*Probability an infection occurring in year y*	The probability of a vCJD infection occurring in a specific year is a function of exposure in that specific year, which is proportional to the number of BSE cases reported in that specific year (more BSE cases higher probability of getting infected) compared to the total BSE cases for all years through 1996.
III. A.2 c.	$P_{LH\text{-}y}$ – *Probability that the blood of an individual infected in year y will contain vCJD agent in the year 1997* IP_{vCJD} - *The incubation period of vCJD was calculated in the model using a gamma distribution represented by the expression Gamma (4.7, 3.6)*	**Assumption 1:** FXI was made in the UK between 1989 and 1997. The model estimates the risk for using FXI made in 1997, assuming year of 1997 is the worst year because accumulation of vCJD asymptomatic individuals in the donor population. **Assumption 2:** The incubation period of vCJD can be represented by a gamma distribution expressed as Gamma (4.7, 3.6) which gives mean incubation period of 14 years and median estimated incubation period of 13 years. **Assumption 3:** The infectivity of vCJD agent present in the blood of infected individual only when the disease is at the last incubation period
III. A.2 d.	P_{LH}- *Probability of an infected individual having vCJD agent present in their blood (prionemic) in year 1997.*	The probability an individual would have been infected in year y and also have prionemia in year 1997 is the product of $P_{infect\text{-}y}$ and $P_{LH\text{-}y}$. Probability of an infected individual having vCJD agent present in their blood (prionemic) in year 1997 is the sum of this probability for any year from 1980 through 1996.
III. A.2 e.	$P_{vCJD\text{-}LH}$-The prevalence of prionemia	The probability of vCJD occurring in the UK population was

	among the UK population in year 1997 is represented by the equation: $P_{vCJD-LH} = P_{vCJD} \times P_{LH}$	estimated for two distinctly different vCJD prevalences as described previously in section III. A. 1.
III. A. 3.	**Estimation of probabilities that a plasma pool contains a vCJD donation and probable number of vCJD donation per plasma pool**	
III. A. 3. a.	**D_{Tpool}** - *Total number of vCJD donations per pool*	Production of FXI included the pooling of plasma donations recovered from whole blood from approximately 20,000 donations
III. A. 3. b.	*D_{vCJD} -Probable number of vCJD donors or donations present per plasma pool*	The number of vCJD donors per plasma pool is represented by a binomial distribution defined by two arguments alpha (α) and beta (β) (represented in the model by the expression Riskbinomial (α, β)). Alpha represents the probability of a donor to be prionemia when donating, which is the prevalence of prionemia among the UK population in year 1997 ($P_{vCJD-LH}$ calculated in III.A.2.e). Beta is the total number of donors per plasma pool (D_{Tpool}), which are 20,000 in this case, represented by the expression: D_{vCJD} = Riskbinomial (α, β) = Riskbinomial ($P_{vCJD-LH}$, D_{Tpool})
III. A. 3. c.	*$P_{vCJD-pool}$ –Probability a plasma pool containing any vCJD donor (donation)*	Probability a plasma pool containing any vCJD donor (donation) was: 1 minus the probability a plasma pool would contain any vCJD donor (donation). $P_{vCJD-pool}$= 1- Cumulative frequency of Binomial(D_{Tpool}, $P_{vCJD-LH}$), at x=0
III. A.4. Estimation of Quantity of vCJD agent per donation and in plasma pools used in manufacturing UK FXI		
III. A.4.a.i.	**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.4.a.ii.	**I_{bl}** - *Infectivity of vCJD (or i.c.ID_{50}s) present in infected blood per ml*	The model used a log normal statistical distribution to represent the variability and uncertainty of the quantity of infectivity in blood. It was assumed that whole blood potentially carries a minimum of 0.1 i.c. ID_{50} per ml, a 5^{th} percentile of 2 i.c. ID_{50} per ml, a most likely of amount of 12 i.c. ID_{50} per ml, a 95^{th} percentile of 30 i.c. ID_{50} per ml and a maximum of 1,000 i.c. ID_{50} per ml.
III. A.4.a.iii.	**$I_{Pl-perc}$** - *Percentage infectivity associated with plasma (i.c.ID_{50}/ml)*	The model uses the more conservative of the two outcomes and assumes that 58% of infectivity is associated with plasma.
III. A. 4.a.iv.	**I_D** - *Total infectivity (or i.c.ID_{50}) per vCJD recovered plasma donation*	One ID_{50} is the amount of material containing infectious agent that has a 50% probability of causing infection in an individual or population.
III. A. 4.a.v.	**A_{ic-iv}** - *Adjustment for intravenous route of infection*	Exposure to infectivity by the i.v. route is between 1 and 10 times less efficient at causing infection than introduction via the intracerebral route.
III. A. 4.b.	**$I_{iv-pool}$** - *Total intravenous infectivity or i.v.ID_{50} per plasma pool of 20,000 donors*	
III.B. Total i.v. ID_{50} per vial after processing / production 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 FXI* **$R_{W\%}$** - *Percentage of pool used to manufacture FXI*	800 kg of material was removed and used to produce FXI. Approximately 16% of starting plasma material from 20,000 donations was used in the manufacture of FXI.
III.B.2.	**R_{Log}** - *Log reduction in ID_{50}s during processing*	Processing reduction is represented by a triangular statistical distribution representing a reduction in ID_{50}s during processing of (0, 2,4) Log_{10} i.v. ID_{50}/ml (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_{50} vCJD agent may be reduced the percentage of pools and vials containing the agent still remains the same.
III.B.4.	$\mathbf{Y_{FI}}$ - *Total yield of FXI from plasma pool*	The yield of FXI per kg plasma was approximately 150 to 180 u, subsequently the model estimates the total yield of FXI as 120,000 to 144,000 u per batch of 800 kg starting material. FXI was distributed in vials of 1,000 u each.
III.C. Utilization by patients with FXI deficiency undergoing Surgery		
III.C.1.	*Total Dose for Pre- and Post-surgical treatment with FXI*	**Scenario 1** – Treatment of a 60kg individual with FXI (20 - 50 u/kg) once during or after surgery for a total patient dose of approximately 3,000 u. **Scenario 2** - Treatment of a 60kg individual both pre- and post-surgery with a total of approximately 9,000 u of FXI. **Scenario 3** - Treatment of a 60kg individual both pre- and post-surgery with a total of approximately 15,000 u of FXI.

Appendix C

Table C. Potential Probability and Number of vCJD Donations in Plasma Pool expressed with mean, median and 5th- 95th percentile values. (Expanded Table 7 from document).

	MODEL OUTPUT USING LOWER PREVALENCE ESTIMATE *vCJD Case Prevalence from epidemiological modeling ~4 per million (Clark and Ghani, 2005)*			***MODEL OUTPUT USING HIGHER PREVALENCE ESTIMATE*** *vCJD Infection estimate from tissue surveillance study 1 in 4,225 (Hilton, et al 2004)*		
	Mean	**Median**	**5th- 95th percentiles**[a]	**Mean**	**Median**	**5th- 95th percentiles**[a]
Probability pool contains vCJD donation	1.6%	1.6%	1.1% -2.1%	50%	68.5%	18% - 77%
Number vCJD donations per pool	0.02	0	0 – 0[b]	0.75	1.0	0 - 3

[a] The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model are expected to fall within this defined interval at least 90% of the time.
[b] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FXI recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FXI plasma pool would be rare and more than 90% of FXI product vials would not be predicted to contain vCJD agent.

Appendix D

Table D. –Potential Exposure and Potential Risk per Person per FXI Treatment Scenario.

Hypothetical scenarios provide an estimate of the magnitude of potential exposure to vCJD agent i.v. ID_{50} and potential risk that might occur per treatment course. A treatment course might include prophylactic treatment prior to a surgery, or medical procedure and possibly several post-surgical or post-procedure treatments with FXI. (Expanded Table 8 from document to include median exposure and risk estimates).

			MODEL OUTPUT USING LOWER PREVALENCE ESTIMATE *vCJD Case Prevalence from epidemiological modeling ~4 per million (Clark and Ghani, 2005)*		***MODEL OUTPUT USING HIGHER PREVALENCE ESTIMATE*** *vCJD Infection estimate from tissue surveillance study 1 in 4,225 (Hilton, et al 2004)*	
Scenario	**Quantity FXI Utilized (u*)**	**Central tendency measure and percentiles**	**Potential exposure to vCJD i.v. ID_{50}**	**Potential vCJD risk per person**	**Potential exposure to vCJD i.v. ID_{50}**	**Potential vCJD risk per person**
Scenario 1: Treatment 3,000 u	3,000 u	Mean: Median[c]: 5th-95th perc[d]:	3.11×10^{-3} [a] 0 0 – 0[e]	1 in 643 [b] 0 0 – 0[e]	0.12[a] 0.007 0 – 0.57	1 in 17 [b] 1 in 286 0 – 1 in 3.5
Scenario 2: Treatment 9,000 u	9,000 u	Mean: Median[c]: 5th-95th perc[d]:	9.33×10^{-2} [a] 0 0 – 0[e]	1 in 214 [b] 0 0 – 0[e]	0.36[a] 0.021 0 – 1.70	1 in 5.6 [b] 1 in 95 0 – 1 in 1.2
Scenario 3: Treatment 15,000 u	15,000 u	Mean: Median[c]: 5th-95th perc[d]:	1.55×10^{-2} [a] 0 0 – 0[e]	1 in130 [b] 0 0 – 0[e]	0.59[a] 0.036 0 – 2.86	1 in 3.4 [b] 1 in 56 0 – 1 in 1

*u - represents units of FXI – and is equivalent to the term "unit" or "units" used in this document

[a] Mean vCJD i.v. ID_{50} (per treatment course) - the average predicted quantity of vCJD agent an individual in a specific treatment group is predicted to receive based on the model.

[b] Mean potential vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential vCJD risk = Total mean quantity i.v. ID_{50} (per treatment course) x 0.5 (50 % chance infection - ID_{50})

[c] Median – A measure of central tendency that reports the value of the exposure and risk estimate at the 50th percentile

[d] The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.

[e] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FXI recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FXI plasma pool would be rare and more than 90% of FXI product vials would not be predicted to contain vCJD agent.

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