APPENDIX A

Supplemental technical information for the FDA Risk Assessment

The sections in this appendix provide additional technical information and details of data and modeling approaches used in specific sections (but not all sections) of Section IV. The heading and numbering of each section in this appendix mirrors the sections in "Section IV. Exposure Assessment" portion of the risk assessment.

A- IV. A. Estimation of vCJD Prevalence in the United Kingdom (Module 1)

A-IV. A. 3. Estimation of age-specific vCJD prevalence based on the age distribution of diagnosed vCJD cases in the UK

Cases of vCJD occur in relatively young individuals (median age of 28 years) compared to classic CJD. Blood and plasma donors are usually at the age 18-40, among whom the vCJD prevalence would be expected to be higher than the prevalence among general population. Because age specific rates of donation and vCJD infection would likely have a large effect on the final risk estimate the FDA model carefully characterizes the age specific prevalence of vCJD and donation rate. Throughout the FDA model, age specific vCJD prevalence rates are calculated for each five year age group beginning at age group of 10 – 14 yrs, 15-19 yrs and so on – and applied in estimating vCJD risk and prevalence for the residents of different geographic regions and the US blood and plasma donors who traveled to those regions. The percentage of reported vCJD cases by age is shown in **Table A-4.3**. The model assumes that the age-specific percentage and prevalence of incubating asymptomatic cases reflects the same age-specific trend as for reported cases of symptomatic vCJD and deaths from vCJD.

Table A-4.3. Reported vCJD cases in the UK and percent of US Source Plasma and blood (recovered plasma) donors by age groups

Age group	<10	10-14	15-19	18-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	>70
Reported vCJD cases in UK (through 2003)[a]	0	5	27		32	30	22	13	5	3	5	0	5		
(%)		(3.4%)	(18.4%)		(21.8%)	(20.4%)	(14.9%)	(8.8%)	(3.4%)	(2%)	(3.4%)	(0%)	(3.4%)		
Age distribution of US Source Plasma donors (%)[b]	0	0	0	12%	29.3%	14.1%	14.1%	9.6%	9.6%	5.8%	5.8%	0%	0%	0%	0%
Age distribution of US Blood (Recovered plasma) donors[c]	0	0	0	5%	13%	8%	10%	12%	13%	12%	11%	7%	4%	5%	0%

[a]Hilton *et al.* 2004

[b]Plasma Protein Therapeutics Association (Jan 07, 2005). Where data were organized in broader age group we allocated donor equally among smaller 5 year age groups

[c] Data provided to FDA by Westat in 2002

Some of the general variables for generating age specific estimates from the model are described below.

Variable: *age* - Age of vCJD cases in 5-year increments

Variable: $vCJD_{UK(age)}$ - Reported vCJD cases in the UK by 5-year age groups (through 2003) beginning at 10 – 14 yrs, 15-19 yrs and so on.

Data used in the model: Data on the vCJD cases in the UK was derived from Hilton et al. (2004). The data includes cases through the end of 2003.

Variable: $Perc_{vCJD(age)}$- Percentage vCJD cases attributed by each age group from 10 – 14 yrs, 15-19 yrs and so on.

Assumption used in the model: We assume each of four age groups, 55-59 yrs, 60-64 yrs, 65-69 yrs and 70-74 yrs, contributes same percentage in vCJD cases.

For the four (five-year) age groups from 55-74yrs we assumed an equal percentage of cases were present in each of the four groups since there were very few vCJD cases in this age range. To estimate the percentages for each group we identified five reported cases (specifically, three reported cases in the age-specific prevalence grouping shown in Hilton et al. (2004) for persons aged 55-74 yrs and two cases of blood transfusion vCJD (each > 64 yrs of age) (Llewelyn 2004, Peden 2005)) in the 55-74 yr age range. The five cases in the 55-74 yr old age group are shown in **Table A-4.3**. We assumed an average of 1.25 cases for each of the four age groups from the ages of 55-74 yrs and divided by the total number of vCJD cases for all age groups to get the percentage of cases for each of the four sub age groups, 55-59 yrs, 60-64 yrs, 65-69 yrs and 70-74 yrs.

The percentage of vCJD cases in the UK from each age group is represented by the equation:

$$Perc_{vCJD(age)} = (vCJD_{UK(age)} / \sum_{age=0-4}^{>85} vCJD_{UK(age)}) \times 100\% \qquad \textbf{(IV. A. 1-1)}$$

A-IV. A. 3. a. Estimating the UK vCJD prevalence predicted by epidemiological modeling (Clarke and Ghani 2005) for each age group

Variable: $vCJD_{since2002}$-Predicted clinical vCJD cases in the UK from 2002 afterward (cases). Predicted clinical cases from 2002 afterward include 32 vCJD cases diagnosed in 2002 and 2003 and 70 (95% CI of 10-190) future cases between 2004 and 2080 predicted by Clarke and Ghani (2005), which give a total of 102 cases (95% CI: 42-222 cases) after 2002.

Variable: $Asym\text{-}vCJD_{(age)}$ - Number of asymptomatic vCJD infected individuals from a specific age group in year 2002.

$$Asym\text{-}vCJD_{(age)} = vCJD_{since2002} \times Perc_{vCJD(age)} \qquad \textbf{(IV.A.2-4)}$$

Variable: $Prev_{Asym\text{-}vCJD(age)}$- Prevalence of asymptomatic vCJD infected individuals in the UK by age groups (cases/million).

The prevalence of asymptomatic vCJD cases in the UK by age group is estimated using the equation:

$$Prev_{Asym\text{-}vCJD(age)} = Asym\text{-}_{vCJD(age)} / Pop_{UK(age)} \quad \textbf{(IV.A.2-5)}$$

A-IV. A. 3. b. Estimating the UK vCJD prevalence derived from tissue surveillance for each age group

For the risk assessment model we converted the 3 in 12,674 presumptive positive rate to an average rate of vCJD in the UK population of 1 in 4,225 (and used the 1 / 20,300 to 1 / 1,450 at 95% CI; proportions were converted from the 95% CI reported by Hilton et al (2004)). Demographic information of reported vCJD cases (**Table A-4.3**) indicated that the younger population (20 -29 yrs of age) 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. Assuming the sensitivity and specificity of the testing method is 100%, the estimated rate of 1 in 4,225 translates roughly to a vCJD prevalence of 237 cases per million (95% CI: 49 – 692 cases per million) for all age groups. The authors (Hilton et al 2005) indicated that approximately 60% of the samples tested (from 7,600 patients) came from patients 20-29 years of age. Among the 20-29 year old group we calculated a vCJD prevalence of approximately 400 cases 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 by the total donor population we were able to estimate the number of possible incubating vCJD cases in each US donor age group. We assumed that a plasma pool used to manufacture pdFVIII product in the US in the year 2002 consisted 6,000 to 360,000 donations, and several donations in the pool likely came from the same donor. 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.

Variable: $Prev_{Asym\text{-}vCJD(20\text{-}30)}$ Prevalence of asymptomatic vCJD infected individuals in the UK 20-30 year old age group (cases/million)

Assumptions used in the model: The vCJD infectious agent is present in the blood of the individual when the the accumulation of prion protein can be detected in lymphoreticular tissue. Prevalence of vCJD asymptomatic individuals in the UK 20-30 year old age group is likely to be 400 cases/million, 95% CI=100-1200 cases/million. The values for this variable were estimated from the Hilton *et al* studies (2000, 2002, 2004).

Variable: $Pop_{UK(age)}$- Population in the UK by age groups (Thousands).

Data used in the model: The data for UK population were sourced from UK government statistics (UK National Statistics, 2005). Where UK data were organized in broader categories of 10 to 15 years we allocated population equally among smaller 5 year age groups.

Variable: $Asym\text{-}vCJD_{(20\text{-}30)}$ - The number of asymptomatic vCJD infected individuals in the 20-30 yr-old UK age group. This variable is represented by the equation:

$$Asym\text{-}vCJD_{(20\text{-}30)} = Prev_{vCJD(20\text{-}30)} \times Pop_{UK(20\text{-}30)} \quad \text{(IV.A.2-1)}$$

Variable: $Asym\text{-}vCJD_{(age)}$ - Number of asymptomatic vCJD infected individuals in the UK by age groups

Assumptions used in the model: Number of asymptomatic vCJD infected individuals from an age group is proportional to the percentage of reported vCJD cases from that age group. The age distribution of asymptomatic vCJD cases was assumed to be the same as that of symptomatic cases.

The number of asymptomatic vCJD individuals in the UK per age group was estimated using the following equation:

$$Asym\text{-}vCJD_{(age)} = Asym\text{-}vCJD_{(20\text{-}30)} \times (Perc_{vCJD(age)} / Perc_{vCJD(20\text{-}30)}) \quad \text{(IV.A.2-2)}$$

Variable: $Prev_{Asym\text{-}vCJD(age)}$- Prevalence of asymptomatic vCJD infected individuals in the UK by age groups (cases/million).

The prevalence of asymptomatic vCJD cases in the UK by age group is estimated by the equation:

$$Prev_{Asym\text{-}vCJD(age)} = Asym\text{-}_{vCJD(age)} / Pop_{UK(age)} \quad \text{(IV.A.2-3)}$$

A-IV. B. Estimation of vCJD Prevalence in US Plasma Donors and Plasma Pools (Module 2)

A-IV. B. 1. a. Annual US plasma donors and characterization by age

A-IV. B. 1. b. Source Plasma collection in the United States: characterized by donor age

Variable: DN_S – Annual number of Source Plasma units used to make pdFVIII .

Assumption used in the model: It was assumed that, on average, 3.3 million units of Source Plasma were used in each year to make pdVIII. It was further assumed that there is a 10% standard deviation in the number of Source Plasma units used to make pdFVIII for any given year.

Data used in the model: The annual number of Source Plasma units was back calculated based on annual units of pdVIII product made from Source Plasma, the average yield of pdFVIII (187 units per liter

plasma) and average volume of single unit of Source Plasma (700 ml per unit). The information on annual units of pdFVIII made from plasma collected in the US, yield of factor VIII and unit volume of plasma were collected from pdFVIII manufacturers.

Variable: DR_S **–**Annual number of donors who contribute Source Plasma for manufacture of pdFVIII.

Assumption used in the model: It was assumed that there are approximately 1 million Source Plasma donors in the US each year. It was further assumed that Source Plasma from any individual donor may be used to make pdFVIII. Therefore, we calculated that there were approximately 1 million donors who contributed Source Plasma for the manufacture of pdFVIII. It was further assumed that there could be a 10% standard deviation in the number of donors in any given year.

Variable: ***Age*** **–** Age information for US plasma donors was grouped in a two year increment for 18-19 years old because the model assumed that 18 was the minimum age of donation. The remaining population was grouped by 5-year increments – including 20- 24yrs old, 25-29yrs old, and so on

Variable: $DR_{S\text{-}perc(age)}$ **-** The percentage of Source Plasma donors from a given age group.

Data used in the model: Distribution of US Source Plasma donors by age was obtained from the Plasma Protein Therapeutics Association (2005). Where data (PPTA, 2005) were organized in broader age groups of 10 years or 15 years, we generated 5-year age subgroups by allocating the percentage equally among each subgroup.

Variable: $DR_{S(age)}$ **–** The annual Source Plasma donors by age groups who contribute plasma for pdFVIII manufacturing is represented by the equation:

$$DR_{S(age)} = DR_S \times DR_{S-perc(age)} \quad \textbf{(IV.B.1-1)}$$

A-IV. B. 1. c. Recovered plasma collection in the United States: Characterized by donor age

Variable: DN_R **-** Annual units of recovered plasma used to make pdFVIII.

Assumption used in the model: It was assumed that approximately 1,800,000 units of recovered plasma are used to make pdFVIII annually. This estimation was generated by backcalculation beginning with the total quantity of pdFVIII manufactured in the US. It was further assumed that there was a 10% standard deviation in the number of units for any given year.

Data used in the model: The annual number of total units of pdFVIII manufactured from recovered plasma collected in the US was estimated by back calculation. The calculation was based on the total quantity of annual units of pdVIII product made from recovered plasma collected in the US. We can further estimate the number of donations used to make the pdFVIII from recovered plasma using estimates in the literature for the average yield of pdFVIII 187 units per liter of plasma (WFH, 2004) and average volume of single unit of recovered plasma (200 ml per unit). The information on annual units of pdFVIII made from plasma collected in the US was collected from pdVIII manufacturers.

Variable: $DN_{Bl\text{-}perc(age)}$ **–** The percentage of blood units donated by a given age group.

Data used in the model: Distribution of blood units by donor age group was obtained from Westat data provided to FDA in 2002 (Data shown in A-4.3).

Variable: $DN_{R(age)}$ **–** Annual units of recovered plasma used to make pdFVIII by donor age group

$$DN_{R(age)} = DN_R \times DN_{Bl-perc(age)} \quad \textbf{(IV.B.2-1)}$$

Variable: $DR_{R(age)}$ **–** Annual number of donors by age group who contribute recovered plasma that is used for manufacture of pdFVIII

Assumption used in the model: Each unit of recovered plasma used to make pdFVIII comes from different donors. Therefore, number of donors from an age group equals the number of donations from that age group.

The annual number of recovered plasma donors by age group was calculated using the equation:

$$DR_{R(age)} = DN_{R(age)} \quad \textbf{(IV.B.2-2)}$$

Variable: DR_R **-** The annual total of potential recovered plasma donors who contribute the plasma that is used for manufacture of pdFVIII, which was estimated in the model using the summation function:

$$DR_R = \sum_{age=18-19}^{70-74} DR_{R(age)} \quad \textbf{(IV.B.2-3)}$$

A-IV. B. 2. Total plasma donors and donations- for manufacture of pdFVIII in the US

Variable: DR_{Tot} **-** The annual total of potential plasma donors who contribute plasma for pdFVIII manufacturing is estimated by summing the number of Source Plasma donors and recovered plasma donors and is represented by the equation:

$$DR_{Tot} = DR_S + DR_R \quad \textbf{(IV.B.3-1)}$$

Variable: DN_{Tot} **-** The annual total of potential plasma units used to make pdFVIII is estimated by summing the number of Source Plasma donations and recovered plasma donations and is represented by the equation:

$$DN_{Tot} = DN_S + DN_R \quad \textbf{(IV.B.3-2)}$$

A-IV. C. Estimation of the probability that a plasma pool may contain a donation from an infected donor that contains vCJD agent

IV.C. 1. US plasma donors with history of travel to the UK, France or other Countries in Europe: Annual number potentially infected and vCJD agent is present in the blood

A-IV. C. 1. a. US plasma donors with history of travel to the UK: Number of donors potentially infected and vCJD agent is present in the blood

A-IV. C. 1. a. i. US plasma donors with history of travel to the UK: Percentage of donors and duration of travel

The risk of vCJD infection in US plasma donors is a function of the intensity of exposure to the BSE agent. The intensity of exposure is assumed to be proportional to the amount of time spent, or duration of travel, in the UK and the prevalence of BSE in UK cattle during the period from 1980 – 1996. The FDA model used data from the National Blood Donor Travel Survey 1980-1996 (TSEAC 2000) to derive estimates of the percentages of US donors with a history of extended travel or residence ($\geq$ 3 months) in the UK during 1980-1996, and to derive the frequencies for various durations of travel for 3 months or more. The period of 3 months or more corresponds to the length of time in the current policy that defers donors that traveled to or resided in the UK. The travel survey data on blood donors pose a limitation because the survey was conducted on whole blood donors and may not exactly reflect the travel histories of plasma donors. Unfortunately, to our knowledge there is not travel data available on plasma donors. Therefore, we assumed that plasma donor travel characteristics to the UK and other countries in Europe since 1980 are similar to those of whole blood donors and used this information in the FDA risk assessment. Some may argue that plasma donors travel less frequently than their blood donor counterparts so use of data on blood donors may overestimate the risk.

Data used in the model: National Blood Donor Travel Survey 1980-1996 was conducted by the American Red Cross and presented at the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC 2000).

Variable: *i* - The duration interval used to group donors who traveled to the UK from 1980-1996 based on the quantity of time spent in the UK during the period from 1980 – 1996.

Variable: D_i - The average duration of time (in months) for interval *i* representing the duration of travel or residence by US donors in the UK during the period from 1980 – 1996.

Variable: $CumPerc_{BlDR\text{-}UKi}$ – The cumulative percentage of blood donors who traveled to the UK within duration interval *i* or longer**.**

Variable: $Perc_{BlDR\text{-}UKi}$ - Percentage of blood donors who traveled to the UK within duration interval *i.* This variable was converted from $CumPerc_{BlDR\text{-}UKi}$

Variable: $Perc_{BlDR\text{-}UKi/UK}$ **-** The percentage of blood donors who traveled for a specific duration interval *i* among all donors who have ever traveled to the UK is represented by the equation:

$$Perc_{BlDR-UKi/UK} = (Perc_{BlDR-UKi} / CumPerc_{BlDR-UK,i>1day-1month}) \times 100\% \quad \textbf{(IV.C.1.a-1)}$$

A-IV.C.1.a.ii. All US plasma donors with a history of travel to the UK: Percentage and number of donors in each age group by year and duration of travel

For the purposes of our analyses we grouped all donors and donors who traveled to the UK between 1980 and 1996 into age groups of five year increments (20 – 24yrs, 25 – 29 yrs, etc). Because the minimum age of donation is 18, the model also included the donor group 18 & 19 years of age. The percentage of donors in each age group who traveled to the UK between 1980 and 1996 was calculated based on the total annual number donors who traveled to the UK between 1980 and 1996 compared to (or divided by) the total number of donors, and the age specific odds ratio for travel.

As mentioned earlier, data are lacking on the travel characteristics of plasma donors, so the FDA used travel survey data collected from blood donors to estimate past travel history. Because plasma donors are less likely to travel use of these data may yield an overestimate of the actual risk. Characteristics of blood donors on travel including the percentage of donors from each age group who traveled to the UK during period between 1980 and 1996, and distribution of donor travel by duration were applied to plasma donors for estimation of the number of plasma donors from each age group who have traveled or resided in the UK from 1980 to 1996 for specific periods of time ranging from less than 3 months to greater than 5 years duration. Furthermore, the model used data that detailed the number of annual visits of US travelers to the UK to allocate donor travel specifically to an individual calendar year.

- **Calculation of the annual number of blood donors who traveled to the UK from 1980 through 1996**

Blood donors donate whole blood and soon after the liquid plasma portion of whole blood is separated and plasma is called recovered plasma. The model assumes that approximately 200 mls of recovered plasma are produced from a unit of whole blood.

Variable : DR_{Bl}-The annual total number of potential blood donors in the US per year

Data used in the model: There are approximately 8 million individuals who donate blood each year in the United States (Westat, 2002).

Variable: $Perc_{BlDR\text{-}UK}$ **-** Percentage of US blood donors who traveled to the UK during the period from 1980 through 1996.

Data used in the model: Approximately, 22.5% of US blood donors have a history of travel to the UK any time during the period from 1980 through 1996, according to data contained in the National Blood Donor Travel Survey (TSEAC 2000).

Variable: $DR_{Bl\text{-}UK}$ -Total number of blood donors estimated to have traveled to the UK from 1980 through 1996

$$DR_{Bl-UK} = DR_{Bl} \times Perc_{BlDR-UK} \quad \textbf{(IV.C.1.a-2)}$$

- **Calculation of the percentage of blood donors for each specific age group**

Variable: ***Age***- Age of donors grouped in 5 year increments (e.g., 20 – 24 yrs, 25 – 29yrs, etc.) per year and 18-19 yr old age cohort.

Variable: $Perc_{BlDR(age)}$-Percentage blood donors in a specific age group.

Variable: *BLDR(age)*- Annual number of blood donors in a specific age group

$$Perc_{BLDR(age)} = BLDR(age) / \sum_{age=18-19}^{65-69} BLDR(age) \quad \textbf{(IV.C.1.a-3)}$$

Variable: *BLDN*-Annual total number of blood donations in the US.

Variable: $Perc_{BlDN(age)}$- Percentage of blood donations in each specific age group of US donors.

Data used in the model: Percentage of blood donations by age group was obtained from Westat (2002).

Variable: $Freq_{BlDN(age)}$-Average annual number of blood donations from a donor in a specific age group

Data used in the model: Information on the average annual number of donations bydonors in each specific age group was obtained from Westat (2002).

$$BLDR(age) = BLDN \times Perc_{BLDN(age)} / Freq_{DN(age)} \quad \textbf{(IV.C.1.a-4)}$$

Replace *BLDR(age)* in equation IV.C.1.a-3 with equation IV.C.1.a.-4, resulting in the expression:

$$Perc_{BlDR(age)} = (Perc_{BlDN(age)} / Freq_{BlDN(age)}) / \sum_{age=18-19}^{65-69} (Perc_{BlDN(age)} / Freq_{BlDN(age)}) \quad \textbf{(IV.C.1.a-5)}$$

Variable : $\boldsymbol{DR_{Bl}}$-The annual total number of blood donors in the US, which is assumed to be 8 million.

Variable: $DR_{Bl(age)}$- The annual number of blood donors in each five-year age group and the18-19 yr old age cohort.

$$DR_{Bl(age)} = DR_{Bl} \times Perc_{BlDR(age)} \quad \textbf{(IV.C.1.a-6)}$$

Variable: $DR_{Bl\text{-}UK}$ -Total number of US blood donors who have traveled to the UK during the period 1980 - 1996

Variable: $Perc_{BlDR\text{-}UK(age)}$ - The percentage of US blood donors in an age group who traveled to the UK during the period 1980 - 1996.

$$DR_{Bl-UK} = \sum_{age=18-19}^{65-69} (Perc_{BlDR-UK(age)} \times DR_{Bl(age)}) \quad \textbf{(IV.C.1.a-7)}$$

Variable: $Odd_{T(age)}$- Age specific odd ratios for travel compared to the age group 18-19 years.

Data used in the model: The odds ratios for likelihood of travel for each age group were derived from the travel data obtained from 1980-1996 blood donor travel survey. An odds ratio of 1 was assigned to the donor group aged 18-19 years. The odds ratios for other age groups is a function of the travel frequency of those age groups compared to the travel frequency of the age group of 18-19 years

$$Perc_{BlDR-UK(age)} = Odd_{T(age)} \times Perc_{BlDR-UK(18-19)} \quad \textbf{(IV.C.1.a-8)}$$

Replacing the variable, **$Perc_{BlDR\text{-}UK(age)}$** , in equation IV.C.1.a-7 with equation IV.C.1.a-8 the percentage of blood donors in the age group of 18-19 years of age who traveled to the UK was calculated using the following equation:

$$Perc_{BlDR-UK(18-19)} = DR_{Bl-UK} \,/\, \sum_{age=18-19}^{65-69} (Odd_{T(age)} \times DR_{Bl(age)}) \quad \textbf{(IV.C.1.a-9)}$$

A-IV. C. 1. a. ii. a. Number of US <u>Source Plasma</u> donors who traveled to the UK in a specific year from 1980 to 1996 and by age group

Variable: *age* - Age of US plasma donors in groups by 5-year increments and 18-19 yr old age cohort.

Variable: $DR_{S(age)}$ (calculated in section A-IV.B. 1**.) -** The annual number of donors by age group who contribute Source Plasma to make pdFVIII.

Variable: $Perc_{BlDR\text{-}UK(age)}$ (calculated in section A-IV.C.1.a.i.b.**) -** the percentage of blood donors in each age group who traveled to the UK between 1980-1996.

Variable: $DR_{S\text{-}UK(age)}$ - Number of Source Plasma donors who traveled to the UK from 1980 through 1996 by age groups.

Assumptions used in the model: The percentage of Source Plasma donors who traveled to the UK is the same as the percentage of blood donors of the same age group.

The number of Source Plasma donors who traveled to the UK from 1980 to 1996 by age group is represented by:

$$DR_{S-UK(age)} = DR_{S(age)} \times Perc_{BlDR-UK} \quad \textbf{(IV.C.1.a-8)}$$

The risk of vCJD infection in US donors who traveled to the UK was assumed proportional to the relative level of exposure to the BSE agent in each year through the UK food supply. The proportional risk was derived based on the number of BSE-reported cattle in a given year from 1980 through 1996 divided by the total number of BSE cases to date. The model generates categories (or bins) for Source Plasma donors by year of travel and estimates the risk more accurately by incorporating the information about proportional risk due to the BSE epidemic in the UK

In 1996 after the emergence of human vCJD cases the UK government implemented stringent food chain controls that decreased the number of high risk animals and high risk tissues containing BSE agent from entering the human food supply. In the early 1980s human exposure may have begun at a low level as BSE spread among the UK cattle population. The BSE epidemic expanded throughout the 1980s and peaked in 1992, then risk started to decrease as animal feed measures were implemented and more stringent human food chain controls were implemented in 1996. Today, a few hundred cases of BSE are identified in the UK annually – but it is unlikely that the animals or products from BSE-infected animals in the UK enter the human food supply. The model incorporates the changing dynamics of the BSE epidemic since 1980 and accounts for relative changes in the levels of human, specifically US plasma donors, exposure to the BSE agent and possible vCJD infection.

Variable: y - Calendar year of travel.

Variable: V_y - Number of visits by year to the UK by US travelers (in thousands)

Data used in the model: Number of visits by year to the UK by US travelers (UK Government Statistics, 2005).

The yearly distribution of travel visits by each age group was adjusted to account for the minimum age of 18 when a donor can donate plasma or blood. Therefore, in calculating the US donor risk for vCJD the yearly distribution of travel visits by each age group was adjusted to account for this requirement. The model adjusted the potential vCJD exposure for younger donors who were born during the period from 1980 to 1986 and would have essentially a zero chance of being exposed to the BSE agent in the years prior to their birth. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

Assumption used in the model: US Source Plasma donors have similar travel patterns to the US blood donor population, which is assumed to be similar for the larger US population.

Assumption used in the model: It was assumed that no US traveler visited the UK more than once per year. This may potentially overestimate the vCJD risk for US plasma donors (because repeat travel by the

same donor is not addressed) and underestimate it in certain other cases (travelers who visit multiple times per year). FDA found no data that quantified the numbers of multiple visits or repeat visits by the same traveler that likely occurred for US donors with a history of UK travel.

Variable: $V_{y/1996}$ **-** The number of visits to the UK by US travelers in year *y* compared to the number of visits in 1996 is represented by the equation:

$$V_{y/1996} = V_y / V_{1996} \quad \textbf{(IV.C.1.a-9)}$$

Variable: ***age*** **-** Age of US plasma donors in groups of 5-year increments (e.g., 20-24 yrs, etc.) and 18-19 yr old age cohort..

Variable: $DR_{S(age)}$ (calculated in section A-IV.B. 1**.) -** the annual Source Plasma donations by age groups.

Variable: $DR_{S\text{-}UK(age)}$ **-** Number of Source Plasma donors who traveled to the UK from 1980 through 1996 by age group in five-year increments and 18-19 yr old age cohort.

Assumptions used in the model:

- The same percentage of Source Plasma donors traveled to UK as blood donors
- Frequencies of travels are similar among the donors of different age groups.
- Travel rates for the general US population are the same as the travel rate for blood and plasma donors.

The number of Source Plasma donors who traveled to the UK from 1980 to 1996 by age group is represented by:

$$DR_{S-UK(age)} = DR_{S(age)} \times Perc_{DR-UK} \quad \textbf{(IV.C.1.a-5)}$$

Variable: $DR_{S\text{-}UK(age),y}$ **-** the number of Source Plasma donors who traveled to the UK in year *y* by age group

Source Plasma donors with a history of travel to the UK among each age group ($DR_{S\text{-}UK(age)}$) was allocated to individual travel years based on the yearly distribution of visits to the UK by US travelers (UK National Statistics, 2005). The yearly distribution of travel visits by each age group was adjusted to account for the minimum age of 18 when a donor can donate plasma or blood. Therefore, in calculating the US donor risk for vCJD the yearly distribution of travel visits by each age group was adjusted to account for this requirement. The model adjusted the potential vCJD exposure for younger donors who were born during the period from 1980 to 1986 and would have essentially a zero chance of being exposed to the BSE agent in the years prior to their birth. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

Assumption used in the model: US Source Plasma donors have similar travel patterns as the general US population and US blood donors.

The number of US Source Plasma donors who have traveled to the UK in year y between 1980-1996 is represented by the equation:

$$DR_{S-UK(age)y} = DR_{S-UK(age)} \times V_{y/1996} / \sum_{y=1980}^{1996} V_{y/1996} \quad \textbf{(IV.C.1.a-10)}$$

A-IV. C. 1. a. ii. b. US Source Plasma donors with history of travel to the UK: Duration of travel by age group

There were no data that we are aware of that details the travel histories of Source Plasma donors in the US. Travel data for US blood donors was used to estimate travel patterns for Source Plasma donors after an adjustment for the frequency of travel based on the age of Source Plasma donors and the age-specific odds ratios for travel, which was obtained from 1980-1996 Blood Donor Travel Survey (TSEAC, 2000). The model used the data on the number of Source Plasma donors who have traveled to the UK in a specific year and subdivided those individuals into additional categories based on estimated duration of stay. The categories of duration of stay was estimated based on the Blood Donor Travel Survey (TSEAC, 2000). Use of blood donor travel data in the model implicitly assumes that travel rates are similar for both blood and plasma donors. However, it is thought that plasma donors likely travel less and are therefore at lower risk for vCJD, therefore the model results may overestimate the potential vCJD risk for plasma donors.

Variable: *i* - The duration interval used to group blood donors who had traveled to UK from 1980-1996 based on the time they spent in the UK (same variable used above in section A-IV. C. 1. a. i.).

Variable: D_i - The average duration of time for interval *i* (months) (same variable used above in section A-IV. C. 1. i.).

Variable: $DR_{S\text{-}UK(age),y}$ - the number of Source Plasma donors who traveled to the UK in year *y* by age group (calculated in A-IV. C. 1. a. ii. (a))

Variable: $Perc_{BlDR\text{-}UKi/UK}$ - The percentage of blood donors who traveled for a specific duration interval *i* among all donors who have ever traveled to the UK (calculated in A-IV. C. 1. a. i. a)

Variable: $DR_{S\text{-}UK(age)y,i}$ - Number of Source Plasma donors within a specific age group that traveled to the UK in year *y* for a duration of *i* and is represented by the equation:

$$DR_{S-UK(age)y,i} = DR_{S-UK(age)y} \times Perc_{DR-UKi/UK} \quad \textbf{(IV.C.1.a-11)}$$

A-IV. C. 1. a. ii. c. Number of US recovered plasma donors with a history of travel to the UK in a specific year from 1980 – 1996 by age group

Recovered plasma is plasma that is separated or "recovered" from a unit of whole blood soon after the blood is collected. As expected, recovered plasma donor donation characteristics mirror those of whole blood donors. A recovered plasma donor can donate plasma a maximum of six times per year (or once every 54 days)– and on average we assumed a recovered donation is approximately 200 milliliters (versus an average of 700 milliliters for a Source Plasma donation).

Variable: ***y*** **– year of travel** (same variable used above in section A-IV. C. 1. a. ii. a) to the UK during the period 1980 - 1996 by US plasma donors.

Variable: age – age groups of the population in five-year increments (same variable used above in section A-IV. B. 1.).

Variable: $DR_{R(age)}$ **-** number of potential recovered plasma donors per year by age group (described in section A-IV. B. 2).

Variable: $Perc_{BlDR\text{-}UK(age)}$ (calculated in section A-IV.C.1.a.i.b.**) -** the percentage blood donors in each specific age group who have traveled to the UK between 1980-1996.

Variable: $DR_{R\text{-}UK(age)}$ **–** The number of recovered plasma donors who have traveled to the UK from 1980 through 1996 by age group and is represented by the equation:

$$DR_{R-UK(age)} = DR_{R(age)} \times Perc_{BlDR-UK(age)} \qquad \textbf{(IV.C.1.a-12)}$$

The model categorizes US recovered plasma donors by year of travel in order to estimate the potential vCJD risk more accurately by incorporating the information about BSE epidemic in the UK. The number of beef cattle affected each year by the BSE epidemic in the UK changed throughout the epidemic. Donors who visited the UK at the height of the BSE epidemic in 1992, we assumed, were more likely to be exposed to BSE agent (and vCJD risk) than a donor who visited in 1996 after food chain controls were implemented. The model accounts for this changing exposure potential by analyzing US donors who may have traveled to the UK for each year from 1980 through 1996. The number of recovered plasma donors who traveled to the UK was allocated to individual travel year based on the yearly distribution of visits to the UK by US travelers determined from UK travel data.

Variable: $DR_{R\text{-}UK(age)}$ **-** Number of recovered plasma donors traveled to the UK from 1980 through 1996 by age groups (calculated above).

Variable: $V_{y/1996}$ **-** The number of visits to the UK by US travelers in year *y* compared to the number of visits in 1996 (calculated in A-IV.C.1.a. ii. a.).

Data used in the model: Number of visits by year to the UK by US travelers was determined using UK Government Statistics (2005).

Assumption about variable: US recovered plasma donors have a similar travel pattern as the US total population. The yearly distribution of travel visits by each age group was adjusted to account for the minimum age of 18 when a donor can donate plasma or blood. Therefore, in calculating the US donor risk for vCJD the yearly distribution of travel visits by each age group was adjusted to account for this requirement. The model adjusted the potential vCJD exposure for younger donors who were born during

the period from 1980 to 1986 and would have essentially a zero chance of being exposed to the BSE agent in the years prior to their birth. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

The number of recovered plasma donors who traveled to the UK in year *y* by age groups during the period from 1980-1996 is represented by the equation:

$$DR_{R-UK(age)y} = DR_{R-UK(age)} \times V_{y/1996} / \sum_{y=1980}^{1996} V_{y/1996} \quad \textbf{(IV.C.1.a-13)}$$

A-IV. C. 1. a. ii. d. US recovered plasma donors with history of travel to the UK: Duration of travel by age group

Recovered plasma donors who traveled to the UK in a specific year ($DR_{R-UK(age)y}$) in the years 1980-1996 were further partitioned in the model into subgroups or "bins" based on travel duration and by 5-year age groups and 18-19 yr old age cohort. Data on the percentage of blood donors who traveled to the UK since 1980 for a certain duration(s) (TSEAC 2000) was used in this risk assessment.

Variable: *i* - The duration interval used to group blood donors who had traveled to the UK from 1980-1996 based on the time they spent in the UK (same variable used above in section A-IV. C. 1.)

Variable: D_i - The average duration of time for interval *i* (months) (same variable used above in section A-IV. C. 1.)

Variable: $DR_{R-UK(age),y}$ - The number of recovered plasma donors who traveled to the UK in year *y* by age group (calculated in A-IV. C. 1. a. ii. c)

Variable: $Perc_{BlDR-UKi/UK}$ - The percentage of blood donors who traveled for a specific duration interval *i* among all donors who have ever traveled to the UK (calculated in A-IV. C. 1. a. i. a)

Variable: $DR_{R-UK(age)y,i}$- The number of recovered plasma donors among an age group who have traveled to the UK in year, *y* ,for duration of *i* and represented by the expression*:*

$$DR_{R-UK(age)y,i} = DR_{R-UK(age)y} \times Perc_{DR-UKi/UK} \quad \textbf{(IV.C.1.a-14)}$$

A-IV. C. 1. a. iii. US plasma donors with a history of travel to the UK: Adjustment of relative risk to account for variations in BSE risk by specific year and travel duration

As indicated in previous sections the FDA model assumed that the relative vCJD risk for UK residents residing for any five-year period or longer from 1980 through 1996 is assumed to have a value of 1, because the BSE epidemic in UK cattle and exposure of the human population to the BSE agent in the UK was greater than any other country. The relative risk value of 1 equates to 100% of the UK asymptomatic and symptomatic vCJD prevalence, which is difficult to estimate. The relative risk value is assigned based on factors such as domestic UK beef consumption, and the rate and number of vCJD cases, and indigenous BSE cases that may have occurred (TSEAC 2004). BSE was first diagnosed in the United Kingdom in 1986 and the epidemic peaked in 1992, a year when the risk of exposure to the BSE agent would have likely been highest for residents and visitors to the UK. Human exposure risk to the BSE agent would likely have decreased dramatically in 1996 with the culling of animals over 30 months of age from the food production system and the institution of food chain controls to prevent high risk tissues that might contain BSE agent from entering the food and animal food supplies. Presumably there were dramatic variations in the BSE exposure risk, and hence, the human vCJD infection risk that occurred from year to year. Therefore, the model adjusted the vCJD risk for US plasma donors with a history of extended travel or residence in the UK by multiplying by the proportional BSE risk per year (e.g., the BSE exposure risk in a given year compared to the total BSE risk since 1980). Additionally, the model included calculations on the estimated duration of UK travel or residence by US plasma donors based on US donor survey data (TSEAC 2000) to generate a more accurate vCJD risk estimate.

A-IV. C. 1. a. iii. a. Variant CJD risk for individual UK residents from 1980 through 1996

Variable: R_{UK}- The accumulated vCJD risk per UK resident from 1980 through 1996.

Assumption used in the model: The UK population has the highest risk of exposure to BSE or vCJD, we assumed the average accumulated risk per UK individual is 1. Also, the relative risk for UK residents is 1, which is equivalent to the UK vCJD prevalence.

A-IV. C. 1. a. iii. b. US plasma donors with a history of travel to the UK: Adjustment for the proportional individual BSE exposure risk for the UK population per year between 1980 to 1996.

The model calculates the risk and potential magnitude of BSE exposure for donors, in any given year in the UK since 1980, as a function of the number of BSE cases in a specific year divided by the total of all BSE cases since 1980.

Variable: y – year of travel (same as variable used above in section A-IV. C. 1. a. ii. A.) by US plasma donor to the UK from 1980 to 1996.

Variable: BSE_{UKy}- The annual number of reported BSE cases in the UK since 1986 (OIE, 2005).

Variable: R_{UKy}- Proportional BSE exposure risk in the UK by specific year from 1980 to 1996.

Assumptions used in the model:

- The BSE exposure risk, and hence, most of the vCJD risk in the UK occurred largely between 1980 and 1996.
- The vCJD risk in the UK was assumed to be negligible after 1996, when stringent food chain controls were put in place to prevent contamination of beef with high risk tissue.
- The yearly rate of the human exposure risk to the BSE agent in the UK is proportional to the number of reported BSE annual cases in the UK
- The vCJD risk is additive for each year of residency during the specific time period.
- A person residing for five or more years during the time period between 1980 and 1996 in the UK is assumed to have a relative risk of 1 (or 100%), i.e., a probability of vCJD infection that is the same as that of the entire UK population.

The proportional BSE risk in the UK per specific year prior to 1997 is represented by the equation:

$$R_{UKy} = R_{UK} \times BSE_{UKy} / \sum_{y=1980}^{1996} BSE_{UKy} \quad \textbf{(IV.C.1.a-15)}$$

A-IV. C. 1. a. iii. c. US plasma donors with a history of travel to the UK: BSE exposure risk and vCJD risk in year *y* for a period of *i,* during the period from 1980 to 1996.

Variable: $R_{DR\text{-}Uky,,i}$- The potential vCJD risk of an individual US donor who traveled to the UK in specific year during the period 1980-1996 for a specific duration.

The potential vCJD risk for the US plasma donor subpopulation that traveled to the UK in a specific year for a specific duration was calculated using a pro-rated monthly rate, which was calculated based on the proportional BSE exposure risk in the UK in the specific year. The blood donor travel survey conducted by the American Red Cross (TSEAC 2000) collected data on the accumulated stay of donors in the UK from 1980 through 1996, which, for simplicity, was assumed to be the duration of a single, consecutive stay, when calculating the risk.

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Assumptions used in the model:

- Risk of vCJD infection is proportional to the duration of the stay in the UK during the period 1980-1996
- All travelers evaluated completed a single, consecutive stay

As mentioned earlier, any US plasma donor with 5 years or more of accumulated stay in the UK is assumed to have average risk of 1, a risk equal to the average risk of an UK resident and equal to the UK vCJD prevalence.

The BSE exposure risk for US plasma donors with a stay less than or equal to one year – is represented by the equation:

$$R_{DR-UKy,i} = (R_{UKy} / 12) \times D_i \quad \textbf{(IV.C.1.a-16)}$$

for $i_{upper} \leq 1$ years;

The BSE exposure risk for US plasma donors with a stay less than five years but greater than or equal to one year is represented by the equation:

$$R_{DR-UKy,i} = (Average(R_{UKy} : R_{UK(y+Roundup(i_{upper,0})}) / 12) \times D_i \quad \textbf{(IV.C.1.a-17)}$$

for 5 years < $i_{upper} \geq 1$ year;

The BSE exposure risk for US plasma donors with a stay greater than or equal to five – is represented by the equation:

$$R_{DR-UKy,i} = 1 \quad \textbf{(IV.C.1.a-18)}$$

for $i_{upper} \geq 5$ years

A-IV. C. 1. a. iv. US plasma donors with a history of travel to the UK: Probability of potential infection with vCJD based on duration of travel to the UK and age

This section describes the portion of the model that estimates the probability that a US plasma donor in a specific age group, who traveled to the UK for a specific duration during the time-span of 1980 through 1996, was infected with vCJD.

Variable: $Pr_{vCJD\text{-}UK(age)}$ **–** the probability of vCJD infection per individual UK resident of a specific age group

Variable: $Prev_{Asym\text{-}vCJD(age)}$- Prevalence of asymptomatic vCJD infection in the UK for each age groups in five-year increments (e.g., 20-24 yrs, etc.) and the 18-19yr old group (calculated in A-IV.A.3.b.).

$$\Pr_{vCJD\text{-}UK(age)} = \Pr ev_{Asym-vCJD(age)} / 1000000 \quad \textbf{(IV.C.1.a-19)}$$

Variable: $Pr_{vCJD\text{-}DR\text{-}UK(age)y,i}$ **–** The probability of infection for individual US plasma donor of a specific age group who had traveled to the UK in a specific year for a specific duration

Assumption used in the model: Probability of infection is proportional to the risk of exposure

$$\Pr_{vCJD-DR-UK(age)y,i} = \Pr_{vCJD-UK(age)} \times R_{DR-UKy,i} \quad \textbf{(IV.C.1.a-20)}$$

A-IV. C. 1. a. v. Number of all US pdFVIII plasma donors with history of travel to the UK and potentially infected with vCJD

This section of the model estimates the total number of all US plasma donors potentially infected with vCJD during travel to the UK from 1980 through 1996. To derive the total number of donors the model separately estimates the number of potentially infected Source Plasma donors and potentially infected recovered plasma donors (described in the subsequent sections below) and sums the two.

A-IV. C. 1. a. v. a. Number US Source Plasma donors with history of travel to the UK and potentially infected with vCJD during travel to the UK

Plasma is collected from Source Plasma donors in a process called plasmapheresis in which an average of approximately 700 milliliters of plasma are collected. Source Plasma donors donate an average of 14 times per year, but can donate up to 48 times per year.

This component of the model estimates the number of US Source Plasma donors potentially infected with vCJD during travel to the UK from 1980 through 1996.

Variable: $DR_{vCJD\text{-}S\text{-}UK(age)y,i}$- Number of Source Plasma donors potentially infected with vCJD during travel to the UK during 1980-1996 by age, year and duration of travel.

$$DR_{vCJD-S-UK(age)y,i} = Bionomial(DR_{S-UK(age)y,i}, \Pr_{vCJD-DR-UK(age)y,i}) \quad \textbf{(IV.C.1.a-21)}$$

Variable: $DR_{vCJD\text{-}S\text{-}UKy}$ - Number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in the UK.

$$DR_{vCJD-S-UK} = \sum_{Age=18-19\,yrs}^{50-54\,yrs} \sum_{i=1day-3months}^{>=5\,years} DR_{vCJD-S-UK(age)y,i} \quad \textbf{(IV.C.1.a-22)}$$

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}Defy}$- Number of Source Plasma donors potentially infected with vCJD in year y and not deferred by current policy.

$$DR_{vCJD-S-UK-defy} = \sum_{Age=18-19\,yrs}^{50-45\,yrs} \sum_{i=3-5months}^{>=5\,years} DR_{vCJD-S-UK(age)y,i} \quad \textbf{(IV.C.1.a-23)}$$

Current deferral policy (FDA 2002) defers individuals who have history of travel to the UK from 1980 through 1996 for an accumulated residence of 3 months or more from donating blood and plasma. The number of potentially infected donors who meet deferral criteria was calculated by equation:

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}Res}$- Residual risk due to the number of Source Plasma donors potentially infected with vCJD not deferred by current policy

$$DR_{vCJD-S-UK-\mathrm{Re}\,sy} = \sum_{Age=18-19}^{50-54\,yrs} DR_{vCJD-S-UK(age)y,i=1day-3months} \quad \textbf{(IV.C.1.a-24)}$$

A-IV. C. 1. a. v. b. Number of US Source Plasma donors with a history of travel to the UK and potentially infected and with vCJD agent present in their blood

Perhaps the most critical component of the model is the estimation of whether a plasma donation was collected from a vCJD-infected donor that contained infectious vCJD agent in their blood at the time of

donation. Based on data from animal studies, the model assumes that vCJD infectious individuals have infectious vCJD agent present in the blood during the last half of the incubation period. This portion of the model calculates the number of Source Plasma donors who may potentially contain infectious vCJD agent in their blood at the time of donation.

Variable: *y* - The calendar year in which a plasma donor traveled and infected with vCJD.

Assumption used in the model: This risk assessment assesses the risk for pdFVIII product made in 2002.

Variable: $T_{Inf\text{-}2002y}$ - Time Period between infection/travel and year of 2002 when the plasma was collected

Variable: $Pr\text{-}LH_y$ - Probability the disease is in the last half incubation period of the disease (and donor is prionemic), if infected in year y

Variable: $T_{Inf\text{-}2002y}$ - Time period between infection/travel and 2002 when the plasma was collected.

$$T_{Inf-2002y} = 2002 - y \qquad \textbf{(IV.C.1.a-25)}$$

For an individual to have vCJD agent present in their blood and plasma (prionemic) in 2002, the elapsed period of time since infection up to 2002 ($I_{Inf\text{-}2002y}$) should be equal to or greater than the half of incubation period of the disease.

Assumption used in the model: The variability and uncertainty of the incubation period of vCJD is represented mathematically by a gamma distribution, specifically Gamma (4.7, 3.6). A gamma distribution is usually used to represent the time between events, in this case the time from infection to the occurrence 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 in this case is the mean incubation period of 14 years.

Variable: $Pr_{LH\text{-}y}$ -The probability an individual has vCJD agent present in their blood and plasma in year 2002 (the baseline year of the model) was calculated by the expression:

Cumulative frequency of Gamma (4.7, 3.6), at x = 2×(1997-y)

Variable: $DR_{vCJD\text{-}S\text{-}UKy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in the UK.

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}LHy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in the UK and were in the last half incubation period of the disease in 2002 at the time of donation.

$$DR_{vCJD-S-UK-LHy} = Binomial(DR_{vCJD-S-UKy,}\ \Pr_{LH-y}) \qquad \text{(IV.C.1.a-26)}$$

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}defy}$- Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in the UK and met deferral criteria

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}def\text{-}LHy}$ - Total number of Source Plasma donors in the last half incubation period of the disease (prionemic) and met current deferral criteria (FDA 2002).

$$DR_{vCJD-S-UK-Def-LHy} = Binomial(DR_{vCJD-S-UK-Defy,}\ \Pr_{LH-y}) \quad \text{(IV.C.1.a-27)}$$

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}Resy}$- Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in the UK and did not meet deferral criteria

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}Res\text{-}LHy}$ - Total number of Source Plasma donors in the last half of the incubation period of the disease who did not meet current deferral criteria (FDA 2002).

$$DR_{vCJD-S-UK-\mathrm{Re}s-LHy} = Binomial(DR_{vCJD-S-UK-\mathrm{Re}sy,}\ \Pr_{LH-y}) \quad \text{(IV.C.1.a-28)}$$

A-IV. C. 1. a. v. c. Number of US recovered plasma donors with history of travel to the UK and potentially infected with vCJD

Recovered plasma donors donate whole blood from which the plasma is separated out (or recovered). Like blood donors recovered plasma donors donate an average of 1.7 times per year but can donate up to 6 times per year. The model assumes the average amount of plasma in a recovered plasma unit is approximately 200 milliliters.

This component of the model estimates the number of US recovered plasma donors potentially infected with vCJD during travel to the UK from 1980 through 1996.

Variable: $DR_{vCJD\text{-}R\text{-}UK(age)y,i}$ - Number of recovered plasma donors potentially infected with vCJD during travel to the UK during 1980-1996 by age, year and duration of travel

$$DR_{vCJD-R-UK(age)y,i} = Bionomial(DR_{R-UK(age)y,i}, \Pr_{vCJD-DR-UK(age)y,i}) \quad \textbf{(IV.C.1.a-29)}$$

Variable: $DR_{vCJD\text{-}R\text{-}UK\ y}$ - Total number of recovered plasma donors potentially infected with vCJD in year y

$$DR_{vCJD-R-UKy} = \sum_{Age=18-19}^{50-54} \sum_{i=1day-3months}^{>=5\,years} DR_{vCJD-R-UK(age)y,i} \quad \textbf{(IV.C.1.a-30)}$$

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}Defy}$- Number of recovered plasma donors potentially infected with vCJD in year y and deferred by current policy

$$DR_{vCJD-R-UK-Defy} = \sum_{Age=18-19}^{50-54} \sum_{i=3-5months}^{>=5\,years} DR_{vCJD-R-UK(age)y,i} \quad \textbf{(IV.C.1.a-31)}$$

Variable: $DR_{vCJDS\text{-}UK\text{-}Resy}$ - Residual risk due to the number of recovered plasma donors potentially infected with vCJD not deferred by current policy and represented by the equation:

$$DR_{vCJD-R-UK-resy} = \sum_{Age=18-19}^{50-54} DR_{vCJD-R-UK(age)y,i=1day-3months} \quad \textbf{(IV.C.1.a-32)}$$

A-IV. C. 1. a. v. d. Number of US recovered plasma donors with a history of travel to the UK and potentially infected and with vCJD agent present in their blood

As discussed in the sections above the most critical determinant in the model of whether exposure occurs is the estimation of whether a plasma donation was collected from a vCJD infected donor who had infectious vCJD agent in their blood (e.g., was prionemic) at the time of donation. Based on data from animal studies, the model assumes that vCJD infectious individuals have infectious vCJD agent present in the blood during the last half of the incubation period. This portion of the model calculates the number of recovered plasma donors who may potentially have infectious vCJD agent in their blood at the time of donation.

Variable: $Pr_{LH\text{-}y}$ -The probability an individual will have vCJD agent in blood and plasma (prionemic) in year 2002

Variable: $DR_{vCJD\text{-}R\text{-}UKy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in the UK (calculated in A-IV. C. 1. a. v. b)

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}LHy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in the UK and in the last half incubation period of the disease.

$$DR_{vCJD-R-UK-LHy} = Binomial(DR_{vCJD-R-UKy,}\ \Pr_{LH-y}) \quad \text{(IV.C.1.a-33)}$$

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}defy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in the UK and met deferral criteria (calculated in A-IV. C. 1. a. v. c)

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}def\text{-}LHy}$ - Total number of recovered plasma donors in the last half incubation period of the disease who met deferral criteria.

$$DR_{vCJD-R-UK-Def-LHy} = Binomial(DR_{vCJD-R-UK-Defy,}\ \Pr_{LH-y}) \quad \text{(IV.C.1.a-34)}$$

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}Resy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in the UK and did not meet deferral criteria (calculated in A-IV. C. 1. a. v. c).

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}Res\text{-}LHy}$ - Total number of recovered plasma donors in the last half incubation period of the disease who did not meet deferral criteria

$$DR_{vCJD-R-UK-\mathrm{Res}-LHy} = Binomial(DR_{vCJD-R-UK-\mathrm{Res}y,}\ \mathrm{Pr}_{LH-y}) \quad \text{(IV.C.1.a-35)}$$

A-IV. C. 1. a. v. e. Number of <u>all</u> US plasma donors with a history of travel to the UK and potentially infected with vCJD

This section sums the total number of <u>all</u> US plasma donors, predicted by the model to donate to plasma pools used in manufacturing pdFVIII made from plasma collected in the US. This includes <u>Source Plasma</u> donors and recovered plasma donors predicted by the model to be infected with vCJD and arrives at an estimate of the total number of US donors potentially infected with vCJD.

Variable: $DR_{vCJD\text{-}UK}$ - Total number of plasma donors potentially infected with vCJD during travel/residence in the UK

$$DR_{vCJD-UK} = \sum_{y=1980}^{1996} DR_{vCJD-S-UKy} + \sum_{y=1980}^{1996} DR_{vCJD-R-UKy} \quad \text{(IV.C.1.a-36)}$$

Variable: $DR_{vCJD\text{-}UK\text{-}Def}$ - Total number of plasma donors potentially infected with vCJD during travel/residence in the UK and met deferral criteria

$$DR_{vCJD-UK-Def} = \sum_{y=1980}^{1996} DR_{vCJD-S-UK-Defy} + \sum_{y=1980}^{1996} DR_{vCJD-R-UK-Defy} \quad \text{(IV.C.1.a-37)}$$

Variable: $DR_{vCJD\text{-}UK\text{-}Res}$- Total number of plasma donors potentially infected with vCJD during travel/residence in the UK and did not meet deferral criteria

$$DR_{vCJD-UK-\mathrm{Res}} = \sum_{y=1980}^{1996} DR_{vCJD-S-UK-\mathrm{Res}y} + \sum_{y=1980}^{1996} DR_{vCJD-R-UK-\mathrm{Res}y} \quad \text{(IV.C.1.a-38)}$$

A-IV. C. 1. a. v. f. Total of all US plasma donors with a history of travel to the UK and potentially infected and with vCJD agent present in their blood

Again, whether a donor contains vCJD agent in their blood is a pivotal calculation for the model since a donation from such an individual would contain vCJD agent that may find its way into a large plasma pool of thousands of donations that are used to manufacture pdFVIII. This section sums the number of US Source Plasma donors and recovered plasma donors predicted by the model to be infected with vCJD

and contain vCJD agent in their blood and arrives at an estimate of the total number of US donors potentially infected with vCJD and prionemic.

Variable: $DR_{vCJD\text{-}UK\text{-}LH}$ **-** Total number of plasma donors in the last half incubation period of the disease

$$DR_{vCJD-UK-LH} = \sum_{y=1980}^{1996} DR_{vCJD-S-UK-LHy} + \sum_{y=1980}^{1996} DR_{vCJD-R-UK-LHy} \quad \text{(IV.C.1.a-39)}$$

Variable: $DR_{vCJD\text{-}UK\text{-}Def\text{-}LH}$ **-** Total number of plasma donors in the last half incubation period of the disease and met deferral criteria

$$DR_{vCJD-UK-Def-LH} = \sum_{y=1980}^{1996} DR_{vCJD-S-UK-Def-LHy} + \sum_{y=1980}^{1996} DR_{vCJD-R-UK-Def-LHy} \quad \text{(IV.C.1.a-40)}$$

Variable: $DR_{vCJD\text{-}UK\text{-}Res\text{-}LH}$**-** Total number of plasma donors in the last half incubation period of the disease and did not meet deferral criteria

$$DR_{vCJD-UK-\mathrm{Res}-LH} = \sum_{y=1980}^{1996} DR_{vCJD-S-UK-\mathrm{Res}-LHy} + \sum_{y=1980}^{1996} DR_{vCJD-R-UK-\mathrm{Res}-LHy}$$

A-IV. C. 1. b. Estimation of the number of US plasma donors with a history of extended travel to France potentially infected and vCJD agent is present in the blood

A-IV.C.1.b.i. US plasma donors with a history of travel to France: Percentage of donors and travel duration

In this portion, blood donors are characterized by frequency and duration of travel to France since 1980. The risk of vCJD infection is a function of exposure to the BSE agent and is assumed to be proportional to the amount of time spent, or duration of travel, in France since 1980. The FDA model used data from the National Blood Donor Travel Survey 1980-1996 (TSEAC 2000) to derive estimates of the percentages of US donors with a history of extended travel or residence ($\geq$ 5 years) in France since 1980, and to derive the frequencies for various durations of travel for 5 years or more. Since the baseline year to estimate potential vCJD risk for US donors in our model was 2002 trends in the National Blood Donor Travel Survey 1980-1996 (TSEAC 2000) were extrapolated from the year 1997 to 2002 when necessary to estimate potential travel characteristics and risk beyond 1996. The period of 5 years or more corresponds to the length of time in the current policy that defers donors who traveled to or resided in France. The travel survey data on blood donors pose a limitation because the survey was conducted on whole blood donors and may not exactly reflect the travel histories of plasma donors. Unfortunately, to our knowledge there is not travel data available on plasma donors. Therefore, we assumed that plasma donor travel characteristics to the France since 1980 are similar to those of whole blood donors and used this information in the FDA risk assessment. Some may argue that plasma donors travel less frequently than their blood donor counterparts so use of data on blood donors may overestimate the risk.

Data used in the model: National Blood Donor Travel Survey 1980-1996 was conducted by the American Red Cross and presented at the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC 2000).

Variable: *i* - The duration interval used to group donors who had traveled to France from 1980-1996 based on the quantity of time spent in France during the period from 1980 – 1996.

Variable: D_i - The average duration of time (months) for interval *i* representing the duration of travel or residence by US donors in France during the period from 1980 – 1996.

Variable: $CumPerc_{BlDR\text{-}FRi}$ – The cumulative percentage of blood donors who traveled to France within duration interval *i* or longer**.**

Data used in the model: Travel data for US blood donors was obtained from a blood donor survey conducted by the American Red Cross and presented at the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC, 2000).

Variable: $Perc_{BlDR\text{-}FRi}$ - Percentage of blood donors who have traveled to France within duration interval *i.* This variable was converted from $CumPerc_{BlDR\text{-}FRi}$

Variable: $Perc_{BlDR\text{-}FRi/FR}$- The percentage of blood donors who traveled for a specific duration interval *i* among all donors who have ever traveled to France is represented by the equation:

$$Perc_{BlDR-FRi/FR} = (Perc_{BlDR-FRi} / CumPerc_{BlDR-FR,i>1day-1month}) \times 100\% \quad \textbf{(IV.C.1.b-1)}$$

IV. C. 1. b. Estimation of the number of US plasma donors with a history of extended travel to France potentially infected and vCJD agent is present in the blood

A-IV.C.1.b.ii. Number of US plasma donors with a history of travel to France by age group, year of travel and duration of travel

This part of risk assessment calculates the annual number of US source and recovered plasma donors that traveled to France by specific year(s) and for a specific duration of time since 1980 by age. For the purposes of our analyses we grouped all donors and donors who traveled to France since 1980 into age groups of five year increments (20 – 24yrs, 25 – 29 yrs, etc) and the two year cohort for 18 and 19 years of age.

We estimated the frequency of donor travel by age group based on travel data for the US population and donor survey data. First, the total number of blood donors who traveled to France between 1980 and 1996 was estimated by multiplying the total number of US blood donors in a specific year by the percentage of donors (from survey data) who traveled to France. The percentage of donors in each age group that traveled to France since 1980 was calculated based on the total annual number donors who traveled to France since 1980 compared to (or divided by) the total number of donors, and the age specific odds ratio for travel. Finally, the information on the number of donors from each age group who traveled was

calculated by year and duration of travel. The risk of a US donor acquiring vCJD is a function of duration of the stay, as well, the year(s) (since 1980) they resided in France.

- **Calculation of the annual number of blood donors who traveled to France from 1980 through 1996**

Variable : $\boldsymbol{DR_{Bl}}$-The annual total number of potential blood donors in the US

Data used in the model: There are approximately 8 million individuals who donate blood each year in the United States (Westat, 2002).

Variable: $\boldsymbol{Perc_{BlDR\text{-}FR}}$ - The total percentage of US blood donors who traveled to France during the period from 1980 through 1996.

Data used in the model: Approximately, 15.6% of US blood donors reported a history of travel to France during the period from 1980 through 1996, based on the travel data of US blood donors (TSEAC, 2000).

Variable: $\boldsymbol{DR_{Bl\text{-}FR}}$ -Total number of blood donors who have traveled to France during 1980 and 1996

$$DR_{Bl-FR} = DR_{Bl} \times Perc_{BlDR-FR} \qquad \textbf{(IV.C.1.b-2)}$$

Then, the percentage donors in each age group that traveled to France between 1980 and 1996 was calculated based on the total number donors who traveled to France, the number of donors from each age group and the odds ratio of travel for each age group.

Variable: $\boldsymbol{DR_{Bl(age)}}$- Annual number of blood donors from each age group (calculated A-IV.C.1.a)

Variable: $\boldsymbol{Perc_{BlDR\text{-}FR(age)}}$ - The percentage of US blood donors of an age group who traveled to France during the period from 1980 through 1996.

Total number of blood donor who traveled to France equals to the sum of donors from all age groups who have ever traveled to France:

$$DR_{Bl-FR} = \sum_{age=18-19}^{65-69} (Perc_{BlDR-FR(age)} \times DR_{Bl(age)}) \qquad \textbf{(IV.C.1.b-3)}$$

Variable: $\boldsymbol{Odd_{T(age)}}$- Odds ratios of each age group for the likelihood of travel compared to the group of age 18-19 year-olds.

Data used in the model: The odds ratio of travel for each age group was derived from the travel data obtained from 1980-1996 blood donor travel survey (TSEAC 2000). An odds ratio of 1 was assigned to donor group of age 18-19. Odds ratio of other age group represents the frequency of travel of those age groups compared to the group of age 18-19

$$Perc_{BlDR-FR(age)} = Odd_{T(age)} \times Perc_{BlDR-FR(18-19)} \quad \textbf{(IV.C.1.b-4)}$$

Replacing equation IV.C.1.b-4 for $\boldsymbol{Perc_{BlDR\text{-}FR(age)}}$ in equation IV.C.1.b-3, percentage blood donors from age group of 18-19 who have traveled to France can be calculated by following equation:

$$Perc_{BlDR-FR(18-19)} = DR_{Bl-FR} / \sum_{age=18-19}^{65-69} (Odd_{T(age)} \times DR_{Bl(age)}) \quad \textbf{(IV.C.1.b-5)}$$

Then, the percentage of blood donors from other age groups who have traveled to France can be calculated using equation IV.C.1.b-4 (above).

A-IV. C. 1. b. ii. a. Number of US Source Plasma donors with a history of travel to France by age group and specific year of travel

This section of the model computes the number of US Source Plasma donors who traveled to France based on annual total of Source Plasma donors and the estimated percentage of Source Plasma donors who have traveled to France between 1980 and 1996. Travel after 1996 was extrapolated from the percentage donors who travel between 1980 and 1996 and yearly travel data. To factor in travel frequency associated with donor age, the number of donors who have traveled was calculated by age groups.

Variable: *age* - Age of US plasma donors in groups of 5-year increments (20 – 24 yrs, 25 – 29yrs, etc) and the 18-19 year old cohort.

Variable: $\boldsymbol{DR_{S(age)}}$ (calculated in section A-IV.B.1.b.) **-** the annual Source Plasma donations by age groups.

Variable: $\boldsymbol{Perc_{BlDR\text{-}FR(age)}}$ (calculated in section A-IV.C.1.b.i..b.**) -** the percentage blood donors from an age group who have traveled to France between 1980-1996

Variable: $\boldsymbol{DR_{S\text{-}FR(age)}}$ **-** Number of Source Plasma donors who traveled to France from 1980 through 1996 by age group.

Assumptions used in the model: The percentage of Source Plasma donors who traveled to France is the same as blood donors of the same age group.

The number of Source Plasma donors who traveled to France from 1980 to 1996 by age group is represented by:

$$DR_{S-FR(age)} = DR_{S(age)} \times Perc_{BlDR-FR} \quad \textbf{(IV.C.1.b-6)}$$

The model assumes that the risk that a traveler was exposed to the BSE agent in France is associated with the magnitude of the BSE epidemic in the UK in the year of travel. Major exposure risk in France was presumably from consumption of beef imported from the UK that was produced from cattle infected with BSE. The model breaks down Source Plasma donors by year of travel, in order to estimate the potential

US donor vCJD risk more accurately by incorporating the information about the magnitude of the BSE epidemic in the UK in a given year.

Variable: $V_{y/1996}$ - The number of visits to the UK by US travelers in year *y* compared to the number of visits in 1996 (calculated in A-IV. C. 1. a. ii. a.).

Variable: $DR_{S\text{-}FR(age),y}$ - Number of Source Plasma donors with history of travel to France in year *y* by age groups

The number of Source Plasma donors who have traveled to France was allocated to individual travel year based on the yearly distribution of visits to France.

$$DR_{S-FR(age)y} = DR_{S-FR(age)} \times V_{y/1996} / \sum_{y=1980}^{1996} V_{y/1996} \quad \text{(IV.C.1.b-7)}$$

for travel during 1980-1996;

$$DR_{S-FR(age)y} = DR_{S-FR(age)1996} \times V_{y/1996} \quad \text{(IV.C.1.b-8)}$$

for travel after 1996

Assumption used in the model: The yearly frequency and distribution of travel to France by US donors was ascertained from UK travel data and the blood donor survey data (TSEAC 2000). Therefore, in calculating the US donor risk for vCJD, donors the yearly distribution of travel visits by age groups was adjusted to account for the requirement that donors be 18 years of age or older. The model also accounted for the fact that some younger donors born during the period 1980 to 1986 may not have been born and would have essentially a zero chance of being exposed to BSE agent. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

A-IV. C. 1. b. ii. b. Number of US Source Plasma donors and duration of travel to France by age group

There are no data detailing the travel histories of Source Plasma donors available. Travel data for blood donors was used for Source Plasma donors after an adjustment for the frequency of travel based on the age of Source Plasma donors and the age-specific odds ratios for travel, which were obtained from 1980-1996 Blood Donor Travel Survey (TSEAC, 2000).

The model further subdivides the number of Source Plasma donors who traveled to France in a specific year by duration of stay. While there were no specific travel data detailing travel patterns to France since 1980 available for US Source Plasma donors, data on travel patterns for whole blood donors was used as a proxy. Donor travel in the model was subdivided into categories based on the percentage of blood donors

who traveled to France for certain durations (Watanabe, 2000) (>5yrs, ≤5yrs, etc) was used in this risk assessment.

Variable: *i* - The duration interval used to group blood donors who had traveled to France from 1980-1996 based on the time they spent in France (same variable used above in section A-IV. C. 1. a. i.).

Variable: D_i - The average duration of time for interval *i* (months) (same variable used above in section A-IV. C. 1. i.).

Variable: $DR_{S\text{-}FR(age),y}$ - the number of Source Plasma donors who traveled to France in year *y* by age group (calculated in A-IV. C. 1. b. ii.)

Variable: $Perc_{BlDR\text{-}FRi/FR}$- The percentage of blood donors who traveled for a specific duration interval *i* among all donors who have ever traveled to France (calculated in A-IV. C. 1. b. i.)

Variable: $DR_{S\text{-}FR(age)y,i}$ - Number of Source Plasma donors among an age group who have traveled to France in year *y* for a duration of *i* and is represented by the equation:

$$DR_{S-FR(age)y,i} = DR_{S-FR(age)y} \times Perc_{DR-FRi/FR} \quad \textbf{(IV.C.1.b-9)}$$

A-IV. C. 1. b. ii. c. Number of US recovered plasma donors with history of travel to France in a specific year between 1980 and 1996 – and by age group

Recovered plasma is plasma that is separated or "recovered" from a unit of whole blood soon after the blood is collected. As expected, recovered plasma donor donation characteristics mirror those of whole blood donors. A recovered plasma donor can donate plasma a maximum of six times per year – and on average a recovered donation is approximately 200 milliliters (versus an average of 700 milliliters for a Source Plasma donation).

Variable: *y* – Year of travel (same variable used above in section A-IV. C. 1. b. ii. a) to France since 1980 by US plasma donors.

Variable: age – Age of the population by five-year increments (same variable used above in section A-IV. B. 1.).

Variable: $DR_{R(age)}$ - Number of potential recovered plasma donors per year by age group (described in section A-IV. B. 2).

Variable: $Perc_{BlDR\text{-}FR(age)}$ (calculated in section A-IV.C.1.b.i.)- The percentage blood donors from an age group who have traveled to France between 1980-1996

Variable: $DR_{R\text{-}FR(age)}$ - Number of recovered plasma donors who traveled to France from 1980 through 1996 by age groups and is represented by the equation:

$$DR_{R-FR(age)} = DR_{R(age)} \times Perc_{BlDR-FR(age)} \quad \textbf{(IV.C.1.b-10)}$$

The risk a traveler was exposed to BSE in France is proportional to the magnitude of the BSE epidemic in the UK in the year of travel. Because the major exposure risk in France is assumed to be from consumption of BSE contaminated beef imported from the UK , the model subdivides recovered plasma donors and groups them by year of travel. This provides a more precise estimate of the risk by incorporating the specific information on donor and donation characteristics and details that better capture the dynamics of the BSE epidemic in the UK on a year by year basis.

Variable: $V_{y/1996}$ **-** The number of visits to the UK by US travelers in year *y* compared to the number of visits in 1996 (calculated in A-IV.C.1.a)

Variable: $DR_{R\text{-}FR(age),y}$ **-** Number of recovered plasma donors with a history of travel to France in year *y* by age groups

Number of recovered plasma donors who have traveled to France was allocated to individual travel year based on the yearly distribution of visits to the UK by US travelers.

$$DR_{R-FR(age)y} = DR_{R-FR(age)} \times V_{y/1996} / \sum_{y=1980}^{1996} V_{y/1996} \quad \text{(IV.C.1.b-11)}$$

for travel during 1980-1996;

$$DR_{R-FR(age)y} = DR_{R-FR(age)1996} \times V_{y/1996} \quad \text{(IV.C.1.b-12)}$$

for travel after 1996

Assumptions used in the model: The yearly distribution of travel to France by US donors is similar to the yearly distribution of travel to the UK by US donors- this is based on travel data and the blood donor survey (TSEAC 2000). The yearly distribution of travel visits by each age group was adjusted to account for the minimum age of 18 when a donor can donate plasma or blood. Therefore, in calculating the US donor risk for vCJD the yearly distribution of travel visits by each age group was adjusted to account for this requirement. The model adjusted the potential vCJD exposure for younger donors who were born during the period from 1980 to 1986 and would have essentially a zero chance of being exposed to the BSE agent in the years prior to their birth. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

A-IV. C. 1. b. ii. d. US recovered plasma donors with a history of travel to France and specific year of travel and duration of travel by age group

Recovered plasma donors who traveled to France in a specific year ($DR_{R\text{-}FR(age)y}$) since 1980 were further partitioned into the subgroups based on travel duration and by 5-year age groups. Data on the percentage

of blood donors who traveled to France since 1980 for certain duration(s) (TSEAC, 2000) was used in this risk assessment.

Variable: *i* - The duration interval used to group blood donors who had traveled to France from 1980-1996 based on the time they spent in France (same variable used above in section A-IV. C. 1.)

Variable: D_i - The average duration of time for interval *i* (months) (same variable used above in section A-IV. C. 1.)

Variable: $DR_{R\text{-}FR(age),y}$ - The number of recovered plasma donors who traveled to France in year *y* by age group (calculated in A-IV. C. 1. b. iv. c.)

Variable: $Perc_{BlDR\text{-}FRi/FR}$- The percentage of blood donors who traveled for a specific duration interval *i* among all donors who have ever traveled to France (calculated in A-IV. C. 1. b. ii. a.)

Variable: $DR_{R\text{-}FR(age)y,i}$- Number of recovered plasma donors among an age group who have traveled to France in year, *y* ,for duration of *i*.

$$DR_{R-FR(age)y,i} = DR_{R-FR(age)y} \times Perc_{DR-FRi/FR} \quad \textbf{(IV.C.1.b-13)}$$

A-IV.C. 1. b. iii. US plasma donors with history of travel to France: Adjustment of the relative risk for France based on the magnitude of the UK BSE risk and by travel duration in a specific year

As indicated in previous sections the FDA model assumed that the relative vCJD risk for UK residents residing for any five-year period or longer from 1980 through 1996 is assumed to have a value of 1, because exposure to BSE in the UK was greater than any other country. The relative risk value of 1 equates to 100% of the UK asymptomatic and symptomatic vCJD prevalence which is difficult to estimate. The relative risk value for France is 0.05 (or 5% of the UK risk). The relative risk value is assigned based on factors such as domestic UK beef consumption, and the rate and number of vCJD cases, and indigenous BSE cases that may have occurred (TSEAC 2004). France received meat and bone meal from the UK during the BSE epidemic and approximately 5% of its beef was imported from the UK as of August 2006, France reported 20 cases of vCJD in its human population. Additionally, the model included calculations on the estimated duration of travel in France or residence by US plasma donors to generate a more accurate vCJD risk estimate. Current US vCJD geographic deferral policy defers donors with a history of residence in France for a period of 5 years or more since 1980.

A-IV. C. 1. b. iii. a. US plasma donors with a history of travel to France: Average accumulated risk of residence since 1980

Variable: R_{FR} – The cumulative risk of individual residents of France from 1980 till present; assuming that the cumulative risk of a UK individual from 1980 through 1996 is 1.

Assumption used in the model: The average cumulative risk of a resident of France since 1980 is 0.05 relative to 1, the average accumulated risk of UK individual since 1980, based on UK beef imports, vCJD cases and indigenous BSE in France

A-IV. C. 1. b. iii. b. US plasma donors with history of travel to France: Proportional risk of individual resident per year since 1980

Variable: *y* – year (same variable used in A-IV. C. 1. a. iv.)

Variable: BSE_{UKy} (same variable used in A-IV. C. 1. a. iii.)

Variable: BSE_{FRy} - Annual numbers of reported BSE cases in France including indigenous and imported cases

Data used in the model: Data on the annual number of reported BSE cases in France was obtained from the World organization for animal health (OIE) (2005).

Variable: R_{FRy} - Proportional risk in France in a specific year

Assumptions used in the model:

- Variant CJD Risk in France occurred starting in 1980 to the present. Evidence indicates that vCJD and BSE cases are still emerging.
- Risk is additive, and can be pro-rated in a yearly and further monthly basis.
- Yearly rate of the risk in France is proportional to the reported BSE annual cases (including indigenous and imported cases) in France.

A-IV. C. 1. b. iii. c. US plasma donors with a history of travel to France: Potential vCJD risk for donors who traveled in year y for a period of i

Variable: $R_{DR\text{-}FR,i}$ - The risk of an individual US donor who traveled to France in a specific year with a specific duration of travel, assuming a cumulative risk for a UK individual from 1980 through 1996 is 1 (or equivalent to the UK vCJD prevalence for the entire UK population).

The vCJD risk for the US plasma donor subpopulation that traveled to France in a specific year for a specific duration was calculated by applying a prorated monthly rate of risk, which was calculated based on the yearly rate of the risk in France during the year of travel. The blood donor travel survey (TSEAC, 2000) collected information on the accumulated stay of the donors in France from 1980 through 1996, which, for simplicity, was used to calculate the duration of consecutive stay, when calculated the risk.
.

Assumptions used in the model:

- Risk is proportional to the duration of the stay
- All travelers have consecutive stays
- US plasma donor subpopulation having more than 5 years accumulated stay in France have average risk of 0.05, which is the same as the average risk of individual resident of France (equivalent to 5% of the UK vCJD prevalence).

$$R_{DR-FRy,i} = (R_{FRy}/12) \times D_i \quad \text{(IV.C. 1. b•-14)}$$

for i< 1 years;

$$R_{DR-FRy,i} = (Average(R_{FRy} : R_{FR(y+i)})/12) \times D_i \quad \text{(IV.C.1.b-15)}$$

for 5 years <i>=1 year;

$$R_{DR-FRy,i} = 0.05 \quad \text{(IV.C.1.b-16)}$$

for i>= 5 years

A-IV.C. 1. b. iv. US plasma donors with history of travel to France: Probability of vCJD infection for donor of a specific age group, in a specific year, for a specific duration, i

This section describes the portion of the model that estimates the potential probability that a US plasma donor in a specific age group who traveled to France for a specific duration since 1980 was infected with vCJD.

Variable: $Pr_{vCJD\text{-}FR(age)}$ -Probability of vCJD infection in an individual resident of France in a specific age.

Variable: $Pr_{vCJD\text{-}DR\text{-}FR(age)y,i}$ - Probability of infection for individual US plasma donor of a specific age group who have traveled to France in a specific year for a specific duration.

Assumption about variable: Probability of vCJD infection being proportional to the risk of exposure to the BSE agent and represented by the equation:

$$\Pr_{vCJD-DR-FR(age)y,i} = \Pr_{vCJD-UK(age)} \times R_{DR-FRy,i} \quad \textbf{(IV.C.1.b-17)}$$

A-IV.C. 1. b. v. Total number of all US plasma donors with a history of travel to France: Number potentially infected with vCJD

A-IV.C. 1. b. v. a. Number of US Source Plasma donors with a history of travel to France and potentially infected with vCJD

Plasma is collected from Source Plasma donors in a process called plasmapheresis in which approximately 700 milliliters of plasma are collected. Source Plasma donors donate an average of 14 units per year, but can donate up to 48 times per year.

This component of the model estimates the number of US Source Plasma donors potentially infected with vCJD during travel to the UK from 1980 through 1996.

Variable: $DR_{vCJD\text{-}S\text{-}FR(age)y,i}$- Number of Source Plasma donors potentially infected with vCJD during travel to France since 1980 by age, year and duration of travel.

$$DR_{vCJD-S-FR(age)y,i} = Bionomial(DR_{S-FR(age)y,i}, \Pr_{vCJD-DR-FR(age)y,i}) \quad \textbf{(IV.C.1.b-18)}$$

Variable: $DR_{vCJD\text{-}S\text{-}FRy}$ - Number of Source Plasma donors potentially infected with vCJD in year y during travel/residence in France.

$$DR_{vCJD-S-FRy} = \sum_{Age=18-19\,yrs}^{50-54\,yrs} \sum_{i=1day-3months}^{>=5\,years} DR_{vCJD-S-FR(age)y,i} \quad \textbf{(IV.C.1.a-19)}$$

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}Defy}$- Number of Source Plasma donors potentially infected with vCJD in year y and meet deferral criteria.

Current deferral policy defers individuals who have a history of travel to France since 1980 for an accumulated time of over 5 years from donating blood and plasma. The number of potentially infected donors who meet deferral criteria was calculated by equation:

$$DR_{vCJD-S-FR-Defy} = \sum_{Age=18-19}^{50-54\,yrs} DR_{vCJD-S-FR(age)y,i>=5\,years} \quad \textbf{(IV.C.1.a-20)}$$

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}Resy}$- Residual risk due to the number of Source Plasma donors potentially infected with vCJD in year y and not deferred by current policy

$$DR_{vCJD-S-FR-\mathrm{Res}y} = \sum_{Age=18-19\,yrs}^{50-54\,yrs} \sum_{i=1-30days}^{>3-5\,years} DR_{vCJD-S-FR(age)y,i} \quad \textbf{(IV.C.1.a-21)}$$

A-IV. C. 1. b. v. b. Number of US Source Plasma donors with history of travel to France and potentially infected and vCJD agent is present in the blood

Perhaps the most critical component of the model is the estimation of whether a plasma donation was collected from a vCJD infected donor who had infectious vCJD agent in their blood (i.e., was prionemic at the time of donation). Based on data from animal studies, the model assumes that vCJD infectious individuals have infectious vCJD agent present in the blood during the last half of the incubation period. This portion of the model calculates the number of Source Plasma donors who may potentially contain infectious vCJD agent in their blood at the time of donation.

Variable: *y*-The calendar year in which a plasma donor traveled and infected with vCJD

Assumption used in the model: This risk assessment assesses the risk for pdFVIII product made in 2002 (but risk is assumed to be similar up to the year 2006).

Variable: $T_{Inf\text{-}2002y}$-Time Period between infection/travel and year of 2002 when the plasma was collected

Variable: $Pr\text{-}LH_y$-Probability the individual is in the last half incubation period of the disease, if infected in year y

Variable: $T_{Inf\text{-}2002y}$-Time period between infection and travel and 2002 when the plasma was collected

$$T_{Inf-2002y} = 2002 - y \qquad \textbf{(IV.C.1.b-22)}$$

For an individual to have vCJD agent present in their blood and plasma (prionemic) in 2002, the elapsed period of time since infection up to 2002 ($I_{Inf\text{-}2002y}$) should be equal to or less than the remaining half of incubation period of the disease; in another words, the incubation period of the disease should be equal to or less than twice as much as $I_{Inf\text{-}2002y}$.

Assumption used in the model The variability and uncertainty of the incubation period of vCJD is represented mathematically by a gamma distribution, specifically Gamma (4.7, 3.6). A gamma distribution is usually used to represent processes that occur sequentially, in this case infection, incubation period of the disease, etc. The distribution is defined by two parameters (or arguments) that produce the shape of the curve and generates a mean incubation period of 14 years and a median incubation period of 13 years.

Variable: $Pr_{LH\text{-}y}$ -The probability an individual will be prionemic in the year 2002, was determined using the distribution:

Cumulative frequency of Gamma (4.7, 3.6), at x=2×(1997-y)

Variable: $DR_{vCJD\text{-}S\text{-}FRy}$- Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in France (calculated in A-IV. C. 1. b. v. a.)

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}LHy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in France and in the last half incubation period of the disease.

$$DR_{vCJD-S-FR-LHy} = Binomial(DR_{vCJD-S-FRy,}\ \Pr_{LH-y}) \quad \text{(IV.C.1.b-23)}$$

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}defy}$- Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in France and met deferral criteria (calculated in A-IV. C. 1. b. v. a)

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}def\text{-}LHy}$ - Total number of Source Plasma donors in the last-half of the incubation period of the disease who met deferral criteria.

$$DR_{vCJD-S-FR-Def-LHy} = Binomial(DR_{vCJD-S-FR-Defy,}\ \Pr_{LH-y}) \quad \text{(IV.C.1.b-24)}$$

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}Resy}$- Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in France and did not met deferral criteria (calculated in A-IV. C. 1. b. v. a)

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}Res\text{-}LHy}$ - Total number of Source Plasma donors in the last half incubation period of the disease who did not met deferral criteria or were not deferred is represented by the equation:

$$DR_{vCJD-S-FR-\mathrm{Re}s-LHy} = Binomial(DR_{vCJD-S-FR-\mathrm{Re}sy,}\ \Pr_{LH-y}) \quad \text{(IV.C.1.b-25)}$$

A-IV.C. 1. b. v. c. Number of US recovered plasma donors with a history of travel to France and potentially infected with vCJD

Variable: $DR_{vCJD\text{-}R\text{-}FR(age)y,i}$ - Number of recovered plasma donors potentially infected with vCJD during travel to France since 1980 by age, year and duration of travel

$$DR_{vCJD-R-FR(age)y,i} = Bionomial(DR_{R-FR(age)y,i}, \Pr_{vCJD-DR-FR(age)y,i}) \quad \textbf{(IV.C.1.b-26)}$$

Variable: $DR_{vCJD\text{-}R\text{-}FRy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y:

$$DR_{vCJD-R-FRy} = \sum_{Age=18-19}^{50-54} \sum_{i=1day-3months}^{>=5\,years} DR_{vCJD-R-FR(age)y,i} \quad \textbf{(IV.C.1.b-27)}$$

Current deferral policy defers individuals who have history of travel to France since 1980 for an accumulated residence of 5 years or more from donating blood and plasma. The number of potentially infected donors who meet the deferral criteria was calculated by equation:

$$DR_{vCJD-R-FR-Defy} = \sum_{Age=18-19}^{50-54\,yrs} DR_{vCJD-R-FR(age)y,i>=5\,years} \quad \textbf{(IV.C.1.b-28)}$$

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}Resy}$- The residual risk due to the number of recovered plasma donors potentially infected with vCJD in year y and not deferred by current policy

$$DR_{vCJD-R-FR-\mathrm{Re}sy} = \sum_{Age=18-19\,yrs}^{50-54\,yrs} \sum_{i=1-30\,days}^{>3-5\,years} DR_{vCJD-R-FR(age)y,i} \quad \textbf{(IV.C.1.b-29)}$$

A-IV. C. 1. b. v. d. Number of US recovered plasma donors with history of travel to France and potentially infected and vCJD agent is present in the blood

As discussed in the sections on Source Plasma (above) the most critical component of the model is the estimation of whether a plasma donation was collected from a vCJD infected donor who had infectious vCJD agent in their blood (i.e., was prionemic at the time of donation). Based on data from animal studies, the model assumes that vCJD infectious individuals have infectious vCJD agent present in the blood during the last half of the incubation period. This portion of the model calculates the number of recovered plasma donors who may potentially contain infectious vCJD agent in their blood at the time of donation.

Variable: $Pr_{LH\text{-}y}$ -The probability an individual will have vCJD agent present in their blood or present (prionemic) at the time of donation in the year 2002 (calculated in A-IV.C.1.a.v. b.)

Variable: $DR_{vCJD\text{-}R\text{-}FRy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residence in France (calculated in A-IV. C. 1. b. v. c.)

Variable: $DR_{vCJD\text{-}R\text{-}FR\text{-}LHy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residence in France and in the last half incubation period of the disease.

$$DR_{vCJD-R-FR-LHy} = Binomial(DR_{vCJD-R-FRy,}\ \mathrm{Pr}_{LH-y}) \quad \text{(IV.C.1.b-30)}$$

Variable: $DR_{vCJD\text{-}R\text{-}FR\text{-}defy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in France and met deferral criteria (calculated in A-IV. C. 1. b. v. c)

Variable: $DR_{vCJD\text{-}R\text{-}FR\text{-}def\text{-}LHy}$ - Total number of recovered plasma donors in the last half incubation period of the disease who met deferral criteria and presumably were deferred from donation.

$$DR_{vCJD-R-FR-Def-LHy} = Binomial(DR_{vCJD-R-FR-Defy,}\ \mathrm{Pr}_{LH-y}) \quad \text{(IV.C.1.b-31)}$$

Variable: $DR_{vCJD\text{-}R\text{-}FR\text{-}Resy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in France and did not met deferral criteria and were likely not deferred from donation (calculated in A-IV. C. 1. b. v. c.)

Variable: $DR_{vCJD\text{-}R\text{-}FR\text{-}Res\text{-}LHy}$ - Total number of recovered plasma donors in the last half incubation period of the disease who did not meet deferral criteria and were likely not deferred from donation.

$$DR_{vCJD-R-FR-Res-LHy} = Binomial(DR_{vCJD-R-FR-Resy,}\ \Pr_{LH-y}) \quad \text{(IV.C.1.b-32)}$$

A-IV. C. 1. b. v. e. Number of <u>all</u> US plasma donors with history of travel to France and potentially infected with vCJD

This section sums the number of <u>all</u> US plasma donors, predicted by the model to donate to plasma pools used in manufacturing pdFVIII made from plasma collected in the US. This includes <u>recovered</u> plasma donors and <u>Source Plasma</u> donors, and generates an estimate for the total number of donors potentially infected with vCJD during extended travel to France since 1980.

Variable: $DR_{vCJD\text{-}FR}$ - Total number of plasma donors potentially infected with vCJD during travel/residence in France

$$DR_{vCJD-FR} = \sum_{y=1980}^{1996} DR_{vCJD-S-FRy} + \sum_{y=1980}^{1996} DR_{vCJD-R-FRy} \quad \text{(IV.C.1.b-33)}$$

Variable: $DR_{vCJD\text{-}FR\text{-}Def}$ - Total number of plasma donors potentially infected with vCJD during travel/residence in France and meet deferral criteria

$$DR_{vCJD-FR-Def} = \sum_{y=1980}^{2002} DR_{vCJD-S-FR-Defy} + \sum_{y=1980}^{2002} DR_{vCJD-R-FR-Defy} \quad \text{(IV.C.1.b-34)}$$

Variable: $DR_{vCJD\text{-}FR\text{-}Res}$- Total number of plasma donors potentially infected with vCJD during travel/residence in the UK and did not meet deferral criteria

$$DR_{vCJD-FR-Res} = \sum_{y=1980}^{2002} DR_{vCJD-S-FR-Resy} + \sum_{y=1980}^{2002} DR_{vCJD-R-FR-Resy} \quad \text{(IV.C.1.b-35)}$$

A-IV. C. 1. b. v. f. Total number of US plasma donors with history of travel to France and are potentially infected and vCJD agent is present in the blood

Again, whether a donor contains vCJD agent in their blood is a pivotal calculation in the model since a donation from such an individual would contain vCJD agent that may find its way into a large plasma pool of thousands of donations that are used to manufacture pdFVIII. This section sums the number of

US Source Plasma donors and recovered plasma donors predicted by the model to be infected with vCJD and contain vCJD agent in their blood and arrives at an estimate of the total number of US donors potentially infected with vCJD and who are prionemic.

Variable: $DR_{vCJD\text{-}FR\text{-}LH}$ - Total number of plasma donors in the last half incubation period of the disease

$$DR_{vCJD-FR-LH} = \sum_{y=1980}^{2002} DR_{vCJD-S-FR-LHy} + \sum_{y=1980}^{2002} DR_{vCJD-S-FR-LHy} \quad \text{(IV.C.1.b-36)}$$

Variable: $DR_{vCJD\text{-}FR\text{-}Def\text{-}LH}$ - Total number of plasma donors in the last half incubation period of the disease and met deferral criteria

$$DR_{vCJD-FR-Def-LH} = \sum_{y=1980}^{2002} DR_{vCJD-S-FR-Def-LHy} + \sum_{y=1980}^{2002} DR_{vCJD-R-FR-Def-LHy} \quad \text{(IV.C.1.b-37)}$$

Variable: $DR_{vCJD\text{-}FR\text{-}Res\text{-}LH}$ - Total number of plasma donors in the last half incubation period of the disease and did not met deferral criteria

$$DR_{vCJD-FR-Res-LH} = \sum_{y=1980}^{2002} DR_{vCJD-S-FR-Res-LHy} + \sum_{y=1980}^{2002} DR_{vCJD-R-FR-Res-LHy} \quad \text{(IV.C.1.b-38)}$$

A-IV.C. 1. c. Number of US plasma donors with a history of travel to countries in Europe (other than the UK and France) potentially infected and vCJD agent is present in the blood

A-IV.C.1.c.i. US recovered plasma donors with a history of travel to countries in Europe: Percentage of US donors and travel duration

In this portion of the FDA risk assessment, US blood (recovered plasma) donors are characterized by frequency and duration of travel to countries in Europe (other than the UK) during the period 1980-1996. The risk of vCJD infection is a function of exposure to the BSE agent and is assumed to be proportional to the amount of time spent, or duration of travel, in countries in Europe (other than the UK) since 1980. The FDA model used data from the National Blood Donor Travel Survey 1980-1996 (TSEAC 2000) to derive estimates of the percentages of US donors with a history of extended travel or residence ($\geq$ 5 years) in other countries in Europe (other than the UK and France) since 1980, and to derive the frequencies for various durations of travel for 5 years or more. The period of 5 years or more corresponds to the length of time in the current policy that defers blood (recovered plasma) donors who traveled to or resided in European countries (other than the UK).

Data used in the model: National Blood Donor Travel Survey 1980-1996 was conducted by the American Red Cross and presented at the TSEAC in 2000.

Variable: *i* - The duration interval used to group donors who had traveled to countries in Europe from 1980-1996 based on the quantity of time spent in Europe (other than the UK and France) during the period from 1980 – 1996.

Variable: D_i - The average duration of time (in months) for interval *i* representing the duration of travel or residence by US donors in countries in Europe (other than the UK and France) during the period from 1980 – 1996.

Variable: $CumPerc_{BlDR\text{-}EUi}$ – The cumulative percentage of blood donors who traveled to countries in Europe (other than the UK and France) within duration interval *i* or longer**.**

Data used in the model: Travel data for US blood donors was obtained from a blood donor survey conducted by the American Red Cross and presented at the TSEAC in 2000.

Variable: $Perc_{BlDR\text{-}EUi}$ - Percentage of blood donors who traveled to countries in Europe (other than the UK and France) within duration interval *i*. This variable was converted from $CumPerc_{BlDR\text{-}EUi}$

Variable: $Perc_{BlDR\text{-}EUi/EU}$- The percentage of blood donors who traveled for a specific duration interval *i* among all donors who have ever traveled to countries in Europe (other than the UK and France) is represented by the equation:

$$Perc_{BlDR-EUi/EU} = (Perc_{BlDR-EUi} / CumPerc_{BlDR-EU,i>1day-1month}) \times 100\% \quad \textbf{(IV.C.1.c-1)}$$

The following portion of the risk assessment estimated the frequency of travel for each recovered plasma donor by age group based on travel data of blood donors. First, estimates for blood donors who traveled to countries in Europe (other than the UK and France) between 1980 and 1996 was calculated to generate the total number of US blood donors and percentages of donors who traveled. For the purposes of our analyses we grouped all donors and donors who traveled to countries in Europe since 1980 into age groups of five-year increments (20 – 24yrs, 25 – 29 yrs, etc) and for the 18 – 19 year old cohort. The percentage of donors in each age group that traveled to countries in Europe since 1980 was calculated based on the total annual number donors who traveled to Europe since 1980 compared to (or divided by) the total number of donors, and the age specific odds ratio for travel.

- **<u>Calculation of the annual number of blood donors who traveled to countries in Europe (other than the UK and France) from 1980 through 1996</u>**

Variable : DR_{Bl} - The annual total number of potential blood donors in the US.

Data used in the model: There are approximately 8 million individuals who donate blood each year in the United States (Westat, 2002).

Variable: $Perc_{BlDR\text{-}EU}$ - The total percentage of US blood donors who traveled to countries in Europe (other than the UK and France) during the period from 1980 through 1996.

Data used in the model: Approximately, 15.6% of US blood donors have histories of travel to countries in Europe (other than the UK and France) during the period from 1980 through 1996, based on the travel data of US blood donors (TSEAC, 2000).

Variable: $DR_{Bl\text{-}EU}$ -Total number of blood donors who have traveled to countries in Europe (other than the UK and France) during the period 1980 - 1996.

$$DR_{Bl-EU} = DR_{Bl} \times Perc_{BlDR-EU} \quad \textbf{(IV.C.1.c-2)}$$

Then, the percentage of donors in each age group who traveled to countries in Europe (other than the UK and France) between 1980 and 1996 was calculated based on the total number donors who traveled to countries in Europe, the number of donors from each age group, and the odds ratio of travel for each age group.

Variable: $DR_{Bl(age)}$- Annual number of blood donors from each age group (calculated IV.C.1.a)

Variable: $Perc_{BlDR\text{-}EU(age)}$ - Annual percentage of US blood donors of an age group who traveled to countries in Europe during the period from 1980 through 1996.

Total number of blood donor who traveled to countries in Europe (other than the UK and France) equals to the sum of donors from all age groups who have ever traveled to Europe:

$$DR_{Bl-EU} = \sum_{age=18-19}^{65-69} (Perc_{BlDR-EU(age)} \times DR_{Bl(age)}) \quad \textbf{(IV.C.1.c-3)}$$

Variable: $Odd_{T(age)}$- The odds ratio for each five-year age group (e.g. 20-24 yrs, etc.) of travelers was compared to the group of age 18-19 yr olds.

Data used in the model: The odds ratios of travel to countries in Europe (other than the UK and France) for each age group was derived from the travel data obtained from 1980-1996 blood donor travel survey. An odds ratio of 1 was assigned to the donor group of age 18-19 yr olds. The odds ratios for the other age groups were generated by comparing the frequency of travel for those age groups to the group of age 18-19 yr-olds.

$$Perc_{BlDR-EU(age)} = Odd_{T(age)} \times Perc_{BlDR-EU(18-19)} \quad \textbf{(IV.C.1.c-4)}$$

The percentage of blood donors from the age group of 18-19 yr olds who have traveled to countries in Europe (other than the UK and France) can be calculated by the following equation:

$$Perc_{BlDR-EU(18-19)} = DR_{Bl-EU} \,/\, \sum_{age=18-19}^{65-69} (Odd_{T(age)} \times DR_{Bl(age)}) \quad \textbf{(IV.C.1.c-5)}$$

Then, the percentage blood donors from other age groups who traveled to Europe (other than the UK and France) can be calculated using the equation (A-IV.C.1.c-4).

A-IV. C. 1. c. ii. US recovered plasma donors who traveled to countries in Europe: Total number by year of travel, duration of travel and by age group

This part of the risk assessment calculates the annual number of US recovered plasma donors who traveled to countries in Europe (other than the UK and France) since 1980. The number of donors from an age group who traveled was calculated by year and duration of travel. The risk of a US donor acquiring vCJD is a function of duration of the stay, as well as the year(s) (since 1980) they resided in Europe.

A-IV. C. 1. c. ii.a. Number of US recovered plasma donors who traveled to Europe in a specific year between 1980 and 1996 by age group

This portion of the model estimates the potential vCJD risk for US recovered plasma donors with a history of travel to countries in Europe (other than the UK and France). Recovered plasma is derived from single units of Whole Blood as a by-product in the preparation of blood components from whole blood collection and is intended for further manufacturing. As expected, recovered plasma donor donation characteristics mirror those of whole blood donors. A recovered plasma donor can donate plasma a maximum of six times per year – and on average a recovered donation is approximately 200 milliliters (versus an average of 700 milliliters for a Source Plasma donation).

Variable: y **–** year of travel (same variable used above in section A-IV. C. 1. b. ii. a.) to a country in Europe (other than the UK or France) since 1980 by US plasma donors.

Variable: age – Age groups of the population by five-year increments (same variable used above in section A-IV. B. 1.) and the two year cohort for 18 and 19 year olds for US recovered plasma donors who traveled to countries in Europe (other than the UK and France).

Variable: $DR_{R(age)}$ **-** Number of potential US recovered plasma donors per year by age group (described in section A-IV. B. 2.).

Variable: $Perc_{BlDR\text{-}EU(age)}$ (calculated in section A-IV.C.1.b.ii.b.)- The percentage US blood donors by age group who have traveled to countries in Europe (other than the UK and France) between 1980-1996.

Variable: $DR_{R\text{-}EU(age)}$ **-** Number of recovered plasma donors who traveled to countries in Europe (other than the UK and France). from 1980 through 1996 by age group and is represented by the equation:

$$DR_{R-EU(age)} = DR_{R(age)} \times Perc_{BlDR-EU(age)} \quad \textbf{(IV.C.1.c-10)}$$

The risk a traveler was exposed to BSE in Europe is proportional to the magnitude of the BSE epidemic in the UK in the year of travel. Because the major exposure risk in Europe was assumed to be from consumption of beef contaminated with BSE agent imported from the UK. The model groups recovered plasma donors by year of travel. This provides a more precise estimate of the risk by incorporating the (age and year) specific information and details that better capture the dynamics of the BSE epidemic in the UK on a year by year basis. Travel for the years not covered by the UK National Survey 1997 to 2002 relied on extrapolation of trends from 1996 and before to estimate travel characteristics up to the baseline year of 2002 in the model (see equation A-IV.C.1.c-12 (below)).

Variable: $V_{y/1996}$ - The number of visits to the UK by US travelers in year *y* compared to the number of visits in 1996 (calculated in A-IV.C.1.a.)

Variable: $DR_{R\text{-}EU(age),y}$ - Number of recovered plasma donors who traveled to Europe in year *y* by age groups.

The number of recovered plasma donors who have traveled to countries in Europe (other than the UK and France) was allocated to individual travel year based on the yearly distribution of visits to the UK by US travelers.

$$DR_{R-EU(age)y} = DR_{R-EU(age)} \times V_{y/1996} / \sum_{y=1980}^{1996} V_{y/1996} \qquad \text{(IV.C.1.c-11)}$$

for travel during 1980-1996;

$$DR_{R-EU(age)y} = DR_{R} \times V_{y/1996} \qquad \text{(IV.C.1.c-12)}$$

for travel after 1996.

Assumption used in the model: The yearly distribution of travel to countries in Europe (other than the UK and France) by US recovered plasma donors is similar to the yearly distribution of travel to the UK by US travelers. The yearly distribution of travel visits by each age group was adjusted to account for the minimum age of 18 when a donor can donate plasma or blood. Therefore, in calculating the US donor risk for vCJD the yearly distribution of travel visits by each age group was adjusted to account for this requirement. The model adjusted the potential vCJD exposure for younger donors who were born during the period from 1980 to 1986 and would have essentially a zero chance of being exposed to the BSE agent in the years prior to their birth. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

A-IV. C. 1. c. ii. b. Number of US recovered plasma donors who traveled to countries in Europe by specific year of travel and duration of travel by age group

Recovered plasma donors who traveled to countries in Europe (other than the UK and France) in a specific year ($DR_{R\text{-}EU(age)y}$) since 1980 were further partitioned into the subgroups in the model based on travel duration and by 5-year age groups and also the two year cohort of donors 18 and 19 years of age. Data on the percentage of blood donors who traveled to countries in Europe (other than the UK and France) since 1980 for a certain duration(s) (TSEAC, 2000) were used in this risk assessment.

Variable: i - The duration interval used to group blood donors who had traveled to countries in Europe (other than the UK and France) from 1980-1996 based on the time spent (same variable used above in section A-IV. C. 1.).

Variable: D_i **-** The average duration of time for interval *i* (months) (same variable used above in section A-IV. C. 1.)

Variable: $DR_{R\text{-}EU(age),y}$ **-** The number of recovered plasma donors who traveled to countries in Europe (other than the UK and France) in year *y* by age group

Variable: $Perc_{BlDR\text{-}EUi/FEU}$**-** The percentage of blood donors who traveled for a specific duration interval *i* among all donors who have ever traveled to countries in Europe (other than the UK and France) (calculated in A-IV. C. 1. c. i).

Variable: $DR_{R\text{-}EU(age)y,i}$**-** Number of recovered plasma donors within a specific age group who have traveled to countries in Europe (other than the UK and France) in year, *y* ,for duration of *i*.

$$DR_{R-EU(age)y,i} = DR_{R-EU(age)y} \times Perc_{DR-EUi/EU} \quad \textbf{(IV.C.1.c-13)}$$

A-IV.C. 1. c. iii. US recovered plasma donors who traveled to countries in Europe: Adjustment of relative risk for the proportion of exposure to the BSE agent per year and by duration of travel and by age group

As indicated in previous sections the FDA model assumed that the relative vCJD risk for UK residents residing for any five-year period or longer from 1980 through 1996 is assumed to have a value of 1, because exposure to BSE in the UK was greater than that of any other country. The relative risk value of 1 equates to 100% of the UK asymptomatic and symptomatic vCJD prevalence, which is difficult to estimate. Again, based on information in FDA guidance (2002), the relative risk value for France was assumed to be 0.05 (or 5% of the UK risk). The relative risk value is assigned based on factors such as domestic UK beef consumption, and the rate and number of vCJD cases, and indigenous BSE cases that may have occurred (FDA 2002). Countries in Europe (other than the UK and France) received meat and bone meal from the UK during the BSE epidemic and approximately 1.5% of their beef was imported from the UK. Additionally, the model included calculations on the estimated duration of travel or residence in Europe by US plasma donors to generate a more accurate vCJD risk estimate. Current US vCJD geographic deferral policy defers blood donors with a history of residence in countries in Europe (other than the UK and France) for a period of 5 years or more since 1980; this policy does not include Source Plasma donors.

A-IV. C. 1. c. iii. a. Number of US recovered plasma donors with a history of travel to countries in Europe: Average accumulated vCJD risk for donors since 1980, assuming that the average accumulated risk for a UK individual since 1980 is 1

This section calculates the number of US plasma donors with a history of travel to countries in Europe (other than the UK and France) and their average accumulated vCJD risk since 1980, assuming that the average accumulated risk for a UK individual since 1980 is 1.

Variable: R_{EU} **-** Ac**–** The cumulative vCJD risk of an individual resident of countries in Europe (other than the UK and France) from 1980 till now; assuming the accumulated risk of a UK individual from 1980 through 1996 is 1.

Assumption used in the model: The average accumulated vCJD risk for travel to countries in Europe (other than the UK and France) by an individual resident since 1980 was assumed to be 0.015 relative to 1, the average accumulated risk of UK individual since 1980, based on UK. It was assumed that approximately 1.5% or less of the beef imports, imported into many countries since 1980 was imported from the UK. The 0.015 relative risk value also considers the number of human vCJD cases present and the presence of indigenous BSE in European countries (other than the UK and France) since 1980.

A-IV. C. 1. c. iii. b. US plasma donors with a history of travel to countries in Europe: Proportional risk per individual resident per year since 1980

Variable: Y_{epi} **–*y*** Years of BSE epidemic in countries in Europe (other than the UK and France).

Variable: BSE_{UKy} Annual numbers of reported BSE cases in the UK.

Variable: BSE_{EUy} **-** Annual numbers of reported BSE cases in European countries other than the UK and France.

Data used in the model: Data on the annual number of reported cases of BSE in cattle in European countries was obtained from the Orgainization Internationale de Epizootics (OIE) (2005).

Variable: R_{EUy} **-** Proportional vCJD risk for European countries (other than the UK and France) in a specific year

Assumptions used in the model:

- The risk of vCJD and BSE in European countries (other than the UK and France) has been present since 1980 and continues to present day. As of August 2006, very few cases of BSE continue to be reported in European countries (other than the UK and France)..
- The vCJD risk is assumed to be additive, and can be prorated on a yearly or monthly basis.
- The yearly rate of the vCJD risk in European countries (other than the UK and France) is proportional to the reported BSE annual cases in Europe (including indigenous and imported cases)

A-IV. C. 1. c. iii. b. US recovered plasma donors with a history of travel to countries in Europe: Potential vCJD risk for an individual in year y for a period of i since 1980

Variable: $R_{DR\text{-}EUy,,i}$ **-** Risk for individual US donors who traveled to countries in Europe other than the UK and France in a specific year for a specific duration, assuming the accumulative risk of a UK person resident in the years 1980 through 1996 is 1.

The vCJD risk for the US plasma donors with less than 5 years accumulated stay in Europe was calculated based on travel to European countries other than the UK and France in a specific year for a specific duration of travel. Potential exposure risk was calculated using a prorated monthly rate, which was calculated based on the yearly rate of the risk (1 month = 1/12 x yearly risk) in Europe during the year of travel. US plasma donors with a total accumulated stay in countries in Europe (other than the UK or France) of 5 years or more is assumed to have average risk of 0.015, which is the same as the risk of an individual citizen or long-term resident of a country in Europe (other than the UK or France). Information on duration of accumulated stays was collected in the blood donor travel survey; however, for simplicity we assumed all travel was consecutive. The blood donor travel survey (TSEAC 2000) collected information on the accumulated stay of US donors who stayed in Europe (other than the UK or France) from 1980 through 1996. For simplicity, these data were used to estimate the duration of consecutive stay, which was used to calculate the potential vCJD risk for recovered plasma donors.

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Assumptions used in the model:

- Risk is proportional to the duration of the stay
- All the travelers' stays were assumed to be single and consecutive stays.
- US plasma donor subpopulation having 5 or more years accumulated stay in countries in Europe (other than the UK or France) have an average risk of 0.015, which is the same as the average risk of individual European resident.

For < 1 year;

$$R_{DR-EUy,i} = (Average(R_{EUy} : R_{EU(y+i)})/12) \times D_i \qquad \text{(IV. C. 1. c-14)}$$

for 5 years <*i*>=1 year;

$$R_{DR-EUy,i} = 0.015 \qquad \text{(IV. C. 1. c-15)}$$

for *i*>= 5 years

A-IV. C. 1. c. iv. US recovered plasma donors with a history of travel to countries in Europe: Probability of vCJD infection for a donor of a specific age group, who traveled in a specific year for a specific duration, i

This section describes the portion of the model that estimates the potential probability that a US plasma donor in a specific age group, who traveled to countries in Europe (other than the UK or France) for a specific duration since 1980 was infected with vCJD.

Variable: $Pr_{vCJD\text{-}UK(age)}$ – the probability of infection for an individual UK resident of a specific age group (calculated in A-IV. C. 1. a. iv.)**.**

Variable: ***$Pr_{vCJD\text{-}DR\text{-}EU(age)y,i}$*** **-** Probability of infection for an individual US plasma donor of a specific age group who have traveled to countries in Europe other than the UK and France in a specific year with specific duration.

Assumption used in the model: The probability of vCJD infection is proportional to the risk of exposure

$$\Pr_{vCJD-DR-EU(age)y,i} = \Pr_{vCJD-UK(age)} \times R_{DR-EUy,i} \quad \text{(IV.C.1.c-16)}$$

A-IV.C. 1. c. v. Number of US recovered plasma donors with a history of travel to countries in Europe: Number potentially infected with vCJD.

Variable: ***$DR_{vCJD\text{-}R\text{-}EU(age)y,i}$*** **-** Number of recovered plasma donors potentially infected with vCJD during travel to countries in Europe (other than the UK and France) since 1980 by age, year and duration of travel

$$DR_{vCJD-R-EU(age)y,i} = Bionomial(DR_{R-EU(age)y,i}, \Pr_{vCJD-DR-EU(age)y,i}) \quad \textbf{(IV.C.1.c-26)}$$

Variable: ***$DR_{vCJD\text{-}R\text{-}EUy}$*** **-** Total number of recovered plasma donors potentially infected with vCJD in year y

$$DR_{vCJD-R-FRy} = \sum_{Age=18-19}^{50-54} \sum_{i=1day-3months}^{>=5\,years} DR_{vCJD-R-FR(age)y,i} \quad \textbf{(IV.C.1.c-27)}$$

Variable: ***$DR_{vCJD\text{-}R\text{-}EU\text{-}Defy}$*** **-** Number of recovered plasma donors potentially infected with vCJD in year y and deferred by current policy

Current FDA guidance (FDA 2002) recommends deferral of individuals who have history of travel to countries in Europe (other than the UK or France) since 1980 for an accumulated stay of 5 years or more from donating blood. The number of potential vCJD-infected recovered plasma donors who meet current deferral criteria (FDA 2002) was calculated by the equation:

$$DR_{vCJD-R-EU-Defy} = \sum_{Age=18-19}^{50-54} DR_{vCJD-R-EU(age)y,i>=5\,years} \quad \textbf{(IV.C.1.c-28)}$$

Variable: ***$DR_{vCJDS\text{-}EU\text{-}Resy}$*** **–** The residual risk associated with recovered plasma donors potentially infected with vCJD that meet deferral criteria but because of limitations in the donor screening process and are not deferred by current policy; is represented by the equation:

$$DR_{vCJD-R-EU-Resy} = \sum_{Age=18-19}^{50-54} \sum_{i=1-30\,days}^{>=3-5\,years} DR_{vCJD-R-EU(age)y,i} \quad \textbf{(IV.C.1.c-29)}$$

A-IV. C. 1. c. vi. Number of US recovered plasma donors who traveled to countries in Europe: Number potentially infected and vCJD agent is present in the blood

The most critical component of the model is the estimation of whether a plasma donation was collected from a vCJD infected donor that contained infectious vCJD agent in their blood (or was prionemic) at the time of donation. Based on data from animal studies, the model assumes that vCJD infectious individuals have infectious vCJD agent present in the blood during the last half of the incubation period. This portion of the model calculates the number of recovered plasma donors who may potentially contain infectious vCJD agent in their blood at the time of donation.

Variable: $\boldsymbol{Pr_{LH\text{-}y}}$ -The probability an individual was prionemic in year 2002.

Variable: $DR_{vCJD\text{-}R\text{-}EUy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residence in European countries (other than France).

Variable: $\boldsymbol{DR_{vCJD\text{-}R\text{-}EU\text{-}LHy}}$ - Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residence in a country in Europe (other than the UK or France) and are in the last half incubation period of the disease (and has vCJD agent present in their blood).

$$DR_{vCJD-R-EU-LHy} = Binomial(DR_{vCJD-R-EUy,}\ \Pr_{LH-y}) \qquad \text{(IV.C.1.c-30)}$$

Variable: $\boldsymbol{DR_{vCJD\text{-}R\text{-}EU\text{-}defy}}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in European countries (other than the UK or France) and met deferral criteria and were presumably deferred from donation .

Variable: $\boldsymbol{DR_{vCJD\text{-}R\text{-}EU\text{-}def\text{-}LHy}}$ - Total number of recovered plasma donors in the last half incubation period of the disease (and presumably has vCJD agent present in their blood) who met deferral criteria and were presumably deferred from donation.

$$DR_{vCJD-R-EU-Def-LHy} = Binomial(DR_{vCJD-R-EU-Defy,}\ \Pr_{LH-y}) \qquad \text{(IV.C.1.c-31)}$$

Variable: $\boldsymbol{DR_{vCJD\text{-}R\text{-}EU\text{-}Resy}}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in countries in Europe (other than the UK or France) and did not meet the deferral criteria and were likely not deferred .

Variable: $\boldsymbol{DR_{vCJD\text{-}R\text{-}EU\text{-}Res\text{-}LHy}}$ - Total number of recovered plasma donors in the last half of the incubation period of the disease who did not met the deferral criteria and were likely not deferred from donation:

$$DR_{vCJD-R-EU-\mathrm{Res}-LHy} = Binomial(DR_{vCJD-R-EU-\mathrm{Res}y,}\ \mathrm{Pr}_{LH-y}) \quad \text{(IV.C.1.c-32)}$$

A-IV. C. 1. d. Number of US plasma donors deployed by the military in the UK or other countries in Europe and potentially infected with vCJD

A-IV. C. 1. d. i. Percentage of US plasma donors deployed at US military bases in the UK or other countries in Europe during the years 1980 through 1996

Variable: $Perc_{DR\text{-}DOD}$ **-** Percentage of US blood donors who were military residents in countries in Europe for ≥ 6 months from 1980 through 1996.

Assumption used in the model**:** Approximately 2% of US blood donors have been military residents in European countries between 1980-1996 (TSEAC 2002). There were no data for plasma donors, therefore, data for US blood donors was used to estimate the number of US donors stationed in US military facilities during the period 1980-1996

- The FDA model assumed that the same percentage of plasma donors have been in the military and deployed in European countries as blood donors.

A-IV. C. 1. d. ii. Number of US plasma donors deployed by Military in the UK or other countries in Europe by year of deployment since 1980

A-IV. C. 1. d. ii. a. Number of US Source Plasma donors stationed at US military facilities in the UK or countries in Europe during the period from 1980 -1996 by year of deployment

Variable: ***y*** **-** Calendar year of deployment

Variable: ***DODy*** **-** Number of US military residents, their family and dependents who resided on US military facilities in Europe by year from 1980 through 1996.

Assumption used in the model: The risk of BSE exposure and vCJD infection for donors previously deployed to US military facilities in the UK or countries in Europe after 1996 was assumed to be negligible, because it is assumed that most of the risk was associated with imported UK beef. Food chain controls put in place in the UK after 1996 were assumed to reduce the BSE exposure risk to negligible levels (TSEAC, 2002) and shipment of UK beef to US military facilities had stopped in 1996 or earlier.

Variable: ***age*** - age of donors in grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group (same variable used above in section A-IV.C.1.a.ii.)

$$Perc_{DR-DODy} = (DOD_y / \sum_{y=1980}^{1996} DOD_y) \times 100\% \quad \text{(IV.C.1.d-1)}$$

Variable: $DR_{S(age)}$ – Age of donors of Source Plasma (calculated in section A-IV.B. 1.**)**

Variable: $Perc_{DR\text{-}DOD}$ **–** Percentage of Source Plasma donors who have a history of military deployment in Europe since 1980 (calculated in section A-IV. C. 1. d. ii. a.)

Variable: $DR_{S\text{-}DOD(age)}$ **-** Estimated annual number of Source Plasma donors who have history of military deployment in the UK or Europe by age

Assumption about variable: We assumed 3% of Source Plasma donors have a history of military deployment and residence in the UK, France or other countries of Europe during any of the years from 1980-1996 and would have similar donation demographics and characteristics as whole blood donors.

The estimated annual number of Source Plasma donors who have a history of military deployment in Europe by age is represented by the equation:

$$DR_{S-DOD(age)} = DR_{S(age)} \times Perc_{DR-DOD} \quad \text{(IV.C.1.d-2)}$$

Variable: $DR_{S\text{-}DOD(age)y}$ **–** Number estimated annual number of Source Plasma donors who have resided on military bases in Europe by age and deployment year

$$DR_{S-DOD(age)y} = DR_{S-DOD(age)} \times Perc_{DR-DODy} \quad \text{(IV.C.1.d-3)}$$

A-IV. C. 1. d. ii. b. Number of recovered plasma donors with a history of military deployment at US military facilities in the UK or other countries in Europe during the period 1980-1996 by year of deployment

Variable: ***age*** **-** Age of donors grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group. No data for the yearly distribution of deployment of military plasma donors in the UK, France or other countries in Europe was available. The age distribution of donors in the military was estimated from Department of Defense (DOD) data (2005). The donation rate for military staff was estimated using the blood donor survey data (TSEAC, 2002).

Variable: $DR_{R\text{-}(age)}$ **-** Annual number of recovered plasma donors by age

Assumption used in the model: We assumed 3% of recovered plasma donors were grouped by deployment year based on the yearly distribution of military deployment and residence in the UK or Europe during 1980-1996 .(DOD 2005).

$$DR_{R-DOD(age)y} = DR_{R-DOD(age)} \times Perc_{DR-DODy} \quad \text{(IV.C.1.d-4)}$$

Variable: $DR_{R(age)}$ **-** Annual number of recovered plasma donors by age (calculated in section A-IV.B. 2.) grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group

Variable: $Perc_{DR\text{-}DOD}$ - Percentage of recovered plasma donors who have a history of military deployment in the UK and countries in Europe since 1980 (calculated in section A-IV. C. 1. d. ii. a.)

Variable: $DR_{R\text{-}DOD(age)}$ - Estimated annual number of recovered plasma donors who have a history of military deployment in the UK and countries in Europe by age.

Assumption used in the model**:** The same percentage of recovered plasma donors have a history of military deployment as blood donors.

The estimated annual number of recovered plasma donors who have history of military deployment in the UK and countries in Europe by age is represented by the equation:

$$DR_{R-DOD(age)} = DR_{R(age)} \times Perc_{DR-DOD} \quad \text{(IV.C.1.d-5)}$$

Assumption used in the model: The annual distribution of US military service members and their dependents residing on US military bases in Europe represents the yearly distribution of deployment in the UK and countries in Europe of US military recovered plasma donors

$$DR_{R-DOD(age)y} = DR_{R-DOD(age)} \times Perc_{DR-DODy} \quad \text{(IV.C.1.d-6)}$$

A-IV. C. 1. d. iii. Adjustment of the Relative Risk for the proportional variation in the BSE exposure risk in the UK and the military deployment duration per specific year during the period from 1980 - 1996

Variable: R_{Base} - The cumulative vCJD risk of individual military personnel who were deployed and resided in the UK or Europe for the entire period from 1980 through 1996: it is assumed that the accumulated risk is equal to that of a UK resident and is assumed to be 1 (or equal to the UK vCJD prevalence) for this period.

Assumption used in the model: The cumulative risk of US military residents in Europe from 1980 through 1996 is 0.35. This estimate is based on the assumption that approximately 35% of the beef consumed by military personnel in Europe between 1980-1996 was imported from the UK (FDA 2002).

Variable: y – Year of deployment (same variable used above in A-IV. C. 1. d. ii. a.)

Variable: y_{epi} – The specific year of BSE epidemic in the UK.

Assumption about variable: The BSE epidemic in the UK was assumed to have started in 1980 and at first was not detected. The first cases of BSE were reported in 1986.

Variable: BSE_{UKy} - Number of diagnosed BSE cases in the UK by year from 1980 through 1996

Data used in the model: Data are from the World organization for animal health (OIE 2005). Data were not collected for individual years prior to 1997. A total of 446 cases of BSE were reported by European countries (other than the UK) during the time period from 1980 through 1996 and were allocated to individual years by assuming the cases were increasing in a linear fashion by year.

Variable: R_{Basey} - Proportional vCJD risk for donors that resided on US military bases in Europe in a specific year

Assumptions used in the model:

- The vCJD risk for US military facilities in Europe was present from 1980 through 1996. There was negligible vCJD risk after 1996 – the model assumed the major source of vCJD risk for US military bases in Europe was associated with imported UK beef. When food chain controls were implemented in the UK in 1996 – the model assumed the risk to be negligible.
- It was assumed that the vCJD risk was additive and can be prorated on a yearly base.
- The vCJD risk in a specific year was assumed to be proportional to the reported BSE cases in the UK in that specific year.

Proportional vCJD risk in the US military bases in a specific year was calculated by the equation:

$$R_{Basey} = R_{Base} \times BSE_{UKy} / \sum_{y=1980}^{1996} BSE_{UKy} \qquad \text{(IV.C.1.d-7)}$$

Variable: $R_{DR\text{-}DODy}$ - Risk of individual military personnel who lived in Europe for a period of two years starting from deployment year y, and assumes the cumulative risk of a UK individual from 1980 through 1996 is 1.

Assumption used in the model: The model assumed an average of two consecutive years of deployment:

$$R_{DR-DODy} = R_{Basey} + R_{Base(y+1)} \qquad \text{(IV.C.1.d-8)}$$

Variable: $Pr_{vCJD\text{-}UK(age)}$ - Probability of infection for individual UK resident of a specific age group (calculated in A-IV. C. 1.).

Variable: $Pr_{vCJD\text{-}DR\text{-}DOD(age)y}$ - Probability of infection for individual US plasma donor of a specific age group that lived on or near a US military bases in Europe starting from year y with duration of two years

Assumption used in the model: Probability of infection is proportional to the risk of exposure

$$\Pr_{vCJD-DR-DOD(age)y} = \Pr_{vCJD-UK(age)} \times R_{DR-DODy} \qquad \text{(IV.C.1.d-9)}$$

A-IV. C. 1. d. iv. Number of all US plasma donors potentially infected with vCJD during residence at a US military base in the UK or other countries in Europe from 1980 to 1996

The section estimates the number of Source and recovered plasma donors with a history of deployment in the UK or countries in Europe during the period from 1980 through 1996 and sums the number of vCJD cases that may have vCJD agent in their blood (or be prionemic) at the time of donation from each pathway to derive the total number of all donors potentially infected with vCJD that may have vCJD agent in their blood (or be prionemic).

A-IV. C. 1. d. iv. a. Potential number of US Source Plasma donors with a history of military deployment in the UK or other countries in Europe from 1980 to 1996 potentially infected with vCJD

Variable: $DR_{vCJD\text{-}S\text{-}DOD(age)y}$ - Potential number of Source Plasma donors infected during residency on US military facilities in the UK or Europe from 1980-1996 by age, and year of deployment

$$DR_{vCJD-S-DOD(age)y} = Binomial(DR_{S-DOD(age)y}, \Pr_{vCJD-DR-DOD(age)y}) \qquad \text{(IV.C.1.d-10)}$$

Variable: $DR_{vCJD\text{-}S\text{-}DOD}$ - Potential number total of Source Plasma donors infected during residency on US military bases in Europe from 1980-1996 is represented by the expression:

$$DR_{vCJD-S-DOD} = \sum_{y=1980}^{1996} \sum_{age=18-19}^{70-74} DR_{vCJD-S-DOD(age)y} \qquad \text{(IV.C.1.d-11)}$$

A-IV. C. 1. d. iv. b. Potential number of Source Plasma donors with a history of deployment to a US military facility in the UK or other countries of Europe from 1980 to 1996 in the last half incubation period of the disease

This section estimates the number of Source Plasma donors that may potentially be infected with vCJD who may have vCJD agent in their blood (or be prionemic) at the time of donation.

Variable: *y*-The calendar year in which a plasma donor was deployed to a US military base in Europe.

Assumption used in the model: This risk assessment assesses the vCJD risk for pdFVIII product made in 2002 but it is assumed that the potential vCJD risk is similar to the present day risk in 2006.

Variable: $T_{Inf\text{-}2002y}$-Time period between infection/travel and the year 2002 when the plasma was collected.

Variable: $Pr\text{-}LH_y$- Probability that the vCJD disease is in the last half of the incubation period of the disease, if infected in year y and the individual has infectious vCJD agent present in their blood and plasma (or was prionemic).

Variable: $T_{Inf\text{-}2002y}$ - Time period between infection/travel and 2002 when the plasma was collected is represented by the expression:

$$T_{Inf-2002y} = 2002 - y \quad \textbf{(IV.C.1.d-12)}$$

For an individual to be prionemic in 2002, the remaining period of time since infection up to 2002 ($I_{Inf-2002y}$) should be equal to or less than the half of incubation period of the disease.

Assumption used in the model: The variability and uncertainty of the incubation period of vCJD is represented mathematically by a gamma distribution, specifically Gamma (4.7, 3.6). A gamma distribution is usually used to represent processes that occur sequentially or the time between events. In this case it would be the time from infection to the time until the appearance of clinical disease (incubation period of the disease). The distribution is defined by two parameters: one that produces the shape of the curve; and a second generates the scale for the distribution, which in this case is represented by the mean incubation period of 14 years.

Variable: Pr_{LH-y} -The probability an individual was prionemic in year 2002-was calculated by using the cumulative frequency of Gamma (4.7, 3.6), at x=2×(1997-y)

Variable: $DR_{vCJD-S-DODy}$- Total number of Source Plasma donors potentially infected with vCJD in year y during military deployment on European bases (calculated in A-IV. C. 1. d. v. a.).

Variable: $DR_{vCJD-S-DOD-LHy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during military deployment to US military bases in European countries and in the last half incubation period of the disease.

$$DR_{vCJD-S-DOD-LHy} = Binomial(DR_{vCJD-S-DODy,}\ \Pr_{LH-y}) \quad \text{(IV.C.1.d-13)}$$

A-IV. C. 1. d. iv. c. Number of US recovered plasma donors with a history of deployment to a US military base in the UK or other countries in Europe during the period 1980-1996 and potentially infected with vCJD

Variable: $DR_{vCJD-R-DOD(age)y}$ - Potential number of recovered plasma donors infected during deployment and residency on or near US military bases in Europe from 1980-1996 by age, and year of deployment

$$DR_{vCJD-R-DOD(age)y} = Binomial(DR_{R-DOD(age)y,}\ \Pr_{vCJD-DR-DOD(age)y}) \quad \text{(IV.C.1.d-14)}$$

Variable: $DR_{vCJD-R-DOD}$ - Potential number of recovered plasma donors infected during residency on US military bases in Europe from 1980-1996 is represented by the equation:

$$DR_{vCJD-R-DOD} = \sum_{y=1980}^{1996} \sum_{age=18-19}^{70-74} DR_{vCJD-R-DOD(age)y} \quad \text{(IV.C.1.d-15)}$$

A-IV. C. 1. d. iv. d. Recovered plasma donors with a history of deployment to a US military base in the UK or other countries in Europe: Potential number of donors in the last half of vCJD incubation period and vCJD agent is present in the blood

This portion of the model calculates the potential number of vCJD infected recovered plasma donors who are in the last half incubation period of the disease and presumably may contain vCJD agent in their blood (or are prionemic).

Variable: $Pr_{LH\text{-}y}$ -The probability a vCJD-infected donor had vCJD agent present in their blood and plasma at the time of donation (was prionemic) in the year 2002 (calculated in A-IV.C.1.d.v.b).

Variable: $DR_{vCJD\text{-}R\text{-}DODy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during military deployment on or near bases in Europe (calculated in A-IV. C. 1. d. v. c.)

Variable: $DR_{vCJD\text{-}R\text{-}DOD\text{-}LHy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y during military deployment on or near bases in Europe and in the last half incubation period of the disease.

$$DR_{vCJD-R-DOD-LHy} = Binomial(DR_{vCJD-R-DODy,}\ \Pr_{LH-y}) \qquad \text{(IV.C.1.d-16)}$$

A-IV. C. 1. d. iv. e. Number of all vCJD infected plasma donors during deployment to a US military base in a country in Europe from 1980-1996

Variable: $DR_{vCJD\text{-}DOD}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996

$$DR_{vCJD-DOD} = \sum_{y=1980}^{1996} DR_{vCJD-S-DOD} + \sum_{y=1980}^{1996} DR_{vCJD-R-DOD} \qquad \text{(IV.C.1.d-17)}$$

Variable: $DR_{vCJD\text{-}DOD\text{-}Def}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and meet deferral criteria

Assumption used in the model: Current policy defers individuals who have been deployed or resided on a US military base in Europe from 1980 to 1996 for a cumulative stay of 6 months or more. We assumed all US Department of Defense (DOD) deployments are 6 months or longer, and therefore, all individuals have a history of deployment to a US military base in Europe are deferred.

$$DR_{vCJD-DOD-Def} = DR_{vCJD-DOD} \qquad \text{(IV.C.1.d-18)}$$

A-IV. C. 1. d. iv. f. Potential number of all plasma donors in the last half of vCJD incubation period

This portion of the model estimates the potential number of all vCJD infected plasma donors with a history of military service posted at a US military base in the UK or countries in Europe fron 1980-1996 who are in the last half incubation period of the disease and their blood and plasma presumably contain infectious vCJD agent (or are prionemic).

Variable: $DR_{vCJD\text{-}DOD\text{-}LH}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and are in the last half incubation period of the disease

$$DR_{vCJD-DOD-LH} = \sum_{y=1980}^{1996} DR_{vCJD-S-DOD-LH} + \sum_{y=1980}^{1996} DR_{vCJD-R-DOD-LH} \quad \text{(IV.C.1.d-19)}$$

Variable: $DR_{vCJD\text{-}DOD\text{-}Def}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and meet deferral criteria

$$DR_{vCJD-DOD-Def} = DR_{vCJD-DOD} \quad \text{(IV.C.1.d-20)}$$

A-IV. C. 1. d. i. Percentage of US plasma donors deployed at US military bases in the UK or other countries in Europe during the years 1980 through 1996

Variable: $Perc_{DR\text{-}DOD}$ - Percentage of US blood donors who were military residents in countries in Europe for $\geq$ 6 months from 1980 through 1996.

Assumption used in the model**:** Approximately 2% of US blood donors have been military residents in European countries between 1980-1996 (TSEAC 2002). There were no data for plasma donors, therefore, data for US blood donors was used to estimate the number of US donors stationed in US military facilities during the period 1980-1996

- The FDA model assumed that the same percentage of plasma donors have been in the military and deployed in European countries as blood donors.

A-IV. C. 1. d. ii. Number of US plasma donors deployed by Military in the UK or other countries in Europe by year of deployment since 1980

A-IV. C. 1. d. ii. a. Number of US Source Plasma donors stationed at US military facilities in the UK or countries in Europe during the period from 1980 -1996 by year of deployment

Variable: ***y*** **-** Calendar year of deployment

Variable: ***DODy*** **-** Number of US military residents, their family and dependents who resided on US military facilities in Europe by year from 1980 through 1996.

Assumption used in the model: The risk of BSE exposure and vCJD infection for donors previously deployed to US military facilities in the UK or countries in Europe after 1996 was assumed to be negligible, because it is assumed that most of the risk was associated with imported UK beef. Food chain controls put in place in the UK after 1996 were assumed to reduce the BSE exposure risk to negligible levels (TSEAC, 2002) and shipment of UK beef to US military facilities had stopped in 1996 or earlier.

Variable: ***age*** - age of donors in grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group (same variable used above in section A-IV.C.1.a.ii.)

$$Perc_{DR-DODy} = (DOD_y / \sum_{y=1980}^{1996} DOD_y) \times 100\% \qquad \text{(IV.C.1.d-1)}$$

Variable: $DR_{S(age)}$ – Age of donors of Source Plasma (calculated in section A-IV.B. 1**.)**

Variable: $Perc_{DR\text{-}DOD}$ **–** Percentage of Source Plasma donors who have a history of military deployment in Europe since 1980 (calculated in section A-IV. C. 1. d. ii. a.)

Variable: $DR_{S\text{-}DOD(age)}$ **-** Estimated annual number of Source Plasma donors who have history of military deployment in the UK or Europe by age

Assumption about variable: We assumed 3% of Source Plasma donors have a history of military deployment and residence in the UK, France or other countries of Europe during any of the years from 1980-1996 and would have similar donation demographics and characteristics as whole blood donors.

The estimated annual number of Source Plasma donors who have a history of military deployment in Europe by age is represented by the equation:

$$DR_{S-DOD(age)} = DR_{S(age)} \times Perc_{DR-DOD} \qquad \text{(IV.C.1.d-2)}$$

Variable: $DR_{S\text{-}DOD(age)y}$ **–** Number estimated annual number of Source Plasma donors who have resided on military bases in Europe by age and deployment year

$$DR_{S-DOD(age)y} = DR_{S-DOD(age)} \times Perc_{DR-DODy} \qquad \text{(IV.C.1.d-3)}$$

A-IV. C. 1. d. ii. b. Number of recovered plasma donors with a history of military deployment at US military facilities in the UK or other countries in Europe during the period 1980-1996 by year of deployment

Variable: ***age*** **-** Age of donors grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group. No data for the yearly distribution of deployment of military plasma donors in the UK, France or other countries in Europe was available. The age distribution of donors in the military was estimated from Department of Defense (DOD) data (2005). The donation rate for military staff was estimated using the blood donor survey data (TSEAC, 2002).

Variable: $DR_{R\text{-}(age)}$ **-** Annual number of recovered plasma donors by age

Assumption used in the model: We assumed 3% of recovered plasma donors were grouped by deployment year based on the yearly distribution of military deployment and residence in the UK or Europe during 1980-1996 .(DOD 2005).

$$DR_{R-DOD(age)y} = DR_{R-DOD(age)} \times Perc_{DR-DODy} \quad \text{(IV.C.1.d-4)}$$

Variable: $DR_{R(age)}$ **-** Annual number of recovered plasma donors by age (calculated in section A-IV.B. 2.) grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group

Variable: $Perc_{DR\text{-}DOD}$ - Percentage of recovered plasma donors who have a history of military deployment in the UK and countries in Europe since 1980 (calculated in section A-IV. C. 1. d. ii. a.)

Variable: $DR_{R\text{-}DOD(age)}$ **-** Estimated annual number of recovered plasma donors who have a history of military deployment in the UK and countries in Europe by age.

Assumption used in the model**:** The same percentage of recovered plasma donors have a history of military deployment as blood donors.

The estimated annual number of recovered plasma donors who have history of military deployment in the UK and countries in Europe by age is represented by the equation:

$$DR_{R-DOD(age)} = DR_{R(age)} \times Perc_{DR-DOD} \quad \text{(IV.C.1.d-5)}$$

Assumption used in the model: The annual distribution of US military service members and their dependents residing on US military bases in Europe represents the yearly distribution of deployment in the UK and countries in Europe of US military recovered plasma donors

$$DR_{R-DOD(age)y} = DR_{R-DOD(age)} \times Perc_{DR-DODy} \quad \text{(IV.C.1.d-6)}$$

A-IV. C. 1. d. iii. Adjustment of the Relative Risk for the proportional variation in the BSE exposure risk in the UK and the military deployment duration per specific year during the period from 1980 - 1996

Variable: R_{Base} - The cumulative vCJD risk of individual military personnel who were deployed and resided in the UK or Europe for the entire period from 1980 through 1996: it is assumed that the accumulated risk is equal to that of a UK resident and is assumed to be 1 (or equal to the UK vCJD prevalence) for this period.

Assumption used in the model: The cumulative risk of US military residents in Europe from 1980 through 1996 is 0.35. This estimate is based on the assumption that approximately 35% of the beef consumed by military personnel in Europe between 1980-1996 was imported from the UK (FDA 2002).

Variable: y – Year of deployment (same variable used above in A-IV. C. 1. d. ii. a.)

Variable: y_{epi} **–** The specific year of BSE epidemic in the UK.

Assumption about variable: The BSE epidemic in the UK was assumed to have started in 1980 and at first was not detected. The first cases of BSE were reported in 1986.

Variable: BSE_{UKy} **-** Number of diagnosed BSE cases in the UK by year from 1980 through 1996

Data used in the model: Data are from the World organization for animal health (OIE 2005). Data were not collected for individual years prior to 1997. A total of 446 cases of BSE were reported by European countries (other than the UK) during the time period from 1980 through 1996 and were allocated to individual years by assuming the cases were increasing in a linear fashion by year.

Variable: $\mathbf{R_{Basey}}$ **-** Proportional vCJD risk for donors that resided on US military bases in Europe in a specific year

Assumptions used in the model:

- The vCJD risk for US military facilities in Europe was present from 1980 through 1996. There was negligible vCJD risk after 1996 – the model assumed the major source of vCJD risk for US military bases in Europe was associated with imported UK beef. When food chain controls were implemented in the UK in 1996 – the model assumed the risk to be negligible.
- It was assumed that the vCJD risk was additive and can be prorated on a yearly base.
- The vCJD risk in a specific year was assumed to be proportional to the reported BSE cases in the UK in that specific year.

Proportional vCJD risk in the US military bases in a specific year was calculated by the equation:

$$R_{Basey} = R_{Base} \times BSE_{UKy} / \sum_{y=1980}^{1996} BSE_{UKy} \qquad \text{(IV.C.1.d-7)}$$

Variable: $R_{DR\text{-}DODy}$ - Risk of individual military personnel who lived in Europe for a period of two years starting from deployment year y, and assumes the cumulative risk of a UK individual from 1980 through 1996 is 1.

Assumption used in the model: The model assumed an average of two consecutive years of deployment:

$$R_{DR-DODy} = R_{Basey} + R_{Base(y+1)} \quad \text{(IV.C.1.d-8)}$$

Variable: $Pr_{vCJD\text{-}UK(age)}$ - Probability of infection for individual UK resident of a specific age group (calculated in A-IV. C. 1.).

Variable: $Pr_{vCJD\text{-}DR\text{-}DOD(age)y}$ - Probability of infection for individual US plasma donor of a specific age group that lived on or near a US military bases in Europe starting from year y with duration of two years

Assumption used in the model: Probability of infection is proportional to the risk of exposure

$$\Pr_{vCJD-DR-DOD(age)y} = \Pr_{vCJD-UK(age)} \times R_{DR-DODy} \quad \text{(IV.C.1.d-9)}$$

A-IV. C. 1. d. iv. Number of all US plasma donors potentially infected with vCJD during residence at a US military base in the UK or other countries in Europe from 1980 to 1996

The section estimates the number of Source and recovered plasma donors with a history of deployment in the UK or countries in Europe during the period from 1980 through 1996 and sums the number of vCJD cases that may have vCJD agent in their blood (or be prionemic) at the time of donation from each pathway to derive the total number of all donors potentially infected with vCJD that may have vCJD agent in their blood (or be prionemic).

A-IV. C. 1. d. iv. a. Potential number of US Source Plasma donors with a history of military deployment in the UK or other countries in Europe from 1980 to 1996 potentially infected with vCJD

Variable: $DR_{vCJD\text{-}S\text{-}DOD(age)y}$ - Potential number of Source Plasma donors infected during residency on US military facilities in the UK or Europe from 1980-1996 by age, and year of deployment

$$DR_{vCJD-S-DOD(age)y} = Binomial(DR_{S-DOD(age)y}, \Pr_{vCJD-DR-DOD(age)y}) \quad \text{(IV.C.1.d-10)}$$

Variable: $DR_{vCJD\text{-}S\text{-}DOD}$ - Potential number total of Source Plasma donors infected during residency on US military bases in Europe from 1980-1996 is represented by the expression:

$$DR_{vCJD-S-DOD} = \sum_{y=1980}^{1996} \sum_{age=18-19}^{70-74} DR_{vCJD-S-DOD(age)y} \quad \text{(IV.C.1.d-11)}$$

A-IV. C. 1. d. iv. b. Potential number of Source Plasma donors with a history of deployment to a US military facility in the UK or other countries of Europe from 1980 to 1996 in the last half incubation period of the disease

This section estimates the number of Source Plasma donors that may potentially be infected with vCJD who may have vCJD agent in their blood (or be prionemic) at the time of donation.

Variable: *y*-The calendar year in which a plasma donor was deployed to a US military base in Europe.

Assumption used in the model: This risk assessment assesses the vCJD risk for pdFVIII product made in 2002 but it is assumed that the potential vCJD risk is similar to the present day risk in 2006.

Variable: $T_{Inf\text{-}2002y}$-Time period between infection/travel and the year 2002 when the plasma was collected.

Variable: $Pr\text{-}LH_y$- Probability that the vCJD disease is in the last half of the incubation period of the disease, if infected in year y and the individual has infectious vCJD agent present in their blood and plasma (or was prionemic).

Variable: $T_{Inf\text{-}2002y}$ - Time period between infection/travel and 2002 when the plasma was collected is represented by the expression:

$$T_{Inf-2002y} = 2002 - y \quad \textbf{(IV.C.1.d-12)}$$

For an individual to be prionemic in 2002, the remaining period of time since infection up to 2002 ($I_{Inf\text{-}2002y}$) should be equal to or less than the half of incubation period of the disease.

Assumption used in the model: The variability and uncertainty of the incubation period of vCJD is represented mathematically by a gamma distribution, specifically Gamma (4.7, 3.6). A gamma distribution is usually used to represent processes that occur sequentially or the time between events. In this case it would be the time from infection to the time until the appearance of clinical disease (incubation period of the disease). The distribution is defined by two parameters: one that produces the shape of the curve; and a second generates the scale for the distribution, which in this case is represented by the mean incubation period of 14 years.

Variable: $Pr_{LH\text{-}y}$ -The probability an individual was prionemic in year 2002-was calculated by using the cumulative frequency of Gamma (4.7, 3.6), at x=2×(1997-y)

Variable: $DR_{vCJD\text{-}S\text{-}DODy}$- Total number of Source Plasma donors potentially infected with vCJD in year y during military deployment on European bases (calculated in A-IV. C. 1. d. v. a.).

Variable: $DR_{vCJD\text{-}S\text{-}DOD\text{-}LHy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during military deployment to US military bases in European countries and in the last half incubation period of the disease.

$$DR_{vCJD-S-DOD-LHy} = Binomial(DR_{vCJD-S-DODy,}\ \Pr_{LH-y}) \quad \text{(IV.C.1.d-13)}$$

A-IV. C. 1. d. iv. c. Number of US recovered plasma donors with a history of deployment to a US military base in the UK or other countries in Europe during the period 1980-1996 and potentially infected with vCJD

Variable: $\mathbf{DR_{vCJD\text{-}R\text{-}DOD(age)y}}$ - Potential number of recovered plasma donors infected during deployment and residency on or near US military bases in Europe from 1980-1996 by age, and year of deployment

$$DR_{vCJD-R-DOD(age)y} = Binomial(DR_{R-DOD(age)y,}\ \Pr_{vCJD-DR-DOD(age)y}) \quad \text{(IV.C.1.d-14)}$$

Variable: $\mathbf{DR_{vCJD\text{-}R\text{-}DOD}}$ - Potential number of recovered plasma donors infected during residency on US military bases in Europe from 1980-1996 is represented by the equation:

$$DR_{vCJD-R-DOD} = \sum_{y=1980}^{1996} \sum_{age=18-19}^{70-74} DR_{vCJD-R-DOD(age)y} \quad \text{(IV.C.1.d-15)}$$

A-IV. C. 1. d. iv. d. Recovered plasma donors with a history of deployment to a US military base in the UK or other countries in Europe: Potential number of donors in the last half of vCJD incubation period and vCJD agent is present in the blood

This portion of the model calculates the potential number of vCJD infected recovered plasma donors who are in the last half incubation period of the disease and presumably may contain vCJD agent in their blood (or are prionemic).

Variable: $Pr_{LH\text{-}y}$ -The probability a vCJD-infected donor had vCJD agent present in their blood and plasma at the time of donation (was prionemic) in the year 2002 (calculated in A-IV.C.1.d.v.b).

Variable: $DR_{vCJD\text{-}R\text{-}DODy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during military deployment on or near bases in Europe (calculated in A-IV. C. 1. d. v. c.)

Variable: $DR_{vCJD\text{-}R\text{-}DOD\text{-}LHy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y during military deployment on or near bases in Europe and in the last half incubation period of the disease.

$$DR_{vCJD-R-DOD-LHy} = Binomial(DR_{vCJD-R-DODy,}, \Pr_{LH-y}) \quad \text{(IV.C.1.d-16)}$$

A-IV. C. 1. d. iv. e. Number of all vCJD infected plasma donors during deployment to a US military base in a country in Europe from 1980-1996

Variable: $DR_{vCJD\text{-}DOD}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996

$$DR_{vCJD-DOD} = \sum_{y=1980}^{1996} DR_{vCJD-S-DOD} + \sum_{y=1980}^{1996} DR_{vCJD-R-DOD} \quad \text{(IV.C.1.d-17)}$$

Variable: $DR_{vCJD\text{-}DOD\text{-}Def}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and meet deferral criteria

Assumption used in the model: Current policy defers individuals who have been deployed or resided on a US military base in Europe from 1980 to 1996 for a cumulative stay of 6 months or more. We assumed all US Department of Defense (DOD) deployments are 6 months or longer, and therefore, all individuals have a history of deployment to a US military base in Europe are deferred.

$$DR_{vCJD-DOD-Def} = DR_{vCJD-DOD} \quad \text{(IV.C.1.d-18)}$$

A-IV. C. 1. d. iv. f. Potential number of all plasma donors in the last half of vCJD incubation period and have vCJD agent present in the blood

This portion of the model estimates the potential number of all vCJD infected plasma donors with a history of military service posted at a US military base in the UK or countries in Europe fron 1980-1996 who are in the last half incubation period of the disease and their blood and plasma presumably contain infectious vCJD agent (or are prionemic).

Variable: $DR_{vCJD\text{-}DOD\text{-}LH}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and are in the last half incubation period of the disease

$$DR_{vCJD-DOD-LH} = \sum_{y=1980}^{1996} DR_{vCJD-S-DOD-LH} + \sum_{y=1980}^{1996} DR_{vCJD-R-DOD-LH} \quad \text{(IV.C.1.d-19)}$$

Variable: $DR_{vCJD\text{-}DOD\text{-}Def}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and meet deferral criteria

$$DR_{vCJD-DOD-Def} = DR_{vCJD-DOD} \quad \text{(IV.C.1.d-20)}$$

Variable: DR_{Tot} **-** (calculated in section A-IV.B.3.) Annual number of plasma donors

Variable: DR_S **-** (calculated in section A-IV.B.1.) Annual number of Source Plasma donors

Variable: DR_R **-** (calculated in section A-IV.B.2.) Annual number of recovered plasma donors

Variable: $Perc_{DR\text{-}Eurob}$ **-** Percentage of blood donors who were Euroblood recipients

Assumption used in the model: 1.2% plasma donors were Euroblood recipients

Variable: DR_{Eurob} **-** Annual number of plasma donors who were Euroblood recipients

$$DR_{Eurob} = DR_{Tot} \times Perc_{DR-Eurob} \quad \text{(IV.C.1.e-1)}$$

Variable: $DR_{S\text{-}Eurob}$ **-** Annual number of Source Plasma donors who were Euroblood recipients

Assumption used in the model: We assumed 1.2% of US Source Plasma donors were Euroblood recipients

$$DR_{S-Eurob} = DR_S \times Perc_{DR-Eurob} \quad \text{(IV.C.1.e-2)}$$

Variable: $DR_{R\text{-}Eurob}$ **-** Annual number of recovered plasma donors who were Euroblood recipients – represented by the equation:

$$DR_{R-Eurob} = DR_R \times Perc_{DR-Eurob} \quad \text{(IV.C.1.e-3)}$$

A-IV. C. 1. e. Annual number of US plasma donors who have been Euroblood recipients

A-IV. C. 1. e. i. Annual number of US plasma donors who have been Euroblood recipients

A-IV. C. 1. e. ii. Annual number of potential vCJD-infected Euroblood donors and estimated annual units of Euroblood potentially containing vCJD agent

This section of the model estimates the quantity of Euroblood units predicted to have been transfused into US plasma donors in a one year period, the number of European donors involved, the number of possible vCJD infected European Euroblood donors, and the total quantity of vCJD infected units given by the Euroblood donors.

Variable: $DNBl_{UK(age)}$ **-** Blood donations in the UK by age of donors.

Data used in the model: Information about UK blood donors was provided by CDSC (2005).

Variable: $Perc_{DN\text{-}UK(age)}$ **-** Percentage distribution of the blood donations in the UK by donor age, and is represented by equation:

$$Perc_{DN-UK(age)} = DN_{Bl-UK(age)} / \sum_{age=18}^{\geq 65} DN_{Bl-UK(age)} \quad \text{(IV.C.1.e-5)}$$

Variable: $EUBL_{(age)}$ **-** Units of Euroblood that were donated by a specific age group of European donors and transfused into US plasma donors

Total units of Euroblood received by US plasma donors of one year period is allocated by age of European donors based on the age distribution of UK blood donors

Assumption used in the model**:** We assumed the age distribution for Euroblood donors is the same as UK blood donors

$$EUBL_{(age)} = EUBL_{Tot} \times Perc_{DN-UK(age)} \quad \text{(IV.C.1.e-6)}$$

Variable: $DR_{EUBL(age)}$ – The number of European donors were grouped by age in five-year increments (e.g., 20-24 yrs, etc) and the 18-19 yr old group that have contributed Euroblood that may have been transfused into US plasma donors per one year period

Each European donor may give multiple donations in a single year; however the chance of more than one donation from same donor being shipped to the US and used by US plasma donors is expected to be small.

Assumption used in the model: Each unit of Euroblood received by US plasma donors of one year-period came from different European donors and is expressed by the equation:

$$DR_{EUBL(age)} = EUBL_{(age)} \quad \text{(IV.C.1.e-7)}$$

The probability of infection of individual European blood donors is calculated below based on the probability of infection per individual UK resident and the relative risk of a resident in a country elsewhere in Europe (other than France) compared to the risk of a UK resident.

Variable: R_{EU} **–** The cumulative risk of an individual European resident from 1980 till the present; assumes that the cumulative risk of a UK individual from 1980 through 1996 is 1 (same variable as used in (A-IV.C.1.c.iii)

Variable: $Pr_{vCJD\text{-}UK(age)}$ **-** Probability of infection for individual UK resident of a specific age group (same variable as used in (A-IV.C.1. c. iv.).

Variable: $Pr_{vCJD\text{-}EU(age)}$**-**Probability of infection for an individual European resident of a specific age group.

Assumption used in the model: Probability of infection is proportional to the risk of exposure:

$$\Pr_{vCJD\ -EU\ (age)} = \Pr_{vCJD\ -UK\ (age)} \times R_{EU} \quad \text{(IV.C.1.e-7)}$$

Variable: ***$DR_{vCJD\text{-}EUBL(age)}$***-Annual number of infected European donors who contributed Euroblood that was transfused into US plasma donors during a one-year period by age group.

Number of infected Euroblood donors among each age group was estimated using a binomial distribution function with the estimated total number of donors in the subgroup ($DR_{EUBL(age)}$ estimated in section A-IV.C. 1.e. ii) and the probability of infection for the individual of this age group of Euroblood donors ($Pr_{vCJD\text{-}DR\text{-}EUBL(age)}$ estimated in this section A-IV. C. 1. e. ii) as parameters of the distribution.

$$DR_{vCJD-EUBL(age)} = Bionomial(DR_{EULL(age)}, \Pr_{vCJD-EU(age)}) \quad \text{(IV.C.1.e-8)}$$

Variable: ***$EUBL_{vCJD}$*** **-** Total units of infected Euroblood received by US plasma donors of one year period

Potential infected European donor may give multiple donations in a single year, however the chance of more than one donation being from a single infected European donor being shipped to the US, and used by US plasma donors is expected to be small.

Assumption about variable**:** One infected European donor produces one unit of infected Euroblood.

$$EUBL_{vCJD} = \sum_{age=18-19}^{>65} DR_{vCJD-EUBL(age)} \quad \text{(IV.C.1.e-9)}$$

A-IV. C. 1. e. iii. Annual number of plasma donors potentially infected with vCJD via transfusion with Euroblood

A-IV. C. 1. e. iii. a. Annual potential number of vCJD infected plasma donors

Variable: ***$Pr_{vCJD\text{-}EUBL}$*** **-** Probability a single unit of Euroblood contains vCJD agent

$$\Pr_{vCJD-EUBL} = EUBL_{VCJD} / EUBL_{Tot} \quad \text{(IV.C.1.e-10)}$$

Variable: ***$Pr_{vCJD\text{-}EUBL\text{-}Recip}$*** **-** Probability a Euroblood recipient is infected with vCJD

Assumption used in the model: We assumed that a Euroblood recipient is likely infected if he/she receives one unit or more of blood blood from a vCJD-infected donor.

$$\Pr_{vCJD-EUBL-recip} = 1 - Binomdist(0, EUBL_{avg}, \Pr_{vCJD-EUBL}, false) \quad \text{(IV.C.1.e-11)}$$

The Excel function Binomdist (n, N, p, false) calculates the probability of n "success" outcomes in a test, if the outcome of each trial of the test is either "success" or "failure", the probability of getting the outcome of "success" in an individual trial throughout the test is a constant *p*, and the number of trials in the test is *N*. In the problem we addressed here the outcomes are the probability of a donation being from a Euroblood recipient that receives a donation that is either infected or not infected. In equation IV.C.1.e-11, *Binomdist(0, $EUBL_{avg,}$ $Pr_{vCJD\text{-}EUBL,}$ false)* calculated the probability of a recipient receiving no infected unit (n=0), under the condition that average number of units received by a recipient is $EUBL_{avg}$ (N=$EUBL_{avg}$) and probability a single unit of Euroblood being infected is $Pr_{vCJD\text{-}EUBL}$ (p=$Pr_{vCJD\text{-}EUBL}$).

The number of Source and recovered plasma donors infected through transfusion with Euroblood was estimated using a binomial distribution function with the estimated total number of source and recovered plasma donors who have received Euroblood ($DR_{S\text{-}EUBL}$ and $DR_{R\text{-}EUBL}$ estimated in section A-IV.C. 1.e. ii.) and the probability of infection for the individual Euroblood recipient ($Pr_{\ vCJD\text{-}EUBL\text{-}receip}$ estimated in section A-IV. C. 1. e. iii) as parameters of the distribution. The total estimated number of potential plasma donors infected due to transfusion using Euroblood is the sum of potential infected source and recovered plasma donors.

Variable: $DR_{vCJD\text{-}S\text{-}EUBL}$ - Annual Number of <u>Source Plasma</u> donors being infected due to transfusion with a Euroblood unit:

$$DR_{vCJD-S-EUBL} = Binomial(DR_{S-EUBL}, \Pr_{vCJD-EUBL-recip}) \quad \text{(IV.C.1.e-12)}$$

Variable: $DR_{vCJD\text{-}R\text{-}EUBL}$ - Annual number of recovered plasma donors possibly infected via transfusion with a unit of Euroblood

$$DR_{vCJD-R-EUBL} = Binomial(DR_{R-EUBL}, \Pr_{vCJD-EUBL-recip}) \quad \text{(IV.C.1.e-13)}$$

Variable: $DR_{vCJD\text{-}EUBL}$ - Annual number of <u>all</u> plasma donors possibly infected through transfusion with a unit of Euroblood

$$DR_{vCJD-EUBL} = DR_{vCJD-S-EUBL} + DR_{vCJD-R-EUBL} \quad \text{(IV.C.1.e-14)}$$

Variable: $DR_{vCJD\text{-}EUBL\text{-}Def}$- Annual number of plasma donors possibly infected through transfusion with a unit of Euroblood and meet deferral criteria and presumably deferred from donation.

Variable: $DR_{vCJD\text{-}EUBL\text{-}Res}$- Annual number of plasma donors potentially infected via transfusion with a unit of Euroblood and does not meet deferral criteria and likely not deferred from donation.

Under current blood donation policies recipients of Euroblood are not deferred and represented by the expressions:

$$DR_{vCJD-EUBL-Def} = 0 \quad \text{(IV.C.1.e-15)}$$

$$DR_{vCJD-EUBL-\mathrm{Res}} = DR_{vCJD-EUBL} \quad \text{(IV.C.1.e-16)}$$

A-IV. C. 1. e. iii. b. Annual number of plasma donors that received Euroblood and are potentially infected and vCJD agent is present in the blood

Assumption used in the model: All infected Euroblood recipients have vCJD agent present in their blood (prionemic)

Variable: $DR_{vCJD\text{-}EUBL\text{-}Pn}$ **-** Annual number of plasma donors infected via transfusion using Euroblood and are prionemic in 2002

$$DR_{vCJD-EUBL-Pn} = DR_{vCJD-EUBL} \quad \text{(IV.C.1.e-17)}$$

Variable: $DR_{vCJD\text{-}EUBL\text{-}Def\text{-}Pn}$**-** Annual number of plasma donors infected via transfusion using Euroblood, and may have vCJD agent present in their blood and plasma (prionemic) in 2002 and meet deferral criteria

$$DR_{vCJD-EUBL-Def-Pn} = DR_{vCJD-EUBL-Def} \quad \text{(IV.C.1.e-18)}$$

Variable: $DR_{vCJD\text{-}EUBL\text{-}Res\text{-}Pn}$**-** Annual number of plasma donors who are possibly infected with vCJD via transfusion with Euroblood, that had vCJD agent present in their blood and plasma (prionemic) in 2002 and did not meet deferral criteria (likely not deferred)

$$DR_{vCJD-EUBL-\mathrm{Res}-Pn} = DR_{vCJD-EUBL-\mathrm{Res}} \quad \text{(IV.C.1.e-19)}$$

A-IV. C. 1. f. Total number all plasma donors who may potentially be infected with vCJD through all sources of exposure and vCJD agent is present in the blood

Variable: $\mathbf{DR_{vCJD\text{-}S\text{-}Pn}}$ **-** Estimated total annual number of Source Plasma donors infected with vCJD who potentially had the agent present in blood and plasma (prionemic) in 2002:

$$DR_{vCJD-S-Pn} = DR_{vCJD-S-UK-LH} + DR_{vCJD-S-FR-HL} + DR_{vCJD-S-DOD-LH} + DR_{vCJD-S-EUBL-Pn} \quad \text{(IV.C.1.f-1)}$$

Variable: $\mathbf{DR_{vCJD\text{-}R\text{-}Pn}}$ **-** Estimated total annual number of recovered plasma donors potentially infected with vCJD with the agent present in blood and plasma (prionemic) in 2002

$$DR_{vCJD-R-Pn} = DR_{vCJD-R-UK-LH} + DR_{vCJD-R-FR-HL} + DR_{vCJD-R-EU-LH} + DR_{vCJD-R-DOD-LH} + DR_{vCJD-R-EUBL-Pn}$$

(IV.C.1.f-2)

Variable: $\mathbf{DR_{vCJD\text{-}Pn}}$ **-** Total annual number of <u>all</u> US plasma donors potentially infected with vCJD with the agent present in blood and plasma (prionemic) in 2002

$$DR_{vCJD-Pn} = DR_{vCJD-S-Pn} + DR_{vCJD-R-Pn} \quad \text{(IV.C.1.f-3)}$$

A-IV. C. 2. Annual number of all US plasma donors potentially infected with vCJD agent present in the blood and who may not be deferred by questionnaire screening

A-IV. C. 2. a Annual number of US Source Plasma donors potentially infected and vCJD agent is present in the blood that may not be deferred by questionnaire screening

Variable: Eff_{Def} - Effectiveness of US donor deferral policy

Assumption about variable: Based on advice from the TSEAC at the October 31, 2005 meeting, the FDA model assumed 85-99% of potential vCJD infected donors would have been deferred just prior to donation.

Variable: $DR_{vCJD\text{-}S\text{-}Def\text{-}Pn}$ - Estimated annual number of Source Plasma donors potentially infected with and having vCJD agent present in blood and plasma (prionemic) that are deferred by current policy

$$DR_{vCJD\text{-}S\text{–}Def\text{–}Pn} = DR_{vCJD\text{-}S\text{–}UK\text{–}Def\text{–}Pn} + DR_{vCJD\text{-}S\text{–}FR\text{–}Def\text{–}Pn} + DR_{vCJD\text{-}S\text{–}DOD\text{-}Pn} \quad \text{(IV.C.2-1)}$$

Assumption about variable: This population includes the potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) that have long-term travel history to the UK ($\geq$3 mo), and France ($\geq$ 5 yrs); and a history of military deployment (or military dependent, etc.) in Europe from 1980 – 1996.

Variable: $DR_{vCJD\text{-}S\text{-}Res}$ - Estimated annual number of Source Plasma donors potentially infected with vCJD with agent present in blood and plasma (prionemic) that have short term travel history (UK (<3 mo), and France and/or Europe (< 5 yrs); and not deferred by deferral policy.

$$DR_{vCJD\text{-}S\text{–}\mathrm{Res}\text{–}Pn} = DR_{vCJD\text{-}S\text{–}UK\text{–}\mathrm{Res}\text{–}Pn} + DR_{vCJD\text{-}S\text{–}FR\text{–}Def\text{–}Pn} + DR_{vCJD\text{-}S\text{–}DOD\text{-}Pn} \quad \text{(IV.C.2-2)}$$

Assumption about variable: This population includes the potential Source Plasma donors with vCJD with agent present in blood and plasma (prionemic) that have short-term travel history to the UK (< 3 mo), France (< 5 yrs), and a history of receiving Euroblood.

Variable: $DR_{vCJD\text{-}S\text{-}Pn\text{-}NR}$ - Annual total number of potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) and were not removed by deferral screening

Assumption used in model: This includes potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) who meet deferral criteria but for a variety of reasons are not deferred.

$$DR_{vCJD-S-Pn-NR} = DR_{vCJD-S-\mathrm{Res}-Pn} + DR_{vCJD-S-Def-Pn} \times (1 - Eff_{Def}) \quad \text{(IV.C.2-3)}$$

A-IV. C. 2. b Annual number of US recovered plasma donors potentially infected and vCJD agent is present in the plasma that may not be deferred by questionnaire screening

Variable: Eff_{Def} - Effectiveness of donor deferral policy

Assumption about variable: Based on advice from the TSEAC at the October 31, 2005 meeting, the FDA model assumed 85-99% of potential vCJD infected donors would have been deferred just prior to donation.

Variable: $DR_{vCJD\text{-}R\text{-}Def\text{-}Pn}$ - Estimated annual number of potential recovered plasma donors with vCJD agent present in blood and plasma (prionemic) who are deferred by current policy

$$DR_{vCJD\text{-}R\text{–}Def\text{–}Pn} = DR_{vCJD\text{-}R\text{–}UK\text{–}Def\text{–}Pn} + DR_{vCJD\text{-}R\text{–}FR\text{–}Def\text{–}Pn} + DR_{vCJD\text{-}R\text{–}EU\text{–}Def\text{–}Pn} + DR_{vCJD\text{-}R\text{–}DOD\text{-}Pn} \quad \text{(IV.C.2-4)}$$

Assumption about variable: Model includes potential recovered plasma donors with vCJD agent present in blood and plasma (prionemic) that have long term travel history to the UK (≥3 mo), France (≥ 5 yrs), and Europe (≥5 yrs); and history of military deployment, military dependent or related travel or residence in Europe.

There is a possibility that some individuals that traveled to the UK, France, and other countries in Europe since 1980 stayed for periods of time that were shorter than the deferral period, were exposed to BSE agent, and were infected with vCJD. These individuals represent a source of residual risk – or the remaining risk after interventions (in this case donor deferral policies) are applied. The section below addresses the calculation of residual risk for non-deferred at risk donors that traveled for periods of time that were shorter than recommended guidelines.

Variable: $DR_{vCJD\text{-}R\text{-}Res}$ - Annual number of potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) that have short term travel history and are not covered by and deferred by deferral policy.

$$DR_{vCJD\text{-}S\text{–}\mathrm{Res}\text{–}Pn} = DR_{vCJD\text{-}S\text{–}UK\text{–}\mathrm{Res}\text{–}Pn} + DR_{vCJD\text{-}S\text{–}FR\text{–}Def\text{–}Pn} + DR_{vCJD\text{-}S\text{–}DOD\text{-}Pn} \quad \text{(IV.C.2-2)}$$

Assumption about variable: Estimation of the possible vCJD residual risk includes potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) that have short-term travel history to the UK (< 3 mo), France (< 5 yrs), history of travel to Europe and history of receiving Euroblood.

Variable: $DR_{vCJD\text{-}S\text{-}Pn\text{-}NR}$ - Annual total of potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) and were not removed by deferral screening

Assumption used in model: This includes all potential donors with vCJD agent present in blood and plasma (prionemic) that do not meet deferral criteria and who meet deferral criteria but wrongly not deferred.

$$DR_{vCJD-S-Pn-NR} = DR_{vCJD-S-Res-Pn} + DR_{vCJD-S-Def-Pn} \times (1 - Eff_{Def}) \quad \text{(IV.C.2-3)}$$

Variable: $DR_{vCJD\text{-}R\text{-}Pn\text{-}NR}$ - Annual total of potential recovered plasma donors with vCJD agent present in blood and plasma (prionemic) not removed by deferral screening

$$DR_{vCJD-R-Pn-NR} = DR_{vCJD-R-Res-Pn} + DR_{vCJD-R-Def-Pn} \times (1 - Eff_{Def}) \quad \text{(IV.C.2-4)}$$

A-IV. C. 2. c Total number of all US plasma donors potentially infected and vCJD agent is present in the plasma but may not be deferred by questionnaire screening

The total number of <u>all</u> US plasma donors potentially infected with vCJD with agent present in blood and plasma (prionemic) that may not be deferred by questionnaire screening was determined by summing the estimates generated for both Source and recovered plasma donors that may <u>not be deferred</u> by current screening procedures, and is described by the equation:

$$DR_{vCJD-Pn-NR} = DR_{vCJD-S-Pn-NR} + DR_{vCJD-R-Pn-NR} \quad \text{(IV.C.2-5)}$$

A-IV. C. 3. Total number of all US plasma donations potentially containing vCJD agent

Variable: $Freq_{DN\text{-}S}$ –Average frequency of donations from a single <u>Source Plasma</u> donor who contributes Source Plasma for FVIII manufacture (times/year)

Variable: $DN_{vCJD\text{-}S}$ - Annual number of potential vCJD donations of <u>Source Plasma</u>

$$DN_{vCJD-S} = DR_{vCJD-S-Pn-NR} \times Freq_{DN-S} \quad \text{(IV.C.2-6)}$$

<u>Assumption used in the model</u>: The average frequency of donations from a single Source Plasma donor who contributes Source Plasma for a FVIII plasma pool used in manufacturing ranges from ----- and most likely to be --- based on data from pdFVIII manufacturers. [FOI REVIEW]

Variable: $Freq_{DN\text{-}R}$ –The average frequency of donations from a single recovered plasma donor who contribute plasma for pdFVIII manufacture (times/year) is 1.

Variable: $DN_{vCJD\text{-}R}$ - Annual number of potential vCJD donations of recovered plasma

$$DN_{vCJD-R} = DR_{vCJD-R-Pn-NR} \times Freq_{DN-R} \quad \text{(IV.C.2-7)}$$

Assumption used in the model: The average frequency of donations from a single blood donor that contributes recovered plasma for pdFVIII manufacture is 1.

A-IV. C. 4. Probability that a US plasma donation potentially contained vCJD agent among all donations

Variable: $Pr(DN_{vCJD\text{-}S})$ - Probability a donation of Source Plasma contained vCJD agent

Variable: DN_s -Annual units of Source Plasma used to make pdFVIII (calculated in A-IV. B. 1)

$$\Pr(DN_{vCJD-S}) = DN_{vCJD-S} / DN_S \qquad \text{(IV.C.4-1)}$$

Variable: $Pr(DN_{vCJD\text{-}R})$ - Probability a donation of recovered plasma contained vCJD agent.

Variable: DN_R-Annual number of units of recovered plasma used to make pdFVIII from plasma collected in the US (calculated in A-IV. B. 2).

$$\Pr(DN_{vCJD-R}) = DN_{vCJD-R} / DN_R \qquad \text{(IV.C.4-2)}$$

A-IV. C. 5. Probability of a Source or recovered plasma pool potentially containing a vCJD donation(s)

A-IV. C. 5. a. Probability that a plasma pool may contain a specific number of vCJD donations

Assumption used in the model**:** Consistent with manufacturing practices in which commingling of Source and recovered plasma is uncommon, the risk assessment considered plasma pools to consist entirely of only Source Plasma donations or only recovered plasma donations.

Variable: $n_{vCJD\text{-}DN\text{-}pool}$ - Designated number of vCJD donors in a single plasma pool.

Assumption used in the model: The number of vCJD donations in a single vCJD pool could be 0, 1, 2, 3 or 4, but because of the low prevalence of vCJD most of the time there would be 0 vCJD donations in a pool

Variable: $DR_{pool\text{-}S}$ -Size of Source Plasma pool (donors/pool)

Data used in the model: Based on information provided to the FDA by pdFVIII manufacturers, an individual Source Plasma pool may contain 6,000 to 60,000 donors [FOI REVIEW]. A statistical distribution representing the variation in the size (number of donations per pool) of plasma pools used in the manufacture of pdFVIII was generated by combining information on pool size with information on the percentage of market share for several individual pdFVIII products.

Variable: $Pr_{(n_{vCJD\text{-}DR\text{-}pool\text{-}S)}}$- Probability a Source Plasma pool containing $n_{vCJD\text{-}DN\text{-}pool}$ infected donations ($n_{vCJD\text{-}DR\text{-}pool}$ =0, 1, 2, 4)-are determined by density frequency of $DR_{pool\text{-}S}$ at $X=n_{vCJD\text{-}DR\text{-}pool}$

Variable: $DN_{pool\text{-}R}$ -Size of recovered plasma pool (donors/pool)

Data used in the model: Based on information from manufacturers, individual Source Plasma pool may contain 6,000 to 60,000 donors. [FOI REVIEW].

Variable: $Pr_{(}n_{vCJD\text{-}DR\text{-}pool\text{-}S)}$- Probability a Source Plasma pool containing $n_{vCJD\text{-}DN\text{-}pool}$ infected donations ($n_{vCJD\text{-}DR\text{-}pool}$ =0, 1, 2, 4)-are determined by density frequency of $DR_{pool\text{-}S}$ at $X=n_{vCJD\text{-}DR\text{-}pool}$

Variable: $DN_{pool\text{-}R}$ -Size of recovered plasma pool (donors/pool)

Data used in the model: Based on information provided to the FDA by pdFVIII manufacturers, an individual recovered plasma pool may contain 150,000 to 360,000 donors [FOI REVIEW]. As with Source Plasma pools described above, a statistical distribution representing the variation in the size (number of donations per pool) of plasma pools used in the manufacture of pdFVIII was generated.

Assumptions used in the model: The size of recovered plasma pools was represented in the model by using a uniform distribution ranging from 150,000 to 360,000 donations per pool (Figure 4-3) [FOI REVIEW]. – representing the range of pool sizes used by manufacturers of pdFVIII. The uniform distribution provided the best fit for the range of possible recovered plasma pool sizes that may be used in the US to manufacture pdFVIII.

Variable: $Pr_{(}n_{vCJD\text{-}DN\text{-}pool\text{-}R)}$-Probability a recovered plasma pool containing $n_{vCJD\text{-}DN\text{-}pool}$ infected donations ($n_{vCJD\text{-}DN\text{-}pool}$ =0, 1, 2, 4)-are determined by density frequency of $DR_{pool\text{-}R}$ at $X=n_{vCJD\text{-}DR\text{-}pool}$

A-IV. C. 5. b. Probability a plasma pool may potentially contain a vCJD donation(s)

Variable: $Pr(vCJD\text{-}pool_S)$-Probability of a Source Plasma pool containing one or more vCJD donations

$$\Pr(vCJD\_pool_S) = 1 - \Pr(n_{vCJD-DN-poolS} = 0) \quad \text{(IV.C.5-1)}$$

Variable: $Pr(vCJD\text{-}pool_R)$-Probability of a recovered plasma pool containing one or more vCJD donations

$$\Pr(vCJD\_pool_R) = 1 - \Pr(n_{vCJD-DN-pool\ R} = 0) \quad \text{(IV.C.5-2)}$$

Variable: $Pr(vCJD\text{-}pool)$-The Probability that a plasma pool (including Source and recovered plasma pools) contained one or more vCJD donations- The distribution for pool size (or number of donations per pool) incorporated information on pool size.

Variable: $Perc_s$ – Percentage of Source Plasma pools used to manufacture pdFVIII in the US

Variable: $Perc_R$ – Percentage of recovered plasma pools used to manufacture pdFVIII in the US

Assumption used in the model: Estimates suggest that approximately --- of pdFVIII products were made from Source Plasma, and --- were made from recovered plasma.

The probability of either a vCJD donation being present in a Source Plasma pool is represented by the variable ***Pr(vCJD-pool$_S$*** and the probability of a vCJD donation being present in a recovered plasma pool is represented by the variable, ***Pr(vCJD-pool$_R$***, which was calculated in the section above. A discrete distribution (X1, X2; p1, p2) represents two discrete values for the probabilities that a pool may contain a vCJD donation, X1(or ***Pr(vCJD-pool$_S$***) and X2 (or ***Pr(vCJD-pool$_R$***) and the associated probabilities of each value occurring with the probabilities, p1 and p2, respectively. Based on the assumptions above that Source Plasma pools are used more frequently in the manufacture of pdFVIII and, on average contain fewer donations, the probability of a Source Plasma pool containing vCJD agent is different from the probability a recovered plasma pool containing vCJD agent. Overall probability of a single plasma pool (including source and recovered plasma pool) containing vCJD agent is a probability weight based on the percentages of the two types of plasma pools (--- for Source and --- for recovered plasma pools) used to make pdFVIII. *Pr(vCJD-pool)* is sampled from ***Pr(vCJD-pool$_S$*** and ***Pr(vCJD-pool$_R$*** using the discrete distribution:

$$\Pr(vCJD-pools) = Discrete(\ Pr(vCJD\text{-}pool\text{-}s),\ Pr(vCJD\text{-}pool\text{-}R);\ Perc_S,\ Perc_R)\ ) \qquad \text{(IV.C.5-3)}$$

or

$$\Pr(vCJD-pools) = Discrete(\ Pr(vCJD\text{-}pool\text{-}s),\ Pr(vCJD\text{-}pool\text{-}R);\ ---,\ ---)\ )$$

A-IV. D. Annual total number of all plasma pools and number of plasma pools potentially containing a vCJD donation that are used to make pdFVIII in the US

A-IV. D.1. Annual amount of pdFVIII distributed in the US

Variable: IU_{FVIII} -Annual number of all units of human pdFVIII manufactured and distributed in the US .

Data used in the model: Based on data provided to FDA from manufacturers, a total of --- million units of pdFVIII was made and distributed in the US. [FOI REVIEW].

Variable: $Perc_s$ – Represents the percentage of pdFVIII assumed in the model to be made from Source Plasma (same as variable used in A-IV. C. 5. b.)

Variable: $Perc_R$ – Represents the percentage of pdFVIII assumed in the model to be made from recovered plasma (same as variable used in A-IV. C. 5. b.)

Variable:$IU_{FVIII\text{-}S}$ –The total annual number of units of pdFVIII made from Source Plasma and is represented by the equation:

$$IU_{FVIII-S} = IU_{FVIII} \times Perc_s \qquad \text{(IV.D.1-1)}$$

Variable:$IU_{FVIII\text{-}R}$ -The total annual number of units of pdFVIII made from recovered plasma and is represented by the equation:

$$IU_{FVIII-R} = IU_{FVIII} \times Perc_R \qquad \text{(IV.D.1-2)}$$

A-IV. D. 2. Annual total number of all plasma pools used to make pdFVIII and plasma pools with vCJD agent

The total number of plasma pools used to make pdFVIII in the US each year can be back-calculated from the total number of units of human plasma-derived pdFVIII distributed in the US each year. Based on information described in earlier sections, it was assumed that approximately --- of the total pdFVIII supply distributed annually in the US is manufactured from Source Plasma and --- from recovered plasma pools. Information on pool size (number of donors), average number of donations per donor, size of individual recovered plasma donations (200 mls) and Source Plasma donations (700 mls) were used to first determine the amount of plasma present in a pool. Then, data on the average yield of pdFVIII per liter of plasma (187 IU), was used to calculate the total number of Source and recovered plasma pools and the results were summed to determine the total number of plasma pools used to manufacture pdFVIII in the US each year. The total number (or percentage) of plasma pools potentially containing vCJD agent was determined in the model based on pool size and the probability that a pool contained a vCJD agent.

A-IV. D. 2. a. Amount plasma per pool

Variable: $DN_{V\text{-}s}$ – Volume of single unit Source Plasma (ml).

Variable: $DR_{pool\text{-}s}$ – Number donors per Source Plasma pool (same variable as used in A-IV.C. 5).

Variable: $Freq_{DN\text{-}S}$ –Average frequency of donations from a single Source Plasma donor that contribute Source Plasma for pdFVIII manufacture (same variable as used in A-IV.C. 3).

Variable: $V_{pool\text{-}S}$ – Volume of a Source Plasma pool (ml).

$$V_{pool-S} = DR_{pool-S} \times Freq_{DN-S} \times DN_{V-S} \quad \text{(IV. D. 2-1)}$$

Variable: $DN_{v\text{-}R}$ – Volume of single unit recovered plasma (ml).

Variable: $DR_{pool\text{-}R}$ – Number donors per recovered plasma pool (same variable as used in A-IV.C. 5. a.)

Variable: $Freq_{DN\text{-}S}$ –Average frequency of donations from a single recovered plasma donor that contribute recovered plasma for pdFVIII manufacture (same variable as used in A-IV.C. 3)

Variable: $V_{pool\text{-}S}$ – Volume of a recovered plasma pool (ml)

$$V_{pool-R} = DR_{pool-R} \times Freq_{DN-R} \times DN_{V-R} \text{ (IV. D. 2-2)}$$

A-IV. D. 2. b. Annual number of plasma pools used to manufacture pdFVIII in the United States

Variable: $IU_{FVIII\text{-}S}$ -Annual units of pdFVIII made from Source Plasma (calculated in A-IV. D. 1)

Variable: Y_{avg} –Average yield of pdFVIII (IU/L plasma)

Assumption used in the model: Based on the data provided by WFH (1998) and FDA-CBER (2003) we assumed average yield of pdFVIII (including high purity and intermediated purity pdFVIII) being 187 IU per liter plasma.

The total number of Source Plasma pools and recovered plasma pools used each year in manufacturing US pdFVIII are calculated separately in the model. Estimates from each type of pool are then summed to get a total value for all pools.

Variable: $Pool_S$–Annual number Source Plasma pool used to make pdFVIII

$$Pool_s = Round((IU_s / Y_{avg}) / (V_{pool-s} / 1000)) \qquad \text{(IV. D. 2-3)}$$

Variable: $IU_{FVIII\text{-}R}$ -Annual units of pdFVIII made from recovered plasma (calculated in A-IV. D. 1.).

Variable: $Pool_R$–Annual number of recovered plasma pools used to make pdFVIII

$$Pool_R = Round((IU_R / Y_{avg}) / (V_{pool-R} / 1000)) \qquad \text{(IV. D. 2-4)}$$

Finally, the number of possible Source and recovered plasma pools are summed to generate the total number of plasma pools used in the manufacture of pdFVIII in the US.

Variable: Pool–Annual total number of plasma pool used to make pdFVIII

$$Pool = Pool_S + Pool_R \qquad \text{(IV. D. 2-5)}$$

A-IV. D. 2. c. Annual number vCJD plasma pools used to manufacture pdFVIII in the United States

Annual number of vCJD pools is expected to be low because the US vCJD prevalence, even among donors that traveled to the UK, France or other countries in Europe since 1980, is likely very low and presumably varies from year to year. A binomial distribution (n, p) is used to reflect the variation in the number of vCJD pools present in a single year. A binomial distribution is usually used when the number of positive observations (p) or in this case the number of vCJD containing pools is very low compared to the total number of pools (n).

Variable: *$Pr(vCJD\text{-}pool_s)$*- Probability of a Source Plasma pool containing vCJD agent

Variable: $Pool_{vCJD\text{-}S}$ – Annual number Source Plasma pools that contain vCJD agent used to make pdFVIII

$$Pool_{vCJD-S} = Binomial(Pool_{S,} \Pr(vCJD - pool_S) \quad \text{(IV. D. 2-6)}$$

Variable: *Pr(vCJD-pool$_R$)*- Probability of a recovered plasma pool containing vCJD agent

Variable: Pool$_{vCJD-R}$ – Annual number of recovered plasma pools that contain vCJD agent used to make pdFVIII

$$Pool_{vCJD-R} = Binomial(Pool_{R,} \Pr(vCJD - pool_R) \quad \text{(IV. D. 2-7)}$$

Variable: Pool$_{vCJD}$ – Annual total plasma pools that contains vCJD agent used to make pdFVIII

$$Pool_{vCJD} = Pool_{vCJD-S} + Pool_{vCJD-R} \quad \text{(IV. D. 2-8)}$$

A-IV. D. 3. Percentage of pools potentially containing vCJD agent

Variable: Perc $_{vCJD-S-pool}$ -Percentage Source Plasma pools used to make pdFVIII that contains vCJD donations

$$Perc_{vCJD-S-pool} = (Pool_{vCJD-S} / Pool_S) \times 100\% \quad \text{(IV. D. 3-1)}$$

Variable: Perc $_{vCJD-R-pool}$ -Percentage recovered plasma pools used to make pdFVIII that contains vCJD donations

$$Perc_{vCJD-R-pool} = (Pool_{vCJD-R} / Pool_R) \times 100\% \quad \text{(IV. D. 3-2)}$$

Variable: Perc $_{vCJD-pool}$ –Overall percentage plasma pools used to make pdFVIII that contains vCJD donations

A-IV. E. Module 2: Estimation of Quantity of vCJD agent in a plasma pool that contains a donation from a donor potentially infected with vCJD

A-IV.E.1. Quantity of vCJD agent present in a donation of a specific donor potentially infected with vCJD

Variable: I_{bl} – Represents the i.c. ID_{50} present in the blood of individual infected donor (ID_{50}/ml) in the last half of the incubation period of vCJD.

Assumption used in the model: Whole blood collected from a vCJD-infected individual can vary from person to person in the quantity of infectivity it contains. The model used a log normal statistical distribution to represent the variability and uncertainty of the quantity of infectivity in blood. It was assumed that whole blood from an infected person potentially carries a minimum of 0.1 i.c. ID_{50} per ml, a 5^{th} percentile of 2 i.c. ID_{50} per ml, a median of 12 i.c. ID_{50} per ml, a 95^{th} percentile of 30 i.c. ID_{50} per ml and a maximum of 1,000 i.c. ID_{50} per ml. Attempts to identify vCJD infectivity titers in human blood have not been successful, but the assay sensitivity for vCJD *in vitro* and in animal models is limited (Bruce *et al* 2001 and Wadsworth *et al* 2001). Wadsworth *et al* estimated a limit of sensitivity of about 1,000 ID_{50}/ml by their assay meaning that infected blood containing less than 1,000 ID_{50} would not have elicited infection or disease in their animal model, hence infectivity would not have been detected (Wadsworth, 2001).
Variable: $\boldsymbol{I_{pl\text{-}perc}}$ **–** Percent (%) i.v. ID_{50}s associated with plasma

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.

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.

Variable: $\boldsymbol{DN_V}$-Volume of one unit of plasma, depending on plasma type (same as $DN_{V\text{-}S}$ used in A-IV. D. 2 for Source Plasma, same as $DN_{V\text{-}R}$ used in A-IV. D. 2. for recovered plasma)

Variable: $\boldsymbol{I_{DN}}$-Quantity of vCJD agent in one donation of infected plasma (i.v. ID_{50}/ml)

$$I_{DN} = I_{bl} \times DN_V \times I_{Pl-perc} \times A_{iv-ic} \qquad \text{(IV.E.1-1)}$$

A-IV.E. 2. Quantity of vCJD agent in a plasma pool containing a donation from donor potentially infected with vCJD

Variable: $\boldsymbol{DN_{DR}}$ **-** Number of donations from an infected plasma donor, which varies based on type of plasma donated.

Assumption used in the model: We assumed individual infected Source Plasma donor most likely give - donations to a pool, with minimum of 1, maximum of 12 donations. Individual infected recovered plasma donors most likely give only one donation to a pool.

Variable: I_{Pool}- Initial infectivity in an infected plasma pool is represented by the equation:

$$I_{Pool} = I_{DN} \times DN_{DR} \qquad \text{(IV.E.2-1)}$$

A-IV. F. Estimation of the potential quantity of vCJD agent in pdFVIII products manufactured from pool(s) potentially containing a vCJD donation

The FDA model employed three stratifications of clearance:

- $2 – 3$ $\log_{10}$
- $4 – 6$ $\log_{10}$
- $7 – 9$ $\log_{10}$

Each of these levels of clearance was modeled separately. Most of the results are presented for the 4-6 $\log_{10}$ reduction during manufacture processing in the risk characterization section (Section V.) of this risk assessment.

Assumptions used in the model: The model assumed there are potentially three levels of reduction that may be achieved: a lower level of reduction (a range of 2 - 3 $\log_{10}$)-represented by uniform distribution (2, 3), medium level of reduction (a range of 4-6 logs, most likely, 5 $\log_{10}$)-represented by triangular distribution (4, 5, 6) and higher level of reduction (a range of 7-9 $\log_{10}$, most likely, $\log_{10}$)-represented by triangular distribution (7, 8, 9).

Variable: I_{Pool}- Initial infectivity in a specific infected plasma pool (calculated in A-IV. E.2)

Variable: R_{Log}- Potential log reduction in infectivity during processing

Variable: $I_{Pool-Ap}$- Remaining infectivity in a specific infected plasma pool after processing

$$I_{Pool-Ap} = I_{Pool} / 10^{R_{Log}} \qquad \text{(IV.F-1)}$$

Variable: DR_{Pool}- Size of plasma pool (number of donors/pool).

Assumption used in the model: The size of the plasma pools used in manufacturing was assumed to vary from pool to pool. In this risk assessment model, two different general distributions were used to represent frequency distribution of sizes of Source and recovered plasma pool based on the data provided by pdFVIII manufacturers.

Data used in the model: Information for Source Plasma pool size was collected by the FDA from pdFVIII manufacturers. The size of Source Plasma pools ranged from 6,000 donors per pool to 60,000

donors per pool with mean of ------ donations per pool. [FOI REVIEW] The distribution was generated based on the pool size data provided by pdFVIII manufacturers and the market share of the products based on information supplied annually to the FDA by manufacturers. Manufacturers supplied FDA with information on the average number of donations from individuals in the pool.

Data used in the model: Information for recovered plasma pool sizes was collected by the FDA from pdFVIII manufacturers. The size of recovered plasma pool ranged from 150,000 to 360,000 donations per pool. [FOI REVIEW] The distribution was generated based on the pool size data provided by pdFVIII manufacturers and the market share of the products. Manufacturers supplied FDA with information on the average number of donations from individuals in the pool.

Variable: $DN_{DR\text{-}Avg}$-Average number of donations from individual donors in the pool

Assumption used in the model: Data on the average number of donations per donor per pool were provided by manufacturers. We assumed the average number donations from individual donors varied from pool to pool. For Source Plasma, it was assumed to range from -------- donations per donor, with a most likely of ----- donations per donor. [FOI REVIEW] For recovered plasma, it was assumed that the most likely number of donations per donor was only 1.

Variable: DN_V-Volume of one unit of plasma, depending on plasma type (for Source Plasma, same as $DN_{V\text{-}S}$ used in A-IV. D. 2, recovered plasma, same as $DN_{V\text{-}R}$ used in A-IV. D. 2.)

Variable: Y_{FVIII}-Yield of pdFVIII (IU/L plasma)

Assumption used in the model: Based on the data provided by the World Federation of Hemophilia (2004) we assumed pdFVIII yield varies from pool to pool with minimum of 120, most likely of 187 and maximum of 250 IU per liter plasma.

Variable: I_{iu}- Quantity of infectivity in the pdFVIII product made from a specific infected pool (i.v. ID_{50} per IU)

$$I_{IU} = (I_{Pool-Ap} / (DR_{Pool} \times DN_{DR-Avg} \times DN_V)) \times 1000 / Y_{FVIII} \qquad \text{(IV. F-2)}$$

A-IV. G. FVIII utilization by HA and vWD patients and potential exposure to the vCJD agent through use of human pdFVIII

A-IV. G. 1. FVIII utilization and potential exposure to the vCJD agent through use of human plasma-derived FVIII by severe HA patients

This risk assessment provides outputs that estimate the annual exposure for several patient subpopulations with **Severe HA** disease for patients in the following clinical treatment groups:

- Prophylaxis – No inhibitor

- Prophylaxis - With inhibitor
- Prophylaxis - With inhibitor and immune tolerance
- Episodic – No inhibitor
- Episodic - With inhibitor

The study collected a total of 17,848 records, each record representing a single year of medical data for a single HA patient. The comprehensive study collected standardized information on patient demographics, clinical treatment and outcome data. Patient medical records were obtained from treatment sites including: hemophilia treatment centers (HTCs), hospitals, clinics, physician's offices, home-care agencies, nursing homes, prison infirmaries, and dispensers of factor concentrates. The data, abstracted from medical records, tabulated all recorded factor concentrate utilization prescribed by quantity, type, purpose (e.g., prophylaxis, treatment of acute bleeds, or immune tolerance therapy) and total quantity used per calendar year. Among all the records collected in the study from 1993-1998, 1,993 were from HA patients with severe disease that had been treated with human pdFVIII and the records were further grouped into five clinical treatment subcategories based on treatment regimen, including: prophylaxis, no inhibitor; prophylaxis,with inhibitor; prophylaxis, with inhibitor and immune tolerance; episodic, no inhibitor; and episodic, with inhibitor. Data from each of the five subpopulations were analyzed individually using the statistical package "JMP" (SAS Institute, Cary, NC) to generate initial descriptive statistics and distributions of pdFVIII usage by the HA patients. The data containing annual pdFVIII utilization information for patients in each of the five treatment groups were further analyzed using Best Fit software (Palisade Corp, New York) to generate a statistical distribution(s) for each patient treatment group that best reflected the variation in pdFVIII utilization. Overall, the Generalized Beta distribution provided the most reasonable and consistent fit for the pdFVIII utilization data among all of the patient treatment groups. The Generalized Beta distributions were then used in the model to approximate the distribution of utilization of pdFVIII in each of the five HA patient subpopulations. FDA used the original patient data to not only generate statistical distributions for each patient treatment subpopulation. FDA also used the original data to identify the minimum and maximum dosages used by patients in each specific treatment subcategory and truncated each distribution using these values. Graphical representations of the original data and the fitted Generalized Beta distributions are shown in Appendix C. We also provide a summary of the pdFVIII usage data from the CDC sponsored six state study, and also summarize the input Generalized Beta distributions generated with each subset of data in Table A-4.5.

Table A-4.5. Annual usage of pdFVIII by individual HA patients with severe disease-data and input distribution

		Original Data			Input distribution (Generalized Beta distribution)				
Treatment Regimen	**Inhibitor Status**	**n**	**Mean**	**95% CI**	**α**	**β**	**(min, max)**	**Mean**	**95% CI**
Prophylaxis	**No Inhibitor**	**578**	**164394 IU**	**(13574 , 518781)**	1.5159	10.02	(300, 1200000)	157949	(21242, 282316)

	With Inhibitor – No Immune Tolerance	**63**	198781	(7859, 937480	1.4640	6.2861	(2000, 800000)	**190523**	**(26956 , 447639)**
	With Inhibitor – With Immune Tolerance	**62**	569707	(14315, 3222471)	0.8782	5.5081	(100000, 2000000)	**558700**	**(33235, 1592943)**
Episodic	No Inhibitor	**946**	90489	(3001, 345416)	0.9882	10.60	(0, 1000000)	**85270**	**(4633, 244656)**
	With Inhibitor	**151**	169710	(4099, 835729)	0.6950	3.6822	(2200, 1000000)	**160458**	**(5314 , 488906)**

Variable: IU_{Yr} **-** Annual usage of pdFVIII by individual HA patient of a specific clinical group (IU/yr, person)

Variable: IU_{vial} **-** Vial size (IU/vial)

Assumption used in the model: We assumed there were equal numbers of vials for each of the four different package sizes (250, 500, 1000 and 1500 IU/vial) that are distributed in the US.

Variable: $Vial_{Tot}$ **-** Annual number of pdFVIII vials used by individual patient (vials/yr, person)

Assumption used in the model: We assumed individual patient uses pdFVIII products of the same package size throughout the whole year period of 2002 for which the model was run.

$$Vial_{Tot} = IU_{Yr} / IU_{Vial} \qquad \text{(IV.G. 1-1)}$$

Variable: ***Pool*** **-** Annual number of plasma pool used to make pdFVIII (calculated in A-IV.D.2.b.)

Variable: $Pool_{vCJD}$ **-** Annual number of vCJD plasma pool used to make pdFVIII (calculated in A-IV.D.2.c.)

Variable: $Perc_{vCJD\text{-}vail}$ **–** Percentage pdFVIII vials containing vCJD agent

Variable: $Vial_{vCJD}$ **-** Annual number of pdFVIII vials used by individual patient (vials/yr, person)

$$Vial_{vCJD} = Vial_{Tot} \times Perc_{vCJD-vial} \qquad \text{(IV.G. 1-2)}$$

Variable: I_{iu} **-** Quantity of infectivity in the pdFVIII product made from a specific infected pool (i.v. ID_{50} per IU) (calculated in IV. F)

Variable: I_{vr} **-** Annual exposure to vCJD through use of pdFVIII (i.v. ID_{50}/yr, person)

$$I_{yr} = \sum_{i=1}^{Vial_{vCJD}} I_{IU} \times IU_{Vial} \qquad \text{(IV.G. 1-3)}$$

A-IV. G. 2. pdFVIII utilization and annual exposure of severe von Willebrand disease patients

The CDC and six state Hemophilia Surveillance System project conducted from 1993-1998 did not include patients with vWD. We assumed that vWD patients with severe disease would largely use Humate P product only for factor replacement treatment. A search of records in the Hemophilia Surveillance System project data revealed a total of 58 records that indicated Humate P had been used, among which, 8 records indicates patients had developed inhibitor, which are considered uncommon among vWD patients and were excluded from analysis. Among the 58 records, 35 were from Adults (≥15 yrs of age) and 23 records were from young persons (<15 yrs of age). Records for each age group were further grouped by clinical treatment using either a prophylaxis or episodic treatment regimen. Data were initially analyzed individually using the statistical package "JMP" (SAS Institute, Cary, NC) to generate descriptive statistics and statistical distribution(s) for each patient treatment group that best reflected the variation in pdFVIII utilization. The Generalized Beta distribution was identified as the best fit to the pdFVIII utilization data (as determined by using the software Best Fit (Palisade Corp, NY) and was used as the input distribution for pdFVIII usage by individual vWD patients in the model. Graphical representations of the original data and the fitted Generalized Beta distributions are shown in Appendix C. Table A-4.6. summarizes pdFVIII usage data from CDC sponsored study and the input distribution generated based on the data. FDA used data in the CDC and six state Hemophilia Surveillance System project conducted from 1993-1998 to estimate FVIII utilization by all vWD patients. The data represent only a sample of all possible vWD patients with severe disease in the US. FDA estimated that there were approximately 250 patients in the US with Type 3 vWD. To calculate the total number of patients in each age group and treatment regimen group we adjusted the 58 patient population to equal a total of 250 patients by multiplying the patient population in each group by a factor of 4.3 (250/58 = ~4.3). The utilization data for patients in each treatment regimen in the sample population were used in the risk assessment model to generate outputs for the annual exposure to vCJD for all vWD for Adult (>15 yrs of age) and Young (≤15 yrs of age) persons in the US among clinical treatment groups of prophylaxis and episodic.

Table A-4.6. Annual usage of pdFVIII by individual severe vWD patient -data and input distribution We need to update the information in this table – based on new calculations for a total of 58 cases (previously it was 50 cases)

	Original Input Data				Input Distribution (Generalized Beta distribution)				
Treatment Regimen	**n**	**Percent of total population**	**Mean**	**95% CI**	**α**	**β**	**(min, max)**	**Mean**	**95% CI**
Young (≤15 yrs of age)									

Prophylaxis	9	16%	164193	**(9200, 504625)**	0.4523	0.9794	(9200, 504625)	165713	(9346, 479457)
Episodic	14	24%	11122	**(1010, 41850)**	0.3900	1.1973	(1010, 41850)	11045	(1013, 37543)
Adult (>15 yrs of age)									
Prophylaxis	17	29%	187538	(15000, 772800)	0.5741	1.9569	(15000, 7728000)	186880	(15570, 606699)
Episodic	18	31%	845556	(1000, 293800)	0.5855	1.4097	(1000, 293800)	86923	(1361, 260660)

Variable: *IUyr* - Annual usage of pdFVIII by individual vWD patient of a specific clinical group (iu/yr, person)

Variable: IU_{vial} - Vial size (IU/vial)

<u>Assumption used in the model</u>: We assumed that equal numbers of vials in each of three different package sizes (250, 500, 1000 IU/vial) are distributed on the market.

Variable: $Vial_{Tot}$ - Annual number of pdFVIII vials used by individual patient (vials/yr, person)

Assumption used in the model: We assumed individual patients used pdFVIII products of the same package size through out whole year period of 2002 for which the model was run.

$$Vial_{Tot} = IU_{Yr} / IU_{Vial} \qquad \text{(IV.G. 2-1)}$$

Variable: *Pool* - Annual number of plasma pool used to make pdFVIII (calculated in A-IV. D .2.b.).

Variable: $Pool_{vCJD}$ - Annual number of vCJD plasma pool used to make pdFVIII (calculated in A-IV.D.2.c.)

Variable: $Perc_{vCJD\text{-}vail}$ – Percentage pdFVIII vials containing vCJD agent

Variable: $Vial_{vCJD}$ - Annual number of pdFVIII vials used by individual patient (vials/yr, person)

$$Vial_{vCJD} = Vial_{Tot} \times Perc_{vCJD-vial} \qquad \text{(IV.G. 2-2)}$$

Variable: I_{iu}- Quantity of infectivity in the pdFVIII product made from a specific infected pool (iv. ID_{50} per IU) (calculated in IV.F.)

Variable: I_{vr}- Annual exposure of individual vWD patients to vCJD through use of pdFVIII (i.v. ID_{50}/yr, person)

$$I_{yr} = \sum_{i=1}^{Vial_{vCJD}} I_{IU} \times IU_{Vial} \qquad \text{(IV.G. 2-3)}$$