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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 (3.4%)	27 (18.4%)		32 (21.8%)	30 (20.4%)	22 (14.9%)	13 (8.8%)	5 (3.4%)	3 (2%)	5 (3.4%)	0 (0%)	5 (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:

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

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.

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

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:

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

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:

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

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: $DN_{BI\text{-}perc(age)}$ – 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

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

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:

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

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:

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

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:

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

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:

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

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

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

Variable: $Perc_{BIDR\text{-}UKi/UK}$ - 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:

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

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_{BI} 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: $Perc_{BIDR\text{-}UK}$ - 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: $DR_{BI\text{-}UK}$ -Total number of blood donors estimated to have traveled to the UK from 1980 through 1996

$$DR_{BI-UK} = DR_{BI} \times Perc_{BIDR-UK} \quad \text{(IV.C.1.a-2)}$$

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

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

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

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

Variable: $Perc_{BIDN(age)}$- 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: $Freq_{BIDN(age)}$-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).

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

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

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

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

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

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

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

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

$$DR_{BI-UK} = \sum_{age=18-19}^{65-69}(Perc_{BIDR-UK(age)} \times DR_{BI(age)}) \qquad \text{(IV.C.1.a-7)}$$

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

$$Perc_{BIDR-UK(age)} = Odd_{T(age)} \times Perc_{BIDR-UK(18-19)} \qquad \text{(IV.C.1.a-8)}$$

Replacing the variable, $Perc_{BIDR\text{-}UK(age)}$, 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:

$$Perc_{BIDR-UK(18-19)} = DR_{BI-UK} / \sum_{age=18-19}^{65-69}(Odd_{T(age)} \times DR_{BI(age)}) \qquad \text{(IV.C.1.a-9)}$$

A-IV. C. 1. a. ii. a. Number of US Source Plasma 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: $Perc_{BIDR\text{-}UK(age)}$ (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.