most probably via dietary exposure to bovine spongiform encephalopathy (BSE)-contaminated beef (Knight 2004). The leading theory is that the transmissible infectious agent is a prion, or proteinaceous infectious agent, that is an altered but pathogenic form of the PrP protein that is normally present in cells. The altered PrP, herein referred to as PrP^{TSE}, consistent with terminology recommended by the World Health Organization, is highly stable and resistant to degradation by high heat and chemical treatments commonly used to denature infectious agents in the manufacture of plasma derivatives. The incubation period for TSEs is long. The mean incubation period of BSE in cattle is approximately 4.5 years. In humans, vCJD acquired through dietary exposure is thought to incubate approximately 10 –12 years or longer, and individuals become symptomatic only in the last few months of the disease, making early detection very difficult. Confirmation of vCJD requires postmortem examination of brain tissue to confirm diagnosis, but prion protein has been detected in tonsil and appendix tissue of asymptomatic individuals as long as two years prior to the onset of symptoms. There are currently no validated tests available to detect the disease in its early stages of infection or to detect the presence of TSE agents in blood.

Transmission of TSEs through transfusion of blood products in animal models

Transmission of different TSE agents through the transfusion of blood or blood products has been demonstrated in animal models on multiple occasions. At least four studies reported transmission via blood transfusion in the same animal species: sheep experimentally infected with BSE (Houston *et al* 2000), sheep naturally infected with scrapie (Hunter *et al* 2002), hamsters with scrapie (Rohwer 2004), and mice with a human TSE (Brown *et al* 1999).

Brown, Rohwer, Taylor (Taylor *et al* 2000) and others have attempted to estimate the amounts of intracerebral (i.c.) infectivity present in blood, which generally fell between 2 and 20 i.c. ID_{50}/ml. A recent study of scrapie-infected hamsters concluded that approximately 58% of the infectivity present in whole blood was associated with plasma (Gregori *et al* 2004). The model uses this more conservative estimate in the published literature and assumes that 58% of infectivity is associated with plasma.

Transfusion transmission of vCJD in the United Kingdom

In December 2003 the UK government announced that vCJD had likely been transmitted to a 69 year-old patient via blood transfusion. The patient had received non-leukoreduced red blood cells in 1996 from a donor who died three years later of vCJD. This first report was followed by the announcement in July 2004 of another probable case of transfusion-transmitted vCJD. The patient died of a ruptured aortic aneurysm without clinical evidence of vCJD, but postmortem testing detected PrP^{TSE} in spleen tissue and cervical lymph node. In February 2006 a third case of probable transfusion transmitted vCJD was reported in the UK in a 31 year-old male; the patient had received a transfusion eight years earlier from a donor who died of vCJD 20 months after donation. None of the donors were known to have had vCJD at the time of donation.

It is possible that dietary exposure may have been responsible for some or all of the three cases that were reported after red blood cell transfusions; however, the probabilities for occurrence of either a single, or, particularly, two or three such events are small. As Llewelyn *et al* (2004) pointed out in their publication discussing the first presumed transfusion-transmitted case "the age of the patient

was well beyond that of most vCJD cases, and the chance of observing a case of vCJD in a recipient in the absence of transfusion transmitted infection is about 1 in 15,000 to 1 in 30,000." The combined probability that the first two transfusion cases, identified in two elderly patients in a small cohort of transfusion recipients—in an age group underrepresented among vCJD cases—both acquired infection from food is remote.

The presumptive transmission of vCJD via red blood cell transfusion in the UK raises the possibility that plasma derivatives may pose a risk. The UK authorities have notified physicians in the UK and their patients who received plasma derivatives made from plasma from UK donors about the potential for risk of vCJD from these products. These plasma derivative products included coagulation factors, as well as antithrombin III, and intravenous immune globulins. The derivatives of concern were manufactured from plasma of UK donors between 1980 and late in 1999, when--consistent with a decision announced in 1998—UK manufacturers stopped using UK plasma. The last expiry date for any of the UK products was in 2001. To date, no cases of vCJD have been reported in any recipients of plasma derivatives, either in the UK, where the risk is considered greatest, or elsewhere, including in patients who have received human plasma-derived coagulation products from implicated lots (e.g., lots manufactured from a pool containing plasma from a donor subsequently diagnosed with vCJD) made in the UK.

The vCJD risk for travelers with history of extended travel or residence in the UK, France, and other countries in Europe and reduction of risk via donor deferral

Public health control measures, such as surveillance, culling of sick animals, or banning specified risk materials, and others have been instituted relatively recently in many European countries, particularly in those with indigenous cases of confirmed BSE, in order to prevent potentially BSE-infected tissues from entering the human food supply. Since 1996, the UK has instituted some of the most stringent of these control measures, including a program that excludes all animals >30 months of age and prevents high risk tissue from slaughtered animals from entering the human food and animal feed supplies. In June 2000, the European Union Commission on Food Safety and Animal Welfare strengthened the European Union's BSE control measures by requiring all member states to remove specified risk materials from animal feed and human food chains; as of October 1, 2000 such bans had already been instituted in most member states.

Travelers to and residents of the UK, France and other countries in Europe during the period of BSE pandemic concern are possibly at increased risk of vCJD. However, the risk can not be determined precisely due to factors such as the great uncertainty about incubation period of the disease, the sensitivities of each country's surveillance for BSE and vCJD, the compliance with and effectiveness of public health measures instituted in each country to prevent BSE contamination of human food, and the cattle products from one country that are distributed and consumed elsewhere.

In the UK, the current risk of acquiring vCJD from eating beef and beef products appears to be extremely small, perhaps about 1 case per 10 billion servings (CDC, 2005). In the other countries of the world, this current risk, if it exists at all, would not likely be any higher than that in the UK if BSE-related. The implementation of animal and public health control measures has caused the prevalence of BSE to decline. The US blood donor deferral criteria currently in effect focus on the

time (cumulatively 3 months or more) that a person lived in the UK from 1980 through 1996, whereas for the rest of Europe the criteria focus on the time (cumulatively 5 years or more) that a person lived in these countries from 1980 through the present. This deferral policy is expected to reduce the risk of vCJD transmission via blood and plasma donations from potential infected donors.

Two cases of vCJD in US residents with history of residence in the UK

In 2002, the first case of vCJD was reported in the United States in a 22-year-old woman living in Florida. She is believed to have become infected with vCJD during her residence in the UK. The patient was born in Great Britain in 1979 and immigrated to the United States in 1992. In early November 2001, the patient was evaluated for depression and memory loss. In late January 2002, the patient was transported to the United Kingdom where her condition worsened. The diagnosis of vCJD was confirmed by western blot and immunohistochemical analysis. The patient died in June 2004, approximately 32 months after illness onset (Belay *et al* 2005).

A second case of vCJD was diagnosed by the UK National Creutzfeldt-Jakob Disease Surveillance Unit in November 2005 in a 30-year old man who resided in Texas during the period 2001-2005 (CDC 2006). The onset of symptoms occurred in early 2005 while the man was in Texas. He returned to the UK and died of the disease in early 2006. A postmortem examination confirmed the diagnosis of vCJD.

Surveillance studies to detect CJD and vCJD in patients with hemophilia

Studies in the United States

Because of the large number of blood products used, persons with hemophilia might be expected to be at risk of developing transfusion-related vCJD or classical Creutzfeldt-Jakob disease (CJD). However, a study conducted by the US Centers for Disease Control (CDC) (Evatt *et al* 1998) examined the brains of 24 decedents with a history of bleeding disorders and dementia and found no evidence of CJD in any of the cases.

Another study conducted by the CDC and the Hemophilia Treatment Center identified no cases of clinical diagnosis of CJD among over 12,000 HA patients who have been assessed since 1996. (Evatt *et al* 1998)

Studies in the United Kingdom

A study in the UK (reference: Lee *et al* 1998) conducted post mortem histological examination of the brains of 33 hemophilia patients who were treated with coagulant factor concentrates spanning the years from 1962 – 1995 and observed no evidence of vCJD.

In summary, the experimental and epidemiological evidence indicates the risk of blood transmission of vCJD is no longer theoretical but a real possibility. To date, there is no evidence suggesting that either human CJD or vCJD have been transmitted by use of plasma derivative products. However, transmission of vCJD via red blood cell tranfusions has likely occurred (Llewelyn *et al* 2004). Because the vCJD agent may be associated with plasma, it is plausible that plasma derivatives potentially pose a risk of transmitting the disease.

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; Rohwer 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

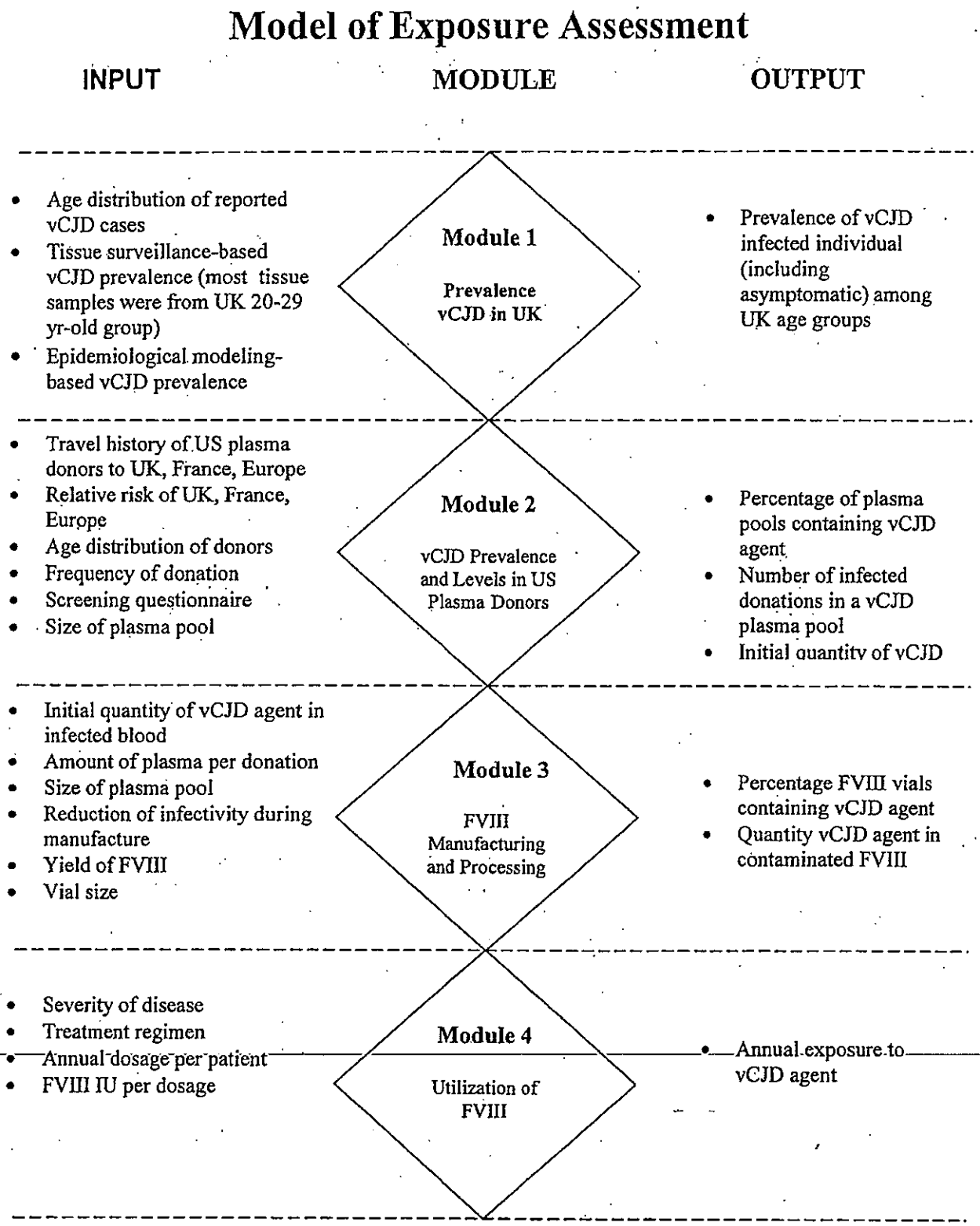
This risk assessment provides outputs that estimate annual exposure for several patient subpopulations with

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 (≥15 yrs of age) and young (≤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	16	16	32	70 (10 – 190)	102 (42 – 222)