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Draft Quantitative Risk Assessment of vCJD Risk Potentially Associated with the Use of Human Plasma-Derived Factor VIII Manufactured Under United States (US) License From Plasma Collected in the US

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EXECUTIVE SUMMARY

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal neurodegenerative disease attributed to human infection with the agent of bovine spongiform encephalopathy (BSE) and is most often transmitted by the consumption of beef products from infected cattle. Cases of vCJD were first reported in humans in the U.K. in 1996 – and as of August 2006, 195 cases have been reported worldwide, with 162 cases in the U.K. Since December 2003, there have also been three reports in the United Kingdom (U.K.) of probable variant Creutzfeldt-Jakob disease (vCJD) transmission by red blood cell transfusions. The donors were healthy at the time of donation, but later developed vCJD. Of the three red blood cell recipients who probably became infected with the vCJD agent after transfusion, two developed vCJD and died from the disease. The third died of an unrelated illness.

The probable transmission of vCJD via red blood cell transfusions raised the possibility that plasma derivatives might also pose a risk of vCJD transmission, although there have as of yet been no reported cases of vCJD in any recipients of plasma derivatives in the U.K., where the risk is considered greatest, or elsewhere in the world. U.K. authorities have notified physicians in the U.K. and their patients who received plasma derivatives made from plasma from U.K. donors about the potential for risk of vCJD from these products. These products included coagulation factors VIII, IX, and XI, as well as antithrombin III, and intravenous immune globulins.

This document "Draft Quantitative Risk Assessment of vCJD Risk Potentially Associated with the Use of Human Plasma-Derived Factor VIII Manufactured Under United States (US) License From Plasma Collected in the US" quantitatively estimates the probability and level of exposure to the vCJD agent and the possible risk of vCJD infection in patients with severe hemophilia A (HA) and von Willebrand disease (vWD) patients with severe disease who have used human plasma-derived Factor VIII (pdFVIII) product manufactured in the US. Because BSE occurs at an extremely low level in US cattle (2 native born cows and 1 cow imported from Canada), the risk of plasma donors acquiring vCJD by consuming domestically produced beef is thought to be very low. Because of concerns about potential exposure to the BSE agent in US blood donors who traveled to or lived in the UK and other at risk European countries, FDA implemented donor deferral policies beginning in 1999. The policies are believed likely to reduce the possible risk from blood donors potentially exposed to BSE agent by ~ 90%. However, it is possible that a small number of non-deferred US donors may have been exposed to the BSE agent during extended travel or residence in the UK, France or other European countries and may be at risk for vCJD. Some of these donors may have been unknowingly infected with vCJD through eating beef from BSE-infected cattle and then contributed donations to plasma pools used to manufacture pdFVIII in the US.

The FDA risk assessment utilizes a computer-based simulation model that evaluates successively the impact on vCJD risk of individual processes used in the production of human pdFVIII starting with plasma donation, extending through manufacturing steps, and finally, addressing utilization by various patient subpopulations. Risk for these 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. A few major elements of the model greatly influence vCJD risk. The most influential of these are manufacturing processes, which may reduce or eliminate the amount of vCJD agent in the final product. The amount of product used by patients in different clinical scenarios also has a significant impact on risk. Additionally, the risk estimate is significantly affected by the prevalence

of vCJD in the United Kingdom population, which is used to estimate vCJD prevalence in US donors who resided in or traveled to the UK and other countries of Europe. The risk assessment model estimates the potential for vCJD exposure and the potential risk of vCJD infection for patients receiving pdFVIII from plasma collected in the US and the accompanying uncertainty of these estimates. Because scientific data on the level of exposure to vCJD agent and the likelihood of certain human health outcomes, such as infection and illness, are lacking, the estimates generated may not be accurate. As a result of these and other large uncertainties, it is not possible to provide a precise estimate of the vCJD risk to patients potentially exposed to the agent through plasma-derived products.

Patients with hemophilia A (HA) have an inherited, recessive, sex-linked bleeding disorder that affects approximately 14,000 individuals in the United States (Soucie et al 1998). FDA estimated that there are approximately 1,800 patients in the US with severe disease who use plasma-derived products. The blood of affected individuals contains functionally abnormal or abnormally low concentrations of FVIII. FVIII is a glycoprotein circulating in blood plasma that is part of the blood coagulation pathway and is critical for the normal clotting of blood. In the case of severe disease, FVIII is <1% of normal. Among severely affected persons, spontaneous bleeding or bleeding at the site of an injury or within a joint is common and can lead to severe disability or death without treatment. The complications of HA can be prevented by appropriate clinical management and treatment with pdFVIII or recombinant FVIII products.

Patients with vWD (Type 3) have an inherited, non-sex linked bleeding disorder associated with abnormal platelet adhesion caused by deficiency in von Willebrand Factor (vWF) activity. FDA estimated that there are approximately 250 patients in the US with severe vWD who use plasma-derived products. Mucosal bleeding is common in patients with vWD due to the platelet adhesion disorder. In some cases there may be a deficiency in FVIII coagulant activity (anti-hemophilic factor) as well. Patients with severe vWD can experience persistent bleeding into joints resulting in pain, degeneration of joints, swelling and loss of range of motion similar to patients with HA. Mild forms of vWD are often treated successfully with desmopressin but more severe forms of the disease usually require treatment with coagulation factor concentrates that contain both vWF and FVIII. Patients who need vWF must use plasma-derived sources of FVIII which contain vWF. No recombinant vWF is currently available.

Results from the Model

An important, yet also highly uncertain parameter in driving the risk assessment results is the estimate used for vCJD prevalence in the UK. The prevalence of vCJD in the UK population was estimated in the model using two different approaches. The first approach to estimating vCJD prevalence in the UK was from a study based on epidemiological modeling that was derived using actual reported vCJD cases in the UK combined with an estimate of future vCJD cases (Clarke and Ghani, 2005). 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. Our calculations, based on the Clarke and Ghani study (2005) and diagnosed cases in 2002 and 2003, yielded a prevalence estimate of approximately 1.8 vCJD cases per million in the UK.

Running the model with this vCJD case prevalence estimate (~1.8 per million) produces an estimate suggesting that, on average, there was a 0.027% likelihood that a plasma pool, which then undergoes manufacturing, will contain at least one donation from an individual whose blood contains the vCJD agent. Therefore, on average, more than 99% of the time the model predicts the product as administered will contain no vCJD agent and this is reflected in the (0 – 0) values for the 5th and 95th percentiles shown for the lower prevalence estimate results in Table I.A. (below).

However, it is possible that the prevalence of vCJD in the UK is higher than that estimated above. This could happen if there are people infected who never develop the disease (but can still spread the infection) or if some individuals take extremely long to become ill. Therefore, a second approach to estimating vCJD infection prevalence was used based on a relatively small tissue surveillance study by Hilton, *et al* (2004), which tested stored tonsil and appendix tissues from the UK for accumulation of abnormal prion protein. It yielded a much higher prevalence estimate of 1 in 4,225 (237 infections per million). This study was not controlled using tissues from a non-BSE exposed population and false positive 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 that may be relevant to transfusion risk and therefore should also be considered. Use of these data as the basis for a vCJD infection prevalence estimate which is then used in the model produces a significantly higher estimate suggesting that, on average, if it were correct, there could be a 2.41% likelihood that a plasma pool, which then undergoes manufacturing, may contain at least one donation from an individual whose blood contains the vCJD agent.

Estimated annual potential vCJD risk associated with human pdFVIII used to treat severe Hemophilia A

Results from the model indicate that it is possible that a donor unknowingly infected with vCJD may have donated plasma used in the manufacture of pdFVIII in the US. Output from the model using the lower UK vCJD prevalence estimate (~1.8 in 1 million) indicated that, on average, there is a 0.027% (95% CI: 0 % - 0 %) likelihood that a plasma pool may contain at least one donation from an individual with the vCJD agent in their blood. Readers may notice that the 5th and 95th percentile intervals for all of the model outputs are from 0 to 0, meaning that the chance of an infected donor donating to a plasma pool would be an infrequent event. This means that at least ninety five percent of the time the model estimates the risk to be zero because vCJD agent was not present in pdFVIII product used during treatment. Again, actual model predictions indicated that, at the lower prevalence, 0.027% of the time the exposure to vCJD may be greater than zero. When the model was run using the higher UK vCJD prevalence estimate (1 in 4,225) to derive an estimate for vCJD prevalence in US plasma donors, the FDA model predicted that, on average, there is an approximately 2.41% (95% CI: 0 % - 10 %) likelihood that a plasma pool will contain at least one donation from an individual with the vCJD agent in their blood. For either set of results, the model assumes that if vCJD agent were present, the amount in a plasma pool would likely be reduced or possibly eliminated by processing steps used during the manufacture of pdFVIII product.

Individuals with HA vary in their degree of FVIII deficiency. For simplicity, the model results and this executive summary specifically address potential vCJD exposure and risk for persons with severe HA. FDA estimates that among the total population of 14,000 HA patients in the United States, approximately 1,800 (Table I.A.) have severe disease and use pdFVIII products. FDA obtained data

on FVIII utilization from the Centers for Disease Control (CDC). The data were generated as part of a collaborative effort between CDC and six states in a study conducted from 1993 –1998. Treatment regimens for HA are administered either as prophylaxis to prevent the occurrence of bleeding episodes or on an episodic basis to control bleeding when it occurs. Additionally, inhibitors may be treated with very high doses of pdFVIII to induce immune tolerance. Assuming these patients are treated with a pdFVIII product that has a 4-6 $\log_{10}$ manufacturing process reduction of vCJD agent, Table I.A. displays model outcomes for patients treated using either prophylaxis or episodic treatment, and with respect to their inhibitor status.

Table I.A. Model Results for all Severe Hemophilia A Patients who use a Hypothetical Plasma-derived FVIII Product with 4-6 $\log_{10}$ Manufacture Process Reduction of vCJD Agent: *Predicted mean potential per person annual vCJD risk using two different UK vCJD prevalence estimates.*

				4 - 6 Log_{10} Reduction	
				Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)	***Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225*** *by Hilton, et al (2004)*
Treatment Regimen	**Inhibitor Status**	**Est. Total Number patients in US**	**Mean quantity FVIII used per person per year (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**
Prophylaxis	No Inhibitor	**578**	**157949 IU[c]** (21242 , 382316)	1 in 4.0 million (0-0)[d]	1 in 54,000 (0 - 1 in 12,000)
	With Inhibitor – No Immune Tolerance	**63**	**190523 IU[c]** (26956 , 447639)	1 in 4.8 million (0-0)[d]	1 in 41,000 (0 - 1 in 9,000)
	With Inhibitor – With Immune Tolerance	**62**	**558700 IU[c]** (33235, 1592943)	1 in 1.3 million (0-0)[d]	1 in 15,000 (0 - 1 in 3,700)
Episodic	No Inhibitor	**946**	**85270 IU[c]** (4633, 244656)	1 in 9.4 million (0-0)[d]	1 in 105,000 (0 - 1 in 24,000)
	With Inhibitor	**151**	**160458 IU[c]** (5314 , 488906)	1 in 8.0 million (0-0)[d]	1 in 48,000 (0 - 1 in 12,000)

[a] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.

[b] The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.

[c] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

[d] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FVIII plasma pool would be rare and more than 90% of FVIII product lots (of vials) would not be predicted to contain vCJD agent.

The risk estimate for the entire severe HA population of 1,800 in the US who use pdFVIII, obtained by summing the total annual exposure and vCJD risk, is shown in Table I.B. Variant CJD risk for US donors with a history of travel to the UK, France or other countries in Europe since 1980 is further adjusted to account for donor age, country, duration and year of travel. Using the lower UK prevalence estimate as a starting point, the model estimates that the total patient population may be exposed to a potential population-based vCJD risk of 1 case observed in 3,077 years of treatment. If the higher vCJD prevalence estimate is used, the model estimates that the total patient population may be exposed to a potential population-based vCJD risk of 1 case observed in 35 years of treatment.

Table I.B. Model Results for Mean Total Population-based Potential vCJD Risk for all Hemophilia A Patients who use a Hypothetical Plasma-derived FVIII Product with 4-6 log_{10} Manufacture Process Reduction of vCJD Agent. Risk estimates were calculated for patients with severe disease, using two different UK vCJD prevalence estimates.

			4 - 6 Log_{10} Reduction	
			Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)	***Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225*** *by Hilton, et al (2004)*
	Est. Total Number severe HA patients in US	**Mean Total quantity FVIII used by all patients per year (5th - 95th perc)[c]**	**Mean population –based potential vCJD risk[a] (5th - 95th perc)[b]**	**Mean population –based potential vCJD risk[a] (5th - 95th perc)[b]**
Mean Total cumulative annual exposure and population risk	**1,800**	**243 million IU[c]**	1 in 3,077 years (0-0)[d]	1 in 35 years (0 - 1 in 8)

[a] Mean population-based potential annual vCJD risk – the risk of potential vCJD infection for the entire population of 1,800 based on animal model dose-response information.

[b] The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.

[c] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

[d] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FVIII plasma pool would be rare and more than 90% of FVIII product lots (of vials) would not be predicted to contain vCJD agent.

Estimated annual potential vCJD risk associated with human pdFVIII used to treat severe von Willebrand disease (vWD)

Individuals with vWD have varying severities of disease; those with Type 3 disease have the severest form of the disease. This executive summary specifically addresses potential vCJD exposure and risk for persons with severe vWD (Type 3) who are assumed to use larger amounts of pdFVIII product and thus, may be at higher risk. FDA estimates that approximately 250 vWD patients have severe vWD disease in the United States and use human pdFVIII products to control their disease (Table II.A.). Results from the risk assessment model for young vWD patients and adult vWD patients treated with pdFVIII product that is assumed to have a 4-6 $\log_{10}$ manufacturing process reduction of vCJD agent are shown in Table II.A. Generally results from the model are expressed for patients with vWD for two groups, either Prophylaxis or Episodic treatment. FDA obtained data on FVIII utilization from the Centers for Disease Control (CDC). The data were generated as part of a collaborative effort between CDC and six states; the study was conducted from 1993 –1998. Annual usage of product by vWD patients was estimated based on an assumption that this patient class largely uses Humate-P®. Totaling the model results for the lower prevalence estimate of ~1.8 per million reveals that the 250 severe vWD patients in the US (Table II.B.) are predicted to have an average potential vCJD infection risk for the population of 1 infection in 28,450 years. At the higher prevalence estimate, the average potential vCJD infection risk for this population is 1 infection in 405 years

Table II.A. Model Results for von Willebrand Disease (vWD) Patients[a] with Severe Disease: Predicted Potential Annual vCJD Risk:

- Assuming a reduction from manufacturing of 4-6 $\log_{10}$, and
- Two different UK vCJD prevalence estimates.

YOUNG vWD (≤ 15 yrs of age)				
			4 - 6 Log_{10} Reduction	
			Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)	***Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225*** *by Hilton, et al (2004)*
	Est. Total Number patients in US	**Mean quantity product used per person per year**	**Mean vCJD risk per person per year[b] (5th - 95th perc)[c]**	**Mean vCJD risk per person per year[b] (5th - 95th perc)[c]**
Prophylaxis	**39**	**165,713 IU[d]** (9876, 454306)	1 In 4.7 million (0-0)[e]	1 in 52,000 (0 - 1 in 13,000)
Episodic	**60**	**11,045 IU[d]** (1025, 34352)	1 in 48 million (0-0)[e]	1 in 971,000 (0 - 1 in 293,000)
ADULT vWD (> 15 yrs of age)				

Prophylaxis	**73**	**186,880 IU[d]** (16910, 539877)	1 In 4.1 million (0-0)[e]	1 in 46,300 (0 - 1 in 11,000)
Episodic	**78**	**86,923 IU[d]** (2182, 240338)	1 In 10 million (0-0)[e]	1 in 1 million (0 - 1 in 24,000)

[a] Number (percent) patients in a CDC sponsored study with 6 states to survey treatment of hemophilia A and B conducted 1993 - 1998. Our analysis included 14 patients (<15yrs) and 28 patients (≥15yrs) (total = 42) on prophylaxis or episodic treatment with Humate P only and no record of inhibitor.

[b] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.

[c] The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.

[d] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

[e] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FVIII plasma pool would be rare and more than 90% of FVIII product lots (of vials) would not be predicted to contain vCJD agent.

Table II.B. Von Willebrand Disease (vWD) patients[a] with Severe Disease: Predicted Total Population-based Potential vCJD Risk:

- *Assuming a reduction from manufacturing of 4-6 log $_{10}$, and*
- *Two different UK vCJD prevalence estimates.*

			4 - 6 Log$_{10}$ Reduction	
			Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)	***Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225*** *by Hilton, et al (2004)*
	Est. Total Number severe vWD patients in US	**Mean Total quantity FVIII used by all patients per year (5th - 95th perc)[c]**	**Mean[b] population –based Potential vCJD risk (5th - 95th perc)[c]**	**Mean[b] population –based Potential vCJD risk (5th - 95th perc)[c]**
Mean total annual exposure and population risk	**250**	**29.9 million IU[d]** (3013, 311745)	**1 in 28,450 years** (0 - 0)[e]	**1 in 405 years** (0 - 1 in 76)

[a] Number (percent) patients in a CDC sponsored study with 6 states to survey treatment of Hemophilia A and B conducted 1993 - 1998. Our analysis included 14 patients (<15yrs) and 28 patients (≥15yrs) (total = 42) on prophylaxis or sodic treatment with Humate P only and no record of inhibitor.

[b] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.

[c] The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.

[d] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

[e] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FVIII plasma pool would be rare and more than 90% of FVIII product lots (of vials) would not be predicted to contain vCJD agent.

Conclusions

Results from the FDA pdFVIII risk assessment model suggest that the risk of vCJD infection from US manufactured pdFVIII generally appears likely to be very low, but may not be zero. For US plasma donors, the major source of vCJD risk is dietary exposure during travel and/or residency in the UK, France, or other countries in Europe since 1980. Although donor deferral criteria in place

since 1999 have reduced the risk of donation by exposed persons, some are not deferred and potentially may donate plasma that contains the vCJD agent. However, the model suggests that the likelihood of a vCJD contaminated plasma pool is low.

Manufacturing processes for human pdFVIII products likely reduce the quantity of vCJD agent, if present, but the level of reduction through manufacturing steps is not precisely known. Clearance of TSE agents in manufacturing appears to vary among products, but has not been measured in standardized studies which might allow more meaningful direct comparisons. Based on currently available experimental studies, it is estimated that pdFVIII products potentially have 4 $\log_{10}$ (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. Assuming a 4-6 $\log_{10}$ manufacturing process reduction, the model predicts that the potential risk per person per year for patients with severe HA using pdFVIII ranges from1 in 15,000 for the higher vCJD prevalence estimate and high product usage to 1 in 9.4 million for the lower vCJD prevalence estimate and low product usage. Due to the wide range of methods used for currently available clearance studies, the results themselves, and gaps in information, it is not possible at this time to determine with any certainty if a specific product may be less or more safe than another.

Although results of the model suggest exposure to vCJD agent is possible, and there is a potential risk of infection that is likely to be very low, it is not possible for the model to provide a *precise* estimate of the vCJD risk in general, or of the actual risk to individual patients. Although the actual risk is highly uncertain, the risk assessment model indicates that the most important factors affecting risk are the clearance of the vCJD agent though manufacturing steps, how much product individuals used, and the vCJD prevalence in the UK donor population.

In considering the results of the risk assessment it is important to note that to date we are not aware of any cases of vCJD having been reported worldwide in patients receiving plasma-derived products, including pdFVIII. This includes patients receiving large amounts of plasma-derived products manufactured from UK plasma donations over a long period of time. This observation also suggests that the actual risk of vCJD infection from pdFVIII is likely to be very low. The absence of cases does not rule out the possibility of exposure that could potentially result in illness in some recipients at some future point in time.

RISK ASSESSMENT

I. INTRODUCTION

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal neurodegenerative disease attributed to human infection with the agent of bovine spongiform encephalopathy (BSE) and is most often transmitted by the consumption of beef products from infected cattle. Cases of vCJD were first reported in humans in the UK in 1996 – and as of August 2006, 195 cases have been reported worldwide, with 162 cases in the UK. Since December 2003, there have also been three reports in the United Kingdom (UK) of probable variant Creutzfeldt-Jakob disease (vCJD) transmission by red blood cell transfusions. The donors were healthy at the time of donation, but later developed vCJD. Of the three red blood cell recipients who probably became infected with the vCJD agent after transfusion, two developed vCJD and died from the disease. The third died of an unrelated illness.

The probable transmission of vCJD via red blood cell transfusions raised the possibility that plasma derivatives might also pose a risk of vCJD transmission, although there have as of yet been no reported cases of vCJD in any recipients of plasma derivatives in the UK, where the risk is considered greatest, or elsewhere in the world. 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 products included coagulation factors VIII, IX, and XI, as well as antithrombin III, and intravenous immune globulins.

Because only 3 cases of BSE (2 that originated in the US, 1 in Canada) have been reported in the US, the US vCJD risk from domestic beef is thought to be very low. However, some US residents (including blood and plasma donors) traveled to the UK, France and other countries in Europe since 1980 and may have been exposed to the BSE agent, and some of these donors may unknowingly be infected with vCJD. The UK had the largest epidemic of BSE among its cattle population and the largest human epidemic of vCJD, which as of August, 2006, reported 162 cases. The UK instituted strong food chain control measures to prevent the entry of high risk cattle tissues into its food supply in 1996; so risk after that time likely decreased considerably. France is considered to rank second in the world for risk for vCJD at this time, albeit at a much lower level than the UK, but higher than many other countries in Europe. As of August 2006 France has reported 20 cases of vCJD. Current US blood and plasma donation policies defer donors with a history of travel or residence to: the UK for a period of three months or longer (1980 – 1996); France, for a period of five years or longer (1980 - present); and other countries in Europe (blood donation only) for 5 years or longer (1980 – present). The CJD geographic donor deferral policy likely removes most of the vCJD risk; however, there may be residual risk in the US donor population for persons who do not meet criteria for donor deferral, or who meet those criteria, but fail to be deferred due to limitations of the donor screening process.

FDA initiated a draft risk assessment of the potential vCJD risk for US manufactured pdFVIII in late 2004. A preliminary draft concept risk assessment model assessing the potential vCJD risks for US manufactured pdFVIII was presented at the February 8, 2005 meeting of the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) for review and comment. The committee largely agreed with the proposed approach. On October 31, 2005, FDA sought advice and

discussion on several risk assessment model inputs to be used in a risk assessment for US manufactured pdFVIII and potential vCJD risks. FDA has incorporated staff, peer reviewer comments, and technical advice provided by the TSEAC at the February 8, 2005 and October 31, 2005 meetings to develop this document "Draft Quantitative Risk Assessment of vCJD Risk Potentially Associated with the Use of Human Plasma-Derived Factor VIII Manufactured Under United States (US) License From Plasma Collected in the US".

This document quantitatively estimates the probability and level of exposure to the vCJD agent and the possible risk of vCJD infection in patients with severe hemophilia A (HA) and von Willebrand disease (vWD) patients with severe (Type 3) disease who have used human pdFVIII product manufactured in the US. Because BSE occurs at an extremely low level in US cattle (2 native born cows and 1 cow imported from Canada), the risk of plasma donors acquiring vCJD by consuming domestically produced beef is thought to be very low. Because of concerns about potential exposure to the BSE agent in US blood donors who traveled to or lived in the UK and other at risk European countries, FDA implemented donor deferral policies beginning in 1999. The policies are believed likely to reduce the possible risk from blood donors potentially exposed to BSE agent by ~ 90%. However, it is possible that a small number of non-deferred US donors may still have been exposed to the BSE agent during extended travel or residence in the UK, France or countries of Europe and may be at risk for vCJD. Some of these donors may have been unknowingly infected with vCJD through eating beef from BSE-infected cattle and then contributed donations to plasma pools used to manufacture pdFVIII in the US.

Scope of the risk assessment

The scope of this FDA risk assessment evaluates the annual potential exposure to the vCJD agent and risk of vCJD infection through human plasma-derived Factor VIII (pdFVIII) product manufactured in the US. Risk for these 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. The FDA risk assessment specifically addresses pdFVIII used to treat patients with severe HA and severe vWD.

The FDA risk assessment utilizes a computer-based simulation model that evaluates successively the impact on vCJD risk of individual processes used in the production of human pdFVIII starting with plasma donation, extending through manufacturing steps, and finally, addressing utilization by various patient subpopulations. A few major elements of the model greatly influence vCJD risk. The most influential are manufacturing processes, which may reduce or eliminate the amount of vCJD agent in the final product. The amount of product used by patients in different clinical scenarios also has a significant impact on risk. Additionally, the prevalence of vCJD in the United Kingdom population, which is used to estimate vCJD prevalence in US donors who resided in or traveled to the UK and other countries of Europe, has a significant effect on the risk estimate.

The risk assessment model estimates the potential for vCJD exposure and the potential risk of vCJD infection for patients receiving pdFVIII from plasma collected in the US and the accompanying uncertainty of these estimates. Because scientific data on the level of exposure to vCJD agent and the likelihood of certain human health outcomes, such as infection and illness, are lacking, the estimates generated may not be accurate. As a result of these and other large uncertainties, it is not possible to

provide a precise estimate of the vCJD risk to patients potentially exposed to the agent through plasma-derived products.

Background

Hemophilia and Factor VIII
Patients with HA have an inherited, recessive, sex-linked bleeding disorder that affects approximately 14,000 individuals in the United States (Soucie et al 1998). FDA estimated that there are approximately 1,800 patients in the US with severe disease who use plasma-derived products. The blood of affected individuals contains functionally abnormal or abnormally low concentrations of FVIII. FVIII is a protein in blood plasma that is part of the blood coagulation pathway and is critical for the normal clotting of blood. In the case of severe disease, FVIII is <1% of normal. Among severely affected persons, spontaneous bleeding or bleeding at the site of an injury or a joint is common and can lead to severe disability or death without treatment. The complications of HA can be prevented by appropriate clinical management and treatment with pdFVIII or recombinant FVIII products.

Patients with vWD have an inherited, non-sex linked bleeding disorder associated with abnormal platelet adhesion caused by deficiency in von Willebrand Factor (vWF) activity. FDA estimated that there are approximately 250 patients in the US with severe vWD who use plasma-derived products. Mucosal bleeding is common in patients with vWD due to the platelet adhesion disorder. In some cases there may be a deficiency in FVIII as well. Patients with severe vWD can experience persistent bleeding into joints resulting in pain, degeneration of joints, swelling and loss of range of motion similar to patients with HA. Mild forms of vWD are often treated successfully with desmopressin but more severe forms of the disease usually necessitate treatment with coagulation factor concentrates that contain both vWF and FVIII. Patients who need vWF must use plasma-derived sources of FVIII which contain vWF. No recombinant vWF is currently available.

FVIII from human plasma is manufactured in a number of different ways. FVIII manufactured from human plasma is purified by fractionation of the protein from large plasma pools containing thousands of donations of plasma. Because thousands of donations are used to assemble the plasma pools used in the manufacturing of pdFVIII, there is a possibility that a donation from a vCJD infected individual may be present in a large plasma pool used to manufacture pdFVIII. In turn, that may lead to exposure of product recipients to the vCJD agent and a risk of infection. Relatively recent advances in pdFVIII production technology, such as [redacted] have likely reduced potential exposure to the vCJD agent. However, further evaluation is necessary to more precisely determine the levels of vCJD clearance afforded by the manufacturing processes for each human pdFVIII product.

There are two approaches for the clinical treatment and control of HA using pdFVIII: (1) episodic treatment and (2) prophylaxis. Episodic treatment involves the administration of FVIII in response to bleeding episodes resulting from trauma or during and after surgery. Prophylaxis treatment requires administration of clotting factor concentrates on a regularly scheduled basis necessary to maintain a minimal level of FVIII (common acceptable trough level is 2-5% of base line level) to prevent bleeding episodes. In view of the demonstrated benefits of prophylaxis, the Medical and Scientific Advisory Council (MASAC) recommends that prophylaxis starting at an early age be considered as an optimal therapy for individuals with severe HA (MASAC 2001). Prophylaxis treatment requires

higher doses of FVIII than episodic treatment (Linden, Kolakoski *et al* 2003; Globe, Curtis *et al* 2004) and thus presents a potentially higher risk of vCJD to the patients than episodic treatment when human pdFVIII is used. Also, some HA patients develop antibodies to FVIII, called inhibitors, that limit the effectiveness of FVIII used in treatment. Inhibitors can develop with the use of either recombinant FVIII or pdFVIII products. In some cases the development of inhibitors is treated with immune tolerance therapy in which large doses of one million or more units of pdFVIII may be administered. Because of the large doses of pdFVIII used, immune tolerance therapy can pose a potential risk for vCJD exposure if vCJD agent were present in the pdFVIII product. As a simplifying assumption in the model we assumed that in a given year a patient received either exclusively prophylaxis treatment or episodic treatment, but not both.

Risk Assessment Framework

This risk assessment generally follows the four step paradigm described by the National Research Council (NRC, 1983) and consists of: (1) hazard identification, (2) hazard characterization, (3) exposure assessment, and (4) risk characterization. The hazard identification portion of the risk assessment provides an in-depth overview and analysis of all data and information sources to establish a causal relationship between the hazard and adverse effects on humans. The hazard characterization component (also known as dose-response) relates the information in the exposure assessment, which determines the dose, to the probability of adverse consequence(s) such as infection, illness, etc., expected at a given dose at the individual, subpopulation, or population level. 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. Risk Characterization integrates the information from the hazard identification, hazard characterization and exposure assessment sections to characterize the probability and consequences of risk for individuals and populations.

II. HAZARD IDENTIFICATION

The hazard identification portion of the risk assessment provides an in-depth overview and analysis of information from laboratory studies, epidemiological studies, the scientific literature, government reports and other credible or peer-reviewed sources of data that establish a causal relationship between the hazard and adverse effects on humans. In this risk assessment, the vCJD agent is the hazard, and potential exposure can occur in individuals who use plasma-derived products that may have been manufactured from plasma that may have contained a donation(s) from a vCJD-infected individual. To date, there is no epidemiological evidence suggesting that vCJD has been transmitted by use of plasma derivative products. However, the probable transmission of vCJD to three recipients of red blood cell products donated by donors later diagnosed with vCJD in the UK raises the possibility of vCJD transmission via plasma-derived products.

Human vCJD was first reported in the United Kingdom in 1996 (Will *et al* 1996). As of August 2006 over 195 cases, 162 of them in the UK, have been reported worldwide. Both vCJD and BSE belong to a class of fatal neurodegenerative diseases known as transmissible spongiform encephalopathies (TSEs). There is strong evidence and general agreement that vCJD results from infection of humans

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; 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.

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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

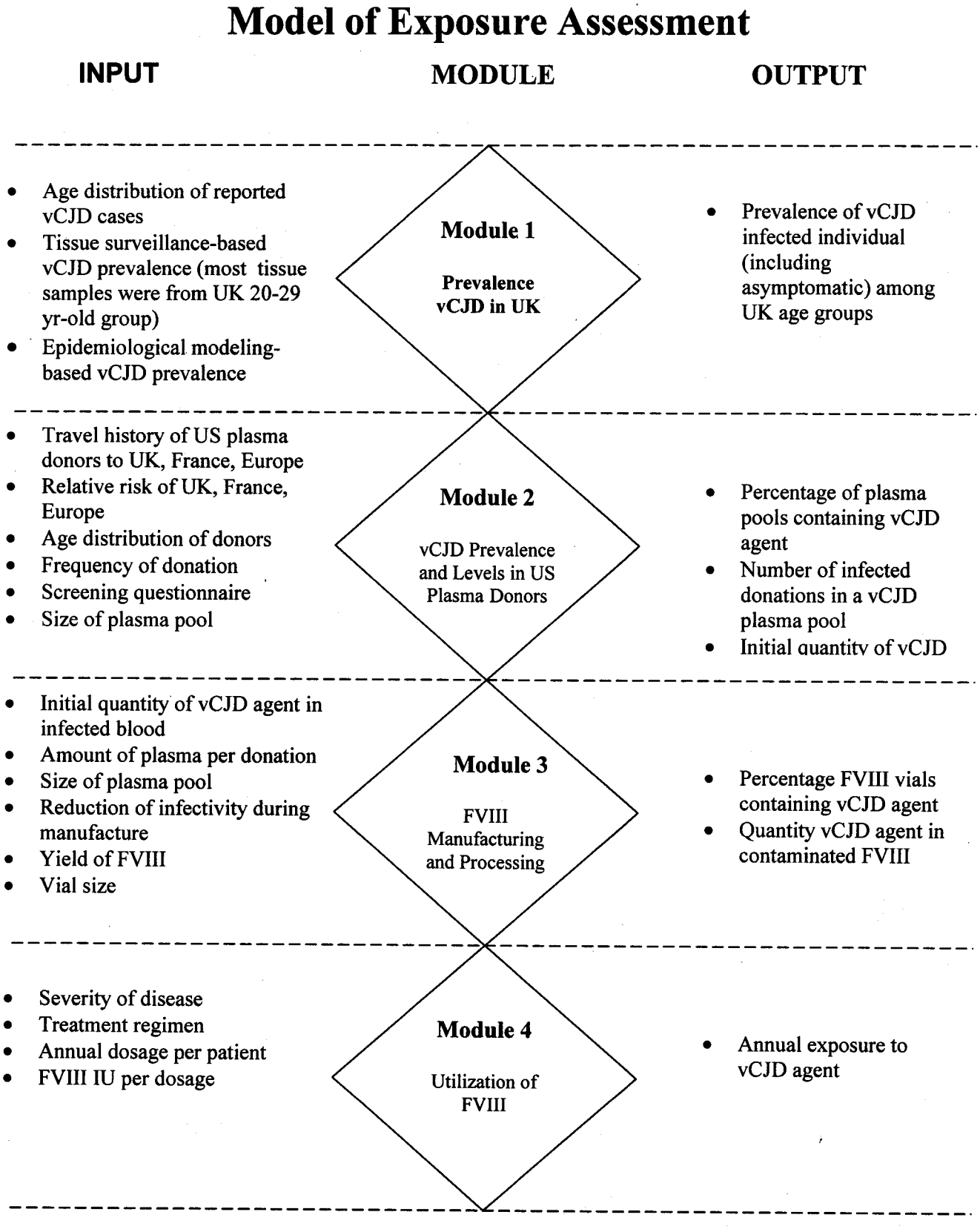
This risk assessment provides outputs that estimate annual exposure for several patient subpopulations with

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	16	16	32	70 (10 – 190)	102 (42 – 222)

cases					

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	27		32	30	22	13	5	3	5	0	5		
(%)		(3.4%)	(18.4%)		(21.8%)	(20.4%)	(14.9%)	(8.8%)	(3.4%)	(2%)	(3.4%)	(0%)	(3.4%)		
Age distribution of US Source Plasma donors (%)[b]	0	0	0	12%	29.3%	14.1%	14.1%	9.6%	9.6%	5.8%	5.8%	0%	0%	0%	0%
Age distribution of US Blood (Recovered plasma) donors[c]	0	0	0	5%	13%	8%	10%	12%	13%	12%	11%	7%	4%	5%	0%

[a]Hilton *et al.* 2004

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

[c] Data provided to FDA by Westat in 2002

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 duration of the travel based on survey information of travel history for whole blood users. Also considered in the model is the type of donation – whether Source Plasma or for recovered plasma, since the number of donations by an individual per year varies dramatically for these two types of plasma. Finally, the model assumes that *a plasma donation from a vCJD infected individual contains the infectious vCJD agent*, and thus poses a potential risk, if the individual is in the last half of the incubation period for the disease (and likely prionemic). However, current deferral policies prevent potentially infected donors with a history of extended travel or residence to BSE countries since 1980 from donating blood. *This geographic deferral policy effectively lowers the prevalence of vCJD in the US donor population by removing donors with a history of extended travel or residence in the UK and other countries in Europe since 1980.* The FDA risk assessment incorporates the effectiveness of current geographic deferral policy in reducing the risk of vCJD transmission through plasma derivatives. The final outputs or results from the model offer estimates of the potential number of Recovered and Source Plasma donors who may be infected with vCJD, and the model further derives an estimate of the number of infected donors who may actually have agent in their blood at the time of donation.

FDA evaluated a number of possible sources of exposure to the BSE agent that could potentially result in infection with vCJD in US plasma donors. The model and risk assessment assumes that the greatest potential vCJD risk for US plasma donors was likely associated with exposure to the BSE agent during extended travel or residence in the United Kingdom (for 3 months or more from 1980 – 1996), or France and other countries in Europe (5 or more years since 1980).

The following sections in the document describe in detail our mathematical approach for modeling and estimating the risk for US plasma donors who lived or resided in:

- United Kingdom from 1980 – 1996 for $\geq$ 3 months (Described in Appendix A - section A-IV.C.1.a.)
- France - since 1980 for $\geq$ 5 years (Described in section IV.C.1.b. and in Appendix A – sections in A-IV.C.1.b.)
- Other countries in Europe – since 1980 for $\geq$ 5 years (does not include plasma donors) (Described in section IV.C.1.c. and in Appendix A – sections in A-IV.C.1.c.)
- US Military personnel or their dependents – deployed in UK or other countries in Europe since 1980 (Described in section IV.C.1.d. and in Appendix A – sections in A-IV.C.1.d.)
- Euroblood recipients in US – that received blood collected from donors in Europe (Described in section IV.C.1.e. and in Appendix A – sections in A-IV.C.1.e.)

Dietary exposure in the US through consumption of domestic beef potentially contaminated with BSE agent was considered negligible based on our calculations, and was not included in the final model of this risk assessment.

Assumption used in the model: The BSE exposure risk for an individual on extended travel or during residence to the UK, France, or other countries in Europe since 1980 is proportional to the duration of the stay or time spent. For instance a person who lived in the UK for one year has one-fifth the risk of a donor who spent five years.

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

The model considered all major potential sources of vCJD infection for US plasma donors. The most likely cause of vCJD is dietary exposure of donors to the BSE agent through the consumption of BSE-contaminated beef during travel to a country where BSE was present in the cattle population. Accordingly, the greatest risk of BSE exposure in the UK likely occurred during the period from 1980 to 1996. The BSE exposure risk for France was likely lower than that of the UK and likely present since 1980. Also, other countries in Europe likely posed an even lower risk than France of human exposure to the BSE agent since 1980. Generally, because of the higher prevalence of BSE in the UK in the late 1980s and early-to-mid-1990s and the higher occurrence of vCJD in the UK human population (currently 162 cases as of August 2006), US donors who traveled to the UK from 1980 through 1996 are likely at higher risk for vCJD infection than donors who traveled to other European countries in the same time period. This model uses the concept of relative risk to estimate the vCJD risk (and prevalence) for a donor population – a value of 1 is used for the UK and this is equal to the vCJD prevalence. Relative risk is used to compare the risk of other regions to that of the UK and is estimated based on factors such as amount of contaminated feed, percentage of meat from the UK, number of cases of BSE, vCJD, etc. In subsequent sections on estimating risk for donors that traveled to France, France is assumed to have a relative risk of 0.05, since they received about 5% of their beef and feed supply from the UK and also have reported domestically-acquired vCJD cases.

The potential vCJD risk faced by US plasma donors exposed to vCJD during travel or residence in the UK (since 1980) is assumed in the model to be proportional to the time a donor spent in the UK (or France or other countries in Europe), and also a function of the age of the donor, and year of travel. Duration of travel is an indicator of possible exposure and we assumed that the probability of exposure was proportional to the time spent in the UK from 1980 - 1996. The longer the duration of travel, the higher the risk of human exposure to the BSE agent. The magnitude of possible exposure to the BSE agent is also influenced by the specific year of travel. The risk is the highest when travel took place during the peak of BSE epidemic in 1992. The FDA risk assessment grouped plasma donors based on age, destination, duration and year of travel, estimated the number of donors, probability of an individual being infected, and potential number of infected donors for each group. Then, numbers of infected donors from all groups were summed to arrive at an estimate of the total number of potential vCJD infected donors in the US that may contribute to FVIII plasma pools. The vCJD agent may only be present in the blood of an infected person during the last half of the disease. Accordingly, the FDA risk assessment considered only those vCJD infected donors who were in the last half incubation period of the disease as being capable of possibly transmitting the disease to others through their plasma donations.

The FDA risk assessment evaluates the effectiveness of current geographic deferral policy in reducing the risk of vCJD transmission through plasma derivatives. Current policy defers individuals with history of long term travel in BSE epidemic areas since 1980, providing a barrier for donors potentially infected, thus effectively lowering the vCJD prevalence in the US donor population by an estimated 90% or more. However, there may be residual risk associated with donors who do not meet criteria for donor deferral, or who meet those criteria, but fail to be deferred due to limitations of the donor screening process. Although current policy defers US donors that received transfusions while in the UK

or France since 1980, the FDA risk assessment did not estimate the potential vCJD risk for these donors.

Assumption used in the model: vCJD risk for the US plasma donor population is a sum of the risk from all exposure sources.

Assumption used in the model: The FDA risk assessment assumed vCJD agent is present in the plasma of infected person only in the last half of the incubation period of the disease, based on animal studies on vCJD infectivity of blood.

Assumption used in the model: The mean incubation period for vCJD is 14 years, and the median incubation period is 13 years.

The United Kingdom has the highest number of reported BSE and vCJD cases in the world. US plasma donors that traveled to the UK during 1980-1996 are considered at risk of exposure to the BSE agent and possibly infected with vCJD. Donors that traveled to France and other countries in Europe are assumed to be at significantly lower risk since the BSE epidemic in those regions was many times smaller than in the UK. This part of the model further characterizes the plasma donors of each age group who have history of travel or residence to the UK (for $\geq$ 3 months from 1980 – 1996), and France or other countries in Europe (for $\geq$ 5 yrs since 1980), by duration and calendar year of travel, estimated the number of potential donors who may be infected, and number of donor who may be in the last half incubation period (prionemic) at year 2002.

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

This portion of the model calculates the potential vCJD risk for US plasma donors who traveled to the UK since 1980 and estimates the potential number of donors with vCJD agent present in their blood and donated to plasma pools used to manufacture pdFVIII. For blood and plasma donors with a history of travel to the UK FDA guidance (2002) currently recommends that blood and plasma collection centers "....defer blood and plasma donors who have traveled or resided in the U.K. for a cumulative period of 3 or more months between 1980 and the end of 1996." The deferral policy likely eliminates much approximately 90% of the potential vCJD risk associated with donor travel to BSE countries when the disease was present. The model incorporates the effectiveness of the deferral policy in reducing risk. However, residual vCJD risk remains from two sources. One source includes potential risk associated with deferrable donors that continue to donate because of limitations in the donor screening process. The second potential source is associated with donors with a history of travel that is less than the deferrable period (blood or plasma donors with a history of less than 3 months of travel to the UK).

In addition to the effectiveness or deferral policies, the residual risk of vCJD infection in US donors is calculated based on the proportion of time spent in the UK by US donors compared to a UK resident whose risk is equivalent to the UK vCJD prevalence. Additionally, the model considers factors such as calendar year of travel, age of donor, type of donation (Source or recovered plasma), possible incubation period of the disease, and whether vCJD agent is present in the blood of a vCJD infected donor. The outcome of this portion of the model predicts the number of US plasma donors who were

potentially infected with vCJD during travel to the UK (see Table 1). The model also predicts the number of donors that potentially have agent present in their plasma that may possibly donate to plasma pools used to manuafacture pdFVIII in the US.

Additional technical information and details on the model calculations of potential vCJD risk and modeling approaches are provided in Appendix A and described in sections in **A - IV.C.**

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

The FDA risk assessment model assumes that the likely source for vCJD risk in US plasma donors is associated with those donors who have a history of travel to the UK from 1980 – 1996, or travel to France or other countries in Europe since 1980. Presumably the greatest vCJD risk resides with travel to the UK since the BSE epidemic was several orders of magnitude larger and the number of vCJD cases greater than that of any other country or region. However, donors who traveled to France are potentially at risk but that risk is likely significantly lower than that of the UK. France likely imported BSE-contaminated feed materials in the 1980s and 1990s and approximately 5% of its beef was supplied by the UK at the time of its BSE epidemic. To date, France has reported 20 cases of vCJD supporting the notion that there may be vCJD infection risk for US donors that may have traveled to or resided in France since 1980.

The FDA risk assessment model incorporates information from current guidance for geographic donor deferrals for vCJD (FDA 2002) to estimate potential vCJD risk for donors with a history of travel to countries where BSE has occurred. FDA guidance (2002) indicates that for donors with a history of travel to France "we now recommend deferral of blood and plasma donors with a history of 5 or more years of cumulative residence or travel in France since 1980." This portion of the model calculates the potential residual US vCJD risk based on the estimated vCJD prevalence among US plasma donors who traveled to France since 1980 and donated to plasma pools used to manufacture pdFVIII. The residual vCJD risk includes risk associated with donors who do not meet criteria for donor deferral (e.g., donors with a history of less than 5 years of travel to France), or who meet those criteria, but fail to be deferred due to limitations of the donor screening process. The model considers factors such as duration of travel, calendar year of travel, age of donor, type of donation (Source or recovered plasma), possible incubation period of the disease, and whether vCJD agent is present in the blood of a vCJD infected donor. The outcome of this portion of the model predicts the number of US plasma donors potentially infected with vCJD and results are shown in Table 4.4. The model goes on to predict the number of donors with a history of travel to France infected with vCJD that may potentially have agent present in their blood at the time of donation.

Additional technical details on the model calculations of potential vCJD risk for donors with a history of travel to France can be found in Appendix A – in sections under A-IV. C.1.b.

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

The FDA risk assessment model incorporates information from current guidance for geographic donor deferrals for vCJD (FDA 2002) in estimating potential vCJD risk for donors with a history of travel to countries where BSE has occurred. The model quantifies potential residual vCJD risk for US plasma donors. The model assumes that the residual vCJD risk likely originates from two sources, one source of potential risk is associated with donors with deferrable risk that continue to donate due to limitations in the donor screening process. The second source of vCJD risk is associated with donors with a history of travel that was less than the deferrable period (blood donors with a history of less than 5 years of travel to Europe). FDA guidance (2002) indicates that for donors with a history of travel to countries in Europe (other than the UK) "the current recommendation is to exclude from transfusion use, blood and blood components from donors with a history of 5 or more years of residence or travel in Europe outside of the UK". Furthermore, for donors with a history of travel to countries in Europe (other than the UK and France) the FDA guidance (FDA 2002) states "...we do not recommend that you defer Source plasma donors who have lived or traveled in Europe for 5 or more years".

The FDA risk assessment model reflects FDA guidance for vCJD deferral of Source Plasma and recovered plasma donors. Because the guidance recommendations for each type of plasma were different the model estimated the potential vCJD risk as follows:

- Recovered plasma donors – the FDA risk assessment **calculated** the potential vCJD risk because deferral was **recommended** for donors with a history of 5 or more years of residence or travel to countries in Europe (other than the UK)
- Source Plasma donors - the FDA risk assessment did **not calculate** the potential vCJD risk because deferral was **not recommended** for donors with a history of 5 or more years of residence or travel to countries in Europe (other than the UK and France).

The term "countries in Europe" as used in this portion of the risk assessment is defined as all countries in Europe (other than the UK and France). The UK and France BSE risk is assumed to be higher than that of other countries in Europe, therefore the potential donor vCJD risk for donors with a history of residence or travel to the UK and France described in sections IV.C. 1. a. and IV.C. 1. b.(and sections in Appendix A – under sections A-IV.C. 1. a. and A-IV.C. 1. b.), respectively, of this document. Also, US donors with a history of residence on US military bases in Europe may have a higher potential vCJD risk so their risk was calculated separately and is described in section IV.C.1.d.

This portion of the model calculates the vCJD prevalence, or number of US blood donors who traveled to other countries in Europe (other than the UK and France) since 1980 and were potentially infected with vCJD and donated to recovered plasma pools used to manufacture pdFVIII. Recovered plasma is plasma that is separated or "recovered" from a unit of whole blood soon after the blood is collected. The model considers factors such as duration of travel, calendar year of travel, age of donor, type of donation, possible incubation period of the disease, and whether vCJD agent is present in the blood of a vCJD infected donor. The outcome of this portion of the model predicts the number of US blood (recovered plasma) donors who are potentially infected with vCJD and have agent present in their plasma.

The model assumes that one of the most likely sources for vCJD risk in US plasma donors is associated with those donors who have a history of travel to the UK from 1980 – 1996, and France and other countries in Europe since 1980. Text in subsequent sections of this document will specifically discuss the potential vCJD infection risk for US plasma donors with a history of travel to countries in Europe (other than the UK and France) since 1980. Presumably the greatest vCJD risk resides with travel to the UK since 1980 since the BSE epidemic was several orders of magnitude larger and the number of vCJD cases greater than that of any other country or region. France is likely at significantly lower risk than the UK but the risk is still likely higher than the vCJD risk of other countries in Europe. There have been 20 cases of vCJD reported in France as of August 2006.

Donors who traveled to other countries in Europe (other than the UK or France) are potentially at risk but that risk is likely significantly lower than that of the UK, and France. Many European countries (other than the UK and France) likely imported BSE-contaminated feed materials in the 1980s and 1990s and approximately 1.5% of their beef may have been imported from the UK at the time of its BSE epidemic. The potential for BSE exposure to donors who traveled to or resided in other countries in Europe is possible. Hence, there may be a vCJD infection risk for blood donors who may have traveled to or resided in a European country (other than the UK and France) for periods greater than 5 years since 1980. The current US vCJD geographic deferral policy defers blood donors with a history of travel or residence in a country in Europe (other than the UK and France) for 5 years or more since 1980. Source Plasma donors who resided in a country in Europe (other than the UK and France) are not deferred from donation. Because Source Plasma donors are not deferred from donation, their risk is not estimated by the model. Therefore, this portion of the model only estimates potential vCJD risk for US recovered plasma donors who traveled to countries in Europe (other than the UK) since 1980.

Additional technical details on the model calculations of potential vCJD risk for donors with a history of travel to countries in Europe (other than the UK and France) can be found in Appendix A – in sections under A-IV. C.1.c.

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

The FDA risk assessment model incorporates information from current guidance for geographic donor deferrals for vCJD (FDA 2002) in estimating potential vCJD risk for donors with a history of travel to countries where BSE has occurred. The FDA guidance (2002) indicates that for donors with a history of service on US military bases in Europe "we recommend that you should indefinitely defer current and former US military personnel, civilian military personnel, and their dependents who were stationed at European bases for 6 months or more during the time periods outlined (in the document)".

The model quantifies potential residual vCJD risk for deferrable donor populations. The residual vCJD risk likely includes two possible sources of risk. One source of risk is associated with donors with deferrable risk that continue to donate because of limitations in the donor screening process. A second possible source of risk is associated with donors who have a history of travel that is less than the deferrable period (blood donors with a history of less than 5 years of travel to Europe). For the purposes of this risk assessment we assumed that exposure to the BSE agent and potential vCJD infection of military personnel or dependents may have occurred during their deployment to US military bases in the UK, France and other European countries during the period from 1980 through 1996, through consumption of BSE contaminated beef procured for use on US military bases from the UK.

Exposure via UK beef likely varied but the model assumes that up to 35% of beef consumed on military bases in Europe came from the UK. The model assumes that approximately 2% of US blood and plasma donors may have been military, military family or their dependents posted to US military bases in the UK or elsewhere in Europe from 1980 through 1996 (TSEAC, 2002). It was further assumed that the average deployment period was 2 years. Because data on military service of plasma donors was not available, the risk assessment used data available on military deployment by whole blood donors.

Additional technical details on the model calculations of potential vCJD risk for donors with a history of military service in countries in Europe can be found in Appendix A – in sections under A-IV. C.1.d.

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

Euroblood is whole blood that was collected at several different collection centers in Europe and shipped to and used by transfusion centers in the United States. The practice was stopped in 2002 with the implementation of geographic vCJD deferrals. The blood was used largely on in the New York City metropolitan area and possibly in other areas on the east coast of the US

The model assumed that a total of 1.2% of US blood donors may have received Euroblood (TSEAC, 2002). To our knowledge there are no specific data available for plasma donors, therefore, data for blood donors was used in this risk assessment.

Assumption used in the model: All infected Euroblood recipients have vCJD agent present in their blood and plasma (prionemic)

IV. C. 1. f. Total number all plasma donors who may potentially be infected with vCJD through all sources of exposure and vCJD agent is present in the blood

This portion of the model sums the total number of all potential US donors that may have been infected with vCJD from different sources. The model estimates the total number of all plasma donors who may be infected with vCJD during extended residence, travel or military service in the UK, France, or other countries of Europe. Potential vCJD risk is also estimated for donors that may have received Europblood. Furthermore, the model estimates the number of total US donors potentially infected with vCJD and have agent present in their plasma.

Variable: $\mathbf{DR_{vCJD\text{-}Pn}}$ - Total annual number of <u>all</u> US plasma donors potentially infected with vCJD with the agent present in blood and plasma (prionemic) in 2002

$$DR_{vCJD-Pn} = DR_{vCJD-S-Pn} + DR_{vCJD-R-Pn} \qquad \text{(IV.C.1.f-3)}$$

Additional technical information and details of analyses and modeling approaches for estimating potential vCJD in the model are provided in Appendix A under section **A - IV.C.1.**

IV. C. 2. Annual number of all US plasma donors potentially infected with vCJD agent present in the blood and who may not be deferred by questionnaire screening

No validated test is currently available to detect the presence of vCJD agent in blood or plasma. The donor questionnaire, administered to all blood donors, can be used to potentially screen donors for potential vCJD risk based on travel history, specifically involving extended travel to the UK, France or other countries in Europe where BSE was known to occur. In 1999 the FDA implemented a donor deferral policy aimed at reducing the potential risk of donations from those potentially exposed to the BSE agent during extended travel to the UK, France and other countries of Europe. Current policies (FDA 2002) defer blood and plasma donors:

- diagnosed with vCJD or other forms of CJD
- at increased risk for CJD, e.g. the donors have received a dura mater transplant, or human pituitary-derived growth hormone; the donors have blood relatives diagnosed with CJD
- with a history of a 3-month or longer travel/residency period in the UK between 1980-96
- with a history of a 5-year or longer travel/residency period in France since 1980
- current or former US military personnel, civilian military personnel, and their dependents resided in Northern Europe for 6 months or more between 1980-90, or resided in military bases elsewhere in Europe for 6 months or more from 1980 to 1996
- received a transfusion of blood or blood components in the UK since 1980
- injected bovine insulin since 1980 unless it is confirmed that injected bovine insulin was not made after 1980 from UK cattle, and
- whole blood donors with a 5-year or longer travel/residency period in Europe (other than the UK) since 1980

Deferral of donors with a history of travel to BSE countries is an effective tool for eliminating a significant portion of potential vCJD risk in US donors. The model incorporates information on the effectiveness of US deferral policies in reducing potential vCJD risk and potential vCJD prevalence in the US donor population.

Assumption about variable: Based on advice from the TSEAC at the October 31, 2005 meeting, the FDA model assumed 85-99% of potential vCJD infected donors would have been deferred just prior to donation.

Assumption about variable: Model includes potential recovered plasma donors with vCJD agent present in blood and plasma (prionemic) that have long term travel history to the UK (≥3 mo), France (≥ 5 yrs), and Europe (≥5 yrs); and history of military deployment, military dependent or related travel or residence in Europe.

There is a possibility that some individuals that traveled to the UK, France, and other countries in Europe since 1980 stayed for periods of time that were shorter than the deferral period, were exposed to BSE agent, and were infected with vCJD. These individuals represent a source of residual risk – or the remaining risk after interventions (in this case donor deferral policies) are applied. The section below addresses the calculation of residual risk for non-deferred at risk donors that traveled for periods of time that were shorter than recommended guidelines.

The total number of all US plasma donors potentially infected with vCJD with agent present in blood and plasma (prionemic) that may not be deferred by questionnaire screening was determined by summing the estimates generated for both Source and recovered plasma donors that may not be deferred by current screening procedures.

Specific technical information and details of analyses and modeling approaches in estimating the effectiveness of donor deferral policies in reducing potential vCJD risk in US donors are provided in Appendix A under section **A - IV.C.2.**

Model Results:
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.

The FDA FVIII risk assessment model uses the concept of relative risk to semi-quantitatively estimate the vCJD risk for US plasma donors with a history of travel to the UK, France and other countries of Europe since 1980. Relative risk is the vCJD risk in a population relative to the UK vCJD relative risk of 1 (or 100%), which is equal to the prevalence of vCJD in the UK. Elements used in the model to calculate vCJD risk for travelers include travel destination (UK, France or other countries of Europe), duration of travel, specific year of travel, and age of donor. The estimated vCJD risk for all potential routes was summed to generate the total mean predicted number of potential vCJD-infected plasma donors in the US. Because of current policies, a blood or plasma donor potentially infected with vCJD has a high probability (85% - 99% chance) of being deferred from donation. Since 2002 FDA has recommended that individuals who resided in the UK for a period of 3 months or more from 1980 to 1996, or resided in France or other countries of Europe for a period of 5 years or more since 1980 be deferred from donating blood or plasma. The model assumes the deferral policy in the US is approximately 85% to 99% effective in reducing the vCJD risk for blood and plasma-derived products. **Table 4.4** (below) shows results from the model predicting the mean number per year of potential vCJD-infected donors and the number of potential vCJD donors who are likely not deferred from donation and donate to plasma pools used to manufacture pdFVIII.

Although it is likely that most would be deferred by the current policy, some plasma donors potentially infected with vCJD may not be deferred and may donate to plasma pools used in the manufacture of pdFVIII. Totaling the estimated number of US donors potentially infected with vCJD yields a mean of approximately 0.01 donors per year based on calculations using a vCJD case-based epidemiological model estimated prevalence of ~1.8 in 1,000,000 (Clarke and Ghani 2005), or a mean of approximately 1.160 donors per year using calculations based on a tissue sample surveillance study yielding a prevalence estimate of 1 in 4,225 (Hilton *et al* 2004) (**Table 4.4**).

Table 4.4 Model Results: Annual Number of US plasma donors predicted by model to be potentially infected with vCJD and donate to plasma pools used to manufacture pdFVIII. Results from model provided for two different UK vCJD prevalence estimates. In the table the mean value is shown above with the 5th and 95th percentiles in parentheses below. The total number of vCJD donors for each prevalence estimate has been rounded to nearest decimal place.

	Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)		***Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225*** *by Hilton, et al (2004)*	
	Mean number (5th - 95th perc)[a] US plasma donors with history of travel to:		**Mean number (5th - 95th perc)[a] US plasma donors with history of travel to:**	
	United Kingdom	***France, Europe, or*** **Military Service**	**United Kingdom**	***France, Europe, or*** **Military Service**
Total number vCJD donors for all US pdFVIII pools Prior to screening	*0.0493* (0– 0)[b]	*0.0108* (0– 0)[b]	*5.32* (0– 13)	*0.77* (0 – 3)
Number vCJD donors NOT DEFERRED (ineffective screening)	*0.0035* (0– 0)[b]	*0.0007* (0– 0)[b]	*0.39* (0-2)	*0.056* (0– 0)[b]
Number vCJD donors NOT DEFERRED *(short-term travel <3 mos, UK; <5 yrs, FR and EU)*	*0.0049* (0– 0)[b]	0.0017 (0– 0)[b]	*0.483* (0 – 2)	0.0343 (0– 0)[b]
Total number vCJD infected donors NOT DEFERRED Donate to pdFVIII Plasma Pools	***0.013*** *(0 – 0)[b]*		***1.160*** *(0 – 4)*	

[a] The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.

[b] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of pdFVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a pdFVIII plasma pool would be rare and more than 90% of pdFVIII product lots (of vials) would not be predicted to contain vCJD agent.

IV. D. Annual total percentage of all plasma pools potentially containing a vCJD donation that are used to make pdFVIII in the US

Model Results:
The percentages of source or recovered plasma pools, potentially containing vCJD agent, used to manufacture pdFVIII in the US were estimated by the model. The majority of pdFVIII is manufactured from Source Plasma and the minority from recovered plasma. Manufacturers provided information to FDA on the approximate range and average number of donations per plasma pool which was combined with information on market share to develop two aggregate statistical distributions, one each representing donations for source and for recovered plasma pools. The distributions were used to predict the number of donations per source or recovered plasma pool in the model. The model used information on the number of donations per pool by type (either source or recovered), combined with estimated yield of pdFVIII per pool, and estimated the total number of plasma pools used to manufacture pdFVIII products distributed in the US in 2002.

As a general comment, the number of donations per plasma pool influences the potential exposure risk for infrequent recipients of plasma derivatives. The use of fewer donations and smaller plasma pools during manufacturing would result in a lower percentage of plasma pools potentially containing vCJD agent and potentially expose a lower percentage of infrequent recipients to vCJD (if present). Frequent recipients of plasma-derived products would likely face a similar level of risk of potential vCJD exposure whether large or small numbers of donations per plasma pool are used in manufacturing.

Lower UK vCJD prevalence estimate of ~1.8 in 1,000,000 (based on Clarke and Ghani, 2005). The lower prevalence estimate used in the FDA model suggested that an average of 0.027% of all US plasma pools used to manufacture pdFVIII in the year 2002 potentially contained the vCJD agent (bottom, **Table 4.5**). The lower disease prevalence is associated with model results predicting a much lower percentage of plasma pools potentially containing vCJD agent. In fact, on average >99.9% of the time plasma pools would be predicted not to contain a donation from a vCJD infected donor. Only an average 0.10% recovered plasma pools would be predicted by the model to contain a vCJD donation from a US donor in any given year. Of interest at the lower prevalence, the model predicts that the occurrence of a recovered plasma pool with a vCJD donation would be infrequent (as indicated by 5^{th} and 95^{th} percentile values of 0); occurring (as estimated by the model), at a rate of 1 in 100 years. Also at the lower prevalence, a vCJD donation in a Source Plasma pool would be predicted to be even more infrequent and predicted by the model to occur at a rate of 1 in 200 years.

Higher UK vCJD prevalence estimate of 1 in 4,225 (Hilton et al 2004). The higher prevalence estimate used in the FDA model suggested that an average of 2.41% of all US plasma pools used to manufacture pdFVIII in 2002 were predicted by the model to contain vCJD agent (**Table 4.5**). It should be noted that fewer recovered plasma pools than Source Plasma pools are used in the US annually to produce pdFVIII. Also, recovered plasma pools contain the largest number of plasma donations. Since recovered plasma pools

contain many more donations than Source Plasma pools the likelihood that a recovered plasma pool may contain a donation from an individual potentially infected with vCJD is considerably higher than for a Source Plasma pool. Using the higher UK vCJD prevalence estimate, the model predicts that on average, 9.12% of recovered pools and 0.96% of Source Plasma pools potentially contain vCJD agent.

Table 4.5 Annual Percentage of US Plasma Pools Potentially containing a vCJD Donation. Results from model include only those US plasma pools used annually to manufacture pdFVIII.

- Results provided for two different UK vCJD prevalence estimates.

	Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)		**Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225** by Hilton, et al (2004)	
	Source Mean (5^{th} - 95^{th} perc)[a]	**Recovered** Mean (5^{th} - 95^{th} perc)[a]	**Source** Mean (5^{th} - 95^{th}) perc)[a]	**Recovered** Mean (5^{th} - 95^{th} perc)[a]
Percent pools potentially containing vCJD agent	0.01% (0 – 0%)[b]	0.10% (0 – 0%)[b]	0.96% (0 – 5.88%)	9.12% (0 – 40.17%)
Average percent pools potentially containing vCJD agent	**0.027 %** (0 – 0 %)[b]		**2.41 %** (0 – 10 %)	

[a] The 5^{th}- 95^{th} perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.

[b] For a 5^{th} and 95^{th} percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of pdFVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a pdFVIII plasma pool would be rare and more than 90% of pdFVIII product lots (of vials) would not be predicted to contain vCJD agent.

Additional technical details on the calculation of the annual total percentage of all plasma pools potentially containing a vCJD donation that are used to make pdFVIII in the US are provided in Appendix A in sections under A-IV. D.

IV. E. Module 2: Estimation of Quantity of vCJD agent in a plasma pool that contains a donation from a donor potentially infected with vCJD

Based on limited available data (see below), FDA believes that the quantity of infectivity present in blood from a vCJD infected individual in i.v. ID_{50} is likely represented by a distribution with the following characteristics: Minimum value = 0.1, 5^{th} percentile = 2,

Most likely value = 10, 95th percentile = 30, and Maximum value= 1,000 i.v. ID_{50}. Given the possible parameters, statistical distributions were fitted to the selected parameters using Best Fit part of the @Risk Professional software package (Palisade Corporation, New York). Using the software we determined that a log normal statistical distribution of (2, 12, 30) i.c. ID_{50}/ml (5th percentile, most likely, and 95th percentile) with minimum and maximum of 0.1 and 1,000, respectively, provided the best fit.

Conclusions from several research groups arrive at somewhat similar estimates for the quantity of infectivity that might be present in the whole blood of mice and hamsters. Using a mouse model and human CJD Brown *et al* (1999) found a range from 0.5 to 15 mouse i.c. IU per ml which we assumed to be roughly equivalent to 1 to 30 i.c. ID_{50} (assuming a linear dose-response for infectivity). An infectious unit is the quantity of infectivity associated with a 100% probability of infection in recipients and roughly equates to two ID_{50} units (1 IU = 2 ID_{50}). Brown *et al* (1998, 1999) conducted experiments to determine the infectivity of buffy coat material and plasma but not red blood cells. Assuming that red blood cells retain approximately 25% of the infectivity of whole blood, then the infectivity present in whole blood could be estimated to be in the range of approximately 10 i.c. ID_{50} and 20 i.c. ID_{50} per ml. Cervenakova *et al* (2003) found levels as high as 20 – 30 infectious doses per ml (40-60 i.c. ID_{50} per ml) associated with buffy coat and plasma during incubating and symptomatic stages of the disease. Red blood cells were not found to be infectious. Transfusion of blood products using the hamster scrapie model by Rohwer suggests that addition of infectivity levels derived for individual blood components would generate a titer for whole blood of approximately 2 to 20 i.c. ID_{50}/ml. Summarizing the above literature it seems that the range of reported values for infectivity ranged from 0.5 to as high as 30 i.c. ID_{50} with the possibility that at times the infectivity present in blood may exceed this range.

Assumption used in the model: Whole blood collected from a vCJD-infected individual can vary from person to person in the quantity of infectivity it contains. The model used a log normal statistical distribution to represent the variability and uncertainty of the quantity of infectivity in blood. It was assumed that whole blood from an infected person potentially carries a minimum of 0.1 i.c. ID_{50} per ml, a 5th percentile of 2 i.c. ID_{50} per ml, a medium of 12 i.c. ID_{50} per ml, a 95th percentile of 30 i.c. ID_{50} per ml and a maximum of 1,000 i.c. ID_{50} per ml. Attempts to identify vCJD infectivity titers in human blood have not been successful, but the assay sensitivity for vCJD *in vitro* and in animal models is limited (Bruce *et al* 2001 and Wadsworth *et al* 2001). Wadsworth *et al* estimated a limit of sensitivity of about 1,000 ID_{50}/ml by their assay meaning that infected blood containing less than 1,000 ID_{50} would not have elicited infection or disease in their animal model, hence infectivity would not have been detected(Wadsworth, 2001).

IV.E.1. Quantity of vCJD agent present in a donation of a specific donor potentially infected with vCJD

This section of risk assessment estimated quantity of vCJD agent in each vCJD plasma pool that may be used to make pdFVIII. Quantity of infectious agent present in plasma

pools may vary depending on number of infected donations in the pool and the volume of each infected donation.

Variable: $\mathbf{I_{bl}}$ – Represents the i.c. ID_{50} present in the blood of individual infected donor (ID_{50}/ml) in the last half of the incubation period of vCJD.

Assumption used in the model: Whole blood collected from a vCJD-infected individual can vary from person to person in the quantity of infectivity it contains. The model used a log normal statistical distribution to represent the variability and uncertainty of the quantity of infectivity in blood. It was assumed that whole blood from an infected person potentially carries a minimum of 0.1 i.c. ID_{50} per ml, a 5th percentile of 2 i.c. ID_{50} per ml, a median of 12 i.c. ID_{50} per ml, a 95th percentile of 30 i.c. ID_{50} per ml and a maximum of 1,000 i.c. ID_{50} per ml. Attempts to identify vCJD infectivity titers in human blood have not been successful, but the assay sensitivity for vCJD *in vitro* and in animal models is limited (Bruce *et al* 2001 and Wadsworth *et al* 2001). Wadsworth *et al* estimated a limit of sensitivity of about 1,000 ID_{50}/ml by their assay meaning that infected blood containing less than 1,000 ID_{50} would not have elicited infection or disease in their animal model, hence infectivity would not have been detected (Wadsworth, 2001).

Variable: $I_{pl\text{-}perc}$ – Percent (%) i.v. ID_{50}s associated with plasma

Studies in animal models have shown that greater than 50% of transmissible spongiform encephalopathy agent present in whole blood is associated with plasma. Experiments by Gregori *et al.* (2004) using a hamster – sheep scrapie model showed that approximately 58% of infectivity in whole blood is associated with plasma.

Assumption used in the model: The model assumes that 58% of infectivity is associated with plasma.

Studies with mouse-adapted scrapie agent suggest that the i.v. route of administration is approximately 10 times less efficient in causing infection than the intracerebral route (Kimberlin *et al* 1996). Brown *et al* (1999) used a mouse-adapted human TSE agent to show that i.v. injection of plasma was about seven times less efficient and i.v. injection of buffy coat approximately 5 times less efficient than were i.c. inoculations of the same materials in transmitting infection. Based on discussion and advice from the FDA Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC, 2005) the range of efficiency of the i.v. route (versus the i.c. route) was assumed in the model to range between the values of 1 and 10.

Assumption used in the model: Exposure to infectivity by the i.v. route is between 1 and 10 times less efficient at causing infection than introduction via the intracerebral route. Using a value of 1 for the ratio of the lower bound of the efficiency is a conservative estimate and assumes that theoretically there would be no difference between the efficiency in initiating infection between the i.c. and i.v. routes.

IV.E. 2. Quantity of vCJD agent in a plasma pool containing a donation from donor potentially infected with vCJD

The quantity of vCJD agent potentially present in a donation from a US donor infected with vCJD will be diluted out in a plasma pool among plasma from thousands of other donations. This section calculates the quantity of agent potentially present in a plasma pool potentially containing a donation that contained vCJD agent.

Assumption used in the model: We assumed only one infected donor per plasma pool, because based on the calculation in section IV. C. 5. the prevalence of vCJD in the US is very low and the chance a pool involves multiple donations from vCJD infected donors is small.

Variable: DN_{DR} - Number of donations from an infected plasma donor, which varies based on type of plasma donated.

Assumption used in the model: We assumed individual infected Source Plasma donor most likely give [redacted] donations to a pool, with minimum of 1, maximum of 12 donations. Individual infected recovered plasma donors most likely give only one donation to a pool.

Variable: I_{Pool}- Initial infectivity in an infected plasma pool is represented by the equation:

$$I_{Pool} = I_{DN} \times DN_{DR} \qquad \text{(IV.E.2-1)}$$

Module 3: Reduction in the quantity of vCJD agent during manufacture of pdFVIII

The plasma separated from whole blood is a protein rich, straw-colored liquid that contains FVIII, a number of other clotting factors, immune globulins, serum albumin and a number of other proteins. Individual proteins, such as FVIII, can be purified by dividing or fractionating the plasma into its various protein components. Fractionation steps may include alcohol precipitation, size exclusion, affinity chromatography, etc. The quantity of vCJD agent present in plasma-derived products may be reduced through removal of the agent during the fractionation process. Although the quantity of agent may be significantly reduced, it may not be entirely eliminated.

Common viral inactivation procedures such as heating, solvent-detergent treatment, and UV irradiation have little effect on the quantity of TSE infectivity present in plasma and plasma derivatives. However, several research studies suggest that TSE infectivity in plasma may be partially removed during the fractionation process. The plasma fractionation procedures, which may remove vCJD infectivity, are summarized in **Table 4.6.** (Lee et al. 2000; Stenland *et al.* 2002; Foster 2004; Foster, *et al.* 2004).

For a specific pdFVIII product, usually only one or two processing steps have been studied for potential reduction of infectivity. Experimental designs of these studies are not standardized; therefore, study results are not directly comparable. In order to achieve a high concentration of vCJD infectivity in initial materials, many studies used vCJD infected brain homogenate as spiking material, which may not mimic the physical form of infectious agent in the blood. Considering the uncertainty in the degree of reduction that can be achieved during various pdFVIII manufacturing processes, this risk assessment models three levels of potential reduction in infectivity, 2-3 $\log_{10}$, 4-6 $\log_{10}$ and 7-9 $\log_{10}$.

Table 4.6 Reduction factor (RF) of fractionation procedures

Fractionation Procedures	RF ($\log_{10}$ ID_{50})	References
Cryoseparation	0-1	(Foster *et al* 2000; Farrugia 2002; Lee *et al* 2002)
General fractionation		
3% PEG	1-3	(Farrugia 2002; Lee *et al* 2002)
11.5% PEG	2-4	(Farrugia 2002)
$Zn+Al(OH)_3$	1.7	(Foster *et al* 2000)
Ion exchange	2.7-3.5	(Foster *et al* 2000; Cervenakova *et al* 2002)
Membrane filtration	1	(Foster *et al* 2000)
Immunopurification	4.4-6.3	(Foster, Welch *et al* 2000; Cervenakova *et al* 2002)

IV.E. 3. Model results: Estimates of the per vial vCJD infection risk for US manufactured pdFVIII (Module 3)

The mean potential risk of vCJD infection per 1,000 IU vial of US manufactured pdFVIII is shown in **Table 4.7**. The mean potential per vial vCJD risk per year is a function of two factors:

1) Percentage of pdFVIII vials containing vCJD agent and,
2) Quantity of agent (i.v. ID_{50}) present in each vial.

If vCJD agent were present in US plasma pools, the risk assessment model assumed that the quantity of agent was likely reduced by manufacturing processes used to produce purified pdFVIII. Based on currently available experimental studies, it is estimated that pdFVIII products potentially have 4 $\log_{10}$ (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. **Table 4.7** shows potential risks associated with products attaining a 4-6 $\log_{10}$ level of reduction during manufacture. Results are shown only for 1,000 IU vials but the model assumed that the final purified pdFVIII product was packaged with equal likelihood into vial sizes of 250, 500, 1,000 and 1,500 international units (IU).

Per vial vCJD risk: Results based on lower epidemiological model estimated prevalence of ~1.8 in 1,000,000 (Clarke and Ghani, 2005). The per vial risk provides an estimate of the potential vCJD infection risk for a 1,000 IU vial of pdFVIII product manufactured from plasma collected from US donors. The model generated estimates of per vial risk using the lower prevalence estimate *(based on Clarke and Ghani 2005)* and results are shown in **Table 4.7**. Based on the lower prevalence estimate the average percent of plasma pools containing the vCJD agent is estimated to be 0.027%. Assuming a clearance of 4-6 $\log_{10}$ the model estimates that the average quantity of i.v. ID_{50} per vial is 3.59×10^{-5} for vials produced from a contaminated pool. This result can be interpreted to mean that only 1 in 55,710 vials made from a contaminated pool would contain an infectious dose of vCJD. Combining these estimates yields an average risk per vial of 1 in 210 million. Alternatively, this could be taken to mean that a patient would need to infuse 210 million vials of product before accumulating one full infectious dose of vCJD.

At this lower prevalence estimate, there is a lower probability that plasma pools contain a donation from a donor potentially infected with vCJD, and a pdFVIII vial would be much less likely to contain vCJD agent. Although the probability (0.027%) is lower, the mean quantity of vCJD agent (iv ID_{50}) and risk of exposure to vCJD agent (1 in 55,710) per vial derived from a pool containing a single vCJD donation would likely be unaffected by prevalence. Readers may notice that the 5^{th} and 95^{th} percentile intervals for all of the model outputs using the lower prevalence estimate (~1.8 per million) are from 0 to 0, meaning that the chance of an infected donor donating to a plasma pool would be an infrequent event. Greater than 99% of the time (on average) the model estimates the risk to be zero because vCJD agent was not present in pdFVIII product used during treatment. Again, the model predicts that, on average, 0.027% of the time the exposure to vCJD may be greater than zero.

Per vial vCJD risk: Results based on higher surveillance prevalence estimate of 1 in 4,225 (Hilton, et al 2004). The per vial risk provides an estimate of the potential vCJD infection risk for a 1,000 IU vial of pdFVIII product manufactured from plasma collected from US donors. The model generated estimates of per vial risk using the higher prevalence estimate (Hilton, et al 2004) and results are shown in **Table 4.7**. Using the higher prevalence estimate the average percent of plasma pools containing the vCJD agent is estimated to be 2.41%. Assuming a clearance of 4-6 $\log_{10}$ the model estimates that the average quantity of i.v. ID_{50} per vial is 3.59×10^{-5} for vials produced from a contaminated pool. This result can be interpreted to mean that only 1 in 55,710 vials made from a contaminated pool would contain an infectious dose of vCJD. Combining these estimates yields an average risk per vial of 1 in 2.3 million. Alternatively, this could be taken to mean that a patient would need to infuse 2.3 million vials of product before accumulating one full infectious dose of vCJD. Again, although the probability (2.41%) is higher at the higher prevalence, the mean quantity of vCJD agent (iv ID_{50}) and risk of exposure to vCJD agent (1 in 55,710) per vial derived from a pool containing a single vCJD donation would likely be unaffected by prevalence.

Table 4.7 Annual Predicted per Vial vCJD Infection Risk for US Manufactured pdFVIII from Model:

- Results for 1,000 IU vial
- Assumed manufacturing process reduction of 4-6 $\log_{10}$, and
- Two different UK vCJD prevalence estimates.

	4 - 6 $\log_{10}$ Reduction					
	Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)			Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225 by Hilton, et al (2004)		
Type of Plasma Pool	**Percentage FVIII vials with vCJD agent** (5^{th}, 95^{th} perc)[c]	**Quantity iv ID_{50}[a] per vial*** (5^{th}- 95^{th} perc)[c]	**Mean potential per vial vCJDrisk[b]** (5^{th}- 95^{th} perc)[c]	**Percentage FVIII vials with vCJD agent** (5^{th}, 95^{th} perc)[c]	**Quantity iv ID_{50}[a] per vial*** (5^{th}- 95^{th} perc)[c]	**Mean** potential per vial vCJDrisk[b] (5^{th}- 95^{th} perc)[c]
Source	**0.01%** (0 – 0%)[d]	**4.36×10^{-5}** (4.51×10^{-6} – 1.43×10^{-4})	**1 in 459 million** (0, 0)[d]	**0.96%** (0 – 5.88%)	**4.36×10^{-5}** (4.51×10^{-6} – 1.43×10^{-4})	**1 in 4.8 million** (0, 1 in 238,000)
Recovered	**0.10%** (0 – 0%)[d]	**2.56×10^{-6}** (3.13×10^{-7} – 8.12×10^{-6})	**1 in 800 million** (0, 0)[d]	**9.12%** (0 – 40.17%)	**2.56×10^{-6}** (3.13×10^{-7} – 8.12×10^{-6})	**1 in 8.6 million** (0,1 in 613,000)
Average of all vials	**0.027 %** (0 – 0%)[d]	**3.59×10^{-5}** (8.18×10^{-7} – 1.29×10^{-4})	**1 in 210 million** (0, 0)[d]	**2.41 %** (0 – 10 %)	**3.59×10^{-5}** (8.18×10^{-7} – 1.29×10^{-4})	**1 in 2.3 million** (0, 1 in 155,000)

*Mean i.v. ID_{50} in vials containing vCJD agent

[a] iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.

[b] Mean potential annual per vial vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Percentage vials with vCJD agent x mean quantity iv ID_{50} per year x 0.5 (50 % chance infection from ID_{50})

[c] The 5^{th}- 95^{th} perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.

[d] For a 5^{th} and 95^{th} percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of pdFVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a pdFVIII plasma pool would be rare and more than 90% of pdFVIII product lots (of vials) would not be predicted to contain vCJD agent.

IV. F. Estimation of the potential quantity of vCJD agent in pdFVIII products manufactured from pool(s) potentially containing a vCJD donation

This section of the risk assessment models each infected plasma pool to estimate the potential reduction in infectivity for each pool during manufacturing processing, and to estimate the quantity of any remaining infectivity (I,v, ID_{50}s) in the pdFVIII product made from each pool.

The levels of reduction of vCJD agent achieved during manufacturing and processing varies among the pdF VIII products on the market. To our knowledge, the total level of reduction in vCJD agent achieved during manufacturing for any pdFVIII product on the market is not known. However, the levels of TSE clearance and reduction for some of the individual fractionation steps (or similar steps) used in the manufacture of some pdFVIII products is known. Based on TSE clearance studies in the published literature and manufacturers' data available to the FDA, FDA staff believe that the plasma-derived products currently on the market employ manufacturing processes that achieve a clearance of vCJD agent of 4 $\log_{10}$ or greater in the final pdFVIII product. The FDA model employed three stratifications of clearance:

- 2 – 3 $\log_{10}$
- 4 – 6 $\log_{10}$
- 7 – 9 $\log_{10}$

Each of these levels of clearance was modeled separately. Most of the results are presented for the 4-6 $\log_{10}$ reduction during manufacture processing in the risk characterization section (Section V.) of this risk assessment.

Module 4: FVIII utilization and annual exposure

Background

Patients with hemophilia A (HA) have an inherited – recessive, sex-linked bleeding disorder that affects approximately 14,000 individuals in the United States (Soucie *et al* 1998). FDA estimated that there are approximately 1,800 patients in the US with severe disease who use plasma-derived products. The blood of affected individuals contains functionally abnormal or abnormally low concentrations of FVIII. FVIII is a protein in blood plasma that is part of the blood coagulation pathway and is critical for the normal clotting of blood. In the case of severe disease, FVIII is <1% of normal. Among severely affected persons, spontaneous bleeding or bleeding at the site of an injury or a joint is common and can lead to severe disability or death without treatment. The complications of HA can be prevented by appropriate clinical management and treatment with pdFVIII or recombinant FVIII products.

Traditionally, HA patients were treated with factor concentrates only when bleeding occurred, which is called episodic treatment. Currently, the adoption of a preventative form of treatment or prophylaxis therapy is increasing. Prophylactic therapy refers to treatment regimens that seek to prevent bleeding events with regular infusions of clotting factor concentration. Prophylactic treatment greatly decreases the likelihood of adverse events such as joint hemorrhage, and effectively prevented the development of chronic joint arthropathy and disability, but requires higher use of FVIII product than episodic treatment.

Patients with vWD have an inherited, non-sex linked bleeding disorder associated with abnormal platelet adhesion caused by deficiency in von Willebrand Factor (vWF) activity. FDA estimated that there are approximately 250 patients in the US with severe vWD who use plasma-derived products. Mucosal bleeding is common in patients with vWD due to the platelet adhesion disorder. In some cases there may be a deficiency in FVIII as well. Patients with severe vWD can experience persistent bleeding into joints resulting in pain, degeneration of joints, swelling and loss of range of motion similar to patients with HA. Mild forms of vWD are often treated successfully with desmopressin but more severe forms of the disease usually necessitate treatment with coagulation factor concentrates that contain both vWF and FVIII. Patients who need vWF must use plasma-derived sources of FVIII which contain vWF. No recombinant vWF is currently available.

IV. G. FVIII utilization by HA and vWD patients and potential exposure to the vCJD agent through use of human pdFVIII

The potential exposure of an individual HA or vWD patient or patient population with severe disease to the vCJD agent through use of pdFVIII was estimated in the model based on the:

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

IV. G. 1. FVIII utilization and potential exposure to the vCJD agent through use of human plasma-derived FVIII by severe HA patients

The quantity of pdFVIII utilized by an individual patient is dependent on the severity of the disease and the treatment regimen. Plasma-derived FVIII utilization and the size of each of the severe HA clinical treatment subpopulations were estimated using data from a Centers for Disease Control (CDC) sponsored study by 6 states by Hemophilia A patients from 1993-1998. This risk assessment provides outputs that estimate the annual exposure for several patient subpopulations with **Severe HA** disease for patients in the following clinical treatment groups:

- Prophylaxis – No inhibitor
- Prophylaxis - With inhibitor
- Prophylaxis - With inhibitor and immune tolerance

- Episodic – No inhibitor
- Episodic - With inhibitor

Because patients with severe HA are likely to use higher quantities of pdFVIII product we reasoned that they would be at potentially greater risk, than those with moderate or mild hemophilia, if the vCJD agent were present in US manufactured product.

A summary of the utilization data used for the model are provided in the table below. Additional technical details of the analysis of FVIII utilization for this population are described in section A-IV.G. of Appendix A.

Table 4.8. Annual usage of pdFVIII by individual HA patients with severe disease-data and input distribution

			Input distribution		
Treatment Regimen	**Inhibitor Status**	**n**	**(min, max)**	**Mean**	**95% CI**
Prophylaxis	**No Inhibitor**	**578**	(300, 1200000)	157949	(21242, 282316)
	With Inhibitor – No Immune Tolerance	**63**	(2000, 800000)	**190523**	**(26956 , 447639)**
	With Inhibitor – With Immune Tolerance	**62**	(100000, 2000000)	**558700**	**(33235, 1592943)**
Episodic	No Inhibitor	**946**	(0, 1000000)	**85270**	**(4633, 244656)**
	With Inhibitor	**151**	(2200, 1000000)	**160458**	**(5314 , 488906)**

IV. G. 2. pdFVIII utilization and annual exposure of severe von Willebrand disease patients

The CDC and six state Hemophilia Surveillance System project conducted from 1993-1998 did not include patients with vWD. We assumed that vWD patients with severe disease would largely use Humate P product only for factor replacement treatment. A search of records in the Hemophilia Surveillance System project data revealed a total of 58 records that indicated Humate P had been used, among which, 8 records indicates patients had developed inhibitor, which are considered uncommon among vWD patients and were excluded from analysis. Among the 58 records, 35 were from Adults (≥15 yrs of age) and 23 records were from young persons (<15 yrs of age). Records for each age group were further grouped by clinical treatment using either a prophylaxis or episodic treatment regimen. Data were initially analyzed individually using the statistical package "JMP" (SAS Institute, Cary, NC) to generate descriptive statistics and statistical distribution(s) for each patient treatment group that best reflected the variation in pdFVIII utilization. The Generalized Beta distribution was identified as the best fit to the pdFVIII utilization data (as determined by using the software Best Fit (Palisade Corp, NY) and was used as the input distribution for pdFVIII usage by individual vWD patients in the model. Graphical representations of the original data and the fitted Generalized Beta distributions are shown in Appendix C. Table 4.9. summarizes pdFVIII usage data from CDC sponsored study and the input distribution generated based on the data. FDA used data in the CDC and six state Hemophilia Surveillance System project conducted from 1993-1998 to estimate FVIII utilization by all vWD patients. The data represent only a sample of all possible vWD patients with severe disease in the US. FDA estimated that there were approximately 250 patients in the US with Type 3 vWD. To calculate the total number of patients in each age group and treatment regimen group we adjusted the 58 patient population to equal a total of 250 patients by multiplying the patient population in each group by a factor of 4.3 (250/58 = ~4.3). The utilization data for patients in each treatment regimen in the sample population were used in the risk assessment model to generate outputs for the annual exposure to vCJD for all vWD for Adult (>15 yrs of age) and Young (≤15 yrs of age) persons in the US among clinical treatment groups of prophylaxis and episodic. The FVIII utilization data were used to calculate the potential vCJD risk for vWD patients; these results are shown in Tables 5.2A and 5.2B.

Table 4.9. Annual usage of pdFVIII by individual severe vWD patient -data and input distribution

Treatment Regimen	n	(min, max)	Mean	95% CI
Young (≤15 yrs of age)				
Prophylaxis	9	(9200, 504625)	165713	(9346, 479457)
Episodic	14	(1010, 41850)	11045	(1013, 37543)
Adult (>15 yrs of age)				
Prophylaxis	17	(15000, 772800)	186880	(15570, 606670)
Episodic	18	(1000, 293800)	86923	(1362, 260660)

V. RISK CHARACTERIZATION

The risk characterization section of the risk assessment integrates information from the hazard identification, hazard characterization and the exposure assessment components to arrive at estimates of the risks posed by a hazard.

In this risk assessment data for hazard characterization are lacking, so we could not develop a human vCJD dose-response. The dose-response relationship provides information needed to use the exposure (dose) assessment results to estimate the probability of adverse responses including infection, illness or mortality – based on assessment of exposure (dose) to the hazard. Many TSE models and risk assessments, including our model, use the ID_{50}, or amount of material that leads to infection in 50% of the population, as a semi-quantitative estimate of the amount of TSE agent. The ID_{50} has been derived from rodent animal models and may or may not approximate infection and occurrence of vCJD in humans. This lack of knowledge about the animal data and how they relate to actual human clinical vCJD outcomes adds considerable uncertainty to the risk estimates generated by the model. The FDA risk assessment interprets the ID_{50} as representing a linear dose-response relationship or linear relationship between exposure and the probability of infection. 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.

The final results of this risk assessment provide estimates of potential annual exposure and annual vCJD infection risk for patients with severe HA and for patients with severe vWD for pdFVIII manufactured from plasma collected in the US. The risk was estimated by applying the linear ID_{50} dose-response relationship, which provides a probability of vCJD infection in the two populations and various subpopulations within the two groups. Given the limited data available FDA believes that any extrapolation or interpretation has limited utility in actually estimating outcomes such as infection and illness. Therefore, any estimate of the risk based on estimates of exposure to the vCJD agent through use of pdFVIII will be imprecise and extremely uncertain.

V.A. THE MODEL

This risk assessment and simulation model links the available scientific and epidemiological data together to mathematically approximate the processes (predicted presence of vCJD in UK population, manufacturing, reduction of vCJD agent, and patient utilization) leading to potential exposure of US patients to vCJD agent present in US-manufactured pdFVIII. A summary of the variables, parameters and equations used in the model were described in Section III. Exposure Assessment and a summary of the variables and equations, data, and assumptions used in the model are provided in Appendix A. The model was run using @Risk software package (Palisades Corp, NY) to conduct the Monte Carlo analysis. Simulations of 10,000 iterations were run.

The risk assessment uses Monte Carlo simulation to randomly draw values from probability input distributions (which are statistical representations of input data) once per iteration; thousands of iterations are used to generate the model outputs as risk estimates. This simulation method is often used in situations when a model is complex, non-linear, or involves several uncertain parameters. The output generated is usually an aggregate distribution whose shape can be summarized using measures of central tendency (mean, median, mode) or with boundaries such as the 95% confidence interval (CI), the 5^{th} and 95^{th} percentiles (representing the 90% CI) or the range, bounded by the minimum and maximum values generated as part of the output. The strength of Monte Carlo analysis is that it generates resulting risk estimates as statistical distributions, which reflect the underlying uncertainty and variability of the original input data and parameters.

V. B. Model results: Estimated annual potential exposure to vCJD i.v. ID_{50} and potential vCJD risk through human pdFVIII used to treat severe HA

Individuals with HA vary in their degree of FVIII deficiency. Although the clinical spectrum generally can range from severe, to moderate, and to mild disease, this assessment specifically addresses potential vCJD exposure and risk for persons with severe HA. Among an estimated 14,000 HA population in the United States, approximately 50% have severe disease and 25% of all HA patients use human pdFVIII products. FDA

estimated that there are a total of approximately 1,800 HA patients **(Tables 5.1A. and 5.1B.)** with severe disease in the US that use human pdFVIII products. Although the estimated risk is very low, it is possible that some patients using human pdFVIII may potentially be exposed to vCJD agent if present in US manufactured product.

Estimation of PdFVIII product utilization by patients with severe HA. FDA obtained data on human plasma-derived FVIII utilization from the Centers for Disease Control (CDC). Data in the study were collected as part of a collaborative effort between CDC and six states during the time period 1993 – 1998. A summary of study results for New York State are described in Linden, et al. (2003). The comprehensive study collected standardized patient demographic, clinical, treatment and outcome data. Patient medical records were obtained from treatment sites including: hemophilia treatment centers (HTCs), hospitals, clinics, physician's offices, home-care agencies, nursing homes, prison infirmaries, and dispensers of factor concentrates. The data abstracted from medical records tabulated all factor concentrate utilization prescribed by quantity, type, purpose (e.g., prophylaxis, treatment of acute bleeds, or immune tolerance therapy) and total quantity used per calendar year.

The data on quantity of pdFVIII product utilized annually were used to develop statistical distributions of product usage for patients by treatment group. The mean quantities of products utilized by HA patients on different treatment regimens are shown in **Table 5.1A. and 5.1B**. Approximately 1,100 records for patients utilizing pdFVIII were analyzed in this study. The percentage of each patient subpopulation in proportion to the total HA population in the CDC-Six State study was used to extrapolate the estimated number of total individuals in each patient subpopulation. From the study results, we estimated that there are a total of approximately 1,800 persons with severe HA in the US who use pdFVIII.

Results from the risk assessment model for patients with severe HA who are treated with pdFVIII product with a 4-6 $\log_{10}$ manufacturing process reduction of vCJD agent are shown in **Tables 5.1A. and 5.1B.** Generally results are expressed for patients in several different HA clinical treatment groups including:

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

Potential exposure of severe HA patients to vCJD agent: Results based on lower epidemiological model estimated prevalence of ~1.8 in 1,000,000 (based on Clarke and Ghani, 2005). The model estimates that severe HA patients treated using a prophylaxis regimen, with inhibitor, with immune tolerance and treated with a pdFVIII product (with 4-6 $\log_{10}$ reduction of vCJD agent) has the highest pdFVIII usage of the groups we examined and potentially face the highest risk among HA patients. **Table 5.1A.** indicates that approximately 62 severe HA patients in a prophylaxis treatment regimen with inhibitor and immune tolerance use an average of 558,700 IU per person per year and are potentially

exposed to an average of 1.57×10^{-6} i.v. ID_{50} per person per year; representing an average potential vCJD risk of 1 in 1.3 million per person per year. If all of the assumptions in the model are correct at this lower estimated prevalence, this risk may yield 1 vCJD infection in an average of approximately 21,000 years of treatment among severe HA patients who are in a prophylaxis treatment regimen with inhibitor and immune tolerance. As mentioned earlier the 5th and 95th percentile intervals for all of the model outputs using the lower prevalence estimate (~1.8 per million) in **Table 5.1A.** are from 0 to 0 meaning that the chance of an infected donor donating to a plasma pool would be an infrequent event. Greater than 99% of the time (on average) the model estimates the risk to be zero because vCJD agent was not present in pdFVIII product used during treatment. However, the model predicts that 0.027% of the time the exposure to vCJD agent may be greater than zero, and there is a possible but low risk of vCJD infection.

The risk for the entire population is calculated by summing the cumulative risk potential of vCJD exposure and risk **(Table 5.1B.).** Using the lower prevalence estimate, the model predicts that the approximately 1,800 severe HA patient population in the US uses a total of approximately 243 million IU pdFVIII and is exposed to an average of 6.50×10^{-4} i.v. ID_{50}. This total annual exposure for the entire severe HA population in the US is equivalent to a mean potential population-based vCJD risk of 1 in 3,077. At this expected level of risk, 1 vCJD infection would be predicted to occur in 3,077 years of treatment for the entire population of 1800 severe HA patients that use pdFVIII.

Potential exposure of severe HA patients to vCJD agent: Results based on higher surveillance prevalence estimate of 1 in 4,225 (Hilton, et al 2004). The model estimates that severe HA patients in a prophylaxis regimen, with inhibitor, with immune tolerance and treated with a pdFVIII product (with 4-6 $\log_{10}$ reduction of vCJD agent) potentially face the highest expected risk among HA patients. **Table 5.1A.** indicates that approximately 62 severe HA patients in a prophylaxis treatment regimen with inhibitor and immune tolerance use an average of 558,700 IU per person per year, and are potentially exposed to an average of 1.30×10^{-4} i.v. ID_{50} per person per year, using the higher prevalence estimate. This represents an average potential vCJD risk of 1 in 15,000 per person per year for the treatment group. If all of the assumptions used in the model are correct and considering the total number of 62 patients in this category (or population-based risk), this expected risk would yield 1 vCJD infection in 240 years of treatment among the patients under this category.

The risk for the entire severe HA population is calculated by summing the cumulative risk potential of vCJD exposure and risk from all individual patients under five categories (prophylaxis with no inhibitor, prophylaxis with inhibitor, prophylaxis with inhibitor and immune tolerance, episodic with no inhibitor and episodic with inhibitor) **(Table 5.1B.).** Using the higher surveillance estimate, the model predicts that the approximate total of 1,800 severe HA patient population in the US uses a total of approximately 243 million IU pdFVIII, and is exposed to an average of 5.67×10^{-2} i.v. ID_{50} per year. This total annual exposure for the entire severe HA population in the US is equivalent to a mean potential

population-based vCJD risk of 1 in 35, i.e., 1 vCJD infection would be predicted to occur in 35 years of treatment in this 1800 severe HA patient population.

Table 5.1A. Model Results for All HA Patients who use a Hypothetical Factor VIII Product with 4-6 log_{10} Manufacture Process Reduction of vCJD Agent: ***Predicted Annual per Person Exposure to vCJD i.v. ID_{50} and Mean Potential per Person Annual vCJD Risk:***

- For patients with SEVERE disease, and
- Two different UK vCJD prevalence estimates.

				4 - 6 Log_{10} Reduction			
				Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)		**Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225** by Hilton *et al* (2004)	
Treatment Regimen	**Inhibitor Status**	**Est. Total Number patients in US**	**Mean quantity FVIII used per person per year (5^{th} - 95^{th} perc)**	**Mean exposure to vCJD iv ID_{50}[a] per person per year (5^{th} - 95^{th} perc)[c]**	**Mean potential vCJD risk per person per year[b] (5^{th} - 95^{th} perc)[c]**	**Mean exposure to vCJD iv ID_{50}[a] per person per year (5^{th} - 95^{th} perc)[c]**	**Mean potential vCJD risk per person per year[b] (5^{th} - 95^{th} perc)[c]**
Prophylaxis	No Inhibitor	**578**	**157949 IU[d]** (21242 , 382316)	**4.99×10^{-7}** (0-0)[e]	1 in 4.0 million (0-0)[e]	**3.67×10^{-5}** (0 - 1.72×10^{-4})	1 in 54,000 (0 - 1 in 12,000)
	With Inhibitor – No Immune Tolerance	**63**	**190523 IU[d]** (26956, 447639)	**4.21×10^{-7}** (0-0)[e]	1 in 4.8 million (0-0)[e]	**4.86×10^{-5}** (0 - 2.17×10^{-4})	1 in 41,000 (0 - 1 in 9,000)
	With Inhibitor – With Immune Tolerance	**62**	**558700 IU[d]** (33235, 1592943)	**1.57×10^{-6}** (0-0)[e]	1 in 1.3 million (0-0)[e]	**1.30×10^{-4}** (0 - 5.39×10^{-4})	1 in 15,000 (0 - 1 in 3,700)
Episodic	No Inhibitor	**946**	**85270 IU[d]** (4633, 244656)	**2.12×10^{-7}** (0-0)	1 in 9.4 million (0-0)[e]	**1.91×10^{-5}** (0 - 8.50×10^{-5})	1 in 105,000 (0 - 1 in 24,000)
	With Inhibitor	**151**	**160458 IU[d]** (5314, 488906)	**2.49×10^{-7}** (0-0)[e]	1 in 8.0 million (0-0)[e]	**4.19×10^{-5}** (0 - 1.67×10^{-4})	1 in 48,000 (0 - 1 in 12,000)

[a] iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.

[b] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Total mean quantity iv ID_{50} per year x 0.5 (50 % chance infection from ID_{50})

[c] The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.
[d] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.
[e] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of pdFVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a pdFVIII plasma pool would be rare and more than 90% of pdFVIII product lots (of vials) would not be predicted to contain vCJD agent.

Table 5.1B. Model Results for Total Population-based Exposure and Potential vCJD Risk for All Hemophilia A patients who use a Hypothetical pdFVIII Product with 4-6 log_{10} Manufacture Process Reduction of vCJD Agent:

Predicted annual per person exposure to vCJD i.v. ID_{50} and mean potential per person annual vCJD risk:

- For patients with SEVERE disease, and
- Two different UK vCJD prevalence estimates.

			4 - 6 Log_{10} Reduction			
			Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)		Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225 by Hilton *et al* (2004)	
	Est. Total Number severe HA patients in US	Mean Total quantity FVIII used by all patients per year (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]	Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]	Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]
Mean total annual exposure and population risk	1,800	243 million IU[d]	6.50×10^{-4} (0-0)[e]	1 in 3,077 years (0-0)[e]	5.67×10^{-2} (0 - 2.52×10^{-1})	1 in 35 years (0 - 1 in 8)

[a] iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.
[b] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Total mean quantity iv ID_{50} per year x 0.5 (50 % chance infection from ID_{50})
[c] The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.
[d] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.
[e] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of pdFVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a pdFVIII plasma pool would be rare and more than 90% of pdFVIII product lots (of vials) would not be predicted to contain vCJD agent.

V. C. Model results: Estimated annual potential exposure to i.v. ID_{50} vCJD agent and potential vCJD risk through human pdFVIII used to treat severe von Willebrand disease (vWD)

Individuals with von Willebrand disease (vWD) vary in severity of disease, those with Type 3 disease have severe disease; this assessment specifically addresses potential vCJD exposure and risk for persons with severe vWD. FDA estimates that approximately 250 vWD patients have severe vWD disease in the United States and use human plasma-derived FVIII products to control their disease (Tables 5.2A. and 5.2 B.) The FDA model suggests that it is possible that some of these vWD patients using human pdFVIII may potentially be exposed to vCJD agent if present in US manufactured product. Results from the risk assessment model for patients with vWD and treated with pdFVIII product with a 4-6 $\log_{10}$ manufacturing process reduction of vCJD agent are shown in Tables 5.2A. and 5.2 B. Generally results are expressed for patients with von Willebrand disease (vWD) clinical treatment groups of either Prophylaxis or Episodic treatment.

Table 5.2A. Results von Willebrand Disease (vWD) patients[1] with Severe Disease: Predicted Potential Annual Exposure to vCJD i.v. ID_{50} and vCJD Risk:

- Assuming a processing reduction of 4-6 $\log_{10}$, and
- Two different UK vCJD prevalence estimates.

			4 - 6 $\log_{10}$ Reduction			
			Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)		Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225 by Hilton, et al (2004)	
	Est. Total Number patients in US	Mean quantity product used per person per year (5^{th} - 95^{th} perc)[c]	Mean exposure to vCJD iv ID_{50}[a] per person per year (5^{th} - 95^{th} perc)[c]	Mean potential vCJD risk per person per year[b] (5^{th} - 95^{th} perc)[c]	Mean exposure to vCJD iv ID_{50}[a] per person per year (5^{th} - 95^{th} perc)[c]	Mean potential vCJD risk per person per year[b] (5^{th} - 95^{th} perc)[c]
Prophylaxis	**39**	**165,713 IU[d]** (9876, 454306)	**4.30×10^{-7}** (0 - 0)[e]	1 In 4.7 million (0 - 0)[e]	**3.81×10^{-5}** (0 - 1.54×10^{-4})	1 in 52,000 (0 - 1 in 13,000)
Episodic	**60**	**11,045 IU[d]** (1025, 34352)	**4.14×10^{-8}** (0 - 0)[e]	1 In 48 million (0 - 0)[e]	**2.06×10^{-6}** (0 - 6.83×10^{-6})	1 in 971,000 (0 - 1 in 293,000)
ADULT vWD (> 15 yrs of age)						
Prophylaxis	**73**	**186,880 IU[d]** (16910, 539877)	**4.89×10^{-7}** (0 - 0)[e]	1 In 4.1 million (0 - 0)[e]	**4.32×10^{-5}** (0 - 1.82×10^{-4})	1 in 46,300 (0 - 1 in 11,000)

Episodic	**78**	**86,923 IU[d]** (2182, 240338)	**1.99×10^{-7}** (0 - 0)[e]	1 In 10 million (0 - 0)[e]	**1.90×10^{-5}** (0 - 8.43×10^{-5})	1 in 1 million (0 - 1 in 24,000)

[1]Number (percent) patients in a CDC sponsored study with 6 states to survey treatment of Hemophilia A and B conducted 1993 - 1998. Our analysis included 14 patients (<15yrs) and 28 patients (≥15yrs) (total = 42) on prophylaxis or episodic treatment with Humate P only and no record of inhibitor.

[a] iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.

[b] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Total mean quantity i.v. ID_{50} per year x 0.5 (50 % chance infection from ID_{50})

[c] The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.

[d] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

[e] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of pdFVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a pdFVIII plasma pool would be rare and more than 90% of pdFVIII product lots (of vials) would not be predicted to contain vCJD agent.

Estimation of Factor VIII product utilization by patients with severe von Willebrand disease. FDA obtained data on pdFVIII utilization, presumably used in the treatment of severe von Willebrand disease, from the Centers for Disease Control (CDC). Details of the CDC – Six state collaborative study are described in the section above (section IV.G.2) on FVIII utilization. Annual usage of product by vWD patients was estimated based on an assumption that this patient class largely uses Humate P. Therefore, only records for patients utilizing Humate P were extracted from the CDC - Six state study conducted from 1993 – 1998 and used to develop statistical distributions of product usage for young vWD (≤15 yrs old) patients and adult vWD (> 15 yrs old) patients. The mean quantity of product utilized per year per patient group is shown in **Table 5.2A.** and **Table 5.2B**.

Table 5.2B. Von Willebrand Disease (vWD) Patients[1] with Severe Disease: Predicted Total Population-based Exposure to vCJD i.v. ID_{50} and Potential vCJD Risk:

- Assuming a processing reduction of 4-6 $\log_{10}$, and
- Two different UK vCJD prevalence estimates.

			4 - 6 Log_{10} Reduction			
			Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)		**Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225** by Hilton *et al* (2004)	
	Est. Total Number severe vWD patients in US	**Mean Total quantity FVIII used by all patients per year (5th - 95th perc)[c]**	**Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]**	**Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]**	**Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]**	**Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]**
Mean total annual exposure and population	**250**	**29.9 million IU[d]**	**7.05×10^{-5}** (0 - 0)[e]	**1 in 28,450 years** (0 - 0)[e]	**4.91×10^{-3}** (0 - 2.59×10^{-2})	**1 in 405 years** (0 - 1 in 76)

risk		(3013, 311745)				

[1]Number (percent) patients in a CDC sponsored study with 6 states to survey treatment of Hemophilia A and B conducted 1993 - 1998. Our analysis included 14 patients (<15yrs) and 28 patients (≥15yrs) (total = 42) on prophylaxis or episodic treatment with Humate P only and no record of inhibitor.

[a]iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.

[b]Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Total mean quantity i.v. ID_{50} per year x 0.5 (50 % chance infection from ID_{50})

[c]The 5th- 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.

[d]IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

[e] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of pdFVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a pdFVIII plasma pool would be rare and more than 90% of pdFVIII product lots (of vials) would not be predicted to contain vCJD agent.

Potential exposure of severe von Willebrand disease patients to vCJD agent: Results based on lower epidemiological model estimated prevalence of ~1.8 in 1,000,000 (Clarke and Ghani, 2005). Adult vWD (>15yrs of age) patients with severe disease on prophylaxis consumed the largest quantities of pdFVIII product annually and may potentially be at greater vCJD risk. Using the lower epidemiological model prevalence estimate, analysis of pdFVIII utilization data indicated that 73 Adult vWD patients on prophylaxis treatment regimen used an average of 186,880 IU and are potentially exposed to an average of 4.89×10^{-7} i.v. ID_{50} per person per year, and representing an average potential vCJD risk of 1 in 4.1 million per person per year **(Table 5.2A.)**. At this level of risk, only 1 vCJD infection would be predicted to occur in an average of approximately 56,000 years. As mentioned earlier the 5th and 95th percentile intervals for all of the model outputs using the lower prevalence estimate (~1.8 per million) in **Table 5.2A.** are from 0 to 0 meaning that the chance of an infected donor donating to a plasma pool would be an infrequent event. Greater than 99% of the time (on average) the model estimates the risk to be zero because vCJD agent was not present in pdFVIII product used during treatment. However, the model predicts that 0.027% of the time the exposure to vCJD agent may be greater than zero, and there is a possible but low risk of vCJD infection.

Totaling the model results reveals that the approximately 250 severe vWD patients in the US used a total of 29.9 million IU, and are potentially exposed to an average total of 7.05×10^{-5} i.v. ID_{50} per year. This represents an average potential vCJD risk of 1 in 28,450 **(Table 5.2B.)** or (as predicted by the model) roughly equal to one vCJD infection observed over a time span of approximately 28,450 years in the population of 250 severe vWD patients.

Potential exposure of severe von Willebrand disease patients to vCJD agent: Results based on higher prevalence estimate of 1 in 4,225 (Hilton et al 2004). At the higher surveillance prevalence estimate, among the vWD patient populations examined by the model, results **(Table 5.2A.)** indicated that adult vWD (>15yrs of age) patients with severe disease on prophylaxis used the largest quantities of pdFVIII product annually and may potentially be at greater vCJD risk. Analysis of pdFVIII utilization data indicated that 73 Adult vWD patients on prophylaxis treatment regimen used an average of 186,880 IU per person per year and are potentially exposed to an average of 4.32×10^{-5} i.v. ID_{50} per person per year, representing an average potential vCJD risk of 1 in 46,300 per person per year **(Table 5.2A.)**. At this level of risk, only 1 vCJD infection would be predicted to occur in an

average of approximately 630 years for the population of 73 Adult vWD patients on prophylaxis treatment regimen.

The potential risk of vCJD infection for the entire population was calculated using the higher surveillance prevalence estimate. The model results shows that the approximately 250 severe vWD patients in the US used a total of 29.9 million IU (**Table 5.2B.**), and are potentially exposed to an average total of 4.91×10^{-3} i.v. ID_{50} per year. This represents an average potential vCJD risk of 1 in 405, i.e., of one vCJD infection observed over a time span of 405 years for the population of 250 severe vWD patients in the U.S.

Range of Predicted annual mean potential per HA patient vCJD risk for pdFVIII (Table 6)
The FDA risk assessment for potential vCJD infection risk for US manufactured pdFVIII generates results for several scenarios that reflect two key factors that greatly influence the final risk estimates including: (1) Reduction in vCJD agent in pdFVIII product during manufacture, and (2) UK vCJD prevalence estimate. As indicated earlier, the model used two widely different prevalence estimates, one lower prevalence estimate based on epidemiological modeling of predicted vCJD cases in the UK (Clarke and Ghani, 2005) of approximately 1.8 in 1 million and one higher prevalence estimate based on surveillance data of UK patient tissue samples (Hilton et al 2004) of 1 in 4,225. The use of these two estimates gives rise to a difference in results generated by the model that vary by an average of approximately 130 fold.

The model evaluated three separate categories of reduction in infectivity including 2-3 $\log_{10}$, 4-6 $\log_{10}$, and 7-9 $\log_{10}$. These three hypothetical categories were chosen to span the possible range of reduction of vCJD agent for pdFVIII products. **Table 5.3A. and 5.3B.** displays model results for a lower prevalence estimate and a higher prevalence estimate at all three levels of reduction. It should be noted that the mean difference between the lowest range of 2-3 $\log_{10}$ and the highest range of 7-9 $\log_{10}$ is nearly 1 million fold (6 $\log_{10}$). These two largest contributors to the final risk estimate also contribute to the greatest uncertainty in the model. Results from the model shown in **Tables 5.3A. and 5.3B.** indicate that there is a difference of approximately 20 to 55 million fold between the lowest and highest risk estimates of each patient group.

Table 5.3A. Range of *Predicted Annual Mean Potential per HA Patient vCJD risk for pdFVIII* – at *three levels of clearance: 7-9 log_{10}, 4-6 log_{10}, and 2-3 log_{10} and at a higher Prevalence and Lower Prevalence estimates and at .*

				7 - 9 Log_{10} Reduction		**4 - 6 Log_{10} Reduction**		**2 - 3 Log_{10} Reduction**	
				Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)	**Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225** by Hilton *et al* (2004)	**Model Output for LOWER vCJD Case Prevalence estimate ~1.8 in 1,000,000 based on** Clark and Ghani (2005)	**Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225** by Hilton *et al* (2004)	**Model Output for LOWER vCJD Case Prevalence estimate ~1.8 in 1,000,000 based on** Clark and Ghani (2005)	**Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225** by Hilton *et al* (2004)
Treatment Regimen	**Inhibitor Status**	**Est. Total Number patients in US**	**Mean quantity product used per person per year (5^{th} - 95^{th})[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**
Prophylaxis	No Inhibitor	**578**	**157949 IU** (21242 , 382316)	1 in 4.1 billion (0-0)[c]	1 in 50 million (0 - 1 in 11 million)	1 in 4 million (0-0)[c]	1 in 54,000 (0- 1 in 12,000)	1 in 15,000 (0-0)[c]	1 in 82 (0 - 1 in 17)
	With Inhibitor – No Immune Tolerance	**63**	**190523 IU** (26956 , 447639)	1 in 3.5 billion (0-0)[c]	1 in 40 million (0 - 1 in 8.8 million)	1 in 4.8 million (0-0)[c]	1 in 41,000 (0- 1 in9,000)	1 in 12,000 (0-0)[c]	1 in 65 (0 - 1 in 13)
	With Inhibitor – With Immune Tolerance	**62**	**558700 IU** (33235, 1592943)	1 in 551 million (0-0)[c]	1 in 15 million (0 - 1 in 3.4 million)	1 in 1.3 million (0-0)[c]	1 in 15,000 (0- 1 in3,700)	1 in 2,700 (0-0)[c]	1 in 24 (0 - 1 in 3)
Episodic	No Inhibitor	**946**	**85270 IU** (4633, 244656)	1 in 3.2 billion (0-0)[c]	1 in 100 million (0 - 1 in 24 million)	1 in 9.4 million (0-0)[c]	1 in 105,000 (0- 1 in 24,000)	1 in 21,500 (0-0)[c]	1 in 159 (0 - 1 in 34)
	With Inhibitor	**151**	**160458 IU** (5314 , 488906)	1 in 4 billion (0-0)[c]	1 in 50 million (0 - 1 in 11 million)	1 in 8 million (0-0)[c]	1 in 23,000 (0- 1 in 12,000)	1 in 23,000 (0-0)[c]	1 in 73 (0 - 1 in 16)

[a] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.

[b] The 5^{th}- 95^{th} perc (percentiles) are the minimum and maximum numbers that define the range constituting the 90% confidence interval. Accordingly, the mean risk estimates from the model should fall within this defined interval at least 90% of the time.

[c] For a 5^{th} and 95^{th} percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of pdFVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a pdFVIII plasma pool would be rare and more than 90% of pdFVIII product lots (of vials) would not be predicted to contain vCJD agent.

This range or difference in the estimates of about 20 -55 million fold is reflected in the higher and lower prevalence results generated by the model shown in **Table 5.3A.** for each HA patient treatment group with severe disease. On closer inspection of the results in **Table 5.3A.** for patients with the most intensive pdFVIII product use, that is, the 62 patients on prophylaxis-with inhibitor and with immune tolerance, the effect of clearance on mean potential vCJD risk across the three ranges of clearance can be seen. At the low end of risk, the mean potential vCJD risk per patient per year risk (at 7-9 $\log_{10}$ and the lower prevalence estimate) is 1 in 551 million. Conversely, the highest risk for this patient group is seen at the 2-3 $\log_{10}$ clearance level and the higher prevalence estimate and is estimated by the model to be an average of 1 in 24. For patients on episodic treatment with no inhibitor who have a less intensive annual use of product, the model predicts the lowest risk (at 7-9 $\log_{10}$ and the lower prevalence estimate) to be 1 in 3.2 billion. The model predicts the highest risk for this group of patients, if they used pdFVIII product with a 2-3 $\log_{10}$ clearance level and the higher prevalence estimate, would be a mean potential per patient risk of 1 in 159.

Table 5.3B. Range of Total Population-based Exposure and Potential vCJD Risk from Model Predicted HA population with severe disease annual vCJD Exposure and Risk associated with use of plasma-derived Factor VIII:

- Lower Prevalence assumptions of Prevalence of 1.8 in 1,000,000 and 7-9 $\log_{10}$ reduction, and
- Higher Prevalence assumptions of Prevalence of 1 in 4,225 and 2-3 $\log_{10}$ reduction.

			7 - 9 $\log_{10}$ Reduction		4 - 6 $\log_{10}$ Reduction		2 - 3 $\log_{10}$ Reduction	
			Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)	Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225 by Hilton et al (2004)	Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)	Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225 by Hilton *et al* (2004)	Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)	Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225 by Hilton *et al* (2004)
	Est. Total Number severe vWD patients in US	Mean Total quantity FVIII used by all patients per year (5^{th} - 95^{th} perc)[b]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c])[c]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c]
Mean total annual exposure and population risk	**1,800**	**243 million IU**	**1 vCJD infection in 1.6 million years** (0-0)[c]	**1 vCJD infection in 35,000 years** (0 -1 in 9,000)	**1 vCJD infection in 3,100 years** (0 -0)[c]	**1 vCJD infection in 40 years** (0 -1 in 10)	**1 vCJD infection in 8 years** (0 -1 in 2)	**~13 vCJD Infections per year** (0- 54 vCJD infections)

[a] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.

[b] **The 5^{th}- 95^{th} perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.**

[c] For a 5^{th} and 95^{th} percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of pdFVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a pdFVIII plasma pool would be rare and more than 90% of pdFVIII product lots (of vials) would not be predicted to contain vCJD agent.

The results from the risk assessment model shown in **Table 5.3A.** show a wide range of difference in the predicted risk and displays the range in our uncertainty and knowledge in

predicting the potential vCJD infection risk for HA patients who use US manufactured human pdFVIII. However, as further scientific information and data become available in the future, the uncertainty in the model may decrease and the estimates of vCJD risk for recipients of pdFVIII may become more precise.

Evaluating the total vCJD infection risk for the severe HA population of 1,800 by summing the total annual exposure (at the higher vCJD Infection prevalence estimated), the model predicts that the population would use a total average of approximately 243 million IU FVIII. If the patient population used product that attained a clearance of 7-9 $\log_{10}$ and assuming the lower prevalence the model predicts that for the total patient population the mean total annual risk would be 1 case in 1.6 million years representing a negligible vCJD risk that would likely not give rise to new cases of the disease. At the other end of the spectrum at the 2-3 $\log_{10}$ clearance level and the higher prevalence the model predicts a mean of approximately 13 vCJD infections per year **(Table 5.3.B.)** for the patient population.

V. D. Sensitivity analysis

Sensitivity analysis is used to identify the input parameter or parameters that have the greatest impact on the risk estimates generated by the model and are done by varying the values of key input parameters and evaluating the effect on the final risk estimate. Our goal in doing these analyses was to identify the key input parameters that have the greatest influence on annual exposure to the vCJD agent. The model was examined and candidate variables for the sensitivity analysis were chosen from the model that exhibited the largest potential for variability and/or uncertainty and those values are listed in Table 5-7. Importance analysis is a type of sensitivity analysis. Our importance analysis used two values, one at the minimum or 5th percentile value and one at the maximum or 95th percentile value to provide a reasonable estimate of impact across the range tested. The results from the importance analysis are displayed as tornado plots (**Figures 2.A., 2.B. and 2.C.**), which graphically shows the relative influence of each input parameter evaluated on the final model estimates. The most influential factors are displayed at the top of the plot and those that are least influential or those with negative influence on the risk are at the bottom of the plot.

For the FVIII risk assessment the output being monitored in the sensitivity and importance analyses was annual exposure (I_{yr}) to vCJD agent quantified in i.v.ID_{50} units. The sensitivity and importance analysis were conducted using the HA patient population on prophylaxis treatment regimens with inhibitor and being treated for immune tolerance as the example population used to do the analyses. This population displayed the largest mean usage and the widest range in product utilization. We assumed that the sensitivity and importance analysis results are representative of all the HA and vWD patient populations included in our study since all of the populations were assumed to differ only by the total average quantity of pdFVIII utilized per year.

The importance analysis was performed for each variable by doing two sets of simulations, each with 5,000 iterations. For each set of simulations the value of one testing variable was set at the minimum or 5th percentile value for the input distribution and the simulation run; for the second run the variable was set at the maximum or 95th percentile value and the simulation run. The importance analysis was run separately each time using one of the three surveillance estimate

ranges. The first analysis used a range of 0.7 to 700 per million, which encompasses the entire range for both the HIGH and LOW prevalence estimates. The second analyses used the higher vCJD Infection prevalence estimate of 1 in 4,225 (or 237 per million) derived from a tissue surveillance study (Hilton et al 2004). This prevalence was based on the variable ($P_{vCJD\text{-}Surv}$) in the model that used data from a tissue surveillance study. To do the sensitivity analysis we used a 5th percentile value of 49 per million and a 95th percentile value of 692 per million. The third set of analyses used the lower vCJD Case prevalence estimate of ~1.8 per million based on epidemiological modeling from actual vCJD occurrence conducted by Clarke and Ghani (2005). This prevalence was ($P_{vCJD\text{-}Epi}$) based on epidemiologic modeling and to do the sensitivity analysis we used a 5th percentile value of 0.7 per million and a 95th percentile value of 4 per million. The results of all simulations and the ranking of input parameters by their importance is represented graphically using a tornado plot shown in **Figures 2.A. , 2.B. and 2.C.** The tornado plot displays the correlations between key inputs in the model and the model output of exposure. A tornado plot prioritizes the various input factors with the most influential factors at the top and those that are least influential or those with negative influence on the risk are at the bottom of the plot.

Table 5.4. Input Variables included in Importance Analysis

Description of variables	Name of input variable	Importance analysis values
Entire range of estimated vCJD prevalence in UK (cases/million)	$Prev_{vCJD\text{-}UK}$	Minimum: 0.7 Maximum: 700
High prevalence estimate of vCJD in UK (cases/million)	$Prev_{vCJD\text{-}UK(Surveillance)}$	5th perc: 49 95th perc: 692
Low vCJD prevalence in UK (cases/million)	$Prev_{vCJD\text{-}UK\ (Epi\ model)}$	5th perc: 0.7 95th perc: 4.0
Efficiency of donor deferral policy	Eff_{Def}	Minimum: 85% Maximum: 99%
Efficiency of i.c. versus i.v. route	$A_{ic\text{-}iv}$	Minimum: 0.1 Maximum: 1
Number of donors per plasma pool	DR_{Pool}	Minimum: 6500 Maximum: 360000
Quantity of i.c. infectivity in infected human blood	I_{bl}	5th perc: 2 95th perc: 30
Manufacturing yield of FVIII (IU/L plasma)	Y_{VIII}	Minimum: 120 Maximum: 250
Log Manufacture Reduction of vCJD agent	R_{Log}	Minimum: 2 Maximum: 9
FVIII used per year (IU/year)	IU_{yr}	5th perc: 10000 95th perc: 4000000

Sensitivity analysis is used to study the quantitative relationship between the input variables and risk output. Same as in importance analysis, output to be monitored in sensitivity analysis is annual exposure (I_{yr}) to vCJD of young HA patients under prophylaxis treatment with inhibitor and immune tolerance treatment. Sensitivity analysis for an input variable consists of multiple simulations. In each simulation the testing input variable is fixed at one value within the input range. Results of sensitivity analysis are presented only for the most important input variables, which were identified by the ranking provided by the importance analysis.

Fig 2. A. Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using prevalence estimate encompassing the range of values for both high and low prevalence from 0.7 to 700 vCJD cases per million UK population. Tornado chart showing impact of input variables on estimated annual exposure of severe HA patient with prophylaxis, inhibitor and immune tolerance treatment

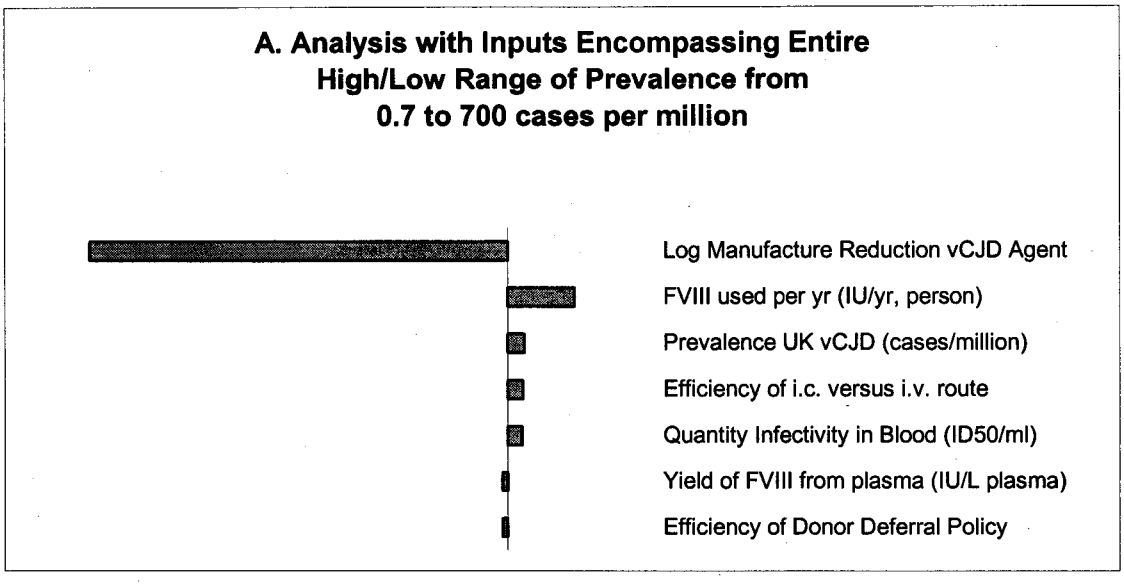


Fig 2. B. FVIII Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using Tissue Surveillance-based (HIGH) prevalence estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of pdFVIII recipients.

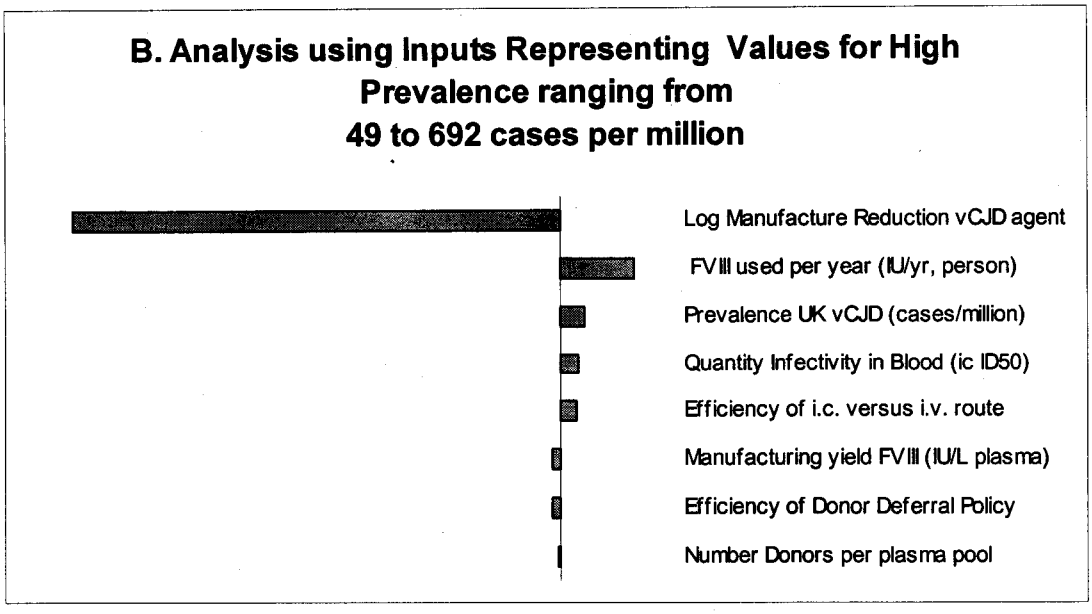
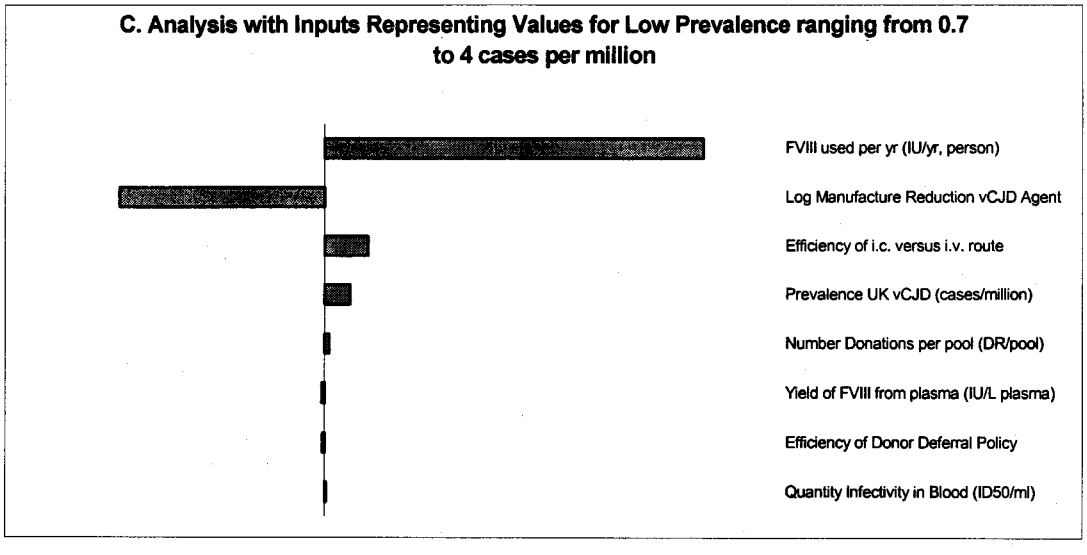


Fig 2. C. FVIII Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using Epi Modeling-based (LOW) prevalence estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of pdFVIII recipients.



Some input variables are used multiple times in the original model, for instance each type of plasma pool (Source or recovered) was modeled on an individual basis. Other examples are pool size ($DR_{pool\text{-}S}$ and $DR_{pool\text{-}R}$), yield (Y_{FVIII}), quantity of i.c. infectivity in the infected human blood (I_{bl}) and the reduction of infectivity during manufacturing (R_{Log}). In importance analysis and sensitivity analysis, when these input variables are tested, we assumed that there was no difference among the pools. When evaluating the impact of a specific variable all other values are held constant during the simulation. When simulating parameters with multiple values (e.g., size of recovered plasma pools) all values are the same for the simulation. The magnitude of changes in risk output associated with changes of input variables are graphed in the tornado chart, which

represents the relative ranking of the input variables by their impacts on the risk outcome. The importance analysis was conducted for three possible ranges of UK vCJD prevalence: one set of analysis for tonsil survey based estimate, one set for epidemiology model-based estimate and another set for the two prevalence estimates combined.

The order of the influence of the specific input factors varies slightly when the importance analysis is conducted using the three difference prevalence estimates. When a higher prevalence estimate was used (either the combined prevalence (0.7 to 700 per million) the tornado plots in **Figures 2.A. and 2.B**. both show that clearance or Log reduction of the vCJD agent ($\mathbf{R_{Log}}$) during the manufacturing process is the dominant factor that influences the annual exposure or risk for a pdFVIII recipient. The importance analysis suggests that changes in the input values for prevalence used in the analysis can cause some visible changes in the rank order of the influence of the various input factors. A change in the rank order of model factors is seen when the lower prevalence estimate of 0.7 to 4 per million is used **(Figure 2. C.).** The dominant factor potentially driving risk then becomes the quantity of pdFVIII used by a patient.

In our importance analysis the five variables that had significant influence on the output of the model were clearance of i.v. ID_{50} from pdFVIII products, pdFVIII use (IU/yr), UK vCJD prevalence, adjustment for the efficiency of transmission via the i.c. route vs. the i.v. route, and the quantity of i.v.ID_{50} in blood. Changes in prevalence did cause the variable parameters to reassort and change rank when the different prevalence estimates were used. Overall, however, they were somewhat similar in asserting their influence on the estimated risk outcome(s), but had significantly less influence when compared to that of reduction of infectivity during processing and manufacture. Although these types of sensitivity analysis and tornado plots are often used to identify influential factors of risk, their use has some limitations. Factors are examined singly or in isolation so interaction among various factors that may influence the risk estimate are not addressed.

General comments on model outputs

The risk estimations in this section of the risk assessment are predicated on the assumption that there is homogeneous mixing and dispersion of vials from all pools among all donors. In reality, vials may not be dispensed homogeneously and it is likely that patients draw from only one or a few manufactured lots of pdFVIII product in a given year. FDA did not have data to model this non-homogeneous dispensing of pdFVIII but the model can be used to estimate the average maximal level of i.v. ID_{50} exposure if on a very rare chance all vials used by a patient in a given year happened to contain vCJD agent.

V. E. Uncertainty and Data Gaps

Uncertainty arises from the absence of information or availability of limited information. In our probabilistic model statistical distributions are used, where possible, to represent the uncertainty of much of the information used in the model. There are uncertainties in the information and the model that we were unable to quantify and that are not represented in the final risk estimates. Some of the difficult to quantify uncertainties are associated with the extrapolation of a human dose-response relationship based on animal data, an assumed linear dose response with no

uncertainty or variability bounds, and assumption of infectivity in the last 50% of the incubation period. We express the uncertainty of the final risk estimates generated from the model using a mathematical mean (average) of exposure in ID_{50} units and the 5^{th} and 95^{th} percentiles, which represent the 90% confidence interval for each estimate. The uncertainty for the risk estimates generated by this FVIII risk assessment model is significant and decision makers should use the results with caution. Similarly, patients and physicians should understand that the uncertainties are too great at this time to determine the presence, absence or degree of actual risk. In the future, additional research and information may be substituted for assumptions or used to improve estimates for the individual parameters and ultimately improve the precision of the final risk estimates generated by the model.

Even considering the associated uncertainty of estimated risks, risk assessment provides an estimate of risk based on the current and known information. It is still a useful tool that can inform the science-based decision making process. It can identify data gaps and research priorities where additional research and information would have the greatest impact on enhancing the final risk estimates. The sensitivity analysis results in Section IV.C. indicated that the risk assessment results are highly dependent upon log reduction of vCJD agent ($\mathbf{R_{Log}}$) during the manufacturing process. The modeled estimates were based upon levels of reduction seen for manufacturing steps of several different types of plasma-derived products that were similar in some but not all respects to those used in the manufacture of FVIII products. More high quality data on the levels of vCJD agent clearance achieved during the pdFVIII manufacturing would likely improve the final risk estimate generated by the FDA model. Given the lack of data on vCJD agent clearance for pdFVIII uncertainty is considerable.

Better information on when infectivity is present in human blood during the incubation period is a critical factor in the model, especially if the higher vCJD infection prevalence estimate (of 1 in 4,225) is in the range of the actual vCJD prevalence, and would improve predictions generated by the model. There are no data available on the level of infectious units or ID_{50} units present in the bloodstream of vCJD infected individuals at the time of blood donation. The model extrapolates an estimate of the level of vCJD agent that might be present in human blood based on data from several animal models. However, the presence and level of agent present in an infected individual at the time of blood donation could differ from our assumption and this adds to the uncertainty of the risk assessment outcomes.

The model estimates exposure to the vCJD agent in the form of intravenous ID_{50} units. Data are not available to estimate the probability of various clinical outcomes, such as infection or illness that might be predicted to arise from exposure to a particular level of agent. Although we did estimate a probability of infection in our model, the uncertainty associated with the estimate is considerable. However, a meaningful dose-response model would need to be generated for vCJD exposure in humans to improve estimates of the probability of adverse clinical outcomes for humans. The type of data needed to generate a dose-response model that would improve the quality of TSE risk assessment predictions would necessitate injection of groups of animals at several different concentrations of ID_{50}, including low doses below 1 ID_{50} using a protocol that mimics transfusion transmission of vCJD in humans. Both infection and duration of the incubation periods at several different i.v. ID_{50} concentrations would be useful endpoints for developing informative dose-response relationships. Given the state of the current TSE science, estimates of the probability of vCJD infection or illness arising from exposure to the vCJD agent are still extremely uncertain. Nevertheless risk assessment is a tool that provides insight into

important factors where additional research is needed into production processes, tools, or strategies that may further reduce vCJD risks and advance product safety for patients.

The manufacturing processes for pdFVIII are highly varied – therefore, any potential clearance of the vCJD agent during production is likely variable and dependent upon the specific steps used to produce the final product. For example, the techniques applied in fractionation process vary from manufacture to manufacture including the sizes of plasma pools used for producing pdFVIII, the yield of products, and the reduction of infectivity during processing varies within a limited range from batch to batch. In addition the utilization of pdFVIII varies from individual to individual. This risk assessment considers the typical production and utilization. Uncertainty from the model should be appreciated. Human plasma-derived FVIII is typically prepared through successive steps of large scale fractionation during the manufacturing process. Cryoprecipitation is the first and a common step in preparation of pdFVIII. Afterward, cryoprecipitate undergoes further fractionation procedures such as precipitation, absorption/desorption, ion exchange and filtration to yield intermediate purity FVIII, [redacted] In certain cases some hospitals may prepare small amount of cryoprecipitate FVIII from small plasma pools (1-8 donations/pool) for special treatment purposes. Preliminary risk assessment results indicated that the risk that vCJD would be transmitted through cryoprecipitated AHF is relatively low due to the small size of plasma pool and small numbers of donors involved. This risk assessment uses 3 ranges of possible clearance of vCJD agent from pdFVIII of 2-3 $\log_{10}$, 4-6 $\log_{10}$, and 7-9 $\log_{10}$ to cover the possible ranges for all pdFVIII products presently in the marketplace.

General comments on model outputs

The risk estimations in this section of the risk assessment are predicated on the assumption that there is homogeneous mixing and dispersion of vials from all pools among all donors. In reality, vials may not be dispensed homogeneously and it is likely that patients draw from only one or a few manufactured lots of pdFVIII product in a given year. FDA did not have data to model this non-homogeneous dispensing of pdFVIII but the model can be used to estimate the average maximal level of i.v. ID_{50} exposure if on a very rare chance all vials used by a patient in a given year happened to contain vCJD agent.

V. F. Conclusions

Results from the FDA pdFVIII risk assessment model suggest that the risk of vCJD infection from US manufactured pdFVIII generally appears likely to be very low, but may not be zero. For US plasma donors, the major source of vCJD risk is dietary exposure during travel and/or residency in the UK, France, or other countries in Europe since 1980. Although donor deferral criteria in place since 1999 have reduced the risk of donation by exposed persons some are not deferred and potentially may donate plasma that contains the vCJD agent. However, the model suggests that the likelihood of a vCJD contaminated plasma pool is low.

Manufacturing processes for human pdFVIII products likely reduce the quantity of vCJD agent, if present, but the level of reduction through manufacturing steps is not precisely known. Clearance of TSE agents in manufacturing appears to vary among products, but has not been measured in standardized studies which might allow more meaningful direct comparisons. Based on currently available experimental studies, it is estimated that pdFVIII products potentially have

4 $\log_{10}$ (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. Assuming a 4-6 $\log_{10}$ manufacturing process reduction, the modeling predicts that the potential risk per person per year for patients with severe HA using pdFVIII ranges from1 in 15,000 for the higher vCJD prevalence estimate and high product usage to 1 in 9.4 million for the lower vCJD prevalence estimate and low product usage. Due to the wide range of methods used for clearance studies currently available, gaps in information, and the results of the model, it is not possible at this time to determine with any certainty if a specific product may be less or more safe than another.

Although results of the model suggest exposure to vCJD agent is possible, and there is a potential risk of infection that is likely to be very low, it is not possible for the model to provide a *precise* estimate of the vCJD risk in general, or of the actual risk to individual patients. Although the actual risk is highly uncertain, the risk assessment model indicates that the most important factors affecting risk are the clearance of the vCJD agent though manufacturing steps, how much product individuals used, and the vCJD prevalence in the UK donor population.

In considering the results of the risk assessment it is important to note that to date we are not aware of any cases of vCJD having been reported worldwide in patients receiving plasma-derived products, including pdFVIII.. This includes patients receiving large amounts of other products manufactured from UK plasma donations over a long period of time. This observation suggests that the actual risk of vCJD infection from pdFVIII is likely to be very low. The absence of cases does not rule out the possibility of exposure that could potentially result in illness in some recipients at some future point in time.

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