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 5th percentile of 2 i.c. ID_{50} per ml, a median of 12 i.c. ID_{50} per ml, a 95th 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. I_{pp} - *Total i.v. ID_{50} present per pool of FXI post-processing*

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

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

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

III.B.4.a. $Y_{f\text{-}kg}$ - *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.

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:

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

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 5th and 95th 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 5th and 95th 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.

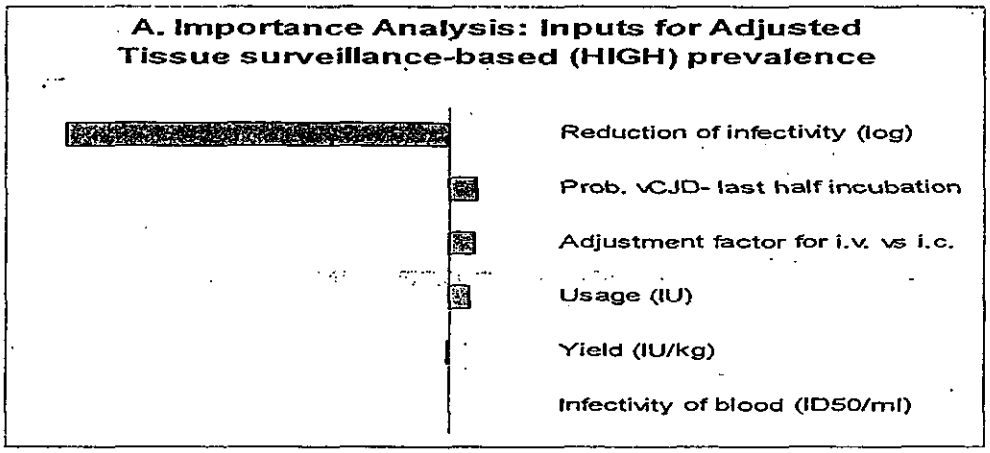
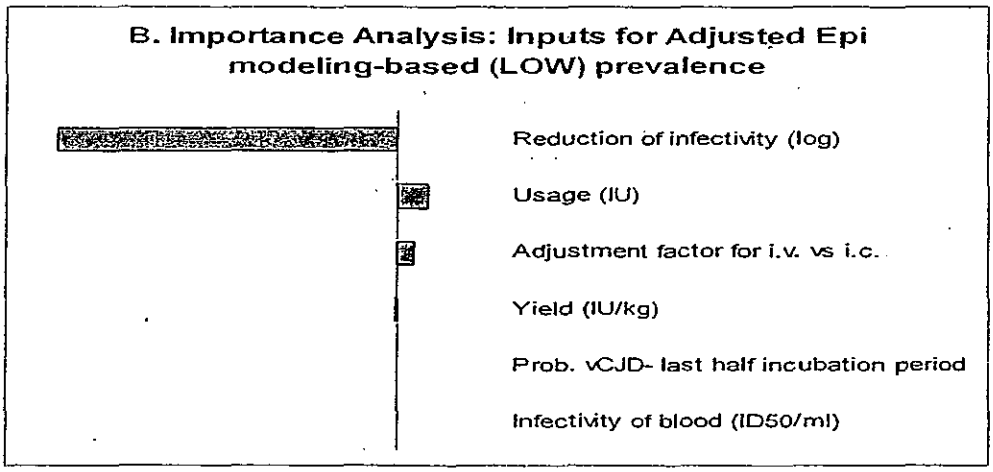


Figure 2. B. FXI Importance Analysis Ranking Influential Factors for Predicted Annual vCJD Exposure (I_{yr}) Using an Adjusted Epidemiological Modeling-Based (LOW) Prevalence Estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of FXI recipients.



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 (R_{Log}) during the manufacturing