

^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 log₁₀ 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 (5 th - 95 th perc) ^c	Mean population -based potential vCJD risk ^a (5 th - 95 th perc) ^b	Mean population -based potential vCJD risk ^a (5 th - 95 th 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 log₁₀ 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 log₁₀, and
- Two different UK vCJD prevalence estimates.

YOUNG vWD (≤ 15 yrs of age)				
			4 - 6 Log₁₀ 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
<i>Prophylaxis</i>	39	165,713 IU^d (9876, 454306)	1 in 4.7 million (0-0) ^e	1 in 52,000 (0 - 1 in 13,000)
<i>Episodic</i>	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 log₁₀, and
- Two different UK vCJD prevalence estimates.

		4 - 6 Log₁₀ 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 total annual exposure and population risk	250	29.9 million IU^d (3013, 311745)	1 in 28,450 years (0 - 0) ^e
			Mean^b population -based Potential vCJD risk (5th - 95th perc)^c
			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 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.

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 log₁₀ (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. Assuming a 4-6 log₁₀ manufacturing process reduction, the model predicts that the potential risk per person per year for patients with severe HA using pdFVIII ranges from 1 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 through 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. ID₅₀/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 recipient 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 transfusions 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 ID₅₀ 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 ID₅₀ is cumulative over a one year period. The ID₅₀ is the common metric used to quantify the infectivity of TSEs. One ID₅₀ 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 ID₅₀ 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 ID₅₀ relationship used in the model was based on infectious TSE units estimated from rodent model studies (Brown 1998, 1999; Rowlier 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 ID₅₀ would suggest a 50% probability of infection, exposure to 0.1 ID₅₀ 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