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 th 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:

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

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.

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:

$$R_{DR\text{-}UKy,I} = (R_{UKy}/12) \times D_i \qquad \text{(IV.C.1.a-16)}$$

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:

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

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:

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

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

Variable: $Prev_{Asym-vCJD(age)}$- 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.).

$$Pr_{vCJD-UK(age)} = Prev_{Asym-vCJD(age)}/100000 \quad \text{(IV.C.1.a-19)}$$

Variable: $Pr_{vCJD-DR-UK(age)y,i}$ – 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

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

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.

APPENDIX A

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.

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

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.

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

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.

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

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

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

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.

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

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.

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

APPENDIX A

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).

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

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).

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

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

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

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

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

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

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

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:

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

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.

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

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.

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

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

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

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

This section sums the total number of all 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 Source Plasma 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

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

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

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

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

Variable: $Perc_{BIDR\text{-}FRI/FR}$ - 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:

$$Perc_{BIDR-FRI\,/\,FR} = (Perc_{BIDR-FRI} / CumPerc_{BIDR-FR,t>1day-1month}) \times 100\% \qquad \text{(IV.C.1.b-1)}$$

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 : DR_{BI}-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: $Perc_{BIDR-FR}$ - 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: DR_{BI-FR} -Total number of blood donors who have traveled to France during 1980 and 1996

$$DR_{BI-FR} = DR_{BI} \times Perc_{BIDR-FR} \qquad \text{(IV.C.1.b-2)}$$

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

Variable: $Perc_{BIDR-FR(age)}$ - 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:

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

Variable: $Odd_{T(age)}$- 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

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

Replacing equation IV.C.1.b-4 for $Perc_{BIDR-FR(age)}$ 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:

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

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

Variable: $Perc_{BIDR-FR(age)}$ (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: $DR_{S-FR(age)}$ - 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:

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

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.

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

for travel during 1980-1996;

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

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: $Perc_{BIDR\text{-}FR/FR}$- 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:

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

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: $Perc_{BIDR\text{-}FR(age)}$ (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: