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 $\log_{10}$ (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. Assuming a 4-6 $\log_{10}$ manufacturing process reduction, the modeling predicts that the potential risk per person per year for patients with severe HA using pdFVIII ranges 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. <u>Risk Management Strategy, Key Message Points, and Communication Strategy</u>

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_{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.

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.

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

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

[e] For a 5^{th} and 95^{th} 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

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EXECUTIVE SUMMARY

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

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

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

The FDA risk assessment utilizes a computer-based simulation model that evaluates successively the impact on vCJD risk of individual processes used in the production of human pdFVIII starting with plasma donation, extending through manufacturing steps, and finally, addressing utilization by various patient subpopulations. Risk for these products was estimated for the baseline year of 2002 but the results and conclusions also are likely to reflect the current vCJD risk for recipients of pdFVIII. A few major elements of the model greatly influence vCJD risk. The most influential of these are manufacturing processes, which may reduce or eliminate the amount of vCJD agent in the final product. The amount of product used by patients in different clinical scenarios also has a significant impact on risk. Additionally, the risk estimate is significantly affected by the prevalence

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

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

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

Results from the Model

An important, yet also highly uncertain parameter in driving the risk assessment results is the estimate used for vCJD prevalence in the UK. The prevalence of vCJD in the UK population was estimated in the model using two different approaches. The first approach to estimating vCJD prevalence in the UK was from a study based on epidemiological modeling that was derived using actual reported vCJD cases in the UK combined with an estimate of future vCJD cases (Clarke and Ghani, 2005). Several factors used in epidemiologic modeling approaches are difficult to quantify and add uncertainty to the final estimated number of future vCJD cases. These factors include: the intensity of human exposure to the BSE agent, incubation period, time of infection, and whether illness will develop in individuals who are not homozygous for methionine at codon 129 of PrP. All cases of vCJD to date have occurred in individuals who are homozygous for methionine at this location. Our calculations, based on the Clarke and Ghani study (2005) and diagnosed cases in 2002 and 2003, yielded a prevalence estimate of approximately 1.8 vCJD cases per million in the UK.