III. HAZARD CHARACTERIZATION

The hazard characterization component (also known as dose-response) relates the information in the exposure assessment, which determines the dose, to the adverse consequence(s) such as infection, illness, etc., at the individual, subpopulation, or population level. Determining dose-response relationships can be difficult to accomplish because data are limited, especially exposure and outcome data for humans. Other factors such as characteristics of the hazard (e.g. strain, chemical make-up, etc.), route of introduction, genetics of exposed individuals, influence the dose-response relationship but are often difficult to characterize. Often in lieu of human data, animal data are used and appropriately extrapolated as best as is possible to estimate the dose-response relationship for humans.

Another challenge is estimating the probability of infection when the exposure to TSEs is small and/or occurs repeatedly over a period of time. It is unknown whether for TSE diseases there is a minimal amount of the agent (presumably the prion protein PrP^{TSE}) or threshold that is needed to initiate infection in an individual. This phenomenon is seen with many other pathogens such as viruses or bacteria, for which infection requires exposure to at least one, and often more, units of the infectious agent. Furthermore, it is not known whether the effects of small multiple exposures over a period of time are cumulative and may result in the possibility of infection and disease equivalent to a single, larger exposure (e.g., via intracerebral injection in laboratory animals). Some risk assessments have made assumptions concerning the exposure and dose for TSE agent that leads to infection. For instance, the Det Norske Veritas (Feb 2003) blood products risk assessment assumes that exposure to infectivity, quantified in ID_{50} units, is cumulative over the period of one year. Based on advice from the TSEAC (2005), and consistent with suggestive data from studies of TSE agents in animal models (Diringer *et al* 1998, Jacquemot, *et al* 2005), FDA also assumes that exposure to vCJD ID_{50} is cumulative over a one year period. The ID_{50} is the common metric used to quantify the infectivity of TSEs. One ID_{50} is defined as the amount of infectious material or tissue that is necessary to initiate infection in 50% of the treated population. The route of exposure to TSE infectious material influences the efficiency of transmission of the disease. Based on advice provided to FDA by the TSEAC (October 31, 2005) the model assumes that transmission via the intravenous (i.v.) route is between 1 and 10 times less efficient than the transmission via the intracranial (i.c.) route.

In estimating the dose-response relationship for TSEs one could use a strict interpretation of the ID_{50} and assume a linear relationship between exposure and infection. In the pdFVIII model FDA assumed there was a linear relationship between the exposure dose of vCJD agent and the probability of infection. The ID_{50} relationship used in the model was based on infectious TSE units estimated from rodent model studies (Brown 1998, 1999; Rowher 2004). We further assumed there was no threshold or minimum dose necessary to initiate infection, that is, exposure to even low quantities of vCJD agent has a probability of initiating infection in an individual, albeit the probability of infection would likely be low at low levels of exposure. The model further assumes that in such a case exposure to 1 ID_{50} would suggest a 50% probability of infection, exposure to 0.1 ID_{50} would suggest a 5% probability of infection, and so on. However, given the lack of information and high degree of uncertainty on the dose-response relationship because of the limited data available for TSE agents, it is plausible that low level exposures, even on a chronic basis, may not attain a threshold or minimum quantity of agent necessary to initiate infection in humans. Again, FDA makes a conservative

assumption that low-level exposure(s) over the period of one year to any quantity of vCJD agent could potentially lead to infection and that there is not a minimum dose necessary to initiate infection.

There are considerable uncertainties in determining the correct form for the vCJD-human dose-response model. For instance, the nature of the dose-response line, its slope, or whether it is more accurately described using a dose-response curve is uncertain because animal data are so limited and human data are not available. The FDA risk assessment estimates the potential individual risk of infection and assumes that a linear interpretation of the rodent model accurately reflects the pathology and progression of vCJD infection and disease in humans, but it may not. Furthermore, exposure to the vCJD agent may not necessarily lead to infection, and vCJD infection may not necessarily produce symptomatic vCJD disease or illness in an individual or population.

IV. EXPOSURE ASSESSMENT

Exposure assessment evaluates the routes of exposure to a hazard, the probability that exposure occurs and the amount (dose) of a hazardous agent to which a person or population may be exposed. This exposure assessment specifically addresses the probability of exposure and, if present, the quantity of vCJD agent that may potentially be present in plasma-derived FVIII products manufactured in the United States. The administration of pdFVIII and, thus, the route of exposure, is intravenous.

Plasma pools consisting of 6,000 or more donations collected from US plasma donors are used as the starting material from which a number of plasma-derived products are purified, including pdFVIII, which is addressed in this assessment. Because of the relatively large number of donations per plasma pool, there is a small probability that even in the United States some of the pools may contain a donation from a donor who may unknowingly be infected with vCJD, but who does not meet criteria for donor deferral, or who meets those criteria but fails to be deferred due to the limitations of the screening process.

Overview of Model for pdFVIII

Module 1 – Estimation of the prevalence of vCJD in the UK. Variant CJD prevalence in the UK was used in our model as the basis for estimating vCJD prevalence in US plasma donors. The model assumes that the major source of potential vCJD in the US would likely be associated with plasma donors with a history of travel and residency in the UK, France or other countries in Europe since 1980 and may have had dietary exposure to the BSE agent during their stay.

Two different data sources were used to estimate UK vCJD prevalence.

- An epidemiological modeling-based approach estimates a UK vCJD case prevalence of approximately ~1.8 cases per million population (Clarke and Ghani 2005).
- A tissue surveillance-based estimate for UK vCJD infection prevalence was generated using data from Hilton *et al* (2004) and yielded a mean estimate of 1 case per 4,225 – but was further adjusted to account for age of patients surveyed.

Module 2 –vCJD Prevalence in US Plasma Donors and Pools. This module estimates the number of US plasma donors that may potentially be infected with vCJD and the percentage/number of pools containing donations with vCJD agent. This module uses survey data to determine US plasma donors potentially at risk for vCJD, including those with a history of:

- Dietary exposure to BSE-contaminated beef during long term travel or residence in the UK (1980-1996), France and other countries in Europe (since 1980),
- Military service - posted on or residing near military facilities in Europe; and
- Transfusion with blood collected in Europe, or Euroblood.

US plasma donors potentially at risk for vCJD were further characterized by:

- Country of travel or residence,
- Specific duration of travel or residence, year of travel or residence,
- Age of donor, rate and frequency of plasma donation,
- Number of donations per pool, and type of plasma pool (source or recovered), and
- Effectiveness of donor deferral policies.

Module 3 - pdFVIII Manufacturing and Processing. This portion of the model calculated the likelihood and number of plasma pools potentially containing vCJD agent and the quantity of agent per plasma pool and pdFVIII vial based on:

- The probability of and predicted quantity of infectivity (i.v. ID_{50}) present per donation and pool
- Reduction in the quantity of potential vCJD agent during manufacture, and
- Total yield or quantity of pdFVIII produced from the plasma pool.

Module 4 - Utilization of pdFVIII by Hemophilia A patients. The potential exposure of an individual HA patient to the vCJD agent through use of pdFVIII was estimated in the model based on:

- the total quantity of pdFVIII used per year, and
- the estimated potential quantity of vCJD agent predicted in the pdFVIII product.

The quantity of pdFVIII utilized by an individual patient is dependent on the severity of the disease and the treatment regimen and was estimated using data from a Centers for Disease Control (CDC) sponsored study by 6 states by HA patients from 1993-1998

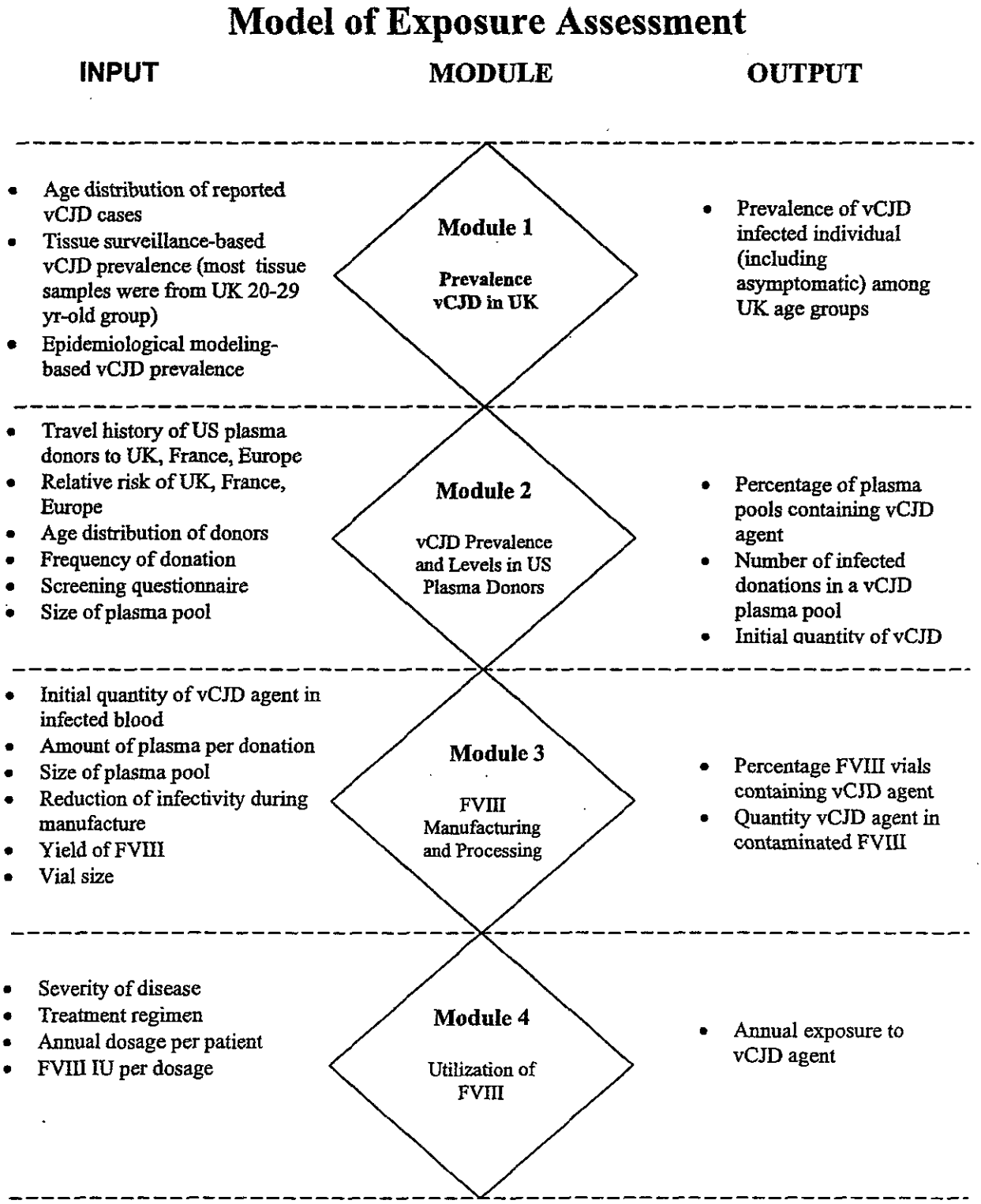
This risk assessment provides outputs that estimate annual exposure for several patient subpopulations with

Severe HA disease for persons in the following clinical treatment groups:

- Prophylaxis
- Prophylaxis plus inhibitor
- Prophylaxis plus inhibitor and immune tolerance
- Episodic
- Episodic plus inhibitor

vWD for adult ($\geq$15 yrs of age) and young ($\leq$15 yrs of age) persons, including those in either clinical treatment group: Prophylaxis or Episodic.

Figure 1 Exposure assessment diagram



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

The potential prevalence of vCJD in the UK was and continues to be dynamic and changes throughout time as people are exposed to the BSE agent, infected with vCJD, develop the disease and eventually die. Variant CJD exposure and infections in the UK population likely occurred in proportion to the UK BSE epidemic which peaked in 1992. The first human vCJD cases were referred to UK public health authorities in 1994. To date, the number of cases per year in the UK reached a maximum of 28 in the year 2000, and since then has been declining annually with a total of 5 deaths in year 2005.

The FDA model assumes that the major source of potential vCJD in the US would likely be associated with plasma donors with a history of travel and residency in the UK, France or other countries in Europe since 1980 and who may have had dietary exposure to the BSE agent during their stay. The potential vCJD prevalence in US plasma donors with a history of travel to BSE countries since 1980 was estimated based on the UK vCJD prevalence. For US donors the UK vCJD prevalence was adjusted based on the proportion of time spent in the UK, the year of travel and age of the donor. Calculation of the potential vCJD risk for donors who traveled to France was estimated relative to the UK risk (or the relative risk), based on the amount of UK beef imports, the number of domestically acquired vCJD cases, and other factors. The relative risk for vCJD for France was assumed to be 0.05 times that of the UK risk (or 0.05 times the UK vCJD prevalence). Applying similar criteria for other countries in Europe their relative risk was assumed to be 0.015 times that of the UK. Risk was calculated in the model for donors by multiplying the UK vCJD prevalence by either 0.05 for travel to France or 0.015 for travel to other European countries and further adjusting the prevalence to account for factors such as the proportion of time spent, the year of travel and age of the donor.

The prevalence of vCJD in the UK is difficult to estimate because of the long incubation period of the disease and a lack of a validated test that can detect infection in its asymptomatic stages. The prevalence of asymptomatic vCJD infections in the UK was estimated in the FDA model using two different approaches based on two different data sources:

- **An epidemiological modeling-based approach that combined information from a study by Clarke and Ghani (2005) and diagnosed vCJD cases for 2002 and 2003 was used to estimate a UK vCJD case prevalence of approximately ~ 1.8 cases per million population.** There are some limitations associated with estimates of future vCJD cases and vCJD incidence in the UK generated by epidemiological modeling based on the current reported vCJD cases. Several factors used in epidemiologic modeling approaches are difficult to quantify and add uncertainty to the final estimated number of future vCJD cases. These factors include: the intensity of human exposure to the BSE agent, incubation period, time of infection, and whether illness will develop in individuals who are not homozygous for methionine at codon 129 of PrP. All cases of vCJD to date have occurred in individuals who are homozygous for methionine at this location. A more detailed description of the derivation of the epidemiological modeling-based estimate and further discussion of the limitations of the approach can be found in section IV. A. 1. below.

- **A tissue surveillance-based estimate for UK vCJD prevalence was generated using the results of a UK study that tested stored tonsil and appendix tissues collected from patients in the 1990s for the accumulation of prion agent (Hilton *et al* 2004).** The study yielded a much higher estimate of 1 in 4,225 (237 infections per million). However, while unconfirmed, the findings from this study provide a higher prevalence estimate and therefore should also be

considered. A total of 3 positive appendix tissues were identified among 12,676 tissue samples tested, yielding a mean UK vCJD prevalence estimate of 1 case per 4,225. This prevalence estimate was further adjusted to account for the age of the patients surveyed (mostly 20 – 29 year olds) to arrive at a total population-based estimate of UK vCJD prevalence.
This study was not controlled using tissues from a non-BSE exposed population, and false positive interpretations of the findings cannot be ruled out. It is also not known whether this staining of appendiceal tissues is a reliable marker for vCJD pre-clinical infection or for an individual's capability to transmit the infection through blood donation. However, while unconfirmed, the findings from this study provide a higher prevalence estimate and therefore should also be considered. A more detailed description of the derivation of the tissue surveillance-based estimate and further discussion of the limitations of the tissue surveillance study can be found in section IV. A. 2. below.

Two spreadsheet models were developed for the FDA risk assessment – one for each of the two prevalence estimates – but otherwise the models were identical in all other ways. We describe the surveillance variables and assumptions in the sections immediately below.

IV. A. 1. UK vCJD prevalence estimated using epidemiological modeling results (Clarke and Ghani 2005) and diagnosed vCJD cases for 2002 and 2003

The first approach used to estimate UK vCJD prevalence in the FDA model relied largely on epidemiological modeling results (Clarke and Ghani 2005) that estimated future 70 vCJD cases in the UK for the years 2004 – 2080. Since the FDA model estimates the baseline vCJD infection risk for pdFVIII product used in the year 2002, we assumed the potential risk for US donors should be calculated based on a UK vCJD prevalence that included all vCJD cases and potentially incubating vCJD infections in the year 2002. Therefore to estimate the number of cases and future vCJD infections in the UK for the years 2002 – 2080 we added the 32 known diagnosed cases in years 2002 and 2003 and the estimated future 70 vCJD cases (Clarke and Ghani 2005). We assumed that the 70 future cases predicted by Clarke and Ghani (2005) would be incubating vCJD infection in 2002. Therefore, the FDA model estimated an average of 102 cases and incubating vCJD infections for the year 2002 and assumed a 95% confidence interval of 42 – 222 cases. The results of the input information and calculations for the number of vCJD cases in the UK in 2002 are summarized in **Table 4.1**. Assuming the population of the UK in 1997 is approximately 58 million, the prevalence of vCJD (United Kingdom Office for National Statistics, 1997) would be a mean of approximately 1.8 vCJD infections per million population (102 potential vCJD cases / 58 million).

Table 4.1. FDA model estimation of UK vCJD cases for years 2002 – 2080.

	Diagnosed vCJD cases in the UK (Health Protection Agency, 2006)			**Estimation of future UK vCJD cases** (Clark and Ghani 2005)	**FDA model: Estimation of UK vCJD cases for years 2002 - 2080**
Year(s)	**2002**	**2003**	Total	**2004 - 2080**	**2002 - 2080**
Number of vCJD cases	16	16	32	70 (10 – 190)	102 (42 – 222)

There are some limitations associated with estimates of future vCJD cases and vCJD incidence in the UK generated by epidemiological modeling based on the current reported vCJD cases. Many of the published models of future vCJD cases or vCJD incidence in the UK, including Clarke and Ghani (2005) and Cooper and Bird (2003), use simplifying assumptions in generating their predictions. Although these simplifying assumptions are a necessary part of vCJD case estimation efforts, they contribute considerable uncertainty to the final case estimates. Generally, the types of assumptions used to estimate vCJD cases fall into four general areas. First, the models must estimate the number of clinical and pre-clinical BSE-infected cattle slaughtered in the UK to estimate the intensity of human exposure to the BSE agent. Second, they assume a level of effectiveness of the 1989 Specified Ban on Offals which was assumed to reduce the quantity of infectious BSE agent in the food supply, thereby reducing human exposure in the UK. Third, the models generate an appropriate mathematical representation (or statistical distribution) for the incubation period, which is represented by many using a unimodal statistical distribution. There may be constraints on the incubation period used in the model (e.g., the vCJD incubation period of all individuals in the population would not exceed 40 years, etc.). Fourth, many of the modeling approaches incorporate age-specific dependencies that influence exposure, susceptibility to the disease, and incubation period. Depending on the assumptions used, estimates of future cases of vCJD have varied considerably. Past estimates of vCJD cases from epidemiological models predicted from 250 to 440 future cases under certain assumptions (d'Aignaux et al 2001). As actual reported vCJD cases peaked in 2000 and have since been declining, predicted estimates of future cases have decreased (Boelle et al 2003, Clarke and Ghani 2005, Cooper and Bird, 2003).

There are additional uncertainties in predicting future vCJD cases that might arise from individuals with different genetic backgrounds and susceptibilities in the UK population. To date, all known cases of vCJD have occurred in individuals that were methionine homozygous (MM genotype) at codon 129 of the prion protein gene (PNRP). Recent research has identified two individuals who were valine homozygous (VV genotype, also called non-MM genotype) at PRNP codon 129 (Ironside *et al* 2006) among the three prion protein positive samples identified by Hilton *et al* (2004). Clarke and Ghani (2005) did incorporate the possibility of wider genetic susceptibilities in some of their estimates of future vCJD cases. However, because no cases of clinical vCJD have been identified in individuals with non-MM genotype, it is uncertain whether these individuals will in fact develop or transmit clinical disease. Therefore, any estimation of the incubation period for potential cases with the non-MM genotype would rely heavily on assumptions, which adds considerable uncertainty to any estimate of the size or number of cases in a possible secondary wave of vCJD cases that might occur in non-MM individuals.

IV. A. 2. UK vCJD Prevalence derived from a Tissue Surveillance study

We used a second approach for estimating UK vCJD prevalence drawing on results from a tissue surveillance study that tested lymphoreticular tissue samples (tonsils and appendices) for prion protein accumulation. The study was a retrospective survey of stored tonsil and appendix tissues surgically removed from UK patients in 1995 and subsequent years. The authors identified appendix samples from 3 patients as positive for lymphoreticular accumulation of prion protein out of a total of 12,674 patient samples tested (Hilton *et al* 2004). No tonsil biopsies showed such findings. The significance of the detection of prion protein in the appendix is not certain, and it is not known whether this test is a reliable marker for either vCJD pre-clinical infection or the ultimate development of disease. Nor is it

known whether or not such detection is a marker for an individual's potential capability to transmit infection through blood donation. Results from the tissue surveillance study are summarized in **Table 4.2.** Assuming the sensitivity and specificity of the testing method is 100%, this translates roughly to a vCJD prevalence of 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.

Table 4.2. Summary of surveillance testing of tonsil and appendix tissues in the UK.

Reference	Ages of population examined	Years tissue taken	Number of positives	Total samples examined	Rate per million (95% CI)
Hilton DA, et al. 2004	10 – 60+ yrs (60% of patients were 20-29 yrs)	1995 - 1999	3 Appendices	14,964 Appendices 1,739 Tonsils 4,029 excluded	237/million (49–692 per million)

There are some possible limitations of using the Hilton *et al* tissue surveillance study in estimating vCJD prevalence. In their tissue survey, Hilton *et al* stressed that there were uncertainties and suggested caution in attempting a prevalence estimate for infection or a prediction of future vCJD cases in the UK based on detection by immunohistochemical staining of lymphoreticular accumulation of prion protein in three of 12,674 adequate tissue samples studied. First, because the stage of vCJD infection during which the appendix first accumulates detectable amounts of abnormal prion protein is not known and because the accumulations might not be uniformly distributed throughout the tissue, the prevalence of infection might have been underestimated. Second, because the study design (lacking examination of a large number of similarly obtained appendices from a non-BSE-epidemic country) did not permit an estimate of specificity of the method or an independent confirmation of results, it is possible that the results might have been false positives leading to an overestimation of prevalence. In their paper the authors stated: "Although immunohistochemical accumulation of PrP in lymphoreticular tissues has not been demonstrated in any disease other than vCJD, the significance of the positive samples in this study is not certain. In one case, the immunohistochemical pattern of immunoreactivity resembled that seen in appendix tissue from pre-clinical and autopsied cases of vCJD, but in the other two cases, a more finely granular pattern of staining was present in relation to follicular dendritic cells, raising the possibility that these may be false positives. However, we have been unable to demonstrate PrP immunoreactivity in a range of other disorders including other human prion diseases, neoplastic disease, or a range of inflammatory conditions."

Assumption used in the model: All vCJD cases that occur after 2002 are incubating in year 2002.

Prevalence of vCJD among the UK population and the vCJD risk from using plasma-derived factor products are expected to be different from year to year since 1980. In this risk assessment, the potential vCJD risk for pdFVIII products was estimated for the baseline year of 2002, but the results and conclusions also are likely to reflect the current vCJD risk for recipients of pdFVIII. Prevalence of vCJD in 2002 for a specific age population in the UK was extrapolated from two estimates of prevalence discussed above based on age information of reported vCJD cases. The prevalence derived from above two different approaches varied by approximately 130 fold. The discrepancy reflects the limitation on the current knowledge of the disease. In order to evaluate the impact of uncertainty in estimation of vCJD prevalence, the FDA risk assessment provides estimated risk outcomes stratified by two estimates of prevalence.

Assumption used in the model: Our model assumed that distribution of asymptomatic cases across age groups would be the same as the distribution of observed symptomatic cases.

Additional technical information and details of analyses and modeling approaches are provided in Appendix A under section **A - IV.A.**

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

The largest source of potential vCJD risk in US plasma donors is presumably associated with donors who traveled to or resided for extended periods of time in the UK, France and other countries of Europe since 1980. These donors might be exposed to the BSE agent in contaminated beef products and infected with vCJD during travel and residence abroad. Other populations in the US at potential risk for vCJD include US military deployed for extended periods of time in the UK or other countries of Europe and individuals in the US who received blood collected in Europe ("Euroblood"). The prevalence of BSE in the US cattle population is very low and therefore there is a very low probability that domestic dietary exposure to the BSE agent would give rise to human vCJD cases. Because of this very low prevalence, risk via US domestic dietary exposure was assumed to be negligible in the model.

This module estimates the annual number of plasma pools that are used to manufacture pdFVIII from plasma collected in the United States, the number of pools that potentially contain a donation from an infected plasma donor, and the potential quantity of vCJD agent that may be present in a positive pool. The potential vCJD risk for US plasma donors is likely associated with dietary exposure to BSE agent during periods of travel or residence in the at-risk geographic areas where BSE occurred. The percentages of blood donors with a history of travel or residency in BSE countries, who are military members who resided in bases in UK and elsewhere in Europe during 1980-1996, and who are recipients of "Euroblood" were obtained from 1980-1996 Blood Donor Travel Survey conducted by American Red Cross (TSEAC 2000). The percentage was calculated by destination (e.g., the UK, France or other European countries) and duration of travel.

Two different types of plasma are used in manufacture of pdFVIII. Source Plasma is collected through plasmapheresis, a process that separates red blood cells from plasma and returns red blood cells to the donor. Recovered plasma is prepared from whole blood units collected from blood donors. Source Plasma accounts for approximately 80% of the total plasma collected annually in the United States, and

recovered plasma accounts for the remaining 20%. Source Plasma donors are usually younger than blood (recovered plasma) donors, and are thought to travel less so presumably their vCJD risk may be somewhat lower than that of blood donors. However, because of their younger age demographic, Source Plasma donors are likely to be more susceptible to vCJD infection. Additionally, Source Plasma pools are usually smaller and contain larger volume donations (an average of 700 milliliters) from fewer donors than recovered plasma pools (average volume of a donation is ~200 milliliters). Plasma from fewer donors reduces the chance that a plasma pool may contain a donation from an infected donor. However, because Source Plasma donors are allowed to donate more frequently, and give more plasma per donation, there is a greater chance that if a vCJD infected donor were in the Source Plasma donor pool that they may contribute multiple donations to a single plasma pool or donate to multiple pools. However, blood deferral policies instituted beginning in 1999 are believed to have reduced the risk of vCJD donations by more than 90%. The effectiveness of the deferral policy in removing potential vCJD risk from the donor and donation pool is included in the FDA model. Because of the unique characteristics and potential differences in risk for Source and recovered plasma donations and plasma pools, the FDA risk assessment modeled Source and recovered plasma pools separately, and considered factors that may result in different risk for pdFVIII product made from each of the two types of plasma.

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

Age is an important factor in estimating potential vCJD risk for US plasma donors. The FDA model is organized by age groups 18 and 19 yr olds, 10-14, 15-29, etc. (by five yr age groups to age 69) and calculates all risk information and makes all adjustments based on age groups. Each of these age groups forms a "bin" and in each of these bins donors are categorized by country of travel, vCJD prevalence (or relative risk) for country of travel, duration of travel, year of travel, type of donation (Source or recovered), donation rate, etc. The output at the end of this portion of the model is an estimation of the number of US donors in each age group that are potentially infected with vCJD. The model further incorporates the effect of FDA donor deferral policies, implemented beginning in 1999, that are believed likely to reduce the possible risk from blood donors potentially infected with vCJD by ~ 90%.

This specific portion of the model estimates potential age specific vCJD risk for both Source and recovered plasma donors. As mentioned above, donor age is an important factor associated with frequency of travel and susceptibility to the disease and influences the vCJD risk for a particular type of donor. For instance, Source Plasma donors as a group are generally younger than recovered plasma donors (see percentages of donors for Source and recovered plasma donors by age group in **Table 4.3**). Also, the younger Source Plasma donor population likely travels less, and thus, likely has a lower potential vCJD risk. However, this lower risk may be offset by the possibility that younger persons may be more susceptible to infection by the vCJD agent. The purpose of this portion of the model is to characterize plasma donors and their donations according to donor age to more accurately estimate the number of potential vCJD infected donors and donations containing vCJD agent. In turn this information will be used to estimate the probability that a plasma pool used in the manufacture of pdFVIII may contain a donation with vCJD agent.

Additional technical information and details of analyses and modeling approaches are provided in Appendix A under section **A - IV.B.**

Table 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

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

The purpose of this section of the model is to estimate the prevalence of vCJD in US donors who may have been exposed to the BSE agent and potentially infected with vCJD during travel, residence, military service in the UK, France or other countries in Europe since 1980. The vCJD prevalence in US donors is then used to estimate the probability that a plasma pool may contain a donation from a vCJDinfected donor with infectious agent in their blood at the time of donation.

The starting material for manufacturing pdFVIII is a plasma pool containing donations from thousands of donors. The probability that a plasma pool contains a donation with vCJD agent is a function of the prevalence of vCJD in the US donor population and the total number of donors and donations present in a pool used to manufacture pdFVIII. For US donors with a history of travel, a key factor in estimating the vCJD risk is the region or country of travel, i.e., the UK, France or other countries in Europe, since 1980. From there we make several adjustments to the vCJD prevalence for US donors. The model incorporates the age of donors into the estimate of vCJD prevalence – donation rate for various age groups is important since the majority of donors are less than 40 years of age. Furthermore, vCJD prevalence for each age group is determined. Since vCJD primarily affects younger persons (median age 28 yrs) and donors are younger – they are at particular risk for vCJD and may unknowingly transmit the agent via donations. The model further adjusts vCJD prevalence based on the year of travel – for instance, a traveler in 1992 that visited the UK at the height of the BSE epidemic faces a higher BSE exposure risk and risk of vCJD infection than someone who traveled to the UK in 1997 after more stringent food controls were implemented in the UK. Also, the model incorporates information on the