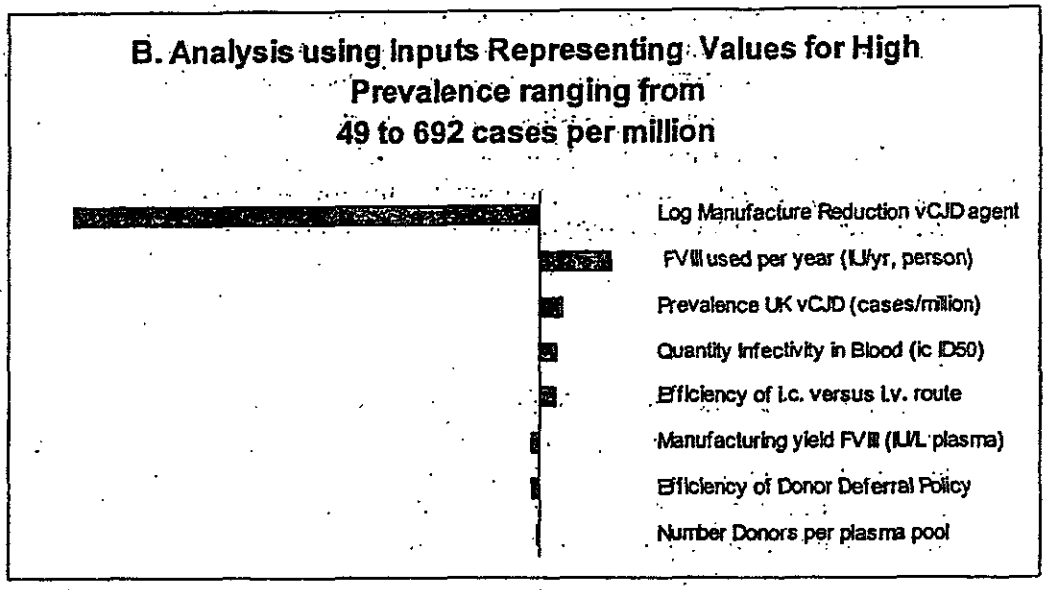
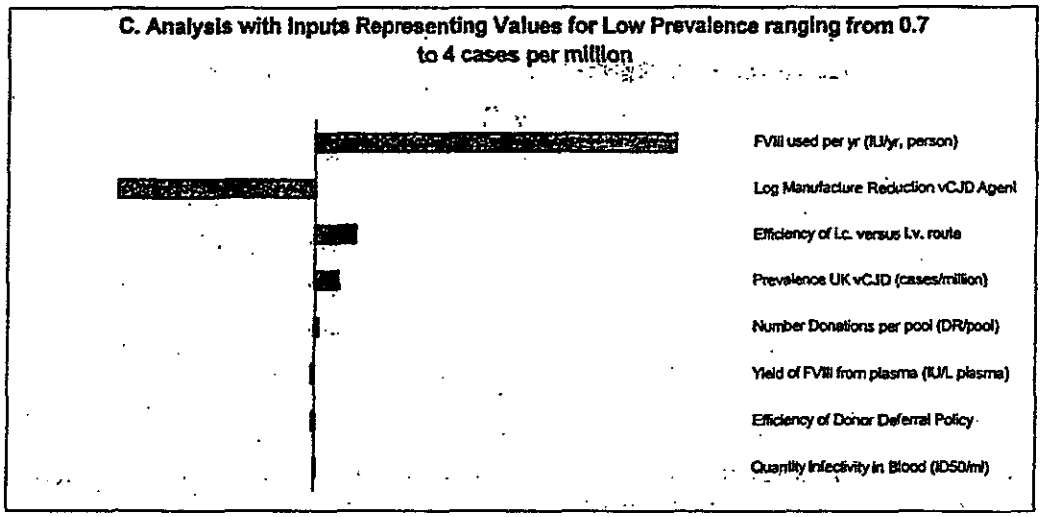


Fig 2. C. FVIII Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using Epi Modeling-based (LOW) prevalence estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of pdFVIII recipients.



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 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_{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.

Communicable Disease Surveillance Centre (CDSC) (2005) Email communication on age distribution of UK plasma donors, May 26, 2005.

Cervenakova L, Brown P, Hammond DJ, Lee CA, Saenko EL.(2002) Factor VIII and transmissible spongiform encephalopathy: the case for safety. Haemophilia. Mar;8(2):63-75.

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 Dec;43(12):1687-94.

CJD Incidents Panel (2004). vCJD and Plasma Products - Recommendations of the CJD Incidents Panel, September 7, 2004.

Det Norske Veritas. Risk Assessment of Exposure to vCJD Infectivity in Blood and Blood Products – for Department of Health. February, 2003. United Kingdom.

Evatt B, Austin H, Barnhart E, Schonberger L, Sharer L, Jones R, DeArmond S. Surveillance for Creutzfeldt-Jakob disease among persons with hemophilia. Transfusion. 1998 Sep;38(9):817-20.

Food and Drug Administration. Guidance for Industry Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products. January 2002.

Foster PR, Welch AG, McLean C, Griffin BD, Hardy JC, Bartley A, MacDonald S,Bailey AC. (2000) Studies on the removal of abnormal prion protein by processes used in the manufacture of human plasma products. Vox Sang. 2000;78(2):86-95.

Foster PR.(2004) Removal of TSE agents from blood products. Vox Sang. Jul;87 Suppl 2:7-10.

Foster PR, Griffin BD, Bienek C, McIntosh RV, MacGregor IR, Somerville RA, Steele PJ, Reid HE.(2004) Distribution of a bovine spongiform encephalopathy-derived agent over ion-exchange chromatography used in the preparation of concentrates offibrinogen and factor VIII. Vox Sang. Feb;86(2):92-9.

Gregori L, McCombie N, Palmer D, Birch P, Sowemimo-Coker SO, Giulivi A, Rohwer RG. (2004). Effectiveness of leucoreduction for removal of infectivity of transmissible spongiform encephalopathies from blood. Lancet 364(9433): 529-531.

http://www.hemophilia.org/bdi/bdi_types9.htm (accessed Oct 26, 2004).

Health Protection Agency of the United Kingdom, Statistics Unit, Centre for Infections. 2006. Incidence of Variant Creutzfeldt-Jakob Disease Deaths in the UK January 1994 – June 2006 at http://www.cjd.ed.ac.uk/vcjdqjun06.htm (accessed August 21, 2006).

Hilton DA, Ghani A, et al. Accumulation of prion protein in tonsil and appendix: review of tissue samples. BMJ 2002; 325:633-634.

Hilton DA, Ghani A, et al. Prevalence of lymphoreticulatar prion protein accumulation in UK tissue samples. J Path 2004; 203:733-739.

Houston F, Foster JD, Chong A, Hunter N, Bostock CJ. Transmission of BSE by blood transfusion in sheep. Lancet 2000; 356:999-1000.

Hunter N, Foster J, Chong A, McCutcheon S, Parnham D, Eaton S, MacKenzie C, Houston F. Transmission of prion diseases by blood transfusion. J Gen Virol 2002; 83:2897-2905.

Ironside JW, Hildon DA, Ghani A, et al. Retrospective study of prion-protein accumulation in tonsil and appendix tissues. Lancet 2000; 355: 1693-1694.

Jacquemot C, Cuche C, Dormont D, Lazarini F. High incidence of scrapie induced by repeated injections of subinfectious prion doses 2005; 79:8904-8908.

Kimberlin, R. (1996). Bovine Spongiform Encephalopathy and Public Health: Some Problem and Solutions in Accessing the Risks. Proceedings of the Third international Symposium on Subacute Spongiform Encephalopathies, Paris.

Lee CA, Ironside JW, Bell JE, Giangrande P, Ludlam C, Esiri MM, McLaughlin JE. Retrospective neuropathological review of prion disease in UK haemophilic patients. Thromb Haemost. 1998 Dec;80(6):909-11.

Lee DC, Stenland CJ, Miller JL, Cai K, Ford EK, Gilligan KJ, Hartwell RC, Terry JC, Rubenstein R, Fournel M, Petteway SR Jr. (2001) A direct relationship between the partitioning of the pathogenic prion protein and transmissible spongiform encephalopathy infectivity during the purification of plasma proteins. Transfusion. 2001 Apr;41(4):449-55.

Linden JV, Kolakoski MH, Lima JE, Du P, Lipton RA. Factor concentrate usage in persons with hemophilia in New York State. Transfusion. 2003 Apr;43(4):470-5.

Llewelyn CA, Hewitt PE, Knight RS, Amar K, Cousens S, Mackenzie J, Will RG. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Lancet. 2004 Feb 7;363(9407):417-21.

Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. (2004) Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. Lancet. 364(9433):527-9.

MESAC Council, 2001

(NBDRC, 2005) The number of annual blood donations is approximately 14,000,000

National Research Council. (1983) Risk Assessment in the Federal Government: Managing the Process. National Academy Press, Washington, DC.

Organization Internationale de Epizootics(OIE) (2005) Table Number of cases of BSE reported in the U.K.. (2006). Data were accessed at http://www.oie.int/eng/info/en_esbru.htm#4 (Accessed on May 30, 2006).

Plasma Protein Therapeutics Association (2004). Data on the age of US plasma donors was obtained from the Plasma Protein Therapeutics Association(2004). Need more info here

Plasma Protein Therapeutics Association (2005). Information on age distribution of plasma donors provided to FDA

Rohwer, Robert presentation at the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) Feb 12, 2004. Recent experimental studies in animals regarding TSE infectivity in blood and transfusion transmission of TSE's - Review of recent experiments in rodents and in sheep.

Stenland CJ, Lee DC, Brown P, Petteway SR Jr, Rubenstein R. (2002) Partitioning of human and sheep forms of the pathogenic prion protein during the purification of therapeutic proteins from human plasma. Transfusion. Nov;42(11):1497-500.

Soucie JM, Evatt B, Jackson D. (1998) Occurrence of hemophilia in the United States. The Hemophilia Surveillance System Project Investigators. Am J Hematol. 1998 Dec;59(4):288-94. Transmissible Spongiform Encephalopathies Advisory Committee (FDA-TSEAC), 2000. Presentation by Kevin Watanabe of the American Red Cross.

TaylorDM, Fernie K, Reichl HE, Somerville RA. 2000. Infectivity in the blood of mice with a BSE-derived agent. J Hosp Infect 46(1):78-79.

Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC), October 31, 2005. Presentations by FDA staff and discussions by TSEAC on FDA's Risk Assessment for Potential Exposure to Variant Creutzfeldt-Jakob Disease in Human Plasma-Derived Antihemophilic Factor (FVIII) Products.

Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC), 2001. Presentation by Alan Williams, FDA

Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) June 1, 2000. Presentation by K. Watanabe.

United Kingdom National CJD Surveillance Unit - Edinburgh, Scotland, 2006. [http://www.cjd.ed.ac.U.K./figures.htm] - Results as of March 31, 2006.

United Kingdom National CJD Surveillance Unit - Edinburgh, Scotland, 2006. *[http://www.cjd.ed.ac.U.K./figures.htm - results as of Aug 4, 2006; accessed on August 14,* 2006)

United Kingdom Office for National Statistics. Ninety Population Trends. Winter, 1997. [http://www.statistics.gov.U.K./downloads/theme_population/PT90book_V2.pdf - Accessed on June 14, 2006]

United Kingdom Office for National Statistics, 2005 accessed at http://statistics.gov.uk/statbase/product.asp?vlnk=1391&More=N on Feb 2, 2005.

Wadsworth JD, Joiner S, Hill AF, Campbell TA, Desbruslais M, Luthert PJ, Collinge J. Tissue distribution of protease resistant prion protein in variant Creutzfeldt-Jakob disease using a highly sensitive immunoblotting assay. Lancet. 2001 Jul 21;358(9277):171-80.

Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, Poser S, Pocchiari M, Hofman A, Smith PG. (1996) A new variant of Creutzfeldt-Jakob disease in the UK. Lancet. 347(9006):921-5.

Westat: Retroviral Epidemiological Donor Study (REDS) were obtained from Westat in Rockville, MD (2002).

World Federation of Hemophilia (WFH). June 4, 2004. (No. 5) Facts and Figures: Contract Fractionation - Revised Edition.

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%

[a]Hilton *et al.* 2004

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

[c] Data 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:

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

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 afterward (cases). Predicted clinical cases from 2002 afterward 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: $Asym\text{-}vCJD_{(age)}$ - Number of asymptomatic vCJD infected individuals from a specific age group in year 2002.

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