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 (5^{th} - 95^{th} perc)[b]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c]	Mean population – based potential vCJD risk[a] (5^{th} - 95^{th} perc)[c]
Mean total annual exposure and population risk	1,800	243 million IU	1 vCJD infection in 1.8 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 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.

[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.

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 th 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_{hl}	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

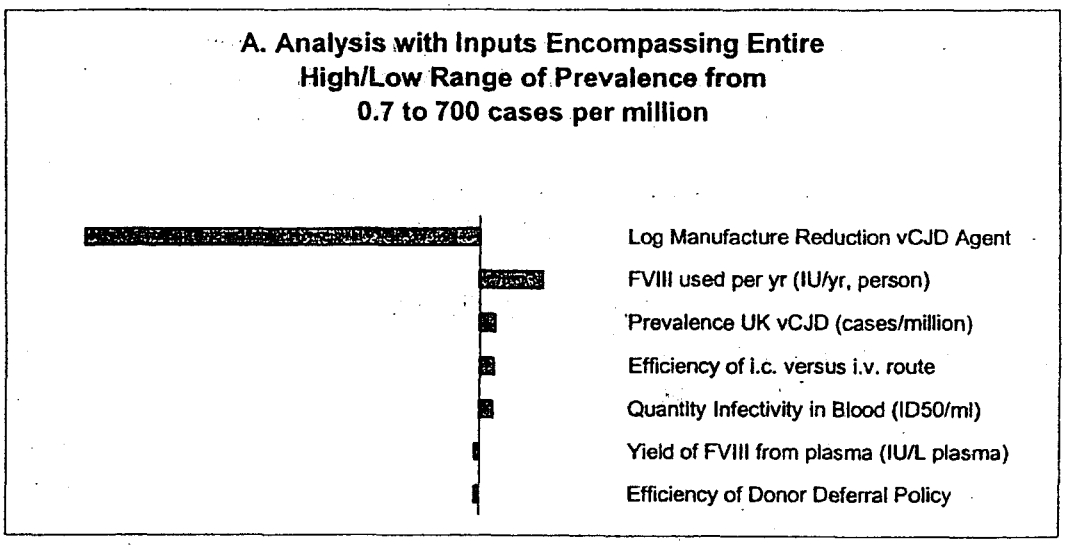


Fig 2. B. FVIII Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using Tissue Surveillance-based (HIGH) prevalence estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of pdFVIII recipients.

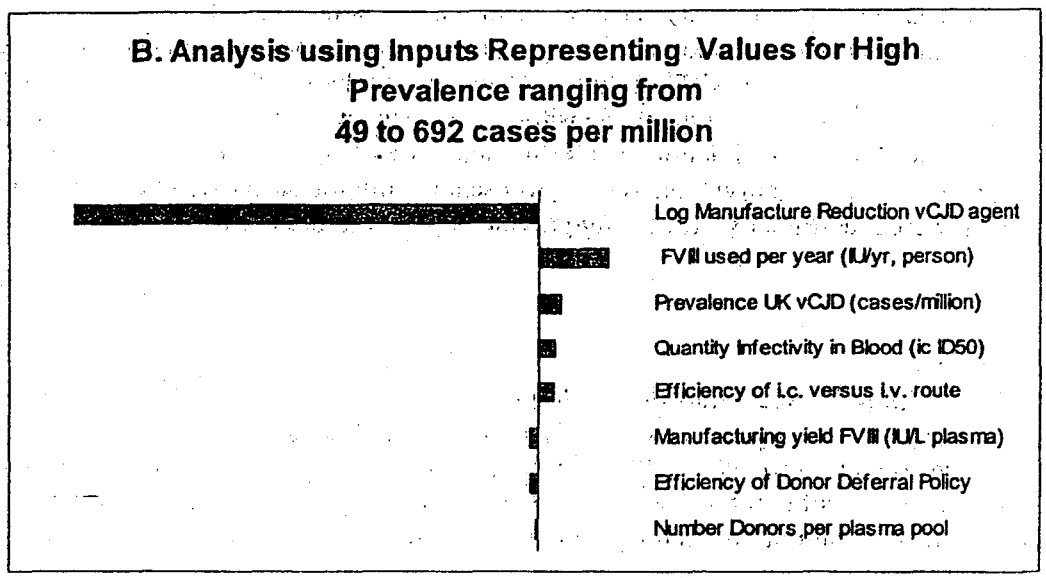
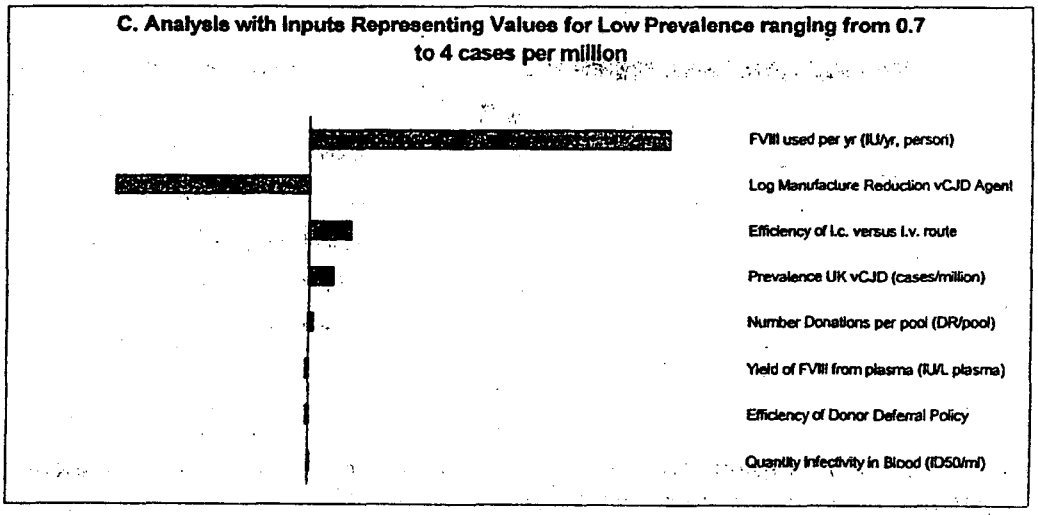


Fig 2. C. FVIII Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using Epi Modeling-based (LOW) prevalence estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of pdFVIII recipients.



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.

In our importance analysis the five variables that had significant influence on the output of the model were clearance of i.v. ID_{50} from pdFVIII products, pdFVIII use (IU/yr), UK vCJD prevalence, adjustment for the efficiency of transmission via the i.c. route vs. the i.v. route, and the quantity of i.v.ID_{50} in blood. Changes in prevalence did cause the variable parameters to reassort and change rank when the different prevalence estimates were used. Overall, however, they were somewhat similar in asserting their influence on the estimated risk outcome(s), but had significantly less influence when compared to that of reduction of infectivity during processing and manufacture. Although these types of sensitivity analysis and tornado plots are often used to identify influential factors of risk, their use has some limitations. Factors are examined singly or in isolation so interaction among various factors that may influence the risk estimate are not addressed.

General comments on model outputs

The risk estimations in this section of the risk assessment are predicated on the assumption that there is homogeneous mixing and dispersion of vials from all pools among all donors. In reality, vials may not be dispensed homogeneously and it is likely that patients draw from only one or a few manufactured lots of pdFVIII product in a given year. FDA did not have data to model this non-homogeneous dispensing of pdFVIII but the model can be used to estimate the average maximal level of i.v. ID_{50} exposure if on a very rare chance all vials used by a patient in a given year happened to contain vCJD agent.

V. E. Uncertainty and Data Gaps

Uncertainty arises from the absence of information or availability of limited information. In our probabilistic model statistical distributions are used, where possible, to represent the uncertainty of much of the information used in the model. There are uncertainties in the information and the model that we were unable to quantify and that are not represented in the final risk estimates. Some of the difficult to quantify uncertainties are associated with the extrapolation of a human dose-response relationship based on animal data, an assumed linear dose response with no

uncertainty or variability bounds, and assumption of infectivity in the last 50% of the incubation period. We express the uncertainty of the final risk estimates generated from the model using a mathematical mean (average) of exposure in ID_{50} units and the 5^{th} and 95^{th} percentiles, which represent the 90% confidence interval for each estimate. The uncertainty for the risk estimates generated by this FVIII risk assessment model is significant and decision makers should use the results with caution. Similarly, patients and physicians should understand that the uncertainties are too great at this time to determine the presence, absence or degree of actual risk. In the future, additional research and information may be substituted for assumptions or used to improve estimates for the individual parameters and ultimately improve the precision of the final risk estimates generated by the model.

Even considering the associated uncertainty of estimated risks, risk assessment provides an estimate of risk based on the current and known information. It is still a useful tool that can inform the science-based decision making process. It can identify data gaps and research priorities where additional research and information would have the greatest impact on enhancin the final risk estimates. The sensitivity analysis results in Section IV.C. indicated that the risk assessment results are highly dependent upon log reduction of vCJD agent (R_{Log}) during the manufacturing process. The modeled estimates were based upon levels of reduction seen for manufacturing steps of several different types of plasma-derived products that were similar in some but not all respects to those used in the manufacture of FVIII products. More high quality data on the levels of vCJD agent clearance achieved during the pdFVIII manufacturing would likely improve the final risk estimate generated by the FDA model. Given the lack of data on vCJD agent clearance for pdFVIII uncertainty is considerable.

Better information on when infectivity is present in human blood during the incubation period is a critical factor in the model, especially if the higher vCJD infection prevalence estimate (of 1 in 4,225) is in the range of the actual vCJD prevalence, and would improve predictions generated by the model. There are no data available on the level of infectious units or ID_{50} units present in the bloodstream of vCJD infected individuals at the time of blood donation. The model extrapolates an estimate of the level of vCJD agent that might be present in human blood based on data from several animal models. However, the presence and level of agent present in an infected individual at the time of blood donation could differ from our assumption and this adds to the uncertainty of the risk assessment outcomes.

The model estimates exposure to the vCJD agent in the form of intravenous ID_{50} units. Data are not available to estimate the probability of various clinical outcomes, such as infection or illness that might be predicted to arise from exposure to a particular level of agent. Although we did estimate a probability of infection in our model, the uncertainty associated with the estimate is considerable. However, a meaningful dose-response model would need to be generated for vCJD exposure in humans to improve estimates of the probability of adverse clinical outcomes for humans. The type of data needed to generate a dose-response model that would improve the quality of TSE risk assessment predictions would necessitate injection of groups of animals at several different concentrations of ID_{50}, including low doses below 1 ID_{50} using a protocol that mimics transfusion transmission of vCJD in humans. Both infection and duration of the incubation periods at several different i.v. ID_{50} concentrations would be useful endpoints for developing informative dose-response relationships. Given the state of the current TSE science, estimates of the probability of vCJD infection or illness arising from exposure to the vCJD agent are still extremely uncertain. Nevertheless risk assessment is a tool that provides insight into

important factors where additional research is needed into production processes, tools, or strategies that may further reduce vCJD risks and advance product safety for patients.

The manufacturing processes for pdFVIII are highly varied – therefore, any potential clearance of the vCJD agent during production is likely variable and dependent upon the specific steps used to produce the final product. For example, the techniques applied in fractionation process vary from manufacture to manufacture including the sizes of plasma pools used for producing pdFVIII, the yield of products, and the reduction of infectivity during processing varies within a limited range from batch to batch. In addition the utilization of pdFVIII varies from individual to individual. This risk assessment considers the typical production and utilization. Uncertainty from the model should be appreciated. Human plasma-derived FVIII is typically prepared through successive steps of large scale fractionation during the manufacturing process. Cryoprecipitation is the first and a common step in preparation of pdFVIII. Afterward, cryoprecipitate undergoes further fractionation procedures such as precipitation, absorption/desorption, ion exchange and filtration to yield intermediate purity FVIII, [redacted] In certain cases some hospitals may prepare small amount of cryoprecipitate FVIII from small plasma pools (1-8 donations/pool) for special treatment purposes. Preliminary risk assessment results indicated that the risk that vCJD would be transmitted through cryoprecipitated AHF is relatively low due to the small size of plasma pool and small numbers of donors involved. This risk assessment uses 3 ranges of possible clearance of vCJD agent from pdFVIII of 2-3 $\log_{10}$, 4-6 $\log_{10}$, and 7-9 $\log_{10}$ to cover the possible ranges for all pdFVIII products presently in the marketplace.

General comments on model outputs

The risk estimations in this section of the risk assessment are predicated on the assumption that there is homogeneous mixing and dispersion of vials from all pools among all donors. In reality, vials may not be dispensed homogeneously and it is likely that patients draw from only one or a few manufactured lots of pdFVIII product in a given year. FDA did not have data to model this non-homogeneous dispensing of pdFVIII but the model can be used to estimate the average maximal level of i.v. ID_{50} exposure if on a very rare chance all vials used by a patient in a given year happened to contain vCJD agent.

V. F. Conclusions

Results from the FDA pdFVIII risk assessment model suggest that the risk of vCJD infection from US manufactured pdFVIII generally appears likely to be very low, but may not be zero. For US plasma donors, the major source of vCJD risk is dietary exposure during travel and/or residency in the UK, France, or other countries in Europe since 1980. Although donor deferral criteria in place since 1999 have reduced the risk of donation by exposed persons some are not deferred and potentially may donate plasma that contains the vCJD agent. However, the model suggests that the likelihood of a vCJD contaminated plasma pool is low.

Manufacturing processes for human pdFVIII products likely reduce the quantity of vCJD agent, if present, but the level of reduction through manufacturing steps is not precisely known. Clearance of TSE agents in manufacturing appears to vary among products, but has not been measured in standardized studies which might allow more meaningful direct comparisons. Based on currently available experimental studies, it is estimated that pdFVIII products potentially have

4 $\log_{10}$ (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. Assuming a 4-6 $\log_{10}$ manufacturing process reduction, the modeling predicts that the potential risk per person per year for patients with severe HA using pdFVIII ranges from1 in 15,000 for the higher vCJD prevalence estimate and high product usage to 1 in 9.4 million for the lower vCJD prevalence estimate and low product usage. Due to the wide range of methods used for clearance studies currently available, gaps in information, and the results of the model, it is not possible at this time to determine with any certainty if a specific product may be less or more safe than another.

Although results of the model suggest exposure to vCJD agent is possible, and there is a potential risk of infection that is likely to be very low, it is not possible for the model to provide a *precise* estimate of the vCJD risk in general, or of the actual risk to individual patients. Although the actual risk is highly uncertain, the risk assessment model indicates that the most important factors affecting risk are the clearance of the vCJD agent though manufacturing steps, how much product individuals used, and the vCJD prevalence in the UK donor population.

In considering the results of the risk assessment it is important to note that to date we are not aware of any cases of vCJD having been reported worldwide in patients receiving plasma-derived products, including pdFVIII.. This includes patients receiving large amounts of other products manufactured from UK plasma donations over a long period of time. This observation suggests that the actual risk of vCJD infection from pdFVIII is likely to be very low. The absence of cases does not rule out the possibility of exposure that could potentially result in illness in some recipients at some future point in time.

REFERENCES

Belay ED, Sejvar JJ, Shieh WJ, Wiersma ST, Zou WQ, Gambetti P, Hunter S, Maddox RA, Crockett L, Zaki SR, Schonberger LB. (2005) Variant Creutzfeldt-Jakob disease death, United States. Emerg Infect Dis. 2005 Sep;11(9):1351-4.

BPL "Guidelines Issued by the UK Haemophilia Centre Directors for the Use of Factor XI Concentrate" draft dated 1/23/2001

Brown P, Rohwer RG, Dunstan BC, MacAuley C, Gajdusek DC, Drohan WN. The distribution of infectivity in blood components and plasma derivatives in experimental models of transmissible spongiform encephalopathy. Transfusion 1998; 38: 810-816.

Brown P, Cervenakova L, McShane LM, Barber P, Rubenstein R, Drohan WN. (1999) Further studies of blood infectivity in an experimental model of transmissible spongiform encephalopathy, with an explanation of why blood components do not transmit Creutzfelt-Jakob disease in humans. Transfusion. Nov-Dec;39(11-12):1169-78.

Bruce ME, McConnell I, Will RG, Ironside JW. Detection of variant Creutzfeldt-Jakob disease infectivity in extraneural tissues. Lancet. 2001 Jul 21;358(9277):208-9.

Centers for Disease Control Universal Data Collection Program (UDC) (2004) Report on the Universal Data Collection Program, Vol.6 No. 2.

Centers for Disease Control, National Center for Infectious Diseases (June 27, 2005) "Bovine Spongiform Encephalopathy and Variant Creutzfeldt-Jakob Disease" from *Health Information for International Travel, 2005-2006* at http://www2.ncid.cdc.gov/travel/yb/utils/ybGet.asp?section=dis&obj=madcow.htm&cssNav=browsecyb (accessed on August 21, 2006).

Centers for Disease Control, National Center for Infectious Diseases (August 14, 2006) "Update: Variant Creutzfeldt-Jakob Disease in a U.K. Citizen Who Had Temporarily Resided in Texas, 2001-2005" at http://www.cdc.gov/ncidod/dvrd/vcjd/other/probablevcjd_texas2001_2005_111805.htm (accessed on Oct 12, 2006).

Cervenakova L, Yakovleva O, McKenzie C, Kolchinsky S, McShane L, Drohan WN, Brown P. Similar levels of infectivity in the blood of mice infected with human-derived vCJD and GSS strains of transmissible spongiform encephalopathy. Transfusion 2003; 43:1687-94.

CJD Incidents Panel. Recommendations of the CJD Incidents Panel. September 4, 2005. Letter found at http://www.hpa.org.uk/infections/topics_az/cjd/vCJDPP-RecoIP.pdf accessed Aug 17, 2006.

Clarke P and Ghani AC. Projections of the future course of the primary vCJD epidemic in the U.K.: inclusion of subclinical infection and the possibility of wider genetic susceptibility. J. R. Soc. Interface 2005; 2:19-31.