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 (5th - 95th perc)[b]**	**Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]**	**Mean potential vCJD risk per person per year[a] (5th - 95th 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