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.

YOUNG vWD (≤ 15 yrs of age)						
			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]
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 - 6.83×10^{-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 - 8.43×10^{-5})	1 in 1 million (0 - 1 in 24,000)

[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.

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 risk	**250**	**29.9 million IU[d]** (3013, 311745)	**7.05×10^{-5}** (0 - 0)[e]	**1 in 28,450 years** (0 - 0)[e]	**4.91×10^{-3}** (0 - 2.59×10^{-2})	**1 in 405 years** (0 - 1 in 76)

[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.

Table 5.3A. Range of *Predicted Annual Mean Potential per HA Patient vCJD risk for pdFVIII* – *at three levels of clearance: 7-9 log_{10}, 4-6 log_{10}, and 2-3 log_{10} and at a higher Prevalence and Lower Prevalence estimates and at .*

				7 - 9 Log_{10} Reduction		4 - 6 Log_{10} Reduction		2 - 3 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)	Model Output for LOWER vCJD Case Prevalence estimate ~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)	Model Output for LOWER vCJD Case Prevalence estimate ~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 product used per person per year (5^{th} - 95^{th})[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**	**Mean potential vCJD risk per person per year[a] (5^{th} - 95^{th} perc)[b]**
Prophylaxis	No Inhibitor	**578**	**157949 IU** (21242 , 382316)	1 in 4.1 billion (0-0)[c]	1 in 50 million (0 - 1 in 11 million)	1 in 4 million (0-0)[c]	1 in 54,000 (0- 1 in 12,000)	1 in 15,000 (0-0)[c]	1 in 82 (0 - 1 in 17)
	With Inhibitor – No Immune Tolerance	**63**	**190523 IU** (26956 , 447639)	1 in 3.5 billion (0-0)[c]	1 in 40 million (0 - 1 in 8.8 million)	1 in 4.8 million (0-0)[c]	1 in 41,000 (0- 1 in9,000)	1 in 12,000 (0-0)[c]	1 in 65 (0 - 1 in 13)
	With Inhibitor – With Immune Tolerance	**62**	**558700 IU** (33235, 1592943)	1 in 551 million (0-0)[c]	1 in 15 million (0 - 1 in 3.4 million)	1 in 1.3 million (0-0)[c]	1 in 15,000 (0- 1 in3,700)	1 in 2,700 (0-0)[c]	1 in 24 (0 - 1 in 3)
Episodic	No Inhibitor	**946**	**85270 IU** (4633, 244656)	1 in 3.2 billion (0-0)[c]	1 in 100 million (0 - 1 in 24 million)	1 in 9.4 million (0-0)[c]	1 in 105,000 (0- 1 in 24,000)	1 in 21,500 (0-0)[c]	1 in 159 (0 - 1 in 34)
	With Inhibitor	**151**	**160458 IU** (5314 , 488906)	1 in 4 billion (0-0)[c]	1 in 50 million (0 - 1 in 11 million)	1 in 8 million (0-0)[c]	1 in 23,000 (0- 1 in 12,000)	1 in 23,000 (0-0)[c]	1 in 73 (0 - 1 in 16)

[a]Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.
[b]The 5^{th}- 95^{th} perc (percentiles) are the minimum and maximum numbers that define the range constituting the 90% confidence interval. Accordingly, the mean risk estimates from the model should fall within this defined interval at least 90% of the time.
[c]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.

This range or difference in the estimates of about 20 -55 million fold is reflected in the higher and lower prevalence results generated by the model shown in **Table 5.3A.** for each HA patient treatment group with severe disease. On closer inspection of the results in **Table 5.3A.** for patients with the most intensive pdFVIII product use, that is, the 62 patients on prophylaxis-with inhibitor and with immune tolerance, the effect of clearance on mean potential vCJD risk across the three ranges of clearance can be seen. At the low end of risk, the mean potential vCJD risk per patient per year risk (at 7-9 log_{10} and the lower prevalence estimate) is 1 in 551 million. Conversely, the highest risk for this patient group is seen at the 2-3 log_{10} clearance level and the higher prevalence estimate and is estimated by the model to be an average of 1 in 24. For patients on episodic treatment with no inhibitor who have a less intensive annual use of product, the model predicts the lowest risk (at 7-9 log_{10} and the lower prevalence estimate) to be 1 in 3.2 billion. The model predicts the highest risk for this group of patients, if they used pdFVIII product with a 2-3 log_{10} clearance level and the higher prevalence estimate, would be a mean potential per patient risk of 1 in 159.

Table 5.3B. Range of Total Population-based Exposure and Potential vCJD Risk from Model Predicted HA population with severe disease annual vCJD Exposure and Risk associated with use of plasma-derived Factor VIII:

- Lower Prevalence assumptions of Prevalence of 1.8 in 1,000,000 and 7-9 log_{10} reduction, and
- Higher Prevalence assumptions of Prevalence of 1 in 4,225 and 2-3 log_{10} reduction.

			7 - 9 Log$_{10}$ Reduction		4 - 6 Log$_{10}$ Reduction		2 - 3 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)	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)	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)[b]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c])[c]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c]
Mean total annual exposure and population risk	**1,800**	**243 million IU**	**1 vCJD infection in 1.6 million years** (0-0)[c]	**1 vCJD infection in 35,000 years** (0 -1 in 9,000)	**1 vCJD infection in 3,100 years** (0 -0)[c]	**1 vCJD infection in 40 years** (0 -1 in 10)	**1 vCJD infection in 8 years** (0 -1 in 2)	**~13 vCJD Infections per year** (0- 54 vCJD infections)

[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] 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.

The results from the risk assessment model shown in **Table 5.3A.** show a wide range of difference in the predicted risk and displays the range in our uncertainty and knowledge in

predicting the potential vCJD infection risk for HA patients who use US manufactured human pdFVIII. However, as further scientific information and data become available in the future, the uncertainty in the model may decrease and the estimates of vCJD risk for recipients of pdFVIII may become more precise.

Evaluating the total vCJD infection risk for the severe HA population of 1,800 by summing the total annual exposure (at the higher vCJD Infection prevalence estimated), the model predicts that the population would use a total average of approximately 243 million IU FVIII. If the patient population used product that attained a clearance of 7-9 $\log_{10}$ and assuming the lower prevalence the model predicts that for the total patient population the mean total annual risk would be 1 case in 1.6 million years representing a negligible vCJD risk that would likely not give rise to new cases of the disease. At the other end of the spectrum at the 2-3 $\log_{10}$ clearance level and the higher prevalence the model predicts a mean of approximately 13 vCJD infections per year **(Table 5.3.B.)** for the patient population.

V. D. Sensitivity analysis

Sensitivity analysis is used to identify the input parameter or parameters that have the greatest impact on the risk estimates generated by the model and are done by varying the values of key input parameters and evaluating the effect on the final risk estimate. Our goal in doing these analyses was to identify the key input parameters that have the greatest influence on annual exposure to the vCJD agent. The model was examined and candidate variables for the sensitivity analysis were chosen from the model that exhibited the largest potential for variability and/or uncertainty and those values are listed in Table 5-7. Importance analysis is a type of sensitivity analysis. Our importance analysis used two values, one at the minimum or 5th percentile value and one at the maximum or 95th percentile value to provide a reasonable estimate of impact across the range tested. The results from the importance analysis are displayed as tornado plots (**Figures 2.A., 2.B. and 2.C.**), which graphically shows the relative influence of each input parameter evaluated on the final model estimates. The most influential factors are displayed at the top of the plot and those that are least influential or those with negative influence on the risk are at the bottom of the plot.

For the FVIII risk assessment the output being monitored in the sensitivity and importance analyses was annual exposure (I_{yr}) to vCJD agent quantified in i.v.ID_{50} units. The sensitivity and importance analysis were conducted using the HA patient population on prophylaxis treatment regimens with inhibitor and being treated for immune tolerance as the example population used to do the analyses. This population displayed the largest mean usage and the widest range in product utilization. We assumed that the sensitivity and importance analysis results are representative of all the HA and vWD patient populations included in our study since all of the populations were assumed to differ only by the total average quantity of pdFVIII utilized per year.

The importance analysis was performed for each variable by doing two sets of simulations, each with 5,000 iterations. For each set of simulations the value of one testing variable was set at the minimum or 5th percentile value for the input distribution and the simulation run; for the second run the variable was set at the maximum or 95th percentile value and the simulation run. The importance analysis was run separately each time using one of the three surveillance estimate

ranges. The first analysis used a range of 0.7 to 700 per million, which encompasses the entire range for both the HIGH and LOW prevalence estimates. The second analyses used the higher vCJD Infection prevalence estimate of 1 in 4,225 (or 237 per million) derived from a tissue surveillance study (Hilton et al 2004). This prevalence was based on the variable ($P_{vCJD\text{-}Surv}$) in the model that used data from a tissue surveillance study. To do the sensitivity analysis we used a 5th percentile value of 49 per million and a 95th percentile value of 692 per million. The third set of analyses used the lower vCJD Case prevalence estimate of ~1.8 per million based on epidemiological modeling from actual vCJD occurrence conducted by Clarke and Ghani (2005). This prevalence was ($P_{vCJD\text{-}Epi}$) based on epidemiologic modeling and to do the sensitivity analysis we used a 5th percentile value of 0.7 per million and a 95th percentile value of 4 per million. The results of all simulations and the ranking of input parameters by their importance is represented graphically using a tornado plot shown in **Figures 2.A. , 2.B. and 2.C.** The tornado plot displays the correlations between key inputs in the model and the model output of exposure. A tornado plot prioritizes the various input factors with the most influential factors at the top and those that are least influential or those with negative influence on the risk are at the bottom of the plot.

Table 5.4. Input Variables included in Importance Analysis

Description of variables	Name of input variable	Importance analysis values
Entire range of estimated vCJD prevalence in UK (cases/million)	$Prev_{vCJD\text{-}UK}$	Minimum: 0.7 Maximum: 700
High prevalence estimate of vCJD in UK (cases/million)	$Prev_{vCJD\text{-}UK(Surveillance)}$	5th perc: 49 95th perc: 692
Low vCJD prevalence in UK (cases/million)	$Prev_{vCJD\text{-}UK\ (Epi\ model)}$	5th perc: 0.7 95th perc: 4.0
Efficiency of donor deferral policy	Eff_{Def}	Minimum: 85% Maximum: 99%
Efficiency of i.c. versus i.v. route	$A_{ic\text{-}iv}$	Minimum: 0.1 Maximum: 1
Number of donors per plasma pool	DR_{Pool}	Minimum: 6500 Maximum: 360000
Quantity of i.c. infectivity in infected human blood	I_{bl}	5th perc: 2 95th perc: 30
Manufacturing yield of FVIII (IU/L plasma)	Y_{VIII}	Minimum: 120 Maximum: 250
Log Manufacture Reduction of vCJD agent	R_{Log}	Minimum: 2 Maximum: 9
FVIII used per year (IU/year)	IU_{yr}	5th perc: 10000 95th perc: 4000000

Sensitivity analysis is used to study the quantitative relationship between the input variables and risk output. Same as in importance analysis, output to be monitored in sensitivity analysis is annual exposure (I_{yr}) to vCJD of young HA patients under prophylaxis treatment with inhibitor and immune tolerance treatment. Sensitivity analysis for an input variable consists of multiple simulations. In each simulation the testing input variable is fixed at one value within the input range. Results of sensitivity analysis are presented only for the most important input variables, which were identified by the ranking provided by the importance analysis.

Fig 2. A. Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using prevalence estimate encompassing the range of values for both high and low prevalence from 0.7 to 700 vCJD cases per million UK population. Tornado chart showing impact of input variables on estimated annual exposure of severe HA patient with prophylaxis, inhibitor and immune tolerance treatment

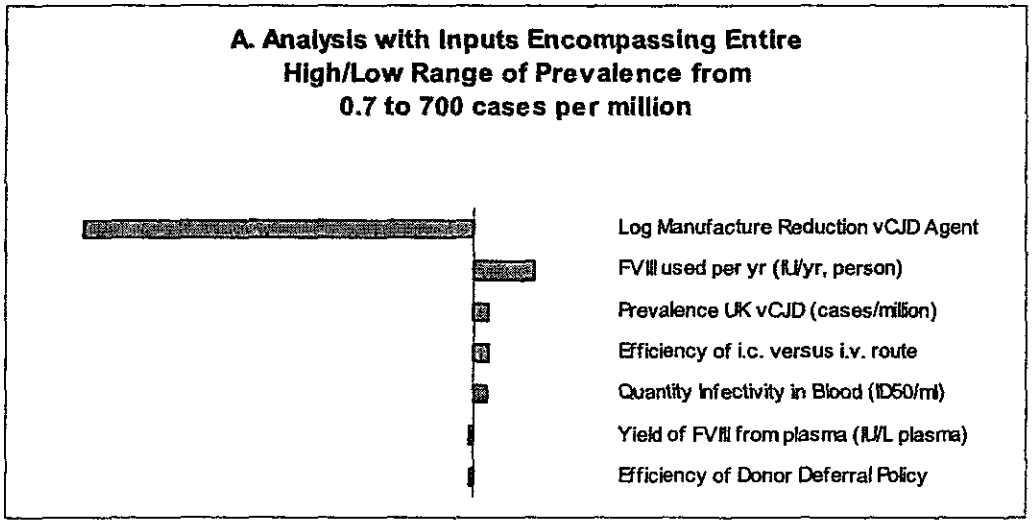


Fig 2. B. FVIII Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using Tissue Surveillance-based (HIGH) prevalence estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of pdFVIII recipients.

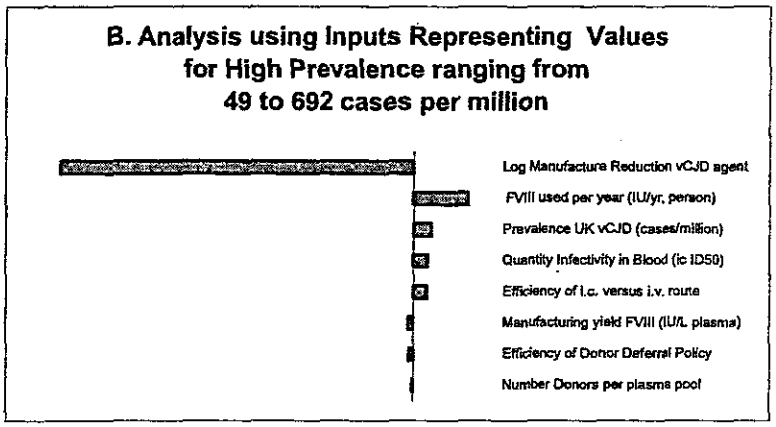
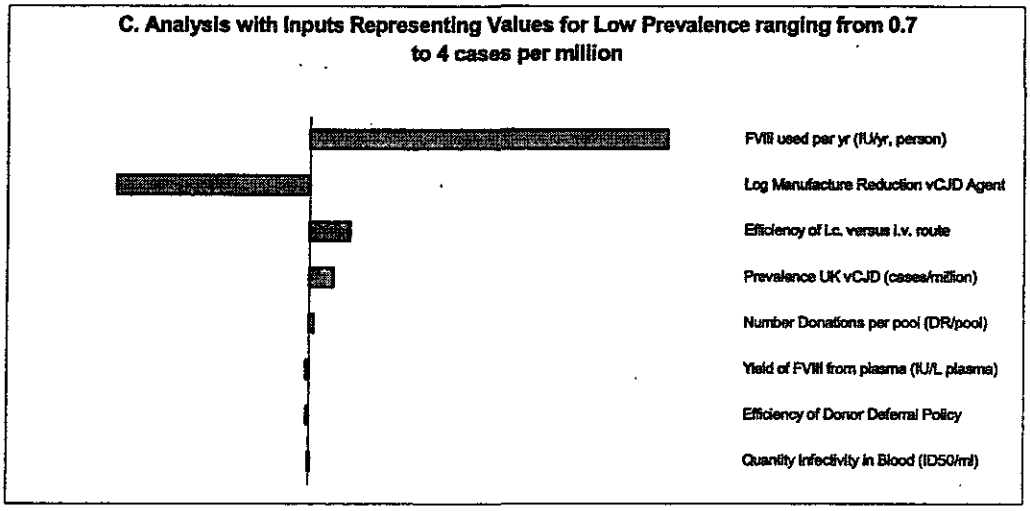


Fig 2. C. FVIII Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using Epi Modeling-based (LOW) prevalence estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of pdFVIII recipients.



Some input variables are used multiple times in the original model, for instance each type of plasma pool (Source or recovered) was modeled on an individual basis. Other examples are pool size ($DR_{pool\text{-}S}$ and $DR_{pool\text{-}R}$), yield (Y_{FVIII}), quantity of i.c. infectivity in the infected human blood (I_{bl}) and the reduction of infectivity during manufacturing (R_{Log}). In importance analysis and sensitivity analysis, when these input variables are tested, we assumed that there was no difference among the pools. When evaluating the impact of a specific variable all other values are held constant during the simulation. When simulating parameters with multiple values (e.g., size of recovered plasma pools) all values are the same for the simulation. The magnitude of changes in risk output associated with changes of input variables are graphed in the tornado chart, which represents the relative ranking of the input variables by their impacts on the risk outcome. The importance analysis was conducted for three possible ranges of UK vCJD prevalence: one set of analysis for tonsil survey based estimate, one set for epidemiology model-based estimate and another set for the two prevalence estimates combined.

The order of the influence of the specific input factors varies slightly when the importance analysis is conducted using the three difference prevalence estimates. When a higher prevalence estimate was used (either the combined prevalence (0.7 to 700 per million) the tornado plots in **Figures 2.A. and 2.B.** both show that clearance or Log reduction of the vCJD agent (R_{Log}) during the manufacturing process is the dominant factor that influences the annual exposure or risk for a pdFVIII recipient. The importance analysis suggests that changes in the input values for prevalence used in the analysis can cause some visible changes in the rank order of the influence of the various input factors. A change in the rank order of model factors is seen when the lower prevalence estimate of 0.7 to 4 per million is used (**Figure 2. C.**). The dominant factor potentially driving risk then becomes the quantity of pdFVIII used by a patient.