

Since 2003, three presumptive transfusion transmitted cases of vCJD have been reported in the UK. Two of the transfusion recipients died of vCJD, whereas the third had vCJD infection detected after death from an unrelated cause. Each had received transfusions of red blood cells from individuals who were asymptomatic at the time of donation, but who later died from vCJD. The strong likelihood that transmission of vCJD occurred via transfusion of red blood cells in the UK increased the concern that products manufactured from the plasma portion of human blood might also pose a risk of vCJD transmission. Note, however, there have been no reported cases of vCJD in any recipients of plasma derived products in the UK, where risk is considered greatest, or anywhere else in the world. In the fall of 2004 UK authorities notified recipients of a number of plasma derivatives that they might be at increased risk of vCJD. These products included coagulation factors VIII, IX, and XI, as well as antithrombin III, and intravenous immune globulins.

Because BSE occurs at an extremely low level in US cattle (only three reported cases: two in US born cattle and one in a cow imported from Canada), and there have been no human cases of vCJD acquired in the US, any risk of plasma donors acquiring vCJD by consuming domestically produced beef is thought to be extremely low. However, it is possible that a small population of US donors may have been exposed to the BSE agent during travel or residence in the UK, France, or other countries of Europe and may therefore be at some risk for vCJD. Some of these donors may have been unknowingly infected with vCJD through dietary exposure and then contributed donations to plasma pools used to manufacture pdFVIII in the U.S. The 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 has developed a computer-based simulation model to try to estimate the potential risk and understand factors involved in determining and potentially reducing the degree of risk. The model and various risk estimate results and uncertainties are presented in the document "A 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" provided as a separate attachment. The results are estimates of 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 the severe form of von Willebrand disease (vWD) (Type 3) who have used human pdFVIII product manufactured in the US.

The parameters used in this risk assessment were derived after receiving recommendations from the TSEAC about another risk assessment, the "Draft Risk Assessment: Potential Exposure to the vCJD agent in United States Recipients of Factor XI Coagulation Product Manufactured in the United Kingdom" at the February 8, 2005 meeting; from discussion at a meeting of the TSEAC on October 31, 2005 on several risk assessment model inputs for plasma derivatives and potential vCJD risks specifically related to pdFVIII; and from peer review by non-FDA experts in risk assessment.

The ranges of uncertainty and variability in the input parameters of the risk assessment are great, resulting in very large uncertainty in the model's outputs that estimate potential risk. Additionally, because scientific data on the level of exposure to the vCJD agent and the

likelihood of certain human health outcomes, such as infection and illness, are lacking, estimates for the infectious risk generated in the risk assessment may not be accurate. For these reasons, it is not possible to provide an actual estimate of the vCJD risk to individual patients potentially exposed to the vCJD agent through plasma-derived products. Additionally, the absence of any reported cases of vCJD in repeatedly exposed recipients of plasma derivatives in the UK, where risk is thought to have been greatest, or anywhere else in the world, further suggests that the actual risk of vCJD from pdFVIII is likely to be very low.

Nevertheless, FDA believes it is appropriate to share both the findings of and the uncertainties in our risk assessment for pdFVIII with physicians, patients, and the general public since it is possible that the risk is not zero. Advice will be sought from the TSEAC in December concerning communication of the findings of the risk assessment and its interpretation, given the very wide range of uncertainty in the estimate of vCJD risk. Advice will also be sought on potential steps that may help to better understand as well as to further reduce any risks.

## **DISCUSSION:**

### **A. Risk Assessment and Interpretation**

The FDA risk assessment estimates the risk of vCJD infection as a function of product exposure for different assumed levels of vCJD infectious agent clearance in manufacturing of pdFVIII and under two assumed levels of vCJD prevalence in the UK. The risk assessment utilizes a probability-based statistical sampling model that evaluates successively the impact on vCJD risk of individual processes used in the production of human pdFVIII beginning with plasma donation, extending through manufacturing steps, and finally, addressing utilization by various representative patient subpopulations. Input data for parameters used in the model such as clearance, vCJD prevalence, and pdFVIII usage are represented as statistical distributions that express the underlying uncertainty and variability. Each run of the model randomly samples one number from the distribution for each parameter; this is done thousands of times to generate a single distribution representing the final risk estimate that expresses, where possible, the accompanying uncertainty of these risk estimates. A sensitivity analysis, conducted by varying values of key parameters within the input range of the model and observing the effect on the predicted outcomes, determined that three major factors in the model greatly influenced potential vCJD risk: reduction of the infectious agent by the manufacturing process, intensity of pdFVIII utilization by the patient, and differing estimates of disease prevalence in the UK.

One of the most influential risk assessment parameters for vCJD risk is the manufacturing process, which may reduce or eliminate the amount of the vCJD agent in the final product. Because of the uncertainty and variability in the levels of vCJD clearance afforded during the manufacturing process for any pdFVIII product, the model evaluated three separate categories of reduction in infectivity that the product may have undergone during manufacturing including 2-3  $\log_{10}$ , 4-6  $\log_{10}$ , and 7-9  $\log_{10}$  reduction. These three categories are meant to span the possible range of uncertainty and variability in reduction of vCJD agent for marketed pdFVIII products. Based on currently available experimental studies, FDA believes that all US licensed pdFVIII products probably achieve at least a 4  $\log_{10}$  of vCJD level of clearance during manufacture.

Another major variable affecting potential risk is the quantity of product used by patients in different treatment groups. For purposes of this model only patients with severe HA were considered because their higher use of product would put them at higher risk than patients with mild or moderate forms of the disease. Severe HA patients account for approximately 50% of the total HA population. Approximately 25% of all HA patients use pdFVIII products, while most others use recombinant FVIII. Data from a CDC sponsored epidemiological study on HA patients were used to generate the statistical distribution of pdFVIII usage by patients. Using these estimates, the risk assessment evaluated different treatment regimens including patients on prophylaxis, prophylaxis plus inhibitor, prophylaxis plus inhibitor plus immune tolerance, episodic treatment, and episodic treatment plus inhibitor. It also evaluated the potential of patients with severe von Willebrand disease (vWD) to be exposed to the risk of infection with vCJD through the use of pdFVIII. These patients must use plasma-derived sources of FVIII/von Willebrand factor because there is presently no recombinant von Willebrand factor.

The prevalence of vCJD in the United Kingdom population was used to estimate vCJD exposure and therefore prevalence in US donors who traveled to the UK, France and other European countries. For purposes of the risk assessment, we used two different estimates of vCJD prevalence in the UK. One estimate is based on epidemiological modeling of actual reported cases and an estimate of future vCJD cases in the UK. The other estimate is based on testing for prion protein in a relatively small tissue (tonsil and appendix) surveillance study. At present it is not possible to know which of the two estimates of vCJD prevalence in the UK provides a better estimate of the true prevalence.

The vCJD case prevalence based on epidemiological modeling of actual reported cases and an estimate of future vCJD cases in the UK yielded an estimate of approximately 1.8 vCJD cases per million. There are a number of limitations to this estimate based on simplifying assumptions that contribute to considerable uncertainty in the final case estimates. These assumptions include the intensity of human exposure to the BSE agent, the length of the incubation period, and how a person's age and genetic background could influence exposure, disease susceptibility, and incubation period. However, it is possible that the prevalence of vCJD in the UK is higher than this estimate if there are people infected who never develop the disease (but can still spread the infection) or if some individuals take an extremely long time to become ill. Therefore, we also used a second approach to estimate vCJD infection prevalence based on testing for prion protein in a relatively small tissue (tonsil and appendix) surveillance study. This approach yielded an estimate of 1 in 4,225 (237 infections per million). Limitations to this study that contribute to uncertainty include the fact that 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 finding of prion protein in tissues is a reliable marker for vCJD pre-clinical infection or for an individual's capability to transmit the infection through blood donation.

After accounting for the age distribution, incubation period, country, year and duration of travel, these two different prevalence estimates have been used to predict the number of vCJD donations that could be present in variably sized pools of US donated plasma.

## Results

See Risk Assessment, including the Executive Summary, and especially Tables I.A and II.A in the Executive Summary and attached here in an Appendix.

### Interpretation

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. Donor deferral criteria in place since 1999 have reduced the risk of donation by exposed persons.

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<sub>10</sub> (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. Assuming a 4-6 log<sub>10</sub> manufacturing process reduction, the modeling 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. While higher levels of clearance are likely to reduce risk, it is not possible at this time to determine with certainty if a specific product may be less or more safe than another due to the wide range of methods used for clearance studies currently available, the results themselves, and gaps in information. Although results of the model suggest that exposure to vCJD agent could occur, and that there is a potential risk of infection that is likely to be generally 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. Despite the uncertainties in the model, we believe this is information that patients and physicians might consider when making treatment decisions.

### **B. Risk Management Strategy, Key Message Points, and Communication Strategy**

#### **Risk Management Strategy**

FDA's current risk management strategy for vCJD has evolved in response to emerging epidemiologic findings and basic scientific developments pertinent to the epidemic. The overall risk management strategy for vCJD includes:

- Deferral of donors at increased risk of vCJD based on epidemiological data, and withdrawal of products at increased vCJD risk
  - Donor deferrals: Guidance since August 1999 (most recently updated in January 2002) to defer donors with "geographic risk," e.g. that visited or resided in countries where BSE prevalence is higher; deferral of donors that used UK-sourced bovine insulin; deferral of donors transfused in the UK since 1980 (note also draft guidance published in August 2006 for deferral of donors transfused in France since 1980).
  - Withdrawal of implicated blood components and plasma derivatives is recommended if a donor is diagnosed with vCJD

- Facilitating development, validation, and information sharing (including product labeling) regarding the performance of manufacturing processes in clearance of TSE agents from blood products.
  - FDA reviews requests for TSE clearance labeling claims which may be approved if detailed, validated TSE clearance study data are provided
  - On September 18, 2006, FDA discussed with TSEAC the feasibility and scientific value of standardized assessments of TSE clearance in the manufacturing processes for pdFVIII. The topic will be addressed again at this meeting
- Facilitating development of candidate donor screening and diagnostic tests for vCJD and other TSEs
  - FDA has held meetings with candidate test kit manufacturers to discuss developmental pathways
  - A public discussion of validation for donor screening tests for vCJD and other TSEs was discussed with the TSEAC on September 19, 2006
- Risk assessment and communication to inform patients and physicians about the current scientific understanding regarding vCJD risk from blood products and to help in informing treatment decisions
  - FDA has engaged in periodic reassessment of TSE epidemiology and pathogenesis to determine whether guidance/policies need to be revisited in light of new information
  - FDA performed risk assessments for potential exposure to vCJD in investigational pdFXI made from plasma donated in the UK, and for pdFVIII made from plasma donated in the US

The risk assessments that FDA has performed for potential exposure to vCJD from licensed pdFVIII made from US plasma has led us to consider further actions. Based on the finding that, despite very large uncertainties in the risk assessment models and generally low risk estimates, the risk of vCJD exposure from these products may not be zero, and we are taking the following steps:

- The risk assessment model has indicated that the level of TSE agent clearance during product manufacturing is one of the most important parameters for vCJD risk. For this reason, FDA seeks to improve our understanding of the actual prion clearance in manufacturing by encouraging standardized clearance studies of the different pdFVIII products, and, potentially, by setting minimum standards for TSE agent clearance.
- Although the risk of vCJD exposure from US pdFVIII products is likely to be very low, and it may not be zero, and FDA is encouraging physicians and patients to consider this risk in making treatment decisions.

#### **DRAFT Risk Communication Messages**

Based on the findings of the risk assessment FDA has developed key message points and additional, background information about the risk of vCJD in pdFVIII made from US donor plasma. They include the following:

#### Key Messages

vCJD (variant Creutzfeldt Jakob Disease, the agent which causes the human form of "Mad Cow Disease") is rare, even in the UK. Infection is not known to have been acquired in the US and there is no evidence that any US plasma donor has had vCJD. FDA has put steps in place to reduce the risk of transmission by deferring plasma donation from individuals with the most potential risk of exposure, those who lived in affected areas for significant time periods. Exposure to vCJD through pdFVIII could still potentially occur if someone traveled or resided briefly in the UK or another area where TSE is present, and became infected without knowing it from eating infected meat, and then donated plasma. While blood transfusion has transmitted vCJD in the UK, pdFVIII products go through additional manufacturing steps likely to help remove the agent and reduce or eliminate the risk of transmitting the disease.

FDA used a computer risk assessment model to help estimate any remaining potential risk to US pdFVIII recipients. While there are still many uncertainties, and it is not possible to estimate risk for specific individuals, the model suggests that any potential risk to the health of most US pdFVIII recipients is likely to be very low. Also, no cases of vCJD have yet been reported in patients receiving such products either in the UK, where the risk is highest, or anywhere else in the world.

Because so much is unknown about vCJD and its incidence, the risk assessment performed by FDA has a lot of uncertainty, making it impossible to precisely estimate any risk. However, we wanted to provide information about the risk assessment so that patients and health care providers can consider the matter, where appropriate, in their treatment decisions.

#### Additional Information

vCJD is a very rare, fatal disease that can infect a person for many years before making people sick by destroying cells in the brain.

Most cases of vCJD have occurred in the UK and individuals there are thought to be at higher risk for the disease than individuals elsewhere.

Beef products contaminated with the infectious agent of BSE are the main cause of vCJD. As of August 2006, world-wide, 195 cases have been reported, 162 of them in the UK. Food risk in the US blood donor population is expected to be very low as there have been only three cases of BSE found in US cattle (two US born, and one imported from Canada) and safeguards are in place to prevent infected beef products, if present, from entering human food.

While most vCJD is due to eating infected beef products, there is convincing evidence that the disease has also been transmitted by red blood cell transfusion. In

the UK, three people who became infected with the vCJD agent had received blood from donors who later developed vCJD

Plasma is the liquid part of blood, after the cells are removed, that is used for manufacture of plasma-derived products such as pdFVIII. Animal studies show that when blood carries this infection, so does the unprocessed plasma.

Manufacturing steps used in making most pdFVIII products appear likely to be effective in removing the agent and may reduce or eliminate most risk even if a vCJD infected donor contributed plasma.

Because so much is unknown about vCJD and its incidence, the risk assessment performed by FDA has a lot of uncertainty, making it impossible to precisely estimate any risk. The risk assessment model suggests that important contributors to risk are how common vCJD is in the donor population, the degree to which the manufacturing process can remove the agent from the products, and the quantity of product that individuals use.

The Public Health Service believes the risk of developing vCJD infection from pdFVIII is likely to be very low, given both the results of the risk assessment and the lack of any reported cases of vCJD in plasma-derived blood products following decades of use, including in the UK, where the risk is considered greatest. For example, for the most common pattern of use (i.e. episodic, no inhibitor) of a pdFVIII product made using processes with a level of clearance believed to be achieved by most manufacturing processes, the model suggests a possible estimated risk of from 1/105,000 to 1/9.4 million infections per person per year, depending on which prevalence estimate is assumed, or a possible total of 1 case in the population of severe HA patients using such products every 35 to 3,077 years. However, there is a great deal of uncertainty in the model, including how effective clearance may be, and it is also possible that not enough time has passed for some people receiving plasma products that contained the vCJD agent to have developed signs of infection. Therefore, while the risk is estimated to be very low, it may not be zero.

While there is no proof of a significant risk at this time, patients and physicians utilizing pdFVIII should be aware of the possibility and consider both the potential risks and benefits of their treatment.

Efforts to better understand and reduce any potential risk of transmission of vCJD by plasma products are ongoing. PHS will provide additional information as it becomes available.

### **Communication Strategy**

Subject to further input from the PHS agencies and possible revisions, the Key Messages and Additional Information cited above are the messages that the FDA, in cooperation with other components of the Public Health Service would utilize for communications with the patient community and health care providers, through various media presentations including government web sites, press, and communications with Hemophilia Treatment Centers and consumer organizations.

APPENDIX

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

				4 - 6 Log <sub>10</sub> 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 <sup>th</sup> - 95 <sup>th</sup> perc) <sup>b</sup>	Mean potential vCJD risk per person per year <sup>a</sup> (5 <sup>th</sup> - 95 <sup>th</sup> perc) <sup>b</sup>	Mean potential vCJD risk per person per year <sup>a</sup> (5 <sup>th</sup> - 95 <sup>th</sup> perc) <sup>b</sup>
Prophylaxis	No Inhibitor	578	157949 IU <sup>c</sup> (21242 , 382316 )	1 in 4.0 million (0-0) <sup>d</sup>	1 in 54,000 (0 - 1 in 12,000)
	With inhibitor - No Immune Tolerance	63	190523 IU <sup>c</sup> (26956 , 447639)	1 in 4.8 million (0-0) <sup>d</sup>	1 in 41,000 (0 - 1 in 9,000)
	With Inhibitor - With Immune Tolerance	62	558700 IU <sup>c</sup> ( 33235 , 1592943)	1 in 1.3 million (0-0) <sup>d</sup>	1 in 15,000 (0 - 1 in 3,700)
Episodic	No Inhibitor	946	85270 IU <sup>c</sup> ( 4633 , 244656)	1 in 9.4 million (0-0) <sup>d</sup>	1 in 105,000 (0 - 1 in 24,000)
	With Inhibitor	151	160458 IU <sup>c</sup> (5314 , 488906)	1 in 8.0 million (0-0) <sup>d</sup>	1 in 48,000 (0 - 1 in 12,000)

<sup>a</sup> Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.

<sup>b</sup> The 5<sup>th</sup> - 95<sup>th</sup> 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.

<sup>c</sup> IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

<sup>d</sup> For a 5<sup>th</sup> and 95<sup>th</sup> 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.A. Model Results for von Willebrand Disease (vWD) Patients<sup>a</sup> with Severe Disease: Predicted Potential Annual vCJD Risk:**

- Assuming a reduction from manufacturing of 4-6 log<sub>10</sub>, and
- Two different UK vCJD prevalence estimates.

<b>YOUNG vWD (≤ 15 yrs of age)</b>				
			<b>4 - 6 Log<sub>10</sub> Reduction</b>	
			<b>Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani ( 2005)</b>	<b>Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225 by Hilton, et al (2004)</b>
	<b>Est. Total Number patients in US</b>	<b>Mean quantity product used per person per year</b>	<b>Mean vCJD risk per person per year<sup>b</sup> (5<sup>th</sup> - 95<sup>th</sup> perc)<sup>c</sup></b>	<b>Mean vCJD risk per person per year<sup>b</sup> (5<sup>th</sup> - 95<sup>th</sup> perc)<sup>c</sup></b>
<i>Prophylaxis</i>	39	165,713 IU <sup>d</sup> (9876, 454306)	1 in 4.7 million (0-0) <sup>e</sup>	1 in 52,000 (0 - 1 in 13,000)
<i>Episodic</i>	60	11,045 IU <sup>d</sup> (1025, 34352)	1 in 48 million (0-0) <sup>e</sup>	1 in 971,000 (0 - 1 in 293,000)
<b>ADULT vWD (&gt; 15 yrs of age)</b>				
<i>Prophylaxis</i>	73	186,880 IU <sup>d</sup> (16910, 539877)	1 in 4.1 million (0-0) <sup>e</sup>	1 in 46,300 (0 - 1 in 11,000)
<i>Episodic</i>	78	86,923 IU <sup>d</sup> (2182, 240338)	1 in 10 million (0-0) <sup>e</sup>	1 in 1 million (0 - 1 in 24,000)

<sup>a</sup> 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.

<sup>b</sup> Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.

<sup>c</sup> The 5<sup>th</sup> - 95<sup>th</sup> 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.

<sup>d</sup> IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

<sup>e</sup> For a 5<sup>th</sup> and 95<sup>th</sup> 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.

**DRAFT**

**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**

**October 15, 2006**

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