

In our importance analysis the five variables that had significant influence on the output of the model were clearance of i.v. ID₅₀ 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.ID₅₀ 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. ID₅₀ 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 ID₅₀ units and the 5th and 95th 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 enhancing 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 ($R_{t,eq}$) 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 ID₅₀ 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 ID₅₀ 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 ID₅₀, including low doses below 1 ID₅₀ using a protocol that mimics transfusion transmission of vCJD in humans. Both infection and duration of the incubation periods at several different i.v. ID₅₀ 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. 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 log₁₀, 4-6 log₁₀, and 7-9 log₁₀ 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. ID₅₀ 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 log₁₀ (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. Assuming a 4-6 log₁₀ manufacturing process reduction, the modeling predicts that the potential risk per person per year for patients with severe HA using pdFVIII ranges from 1 in 15,000 for the higher vCJD prevalence estimate and high product usage to 1 in 9.4 million for the lower vCJD prevalence estimate and low product usage. 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 through 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.

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APPENDIX A

Supplemental technical information for the FDA Risk Assessment

The sections in this appendix provide additional technical information and details of data and modeling approaches used in specific sections (but not all sections) of Section IV. The heading and numbering of each section in this appendix mirrors the sections in "Section IV. Exposure Assessment" portion of the risk assessment.

A- IV. A. Estimation of vCJD Prevalence in the United Kingdom (Module 1)

A-IV. A. 3. Estimation of age-specific vCJD prevalence based on the age distribution of diagnosed vCJD cases in the UK

Cases of vCJD occur in relatively young individuals (median age of 28 years) compared to classic CJD. Blood and plasma donors are usually at the age 18-40, among whom the vCJD prevalence would be expected to be higher than the prevalence among general population. Because age specific rates of donation and vCJD infection would likely have a large effect on the final risk estimate the FDA model carefully characterizes the age specific prevalence of vCJD and donation rate. Throughout the FDA model, age specific vCJD prevalence rates are calculated for each five year age group beginning at age group of 10 – 14 yrs, 15-19 yrs and so on – and applied in estimating vCJD risk and prevalence for the residents of different geographic regions and the US blood and plasma donors who traveled to those regions. The percentage of reported vCJD cases by age is shown in Table A-4.3. The model assumes that the age-specific percentage and prevalence of incubating asymptomatic cases reflects the same age-specific trend as for reported cases of symptomatic vCJD and deaths from vCJD.

Table A-4.3. Reported vCJD cases in the UK and percent of US Source Plasma and blood (recovered plasma) donors by age groups

Age group	<10	10-14	15-19	18-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	>70
Reported vCJD cases in UK (through 2003) ^a (%)	0	5 (3.4%)	27 (18.4%)		32 (21.8%)	30 (20.4%)	22 (14.9%)	13 (8.8%)	5 (3.4%)	3 (2%)	5 (3.4%)	0 (0%)	5 (3.4%)		
Age distribution of US Source Plasma donors (%) ^b	0	0	0	12%	29.3%	14.1%	14.1%	9.6%	9.6%	5.8%	5.8%	0%	0%	0%	0%
Age distribution of US Blood (Recovered plasma) donors ^c	0	0	0	5%	13%	8%	10%	12%	13%	12%	11%	7%	4%	5%	0%

^aHilton *et al.* 2004

^bPlasma Protein Therapeutics Association (Jan 07, 2005). Where data were organized in broader age group we allocated donor equally among smaller 5 year age groups

^cData provided to FDA by Westat in 2002

Some of the general variables for generating age specific estimates from the model are described below.

Variable: age - Age of vCJD cases in 5-year increments

Variable: $vCJD_{UK(age)}$ - Reported vCJD cases in the UK by 5-year age groups (through 2003) beginning at 10 – 14 yrs, 15-19 yrs and so on.

Data used in the model: Data on the vCJD cases in the UK was derived from Hilton et al. (2004). The data includes cases through the end of 2003.

Variable: $Perc_{vCJD(age)}$ - Percentage vCJD cases attributed by each age group from 10 – 14 yrs, 15-19 yrs and so on.

Assumption used in the model: We assume each of four age groups, 55-59 yrs, 60-64 yrs, 65-69 yrs and 70-74 yrs, contributes same percentage in vCJD cases.

For the four (five-year) age groups from 55-74yrs we assumed an equal percentage of cases were present in each of the four groups since there were very few vCJD cases in this age range. To estimate the percentages for each group we identified five reported cases (specifically, three reported cases in the age-specific prevalence grouping shown in Hilton et al. (2004) for persons aged 55-74 yrs and two cases of blood transfusion vCJD (each > 64 yrs of age) (Llewelyn 2004, Peden 2005)) in the 55-74 yr age range. The five cases in the 55-74 yr old age group are shown in Table A-4.3. We assumed an average of 1.25 cases for each of the four age groups from the ages of 55-74 yrs and divided by the total number of vCJD cases for all age groups to get the percentage of cases for each of the four sub age groups, 55-59 yrs, 60-64 yrs, 65-69 yrs and 70-74 yrs.

The percentage of vCJD cases in the UK from each age group is represented by the equation:

$$Perc_{vCJD(age)} = (vCJD_{UK(age)} / \sum_{age=0-4}^{>85} vCJD_{UK(age)}) \times 100\% \quad (IV. A. 1-1)$$

A-IV. A. 3. a. Estimating the UK vCJD prevalence predicted by epidemiological modeling (Clarke and Ghani 2005) for each age group

Variable: $vCJD_{since2002}$ - Predicted clinical vCJD cases in the UK from 2002 onward (cases). Predicted clinical cases from 2002 onward include 32 vCJD cases diagnosed in 2002 and 2003 and 70 (95% CI of 10-190) future cases between 2004 and 2080 predicted by Clarke and Ghani (2005), which give a total of 102 cases (95% CI: 42-222 cases) after 2002.

Variable: $Asym-vCJD_{(age)}$ - Number of asymptomatic vCJD infected individuals from a specific age group in year 2002.

$$Asym-vCJD_{(age)} = vCJD_{since2002} \times Perc_{vCJD(age)} \quad (IV.A.2-4)$$

Variable: $Prev_{Asym-vCJD(age)}$ - Prevalence of asymptomatic vCJD infected individuals in the UK by age groups (cases/million).

The prevalence of asymptomatic vCJD cases in the UK by age group is estimated using the equation:

$$Prev_{Asym-vCJD(age)} = Asym-vCJD(age) / Pop_{UK(age)} \quad (IV.A.2-5)$$

A-IV. A. 3. b. Estimating the UK vCJD prevalence derived from tissue surveillance for each age group

For the risk assessment model we converted the 3 in 12,674 presumptive positive rate to an average rate of vCJD in the UK population of 1 in 4,225 (and used the 1 / 20,300 to 1 / 1,450 at 95% CI; proportions were converted from the 95% CI reported by Hilton et al (2004)). Demographic information of reported vCJD cases (Table A-4.3) indicated that the younger population (20 -29 yrs of age) that was deliberately oversampled in this study may have been more susceptible to the disease. The vCJD prevalence among UK donors might, therefore, be over-represented by the prevalence of 20-29 years age group derived from the surveillance study. Assuming the sensitivity and specificity of the testing method is 100%, the estimated rate of 1 in 4,225 translates roughly to a vCJD prevalence of 237 cases per million (95% CI: 49 – 692 cases per million) for all age groups. The authors (Hilton et al 2005) indicated that approximately 60% of the samples tested (from 7,600 patients) came from patients 20-29 years of age. Among the 20-29 year old group we calculated a vCJD prevalence of approximately 400 cases per million for which we assumed a 95% CI of 100-1200 cases per million.

We then derived the prevalences for the remainder of the UK donor population by determining the proportional difference between the vCJD prevalence from the tissue study group and the number of actual reported vCJD cases for donors in the 20-29 years age group. This proportion was then applied to the remaining age groups in the distribution of reported vCJD cases to determine the prevalence for each age group. By multiplying our extrapolated vCJD prevalence for incubating cases by the total donor population we were able to estimate the number of possible incubating vCJD cases in each US donor age group. We assumed that a plasma pool used to manufacture pdFVIII product in the US in the year 2002 consisted 6,000 to 360,000 donations, and several donations in the pool likely came from the same donor. The estimated prevalence was then used to generate variables and parameters representing the potential number of vCJD donors or donations that might be present in a plasma pool.

Variable: $Prev_{Asym-vCJD(20-30)}$ Prevalence of asymptomatic vCJD infected individuals in the UK 20-30 year old age group (cases/million)

Assumptions used in the model: The vCJD infectious agent is present in the blood of the individual when the the accumulation of prion protein can be detected in lymphoreticular tissue. Prevalence of vCJD asymptomatic individuals in the UK 20-30 year old age group is likely to be 400 cases/million, 95% CI=100-1200 cases/million. The values for this variable were estimated from the Hilton *et al* studies (2000, 2002, 2004).

Variable: $Pop_{UK(age)}$ - Population in the UK by age groups (Thousands).

Data used in the model: The data for UK population were sourced from UK government statistics (UK National Statistics, 2005). Where UK data were organized in broader categories of 10 to 15 years we allocated population equally among smaller 5 year age groups.

Variable: $Asym-vCJD_{(20-30)}$ - The number of asymptomatic vCJD infected individuals in the 20-30 yr-old UK age group. This variable is represented by the equation:

$$Asym-vCJD_{(20-30)} = Prev_{vCJD(20-30)} \times Pop_{UK(20-30)} \quad (IV.A.2-1)$$

Variable: $Asym-vCJD_{(age)}$ - Number of asymptomatic vCJD infected individuals in the UK by age groups

Assumptions used in the model: Number of asymptomatic vCJD infected individuals from an age group is proportional to the percentage of reported vCJD cases from that age group. The age distribution of asymptomatic vCJD cases was assumed to be the same as that of symptomatic cases.

The number of asymptomatic vCJD individuals in the UK per age group was estimated using the following equation:

$$Asym-vCJD_{(age)} = Asym-vCJD_{(20-30)} \times (Perc_{vCJD(age)} / Perc_{vCJD(20-30)}) \quad (IV.A.2-2)$$

Variable: $Prev_{Asym-vCJD(age)}$ - Prevalence of asymptomatic vCJD infected individuals in the UK by age groups (cases/million).

The prevalence of asymptomatic vCJD cases in the UK by age group is estimated by the equation:

$$Prev_{Asym-vCJD(age)} = Asym-vCJD_{(age)} / Pop_{UK(age)} \quad (IV.A.2-3)$$

A-IV. B. Estimation of vCJD Prevalence in US Plasma Donors and Plasma Pools (Module 2)

A-IV. B. 1. a. Annual US plasma donors and characterization by age

A-IV. B. 1. b. Source Plasma collection in the United States: characterized by donor age

Variable: DN_S - Annual number of Source Plasma units used to make pdFVIII .

Assumption used in the model: It was assumed that, on average, 3.3 million units of Source Plasma were used in each year to make pdVIII. It was further assumed that there is a 10% standard deviation in the number of Source Plasma units used to make pdFVIII for any given year.

Data used in the model: The annual number of Source Plasma units was back calculated based on annual units of pdVIII product made from Source Plasma, the average yield of pdFVIII (187 units per liter

plasma) and average volume of single unit of Source Plasma (700 ml per unit). The information on annual units of pdFVIII made from plasma collected in the US, yield of factor VIII and unit volume of plasma were collected from pdFVIII manufacturers.

Variable: DR_S – Annual number of donors who contribute Source Plasma for manufacture of pdFVIII.

Assumption used in the model: It was assumed that there are approximately 1 million Source Plasma donors in the US each year. It was further assumed that Source Plasma from any individual donor may be used to make pdFVIII. Therefore, we calculated that there were approximately 1 million donors who contributed Source Plasma for the manufacture of pdFVIII. It was further assumed that there could be a 10% standard deviation in the number of donors in any given year.

Variable: *Age* – Age information for US plasma donors was grouped in a two year increment for 18-19 years old because the model assumed that 18 was the minimum age of donation. The remaining population was grouped by 5-year increments – including 20- 24yrs old, 25-29yrs old, and so on

Variable: $DR_{S-perc(age)}$ – The percentage of Source Plasma donors from a given age group.

Data used in the model: Distribution of US Source Plasma donors by age was obtained from the Plasma Protein Therapeutics Association (2005). Where data (PPTA, 2005) were organized in broader age groups of 10 years or 15 years, we generated 5-year age subgroups by allocating the percentage equally among each subgroup.

Variable: $DR_{S(age)}$ – The annual Source Plasma donors by age groups who contribute plasma for pdFVIII manufacturing is represented by the equation:

$$DR_{S(age)} = DR_S \times DR_{S-perc(age)} \quad (IV.B.1-1)$$

A-IV. B. 1. c. Recovered plasma collection in the United States: Characterized by donor age

Variable: DN_R – Annual units of recovered plasma used to make pdFVIII.

Assumption used in the model: It was assumed that approximately 1,800,000 units of recovered plasma are used to make pdFVIII annually. This estimation was generated by backcalculation beginning with the total quantity of pdFVIII manufactured in the US. It was further assumed that there was a 10% standard deviation in the number of units for any given year.

Data used in the model: The annual number of total units of pdFVIII manufactured from recovered plasma collected in the US was estimated by back calculation. The calculation was based on the total quantity of annual units of pdVIII product made from recovered plasma collected in the US. We can further estimate the number of donations used to make the pdFVIII from recovered plasma using estimates in the literature for the average yield of pdFVIII 187 units per liter of plasma (WFH, 2004) and average volume of single unit of recovered plasma (200 ml per unit). The information on annual units of pdFVIII made from plasma collected in the US was collected from pdVIII manufacturers.