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 (P_{LH}), adjustment for route of administration ($A_{ic\text{-}iv}$), FXI usage (D_{Tu}) (u), and FXI yield (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 (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.*	$P_{vCJD\text{-}Epi}$	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*	$N_{vCJD\text{-}CE}$	$N_{vCJD\text{-}CE}$, is the sum of 138 reported vCJD cases, $N_{vCJD\text{-}Case}$, and the cases estimated by epidemiological modeling, $N_{vCJD\text{-}Epi}$, 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.*	$N_{vCJD\text{-}Case}$	138 cases
A.1.a.iii.	*Number of future vCJD-infected individuals in UK population based on epidemiological modeling prevalence estimate*	$N_{vCJD\text{-}Epi}$	The cases estimated by epidemiological modeling, $N_{vCJD\text{-}Epi}$, is an estimated 70 future cases
A.1.b.	*Probability of vCJD-infected individual in UK population using the surveillance prevalence estimate*	$P_{vCJD\text{-}Surv}$	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*	BSE_y	BSE case numbers shown in table 6.
A.2 b.	*Probability an infection occurring in year y*	$P_{infect\text{-}y}$	Based on equation: $P_{infect-y} = BSE_y / \sum_{y=1980}^{1996} BSE_y$
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)*	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}	Lognormal distribution 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.iv.	*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: $I_D = D_V \times I_{bl} \times I_{Pl-perc}$
A.4.a.v.	*Adjustment for intravenous route of*	A_{ic-iv}	Uniform distribution

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

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

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*	D_{Pre}	20 – 50 u/kg
C.1.b.	*Post-surgical maintenance of dose 20 – 50 u/kg given every 2 - 3 days*	D_{Post}	20 – 50 u/kg
Output			
C.1.c.	*Total Utilization of FXI*	$D_T = D_{Pre} + D_{Post}$	
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.	$P_{vCJD\text{-}Epi}$ - *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.	$N_{vCJD\text{-}CE}$ - *Estimated Number of vCJD-infected individuals in UK population using recorded vCJD cases (1997 – 2004*) and epidemiological modeling based prevalence estimate*	The variable, $N_{vCJD\text{-}CE}$, is the sum of 138 reported vCJD cases, $N_{vCJD\text{-}Case}$, and the cases estimated by epidemiological modeling, $N_{vCJD\text{-}Epi}$, 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.	$N_{vCJD\text{-}Case}$ - *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.	$N_{vCJD\text{-}Epi}$ - *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.	$P_{vCJD\text{-}Surv}$ - *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.	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.	$P_{infect\text{-}y}$-*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 5th percentile of 2 i.c. ID_{50} per ml, a most likely of amount 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.
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_{it-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.	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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医薬品
医薬部外品　研究報告　調査報告書
化粧品

別紙 3-1

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2007 年 3 月 16 日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称			研究報告の公表状況	Potential vCJD risk from US licensed plasma-derived Factor VIII (pdFVIII, antihemophilic factor) products www.fda.gov/cber/blood/vcjdplasma.htm	公表国 米国	
販売名（企業名）						

研究報告の概要	使用上の注意記載状況・その他参考事項等
英国の赤血球輸血を介した vCJD 伝播例 4 例の報告を受けて，米国 FDA は同国の承認薬である血漿由来血液凝固第 VIII 因子製剤の投与を受けた血友病患者に対しリスク評価を実施した。この評価は，vCJD 誘発物質が血漿分画に存在すると仮定した場合，血漿由来第 VIII 因子製剤の原料となる血漿分画が，アルブミン，免疫グロブリン及び血液凝固第 IX 因子等，他の製剤の血漿分画よりも多く含むと考えられていることから実施された。しかしながら，血漿由来製剤の製造に用いるすべての血漿分画は，vCJD 感染物質を減少，あるいは除去する工程が導入されている。また，英国で採集された血漿由来の血液製剤の大量投与を受けた患者を含め，血液凝固因子障害をもつ患者における vCJD はこれまでに報告されていない。現時点ではこれを正確に評価できないことは明確であるが，米国公衆衛生局は，米国承認薬である血漿由来血液凝固第 VIII 因子製剤の投与を受けた患者への vCJD 感染リスクは極めて低いと推定しており，その他の血漿由来製剤によるリスクはさらに低いと考えている。しかしながら，FDA は予防措置として，BSE 及び vCJD の有病率が米国よりも大幅に上回る欧州を広範囲に旅行した供血者，又は欧州に在住していた供血者を除外するよう勧告した。また，後に vCJD と診断された供血者の血液より製造された血液成分及び血漿由来製剤については回収されることになっている。	BYL-2007-0278

報告企業の意見	今後の対応
米国採取の血漿由来血液凝固第VIII因子製剤によるvCJD感染リスクは極めて低いと推定される。しかしながら，FDA は予防措置として，長期間を欧州で過ごした経験のある供血者を除外するよう勧告している。弊社の血漿分画製剤及びコージネイト FS 又はコージネイト FS バイオセットの製造工程培地で使用されている血漿分画成分は，米国採取の血漿から製造されており（万一，存在しても）感染リスクは極めて低いと考えられる。また，FDA が勧告している追加の予防措置は実施すべきであると考える。	現時点で新たな安全対策上の措置を講じる必要はないと考える。

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