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

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

- Results provided for two different UK vCJD prevalence estimates.

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

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

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

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

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

Based on limited available data (see below), FDA believes that the quantity of infectivity present in blood from a vCJD infected individual in i.v. ID_{50} is likely represented by a distribution with the following characteristics: Minimum value = 0.1, 5th percentile = 2, Most likely value = 10, 95th percentile = 30, and Maximum value= 1,000 i.v. ID_{50}. Given the possible parameters, statistical distributions were fitted to the selected parameters using Best Fit part of the @Risk Professional software package (Palisade Corporation, New York). Using the software we determined that a log normal statistical distribution of (2, 12, 30) i.c. ID_{50}/ml (5th percentile, most likely, and 95th percentile) with minimum and maximum of 0.1 and 1,000, respectively, provided the best fit.

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

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

less than 1,000 ID_{50} would not have elicited infection or disease in their animal model, hence infectivity would not have been detected(Wadsworth, 2001).

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

This section of risk assessment estimated quantity of vCJD agent in each vCJD plasma pool that may be used to make pdFVIII. Quantity of infectious agent present in plasma pools may vary depending on number of infected donations in the pool and the volume of each infected donation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 4.6 Reduction factor (RF) of fractionation procedures

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

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

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

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

If vCJD agent were present in US plasma pools, the risk assessment model assumed that the quantity of agent was likely reduced by manufacturing processes used to produce

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

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

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

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

vCJD. Again, although the probability (2.41%) is higher at the higher prevalence, the mean quantity of vCJD agent (iv ID_{50}) and risk of exposure to vCJD agent (1 in 55,710) per vial derived from a pool containing a single vCJD donation would likely be unaffected by prevalence.

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

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

	4 - 6 Log_{10} Reduction					
	Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)			**Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225** by Hilton, et al (2004)		
Type of Plasma Pool	**Percentage FVIII vials with vCJD agent** (5^{th}, 95^{th} perc)[c]	**Quantity iv ID_{50}[a] per vial*** (5^{th}- 95^{th} perc)[c]	**Mean potential per vial vCJDrisk[b]** (5^{th}- 95^{th} perc)[c]	**Percentage FVIII vials with vCJD agent** (5^{th}, 95^{th} perc)[c]	**Quantity iv ID_{50}[a] per vial*** (5^{th}- 95^{th} perc)[c]	**Mean** potential per vial vCJDrisk[b]** (5^{th}- 95^{th} perc)[c]
Source	**0.01%** (0 – 0%)[d]	**4.36×10^{-5}** (4.51×10^{-8} – 1.43×10^{-4})	**1 in 459 million** (0, 0)[d]	**0.96%** (0 – 5.88%)	**4.36×10^{-5}** (4.51×10^{-8} – 1.43×10^{-4})	**1 in 4.8 million** (0, 1 in 238,000)
Recovered	**0.10%** (0 – 0%)[d]	**2.56×10^{-6}** (3.13×10^{-7} – 8.12×10^{-6})	**1 in 800 million** (0, 0)[d]	**9.12%** (0 – 40.17%)	**2.56×10^{-6}** (3.13×10^{-7} – 8.12×10^{-6})	**1 in 8.6 million** (0,1 in 613,000)
Average of all vials	**0.027 %** (0 – 0%)[d]	**3.59×10^{-5}** (8.18×10^{-7} – 1.29×10^{-4})	**1 in 210 million** (0, 0)[d]	**2.41 %** (0 – 10 %)	**3.59×10^{-5}** (8.18×10^{-7} – 1.29×10^{-4})	**1 in 2.3 million** (0, 1 in 155,000)

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

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

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

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

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

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

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

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

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

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

Module 4: FVIII utilization and annual exposure

Background

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

HA can be prevented by appropriate clinical management and treatment with pdFVIII or recombinant FVIII products.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

V. RISK CHARACTERIZATION

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

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

infection. In such a case exposure to 1 ID_{50} would suggest a 50% probability of infection, exposure to 0.1 ID_{50} would suggest a 5% probability of infection, and so on.

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

V.A. THE MODEL

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

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

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

Individuals with HA vary in their degree of FVIII deficiency. Although the clinical spectrum generally can range from severe, to moderate, and to mild disease, this

assessment specifically addresses potential vCJD exposure and risk for persons with severe HA. Among an estimated 14,000 HA population in the United States, approximately 50% have severe disease and 25% of all HA patients use human pdFVIII products. FDA estimated that there are a total of approximately 1,800 HA patients **(Tables 5.1A. and 5.1B.)** with severe disease in the US that use human pdFVIII products. Although the estimated risk is very low, it is possible that some patients using human pdFVIII may potentially be exposed to vCJD agent if present in US manufactured product.

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

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

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

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

Potential exposure of severe HA patients to vCJD agent: Results based on lower epidemiological model estimated prevalence of ~1.8 in 1,000,000 (based on Clarke and Ghani, 2005). The model estimates that severe HA patients treated using a prophylaxis regimen, with inhibitor, with immune tolerance and treated with a pdFVIII product (with 4-6 $\log_{10}$ reduction of vCJD agent) has the highest pdFVIII usage of the groups we examined