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

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

The probability of a vCJD-infected individual in UK population who will eventually develop symptoms is represented by the variable, $P_{vCJD\text{-}Epi}$. *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*, $N_{pop\text{-}UK1997}$, *in the UK in the year 1997.*

$N_{pop\text{-}UK1997}$ - 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. $N_{vCJD\text{-}CE}$ - *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, $N_{vCJD\text{-}CE}$, is the sum of 138 diagnosed 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) and represented by the equation:

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

III. A.1.a.ii. $N_{vCJD\text{-}Case}$ - *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. $N_{vCJD\text{-}Epi}$ - *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, $N_{vCJD\text{-}CE}$, is the sum of 138 vCJD cases diagnosed between 1997 and 2004, $N_{vCJD\text{-}Case}$, and the 70 future cases since 2004 estimated by epidemiological modeling, $N_{vCJD\text{-}Epi}$; 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. $P_{vCJD\text{-}Surv}$ - *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. $P_{infect-y}$-*Probability an infection occurring in year y - calculated by the equation:*

$$P_{infect-y} = BSE_y / \sum_{y=1980}^{1996} BSE_y$$

That is, the probability of infection with vCJD in a given year ($P_{infect-y}$) 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-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×(1997-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:

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

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. 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. $P_{vCJD\text{-}pool}$-*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:

$P_{vCJD\text{-}pool}$= 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. 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 *(5^{th} percentile, most likely, and 95^{th} 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, 5^{th} percentile = 2, Most likely value = 10, 95^{th} 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 (5^{th} percentile, most likely, and 95^{th} 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