Table 4.9. Annual usage of pdFVIII by individual severe vWD patient -data and 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 and potentially face the highest risk among HA patients. **Table 5.1A.** indicates that approximately 62 severe HA patients in a prophylaxis treatment regimen with inhibitor and immune tolerance use an average of 558,700 IU per person per year and are potentially

exposed to an average of 1.57×10^{-6} i.v. ID_{50} per person per year; representing an average potential vCJD risk of 1 in 1.3 million per person per year. If all of the assumptions in the model are correct at this lower estimated prevalence, this risk may yield 1 vCJD infection in an average of approximately 21,000 years of treatment among severe HA patients who are in a prophylaxis treatment regimen with inhibitor and immune tolerance. As mentioned earlier the 5th and 95th percentile intervals for all of the model outputs using the lower prevalence estimate (~1.8 per million) in **Table 5.1A.** 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. However, the model predicts that 0.027% of the time the exposure to vCJD agent may be greater than zero, and there is a possible but low risk of vCJD infection.

The risk for the entire population is calculated by summing the cumulative risk potential of vCJD exposure and risk **(Table 5.1B.)**. Using the lower prevalence estimate, the model predicts that the approximately 1,800 severe HA patient population in the US uses a total of approximately 243 million IU pdFVIII and is exposed to an average of 6.50×10^{-4} i.v. ID_{50}. This total annual exposure for the entire severe HA population in the US is equivalent to a mean potential population-based vCJD risk of 1 in 3,077. At this expected level of risk, 1 vCJD infection would be predicted to occur in 3,077 years of treatment for the entire population of 1800 severe HA patients that use pdFVIII.

Potential exposure of severe HA patients to vCJD agent: Results based on higher surveillance prevalence estimate of 1 in 4,225 (Hilton, et al 2004). The model estimates that severe HA patients in a prophylaxis regimen, with inhibitor, with immune tolerance and treated with a pdFVIII product (with 4-6 $\log_{10}$ reduction of vCJD agent) potentially face the highest expected risk among HA patients. **Table 5.1A.** indicates that approximately 62 severe HA patients in a prophylaxis treatment regimen with inhibitor and immune tolerance use an average of 558,700 IU per person per year, and are potentially exposed to an average of 1.30×10^{-4} i.v. ID_{50} per person per year, using the higher prevalence estimate. This represents an average potential vCJD risk of 1 in 15,000 per person per year for the treatment group. If all of the assumptions used in the model are correct and considering the total number of 62 patients in this category (or population-based risk), this expected risk would yield 1 vCJD infection in 240 years of treatment among the patients under this category.

The risk for the entire severe HA population is calculated by summing the cumulative risk potential of vCJD exposure and risk from all individual patients under five categories (prophylaxis with no inhibitor, prophylaxis with inhibitor, prophylaxis with inhibitor and immune tolerance, episodic with no inhibitor and episodic with inhibitor) **(Table 5.1B.)**. Using the higher surveillance estimate, the model predicts that the approximate total of 1,800 severe HA patient population in the US uses a total of approximately 243 million IU pdFVIII, and is exposed to an average of 5.67×10^{-2} i.v. ID_{50} per year. This total annual exposure for the entire severe HA population in the US is equivalent to a mean potential

population-based vCJD risk of 1 in 35, i.e., 1 vCJD infection would be predicted to occur in 35 years of treatment in this 1800 severe HA patient population.

Table 5.1A. Model Results for All HA Patients who use a Hypothetical Factor VIII Product with 4-6 log_{10} Manufacture Process Reduction of vCJD Agent: *Predicted Annual per Person Exposure to vCJD i.v. ID_{50} and Mean Potential per Person Annual vCJD Risk:*

- For patients with SEVERE disease, 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)	
Treatment Regimen	**Inhibitor Status**	**Est. Total Number patients in US**	**Mean quantity FVIII used per person per year (5^{th} - 95^{th} perc)**	**Mean exposure to vCJD iv ID_{50}[a] per person per year (5^{th} - 95^{th} perc)[c]**	**Mean potential vCJD risk per person per year[b] (5^{th} - 95^{th} perc)[c]**	**Mean exposure to vCJD iv ID_{50}[a] per person per year (5^{th} - 95^{th} perc)[c]**	**Mean potential vCJD risk per person per year[b] (5^{th} - 95^{th} perc)[c]**
Prophylaxis	No Inhibitor	578	157949 IU[d] (21242 , 382316)	4.99×10^{-7} (0-0)[e]	1 in 4.0 million (0-0)[e]	3.67×10^{-5} (0 - 1.72×10^{-4})	1 in 54,000 (0 - 1 in 12,000)
	With Inhibitor – No Immune Tolerance	63	190523 IU[d] (26956, 447639)	4.21×10^{-7} (0-0)[e]	1 in 4.8 million (0-0)[e]	4.86×10^{-5} (0 - 2.17×10^{-4})	1 in 41,000 (0 - 1 in 9,000)
	With Inhibitor – With Immune Tolerance	62	558700 IU[d] (33235, 1592943)	1.57×10^{-6} (0-0)[e]	1 in 1.3 million (0-0)[e]	1.30×10^{-4} (0 - 5.39×10^{-4})	1 in 15,000 (0 - 1 in 3,700)
Episodic	No Inhibitor	946	85270 IU[d] (4633, 244656)	2.12×10^{-7} (0-0)	1 in 9.4 million (0-0)[e]	1.91×10^{-5} (0 - 8.50×10^{-5})	1 in 105,000 (0 - 1 in 24,000)
	With Inhibitor	151	160458 IU[d] (5314, 488906)	2.49×10^{-7} (0-0)[e]	1 in 8.0 million (0-0)[e]	4.19×10^{-5} (0 - 1.67×10^{-4})	1 in 48,000 (0 - 1 in 12,000)

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

[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 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.

Table 5.1B. Model Results for Total Population-based Exposure and Potential vCJD Risk for All Hemophilia A patients who use a Hypothetical pdFVIII Product with 4-6 log_{10} Manufacture Process Reduction of vCJD Agent:

Predicted annual per person exposure to vCJD i.v. ID_{50} and mean potential per person annual vCJD risk:

- For patients with SEVERE disease, and
- Two different UK vCJD prevalence estimates.

			4 - 6 Log_{10} Reduction			
			Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)		Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225 by Hilton *et al* (2004)	
	Est. Total Number severe HA patients in US	Mean Total quantity FVIII used by all patients per year (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]	Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]	Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]
Mean total annual exposure and population risk	1,800	243 million IU[d]	6.50×10^{-4} (0-0)[e]	1 in 3,077 years (0-0)[e]	5.67×10^{-2} (0 - 2.52×10^{-1})	1 in 35 years (0 - 1 in 8)

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

V. C. Model results: Estimated annual potential exposure to i.v. ID_{50} vCJD agent and potential vCJD risk through human pdFVIII used to treat severe von Willebrand disease (vWD)

Individuals with von Willebrand disease (vWD) vary in severity of disease, those with Type 3 disease have severe disease; this assessment specifically addresses potential vCJD exposure and risk for persons with severe vWD. FDA estimates that approximately 250 vWD patients have severe vWD disease in the United States and use human plasma-derived FVIII products to control their disease (Tables 5.2A. and 5.2 B.) The FDA model suggests that it is possible that some of these vWD patients using human pdFVIII may potentially be exposed to vCJD agent if present in US manufactured product. Results from the risk assessment model for patients with vWD and treated with pdFVIII product with a 4-6 $\log_{10}$ manufacturing process reduction of vCJD agent are shown in Tables 5.2A. and 5.2 B. Generally results are expressed for patients with von Willebrand disease (vWD) clinical treatment groups of either Prophylaxis or Episodic treatment.

Table 5.2A. Results von Willebrand Disease (vWD) patients[1] with Severe Disease: Predicted Potential Annual Exposure to vCJD i.v. ID_{50} and vCJD Risk:

- Assuming a processing 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)	
	Est. Total Number patients in US	Mean quantity product used per person per year (5^{th} - 95^{th} perc)[c]	Mean exposure to vCJD iv ID_{50}[a] per person per year (5^{th} - 95^{th} perc)[c]	Mean potential vCJD risk per person per year[b] (5^{th} - 95^{th} perc)[c]	Mean exposure to vCJD iv ID_{50}[a] per person per year (5^{th} - 95^{th} perc)[c]	Mean potential vCJD risk per person per year[b] (5^{th} - 95^{th} perc)[c]
YOUNG vWD (≤ 15 yrs of age)						
Prophylaxis	39	165,713 IU[d] (9876, 454306)	4.30×10^{-7} (0 - 0)[e]	1 In 4.7 million (0 - 0)[e]	3.81×10^{-5} (0 - 1.54×10^{-4})	1 in 52,000 (0 - 1 in 13,000)
Episodic	60	11,045 IU[d] (1025, 34352)	4.14×10^{-8} (0 - 0)[e]	1 In 48 million (0 - 0)[e]	2.06×10^{-6} (0 - 6.63×10^{-6})	1 in 971,000 (0 - 1 in 293,000)
ADULT vWD (> 15 yrs of age)						
Prophylaxis	73	186,880 IU[d] (16910, 539877)	4.89×10^{-7} (0 - 0)[e]	1 In 4.1 million (0 - 0)[e]	4.32×10^{-5} (0 - 1.82×10^{-4})	1 in 46,300 (0 - 1 in 11,000)

Episodic	78	86,923 IU[d] (2182, 240338)	1.99×10^{-7} (0 - 0)[e]	1 in 10 million (0 - 0)[e]	1.90×10^{-5} ($0 - 8.43 \times 10^{-6}$)	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] iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.

[c] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Total mean quantity i.v. ID_{50} per year x 0.5 (50 % chance infection from ID_{50})

[d] 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.

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

[f] For a 5th and 95th 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.

Estimation of Factor VIII product utilization by patients with severe von Willebrand disease. FDA obtained data on pdFVIII utilization, presumably used in the treatment of severe von Willebrand disease, from the Centers for Disease Control (CDC). Details of the CDC – Six state collaborative study are described in the section above (section IV.G.2) on FVIII utilization. Annual usage of product by vWD patients was estimated based on an assumption that this patient class largely uses Humate P. Therefore, only records for patients utilizing Humate P were extracted from the CDC - Six state study conducted from 1993 – 1998 and used to develop statistical distributions of product usage for young vWD (≤15 yrs old) patients and adult vWD (> 15 yrs old) patients. The mean quantity of product utilized per year per patient group is shown in **Table 5.2A.** and **Table 5.2B.**

Table 5.2B. Von Willebrand Disease (vWD) Patients[1] with Severe Disease: Predicted Total Population-based Exposure to vCJD i.v. ID_{50} and Potential vCJD Risk:

- Assuming a processing 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)	
	Est. Total Number severe vWD patients in US	Mean Total quantity FVIII used by all patients per year (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]	Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]	Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]
Mean total annual exposure and population	250	29.9 million IU[d]	7.05×10^{-5} (0 - 0)[e]	1 in 28,450 years (0 - 0)[e]	4.91×10^{-3} ($0 - 2.59 \times 10^{-2}$)	1 in 405 years (0 - 1 in 76)

risk		(3013, 311745)				

[1]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.

[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 vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Total mean quantity i.v. ID_{50} per year x 0.5 (50 % chance infection from ID_{50})

[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 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.

Potential exposure of severe von Willebrand disease patients to vCJD agent: Results based on lower epidemiological model estimated prevalence of ~1.8 in 1,000,000 (Clarke and Ghani, 2005). Adult vWD (>15yrs of age) patients with severe disease on prophylaxis consumed the largest quantities of pdFVIII product annually and may potentially be at greater vCJD risk. Using the lower epidemiological model prevalence estimate, analysis of pdFVIII utilization data indicated that 73 Adult vWD patients on prophylaxis treatment regimen used an average of 186,880 IU and are potentially exposed to an average of 4.89×10^{-7} i.v. ID_{50} per person per year, and representing an average potential vCJD risk of 1 in 4.1 million per person per year **(Table 5.2A.)**. At this level of risk, only 1 vCJD infection would be predicted to occur in an average of approximately 56,000 years. As mentioned earlier the 5th and 95th percentile intervals for all of the model outputs using the lower prevalence estimate (~1.8 per million) in **Table 5.2A.** 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. However, the model predicts that 0.027% of the time the exposure to vCJD agent may be greater than zero, and there is a possible but low risk of vCJD infection.

Totaling the model results reveals that the approximately 250 severe vWD patients in the US used a total of 29.9 million IU, and are potentially exposed to an average total of 7.05×10^{-5} i.v. ID_{50} per year. This represents an average potential vCJD risk of 1 in 28,450 **(Table 5.2B.)** or (as predicted by the model) roughly equal to one vCJD infection observed over a time span of approximately 28,450 years in the population of 250 severe vWD patients.

Potential exposure of severe von Willebrand disease patients to vCJD agent: Results based on higher prevalence estimate of 1 in 4,225 (Hilton et al 2004). At the higher surveillance prevalence estimate, among the vWD patient populations examined by the model, results **(Table 5.2A.)** indicated that adult vWD (>15yrs of age) patients with severe disease on prophylaxis used the largest quantities of pdFVIII product annually and may potentially be at greater vCJD risk. Analysis of pdFVIII utilization data indicated that 73 Adult vWD patients on prophylaxis treatment regimen used an average of 186,880 IU per person per year and are potentially exposed to an average of 4.32×10^{-5} i.v. ID_{50} per person per year, representing an average potential vCJD risk of 1 in 46,300 per person per year **(Table 5.2A.)**. At this level of risk, only 1 vCJD infection would be predicted to occur in an

average of approximately 630 years for the population of 73 Adult vWD patients on prophylaxis treatment regimen.

The potential risk of vCJD infection for the entire population was calculated using the higher surveillance prevalence estimate. The model results shows that the approximately 250 severe vWD patients in the US used a total of 29.9 million IU (**Table 5.2B.**), and are potentially exposed to an average total of 4.91×10^{-3} i.v. ID_{50} per year. This represents an average potential vCJD risk of 1 in 405, i.e., of one vCJD infection observed over a time span of 405 years for the population of 250 severe vWD patients in the U.S.

Range of Predicted annual mean potential per HA patient vCJD risk for pdFVIII (Table 6)
The FDA risk assessment for potential vCJD infection risk for US manufactured pdFVIII generates results for several scenarios that reflect two key factors that greatly influence the final risk estimates including: (1) Reduction in vCJD agent in pdFVIII product during manufacture, and (2) UK vCJD prevalence estimate. As indicated earlier, the model used two widely different prevalence estimates, one lower prevalence estimate based on epidemiological modeling of predicted vCJD cases in the UK (Clarke and Ghani, 2005) of approximately 1.8 in 1 million and one higher prevalence estimate based on surveillance data of UK patient tissue samples (Hilton et al 2004) of 1 in 4,225. The use of these two estimates gives rise to a difference in results generated by the model that vary by an average of approximately 130 fold.

The model evaluated three separate categories of reduction in infectivity including 2-3 $\log_{10}$, 4-6 $\log_{10}$, and 7-9 $\log_{10}$. These three hypothetical categories were chosen to span the possible range of reduction of vCJD agent for pdFVIII products. **Table 5.3A. and 5.3B.** displays model results for a lower prevalence estimate and a higher prevalence estimate at all three levels of reduction. It should be noted that the mean difference between the lowest range of 2-3 $\log_{10}$ and the highest range of 7-9 $\log_{10}$ is nearly 1 million fold (6 $\log_{10}$). These two largest contributors to the final risk estimate also contribute to the greatest uncertainty in the model. Results from the model shown in **Tables 5.3A. and 5.3B.** indicate that there is a difference of approximately 20 to 55 million fold between the lowest and highest risk estimates of each patient group.