Transmissible Spongiform Encephalopathies Advisory Committee
21st Meeting, June 12, 2009

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, MD 20879

Topic I:

Modified FDA Risk Assessment for Potential Exposure to the Infectious Agent of Variant Creutzfeldt-Jakob Disease (vCJD) in US-licensed Plasma-Derived Factor VIII (pdFVIII)

ISSUE:

Plasma-derived Factor VIII (pdFVIII) products are used by blood clotting disorder patients with von Willebrand disease and some patients with hemophilia A. The announcement in February 2009 by health authorities in the United Kingdom that a vCJD infection had been recognized in a person with hemophilia treated with a UK manufactured "vCJD-implicated" pdFVIII 11 years earlier has prompted FDA to review the potential vCJD risk for US users of US-licensed pdFVIII products and current risk management strategies for such products.

Results from an updated FDA risk assessment model continue to indicate that the estimated risk of the potential for US-licensed pdFVIII products to transmit the agent of vCJD, the human form of "Mad Cow Disease," is highly uncertain but is most likely to be extremely small.

FDA seeks the advice of the Committee on whether additional risk reducing measures are needed (e.g. modifications to current donor deferral policies) to maintain the safety of plasma-derived biologic products and whether FDA should change its communications concerning the risks of vCJD associated with plasma derivatives.

BACKGROUND:

In February 2009 the Health Protection Agency of the United Kingdom (UK) reported a probable case of pre-clinical variant Creutzfeldt-Jakob Disease (vCJD) infection in a man over 70 years of age with hemophilia (http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733818681). Post-mortem examination of the brain found no neuropathological changes suggestive of vCJD, however, examination of the spleen revealed abnormal accumulations of prion protein (PrP) typical of vCJD and not of other forms of CJD. The man, who was in his 70s at death, had been treated 11 years earlier with UK-sourced plasma-derived Factor VIII (pdFVIII) from a "vCJD-implicated" lot, i.e., a lot of pdFVIII manufactured from pooled plasma containing at least one donation from a person who later died of confirmed or probable vCJD.

Variant CJD is a fatal human neurodegenerative disease acquired through infection with the agent that causes bovine spongiform encephalopathy (BSE). vCJD infection is most often acquired by consumption of beef products from infected cattle. The first human cases of vCJD were reported in the UK in 1996 (Will 1996); as of May 2009, 211 definite or probable clinical cases of vCJD have been reported worldwide, 168 of them in the UK (http://www.cjd.ed.ac.uk/). In addition to food-borne cases, four presumptive "secondary" transfusion-transmitted infections with the vCJD agent have also been reported in the UK since 2003 (Llewelyn 2004, Peden 2005, Hewitt 2006, http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733711457?p=1171991026241). Three of the transfusion recipients died of vCJD, while one had vCJD infection detected after death from an unrelated cause. Each person with a secondary vCJD infection had been transfused with red blood cells from donors who were asymptomatic at the time of donation but who later died from vCJD. The probable transmission of vCJD via transfusion of red blood cells in the UK increased the concern that products manufactured from the plasma component of human blood might also pose a risk of vCJD transmission. (Plasma of animals with scrapie—a transmissible spongiform encephalopathy [TSE] used to model vCJD—contains approximately 50% of the total infectious agent present in blood [Gregori 2004].)

After the first descriptions of vCJD, UK authorities, recognizing a possible risk of transmitting vCJD by products derived from human plasma, stopped using UK plasma in their manufacture and began to obtain plasma from the US (http://www.transfusionguidelines.org.uk/docs/pdfs/dl_ps_vcjd_2008-09.pdf). After the first reports of transfusion-transmitted vCJD, UK authorities took the additional step of notifying recipients of a number of plasma derivatives, such as coagulation factors VIII, IX, and XI, as well as antithrombin and intravenous immune globulins, that they might be at increased risk of vCJD and reminded surgeons and dentists to take reasonable precautions to prevent iatrogenic transmission of vCJD (http://www.advisorybodies.doh.gov.uk/acdp/tseguidance/tseguidance_annexj.pdf http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_081170?IdcService=GET_FILE&dID=155914&Rendition=Web).

In 1999, prior to the identification of transfusion-transmitted vCJD, FDA recognized a potential though unknown risk of transmitting vCJD by contaminated blood products. Therefore, consistent with advice from TSEAC, FDA recommended precautionary deferrals of blood and plasma donors who had traveled or lived for six months or longer in the UK from the presumed start of the BSE outbreak in the UK in 1980 until the end of 1996, when the UK had fully implemented a full range of measures to protect animal feed and human food from contamination with the infectious agent causing BSE. In January 2002, FDA recommended enhancing the vCJD geographical donor deferral policy by reducing the time that an otherwise suitable blood donor might have spent in the UK from six to three months. FDA also recommended deferring donors who had spent five or more years in France or cumulatively in any European country listed by the USDA as either having had BSE or having a significant risk of BSE. FDA added certain other measures to reduce potential risk, such as deferring any donor with a history of blood transfusion in the UK after 1979 (http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/ucm095138.ht

m;
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/ucm095143.htm). Taken together, these steps were estimated to have excluded donors representing slightly more than 90% of the potential vCJD risk while deferring about 7% of otherwise suitable donors. Since 2002, TSEAC has several times reviewed FDA vCJD/CJD blood donor deferral policies, most recently advising FDA to recommend deferral of blood donors transfused in France since 1980. FDA has issued draft guidance containing such recommendations (FDA 2006).

Because BSE has been detected in so few US cattle (only three reported cases: two in US-born cattle and one in a cow imported from Canada [http://www.ars.usda.gov/research/publications/publications.htm?SEQ_NO_115=197033]), and because none of the three cases of vCJD recognized in the US appears likely to have resulted from exposure here (two cases in long-time UK residents and a third in a recent immigrant from Saudi Arabia), the risk that US plasma donors might have acquired vCJD infection from US beef is thought to be extremely low. (Because the likelihood of exposure of US donors to the BSE agent in US beef products was judged to be so much lower than likelihood of exposure in UK, its estimated contribution to overall risk seems negligible and—while not ignored in developing FDA Risk Assessments—was not included in the model summarized here.) However, it is possible that a few US donors might have been exposed to the BSE agent during travel or residence in the UK, France, or certain other countries of Europe; such donors are at an uncertain but increased risk for vCJD. A subset of such vCJD-infected donors might have contributed to plasma pools used to manufacture pdFVIII in the US. The FDA-recommended donor deferral policy probably eliminates most of the risk associated with vCJD-infected individuals; however, there could be residual risk from eligible donors who were nonetheless infected during brief stays in foreign countries (Yamada 2006) or from donors who should have been deferred by the screening process, but, for an unknown reason, were not.

FDA Risk Assessment for vCJD and pdFVIII

The recent report from the UK attributing vCJD infection in a person with hemophilia to treatment 11 years earlier with pdFVIII from an implicated batch prompted FDA to re-examine the potential vCJD risk for recipients of US-sourced pdFVIII. FDA presented a previous version of a "*Draft Quantitative Risk Assessment of vCJD Risk Potentially Associated with the Use of Human Plasma-Derived Factor VIII Manufactured Under United States (US) License From Plasma Collected in the US* " at the December 15, 2006 meeting of the TSEAC.

Since 2006, new information has emerged, prompting us to update the risk assessment. FDA is presenting an update of its 2006 computer-based simulation model to estimate the potential risk, to elucidate the most important factors determining the risk, and to identify feasible actions that might reduce the risk. The results are modified estimates of the probability of exposure, possible levels of exposure to the vCJD agent and the possible risk of vCJD infection in several types of patients with severe hemophilia A (HA) or with a severe form of von Willebrand disease (type-3 vWD) who have used pdFVIII product manufactured in US-

licensed facilities. The following overview briefly describes key elements of the FDA risk assessment for vCJD and pdFVIII as first presented and posted online in 2006 (FDA, 2006).

I. Overview of FDA 2006 Risk Assessment Model for vCJD and pdFVIII

Module 1. Estimates of vCJD Prevalence in UK

In our 2006 model, we used the possible UK prevalence of vCJD to estimate the possible prevalence in US plasma donors. The model assumed that the major source of vCJD infection in the US would probably be from plasma donors who traveled or lived in the UK, France or elsewhere in Europe since 1980 and were infected with the BSE agent during their stays.

Two different sources of information were used to estimate possible prevalence of UK vCJD:

- One estimate was based on epidemiological modeling predictions of the number of vCJD cases diagnosed in the UK and a number of assumptions (e.g., incubation period, time of infection, effectiveness of feed ban). The model estimated a prevalence of approximately ~1.8 cases per million persons of the genetically most susceptible genotype (homozygous for methionine at codon 129 of the gene encoding PrP [*PRNP* gene]) and allowed for the possibility that some infected people might have very long asymptomatic incubation periods or never become symptomatic (Clarke and Ghani 2005). The model relied on reports of overt clinical cases of vCJD—all of which, at the time of our FDA 2006 risk assessment, had been in persons homozygous for methionine at codon 129 of the *PRNP* gene. The number of expected cases was therefore restricted to the approximately 40% of the UK population having that genotype; no prediction was offered for the rest of the population.

- A second estimate for UK vCJD infection prevalence was generated using data from a survey of abnormal TSE-associated PrP (recently designated as PrP^{TSE} by a WHO Consultation (http://www.who.int/bloodproducts/cs/TSEPUBLISHEDREPORT.pdf)) in lymphoid tissues reported in 2004 (Hilton 2004), yielding a mean estimate of 1 case per 4,225 persons. The prevalence estimate was further adjusted to account for the difference in age distributions of patients whose tissues were surveyed and of blood donors.

Module 2. Estimates of vCJD Prevalence in US Donors and US Plasma Pools

This module estimated the number of US plasma donors potentially infected with the agent that is responsible for vCJD and, from that, the number and percentage of plasma pools potentially including donations containing the vCJD agent. This module used results of a travel survey of US donors to determine numbers of US plasma donors expected to be at increased risk for vCJD, including those with history of:

- Dietary exposure to BSE-contaminated beef during long-term travel or residence in UK, France and other European countries (since 1980);
- US military service in European countries where beef was obtained from the UK, including US military personnel and associated civilian employees and dependents posted on or residing near military facilities in Europe during certain years; and
- Transfusion with blood collected in Europe ("EuroBlood").

US plasma donors potentially at increased risk for vCJD were further characterized by their:

- Country of travel or residence,
- Specific duration of travel or residence,
- Years of travel or residence,
- Age of donor,
- Rate and frequency of plasma donation,
- Number of donations per pool, and type of plasma pool (Source Plasma or recovered plasma), and
- Effectiveness of donor deferral policies.

Module 3. pdFVIII Manufacturing and Processing

This part of the model calculated the likelihood and number of plasma pools potentially containing vCJD agent and the quantity of agent per plasma pool and FVIII vial based on:

- Probability of and predicted quantities of vCJD infectivity (as animal intravenous 50%-infecting doses [i.v. ID_{50}]) per donation and per pool,
- Reduction in quantity of vCJD agent during manufacture, and
- Total yield or quantity of pdFVIII produced from the plasma pool.

Module 4. Utilization of pdFVIII by Hemophilia A Patients

The potential exposure of an individual with hemophilia A to vCJD agent in pdFVIII was estimated in the model based on:

- Total quantity of pdFVIII used per year, and
- Estimated potential quantity of vCJD agent predicted to be present in the pdFVIII product.

The quantity of pdFVIII utilized by an individual patient depends on the severity of hemophilia and the treatment regimen employed. Those were estimated using data from a study sponsored by the US Centers for Disease Control (CDC) involving patients with hemophilia A in six states from 1993 through 1998. The FDA 2006 Risk Assessment provided outputs that estimated the annual exposures for several subpopulations of patients with severe hemophilia A in the following five clinical treatment groups:

- Patients requiring FVIII prophylaxis but having no FVIII inhibitor and no immune-tolerance treatment;
- Patients requiring FVIII prophylaxis but having FVIII inhibitor (i.e., needing more FVIII to maintain desired coagulation status);
- Patients requiring prophylaxis and having both inhibitor and immune-tolerance treatment;
- Patients requiring only episodic treatments and having no inhibitor; and
- Patients requiring only episodic treatments but having FVIII inhibitor.

Additional Module. VonWillebrand disease (vWD) in Adults (>15 yrs of age) and Young Persons (≤15 yrs of age)

We estimated risk for adult and juvenile patients with vWD in two clinical treatment groups, those requiring:

- Prophylaxis or
- Episodic treatments only.

II. FDA Modified Risk Assessment Model for vCJD and pdFVIII: Updates and Changes in Model Inputs of June 2009

Recently, new scientific information has emerged concerning susceptibility to infection with the vCJD agent. To date, only persons homozygous for methionine at codon 129 of the *PRNP* gene have developed symptomatic vCJD illness that meets the case definition for vCJD. Successful sequencing of the *PRNP* genes from two of the three PrP^{TSE}-positive appendix samples detected during the survey described above (Hilton 2004) found them to be from persons homozygous for valine (VV) at codon 129 (Ironside 2006). The fate of these two persons with *PRNP* codon-129 VV genotypes is not known, although no definite or probable cases of vCJD in persons with that genotype have been reported. One of the four transfusion-transmitted vCJD infections reported since 2003 was in a patient heterozygous for methionine and valine (MV) at that codon (Peden 2004). Furthermore, one individual with the *PRNP* codon-129 MV genotype—apparently not a transfusion recipient—was reported in the UK popular press (Telegraph, December 18, 2008) to have died with CJD suspected "…on a clinical basis only… [but] it does look more likely to be variant CJD than another form of prion disease." (http://www.telegraph.co.uk/health/healthnews/3815384/Hundreds-could-die-as-scientists-identify-first-case-of-second-wave-vCJD.html).

Taken together, these recent findings suggest that it is now more reasonable to assume that the entire general UK population is at risk for vCJD infection, and this assumption has been incorporated throughout the FDA 2009 updated Risk Assessment. Unfortunately, there is still little information available on the duration of the incubation periods for vCJD-infected persons with *PRNP*-129 non-MM genotypes. We assumed that the incubation periods and duration of that part of the incubation period in which vCJD agent is present in blood of infected *PRNP*-129 non-MM individuals is potentially much longer than for *PRNP*-129 MM individuals.

Several inputs have been updated or added to modules 1 and 2 of the model since 2006. Three input parameters, listed below, have been updated since 2006, and three new inputs were recently added to the model to improve assumptions for susceptibility of recipients to vCJD infection.

Updated Inputs:

1. Prevalence estimation of UK vCJD infection
2. Prevalence of UK vCJD infection: Age of susceptible population
3. Time during incubation period when infectivity is present in blood

New Inputs:

4. *PRNP*-129 genotype susceptibility and genotype proportions in US population
5. Distributions of vCJD incubation periods for persons of different *PRNP*-129 genotypes
6. Age distribution of persons with asymptomatic vCJD infections

1. Prevalence Estimation of UK vCJD Infection (updated input)

A key assumption of the FDA vCJD Risk Assessment Model is that most infected donors in the US would probably have become infected through exposure to the BSE agent from consumption of BSE-contaminated beef products during travel to the UK, France and other countries in Europe since 1980. Because prevalence of vCJD infection is highest in the UK, the model used prevalence in the UK population and a relative-risk approach to estimate vCJD exposure, and therefore prevalence of vCJD infection, for US donors who traveled to the UK, France and other European countries. The actual prevalence of vCJD infection in the UK remains unknown and difficult to estimate because of the long incubation periods and because clinical illness appears only during the last few months or years of infection. Because of the uncertainties, the FDA 2006 Risk Assessment used the two different sources of information described above for estimating possible UK prevalence of vCJD infection: a high estimate based on a lymphoid-tissue survey (infection prevalence) and a lower vCJD case prevalence estimate based on registered overt vCJD cases. We still do not know which of the two estimates of UK prevalence of vCJD is better to estimate the possible prevalence of US donors having vCJD agent in their blood at the time of donation. We modified the lower vCJD prevalence estimate (Clarke-Ghani case-based estimate) for this 2009 update of the FDA Risk Assessment to assume that the entire population is susceptible to vCJD infection, including persons with all three possible *PRNP*-129 genotypes: MM, MV and VV. As noted above, the lower vCJD case prevalence estimate was derived using epidemiological modeling of actual reported cases to estimate probable future clinical vCJD cases in the UK (Clarke and Ghani 2005). This estimate of approximately 1.8 vCJD cases per million was used by FDA for the 2006 Risk Assessment. It had a number of limitations associated with its simplifying assumptions; those contributed to considerable uncertainty in final case estimates. Those simplifying assumptions included the intensity of human exposure to the BSE agent, influence of genetics and other factors on susceptibility to infection with BSE agent, length of vCJD incubation periods, and influence of age on exposure to the agent. An

additional limitation is the possibility that the prevalence of vCJD infection in the UK is higher than this estimate if there are people infected but who never develop the disease while still potentially spreading the infection, or—as seems increasingly likely—if some infected individuals become ill but only after an extremely long time.

The higher vCJD infection prevalence was estimated from testing results of a relatively small survey of tonsil and appendix tissue samples saved from UK patients; the samples were examined by immunohistochemistry, seeking accumulations of abnormal PrP^{TSE}. (Such accumulations of abnormal PrP^{TSE} were previously found at autopsies of patients who died with vCJD and in tissue fortuitously saved from surgery during the last two years of incubation period [Hilton 2002]). This approach yielded an unadjusted estimate of 1 vCJD-infected person in 4,225 (237 infections per million [Hilton 2004]) that was then adjusted for patient age and the distribution of reported age-specific vCJD rates. A limitation to this study, contributing to uncertainty of the estimate, was its lack of control by testing a statistically adequate number of similar tissues from non-BSE exposed populations, so that false-positive reactions cannot be ruled out, and specificity and positive-predictive values cannot be evaluated. It also remains unknown whether the finding of PrP^{TSE} in lymphoid tissues by immunohistochemistry, assuming reliability of the method for identifying sub-clinical or pre-clinical vCJD infections, accurately predicts the presence of vCJD agent in blood in a quantity sufficient to transmit infection by transfusion—now repeatedly demonstrated for blood during the last one to three years of incubation period for three donors who later became ill with typical vCJD. (This limitation also applies to the lower prevalence estimate.)

After accounting for the age distribution, incubation period, country, year and duration of travel, we used both prevalence estimates to predict the number of vCJD donations that might make their way into US plasma pools of various sizes. A brief summary comparing changes in the UK vCJD infection prevalence estimates between the FDA December 2006 Risk Assessment Model and the FDA June 2009 updated Model is provided in Table 1 below. The lower vCJD prevalence estimate used for the FDA 2006 Risk Assessment Model was ~1.8 per million; it assumed that vCJD-infected individuals would develop clinically overt vCJD only if they had the *PRNP* codon-129 MM (approximately 40% of the total population). The FDA 2009 Risk Assessment Model now assumes 100% of the population to be susceptible to vCJD infection, yielding a higher prevalence of ~4.5 per million (~1.8 per million x 100% / 40% = ~4.5 per million).

Table 1: Changes in UK vCJD infection prevalence estimates between the FDA December 2006 Risk Assessment Model and FDA June 2009 Updated Model

Input Parameter Name and Description	FDA Model December 2006	FDA Updated Model June 2009
UK vCJD Prevalence Estimates	1) LOWER vCJD Case Prevalence estimate: Predictive modeling estimates; implies initial prevalence **~<u>1.8 per million*</u>** *Estimate based on Clarke and Ghani (2005), assumed only persons homozygous for methionine (MM) at codon 129 of *PRNP* gene would progress to develop clinically overt vCJD	1) LOWER vCJD Case Prevalence estimate: Predictive modeling estimates; implies initial prevalence **~<u>4.5 per million*</u>** *Estimate based Clarke and Ghani (2005) , assumes persons of all 3 *PRNP* genotypes to be equally susceptible to vCJD infection and that some might progress to develop clinically overt vCJD
	2) HIGHER vCJD Infection Prevalence estimate: starting prevalence based on PrP^{TSE} immunohistochemical surveillance study of tonsils and appendices of ~ **<u>1 in 4,225</u>**[#] [#]Estimate based on Hilton et al (2004); assumed persons of all three *PRNP*-129 genotypes (i.e., entire general population)to be susceptible to vCJD infection	2) HIGHER vCJD Infection Prevalence estimate: starting prevalence based on PrP^{TSE} immunohistochemical surveillance study of tonsils and appendices of ~ **<u>1 in 4,225</u>**[#] [#]Estimate based on Hilton et al (2004); assumed persons of all three *PRNP*-129 genotypes (i.e., entire general population) to be susceptible to vCJD infection

2. Prevalence of UK vCJD Infection: Age of Susceptible Population (updated input)

In the UK, vCJD has most often occurred in relatively young persons; the median age at onset of clinical signs is approximately 30 years. Because of this tendency for infection and clinical disease to occur in the relatively young, the FDA December 2006 Risk Assessment Model adjusted prevalence estimates to account for the age-specific rates of observed clinical cases in the UK, where "age" was the age at the onset of symptoms as described in Hilton (Hilton 2004).

The updated FDA June 2009 Risk Assessment Model incorporates an estimate of the age distribution of the population of persons at risk for or susceptible to vCJD infection. The approach further adjusts the age-specific rates of observed clinical cases in the UK at the onset of symptoms (Hilton 2004) that were used in our previous model (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4271b1-index.htm) by subtracting the median incubation period, which is assumed to have a median duration of approximately 12 years (90% CI= 5-35). The resulting mathematical function effectively shifts the age distribution curve at the time of clinical onset left by approximately 12 years to produce a new distribution that represents the population of persons who are at risk or susceptible to vCJD infection (see Figure 1 below). This overall younger population (a median of

approximately 12 years younger) probably provides a better representation of the age distribution of the UK population most susceptible to vCJD infection.

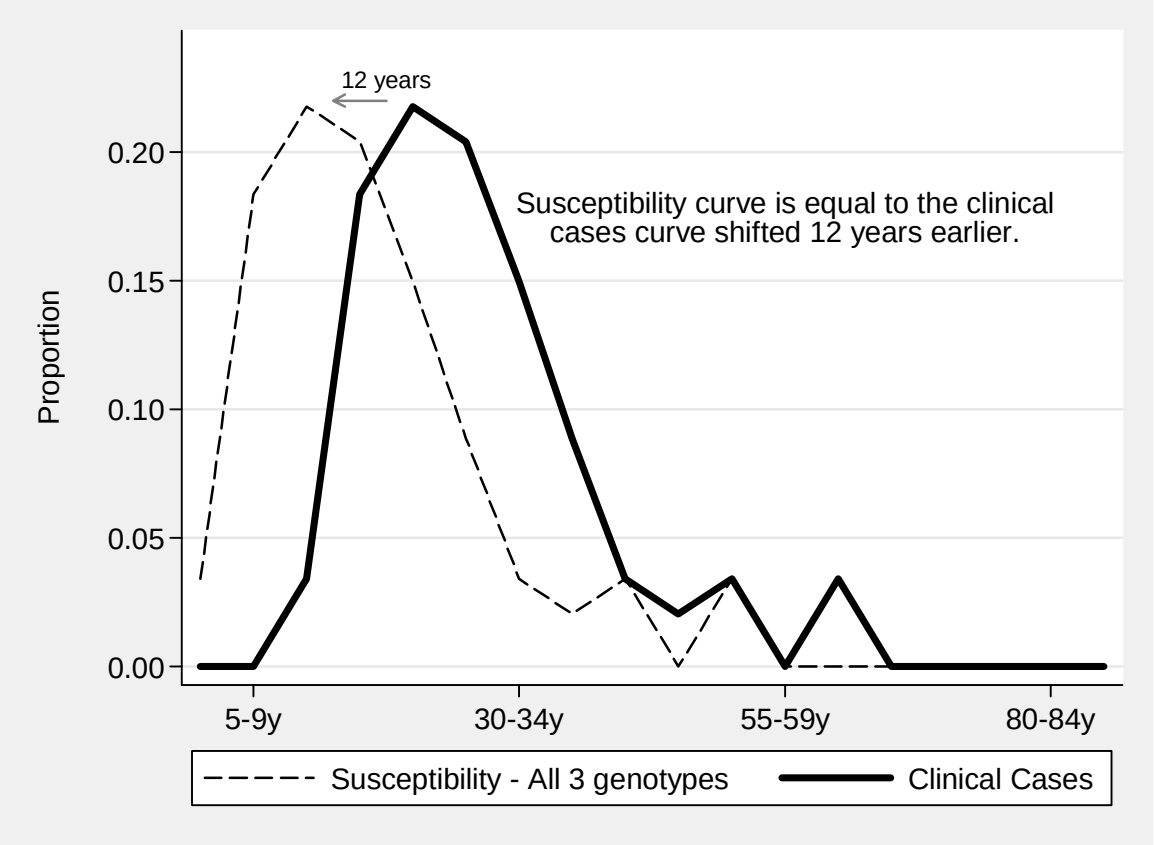

Figure 1. UK vCJD Prevalence: Age of susceptible population. Age of the susceptible population was derived using the distribution for age of persons at the time of clinical onset of vCJD in observed cases (Hilton 2004) and subtracting the median incubation period of approximately 12 years.

3. Time During Incubation Period when vCJD Infectivity Present in Blood (updated input)

The FDA December 2006 Risk Assessment Model assumed that infectious vCJD agent was present in blood of infected persons only during the last half of the incubation period. This assumption was based on a discussion at the October 31, 2005 TSEAC Meeting addressing vCJD risk for plasma derivatives. The updated FDA June 2009 Risk Assessment Model now assumes that infectious vCJD agent is most likely to be present in blood longer—during the last 75% of the incubation period (minimum=50%, maximum=90%). This assumption was updated to reflect results from recent findings from studies in animal models which suggest that TSE agents might appear in blood during the first third of the incubation period (Brown 2007).

4. *PRNP*-129 Genotype Susceptibility and Genotype Proportions in US Population (new input)

The FDA December 2006 Risk Assessment Model assumed that the genetic background of individuals in the population is one factor likely to be associated with susceptibility to vCJD infection. At that time, all known cases of overt vCJD (symptomatic individuals who met the WHO case definition of vCJD) had occurred in individuals with the homozygous *PRNP*-129-MM genotype. Research had revealed presumptive evidence of latent infection in two individuals homozygous for valine at that locus (*PRNP*-129-VV) (Ironside 2006) among the three samples of appendix containing accumulations of PrP^{TSE} reported by Hilton (Hilton 2004). (The third PrP^{TSE}-positive appendix tissue could not be genotyped.) However, because clinical vCJD had never been identified in any individual with a *PRNP*-129-non-MM genotype (*PRNP*-129-MV or *PRNP*-129-VV genotypes), it was impossible to estimate incubation periods for non-MM infected persons—except to conclude that they would be longer than those of *PRNP*-129-MM persons. Furthermore, it was even unclear whether these individuals would ever develop clinical illness or transmit infection. Therefore, to calculate the lower vCJD Case Prevalence estimate, the model assumed that only persons with the *PRNP*-129-MM genotype were susceptible and would—if they lived long enough—eventually develop clinical vCJD. MM persons were assumed to represent approximately 40% of the total donor population in the UK. Persons with *PRNP*-129-non-MM genotypes were not included in the calculation of the LOWER vCJD case prevalence estimate. For the higher vCJD Infection Prevalence estimate (based on the Hilton tissue survey), we assumed that persons of all *PRNP*-129 genotypes—MM, MV and VV—representing 40%, 50% and 10% of the total donor population, respectively were equally susceptible to vCJD infection.

The updated FDA June 2009 Risk Assessment Model now assumes for both the LOWER vCJD Case Prevalence estimate and the HIGHER vCJD Infection Prevalence estimate (based on the tissue survey) that all persons are equally susceptible to vCJD infection. We have also modified our 2006 assumption that only persons with the *PRNP*-129-MM genotype would develop overt vCJD, and our updated 2009 model assumes for the LOWER vCJD Case Prevalence estimate that at least some persons with *PRNP*-129-non-MM genotypes may eventually progress to develop overt vCJD but that many will probably remain asymptomatic for life. We again assume, for modeling purposes, that persons with the *PRNP*-129- MM, -MV, and -VV genotypes comprise 40%, 50% and 10% of the total donor population, respectively, in both the UK and US.

5. Distributions of vCJD Incubation Periods for Persons of Different *PRNP*-129 Genotypes (new input)

The FDA December 2006 Risk Assessment Model assumed a vCJD median incubation period of 13 years and mean incubation of 14 years for persons with the *PRNP*-129-MM genotype. Because little information was available on the incubation period for persons with the *PRNP*-129-MV and -VV genotypes, we assumed their incubation periods to be the same as for persons of the *PRNP*-129-MM genotype. The updated FDA June 2009 Risk Assessment Model assumes a median incubation period of 12 years (90% CI = 5-35) for persons with the *PRNP*-129-MM genotype.

Additional reports of *PRNP*-129-non-MM genotype individuals with immuno-histochemical evidence of vCJD infection detected post-mortem have been published in the literature (Peden 2004, Ironside 2006). Although no case reports of definite or probable vCJD in such

persons have been officially announced, a prudent assumption must be that some of them will eventually develop overt disease and that their blood may contain the infectious vCJD agent for a portion of the incubation period. However, the estimation of incubation periods for people with *PRNP*-129-non-MM genotypes remains complicated and more uncertain than for persons with the *PRNP*-129-MM genotype. Given this considerable uncertainty, we made simplifying assumptions to establish a distribution for the incubation periods of vCJD-infected people with the *PRNP*-129-non-MM genotype. Our updated model assumes the distributions for the incubation periods for vCJD infection to be the same for persons with *PRNP*-129-MV and -VV genotypes with a median of 32 years (90%CI; 25-55 years) and to be normally distributed. The high value of 55 years (95^{th} percentile) was estimated based on the maximum incubation period for kuru (Collinge 2006).

6. Age distribution of persons with asymptomatic infection (new input)

The December 2006 FDA Risk Assessment Model assumed that the age distribution for persons with asymptomatic vCJD infections was the same as the distribution of ages of onset of clinical cases. The updated FDA June 2009 Risk Assessment Model calculates an "Age Distribution of Incubation Periods" (period of asymptomatic infections) by combining the "UK vCJD Prevalence: Age of susceptible population" (input #2, described above) and "Distribution of incubation periods" (input #5 described above).

Model Uncertainty

The ranges of uncertainty and variability in the input parameters of the risk assessment are great, resulting in very large uncertainty in the outputs that estimate potential risk. Uncertainty can result from lack of information or limited information, while variability is usually the inherent difference observed for a particular input parameter. Because scientific data regarding the level of exposure to the vCJD agent and the likelihood of certain human health outcomes, such as infection and illness, are lacking, estimates for the risk of infection generated in the assessment may not be accurate. For those reasons, it is not possible to provide an actual estimate of the vCJD risk to individual patients potentially exposed to the vCJD agent through plasma-derived products.

FDA believes it is nonetheless appropriate to share with the general public both the findings of possible risk and the uncertainties in our assessment for pdFVIII, because it is possible that the risk is not zero. We are seeking the advice of the TSEAC, meeting in June 2009, concerning the findings of the updated risk assessment and its interpretation, given the very wide range of uncertainty in the estimate of vCJD risk. We will also seek advice on steps that might help to estimate risks better and improve risk reduction.

DISCUSSION:

A. Risk Assessment and Interpretation

Current FDA quantitative risk assessments use probabilistic models and Monte Carlo-based methods to sample individual values from statistical distributions of model inputs to produce thousands of theoretically possible individual scenarios that are combined into a single distribution describing the range of predicted outcomes for a risk (Vose 2000). The FDA December 2006 and June 2009 Risk Assessment Models are both intended to estimate the risk of vCJD infection for users of US-licensed pdFVIII as a function of product exposure for different assumed levels of infectious vCJD agent clearance during manufacturing of pdFVIII under each of two assumed levels of prevalence of vCJD infection in the UK (http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/UCM095104.pdf; http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/UCM095106.pdf).

First, after consultations with TSEAC, we outlined the successive steps involved in the manufacture of the product of concern and the events that would need to occur in each step for an infectious agent from a donor to reach the final product. The risk assessment utilizes a probability-based computer-based simulation model to evaluate successively the impact on vCJD risk of individual processes used to produce human pdFVIII beginning with plasma donation, vCJD infection prevalence in plasma donors, manufacturing steps, and, finally, differing levels of utilization of the product by various representative patient subpopulations. Input data for parameters used in the model, such as clearance of infectious vCJD agent by various steps in the manufacturing process and pdFVIII usage, are represented as statistical distributions that express the underlying uncertainties and variability. Each run of the model randomly samples one number from the distribution for each parameter; this is done thousands of times to generate a single distribution representing the final risk estimate that expresses, where possible, the accompanying uncertainty of these risk estimates. A sensitivity analysis, conducted by varying values of key parameters within the input range of the model and observing the effect on the predicted outcomes, determined that three major factors in the model greatly influenced potential vCJD risk: reduction of the infectious agent by the manufacturing process, intensity of pdFVIII utilization by the patient, and differing estimates of disease prevalence in the UK.

One of the most influential risk assessment parameters for vCJD is the manufacturing process, which may reduce the amount of vCJD agent in the final product or even or eliminate it. Because of the uncertainty and variability in the levels of vCJD clearance afforded during the manufacturing process for any pdFVIII product, the model evaluated two separate categories of reduction in infectivity that the product may have undergone during manufacturing including 4-6 $\log_{10}$, and 7-9 $\log_{10}$ reduction. These two categories are meant to span the possible range of uncertainty and variability in reduction of vCJD agent for US-licensed pdFVIII products. Based on currently available experimental studies, FDA believes that all US-licensed pdFVIII products probably achieve at least 4 $\log_{10}$-fold clearance of vCJD infectivity during manufacture.

Laboratory studies using model TSE agents have demonstrated reduction or elimination of TSE infectivity by certain types of manufacturing steps. Analogous to viral clearance studies, the capacity of a manufacturing process to clear TSE agents can be inferred from the results of experiments using validated scaled-down simulations of manufacturing processes and a well-characterized model TSE agent. FDA has recommended that such studies, if submitted for a labeling claim, supply the following information:

- Rationale for animal model selected to assay infectivity;
- Well-characterized bioassay for TSE infectivity;
- Rationale for selection of spiking preparation containing TSE agent;
- Characterization of spiking TSE agent;
- Demonstration of accurately scaled-down manufacturing processes (ordinarily evidenced by producing the desired active product);
- Reproducibility of experiments;
- Estimated $\log_{10}$ of TSE clearance by processing steps (log reduction factor [LRF]);
- Demonstration of "mass balance" (accounting for fate of all input infectivity);
- Demonstration that mechanistically similar clearance steps are or are not additive; and
- Account experimentally for "conditioning" of infectivity ("matrix" effect) because a prior step in the manufacturing process may affect the physical state of TSE agent and in turn affect downstream clearance.

In December 2006, the TSEAC discussed whether a minimum level of TSE clearance (total cumulative LRF) demonstrated by laboratory studies could be defined that enhances safety of plasma-derived products. The concept of a minimum level was agreeable to TSEAC. FDA proposed a total cumulative LRF of 6 log of clearance, based upon estimation of plasma infectivity derived from animal studies, results of the FDA 2006 Risk Assessment for pdFVIII, and including a margin of safety. However, TSEAC felt that, due to insufficient scientific certainty regarding the amounts of vCJD infectivity that might be present and the physical/chemical characteristics of infectivity in human plasma, it was not wise for FDA to recommend a firm minimum LRF (as demonstrated in experimental studies) that would guarantee the safety of pdFVIII prepared by any single manufacturing scheme. In addition, TSEAC members expressed concerns regarding the major limitations of studies involving spiked brain-derived TSE agents into blood or plasma for predicting clearance of endogenous vCJD agent from blood. There was agreement that while current exogenous spiking models have utility and enhance understanding of product safety, their limitations preclude recommending a specific minimum clearance level (http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4271t-unofficial.htm).

To date, FDA has allowed TSE clearance labeling claims for five plasma-derived products.[1] The minimum approved labeling claim has been for products manufactured by processes that demonstrated 6 $\log_{10}$ of clearance for model TSE agents in experimental studies. FDA has encouraged industry studies of pdFVIII manufacturing processes, which were presented to TSEAC in December 2006. The range of clearance offered by single production steps was 2.28 to 4.6 $\log_{10}$. Results of three of four studies were based on prion-protein-binding assays

[1] Carimune® NF, Panglobulin® NF, Privigen® Gamunex®, Thrombate III®

(detecting PrP^{TSE}) rather than infectivity assayed in known susceptible animals; a fourth study assessed clearance by infectivity bioassay (http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4271S1_00-index.htm). This raises questions as to the processes used for clearance of TSE infectivity in the manufacture of the "implicated" pdFVIII product received by the UK hemophilia patient with vCJD infection. Unfortunately, results of clearance studies are not available for that product.

Another major variable affecting potential risk is the quantity of product used by patients in different treatment groups. For purposes of this model, only patients with severe hemophilia A (HA) were considered because their higher use of product puts them at higher risk than patients with mild or moderate forms of the disease. Severe HA patients account for approximately 50% of the total HA population. Approximately 25% of all US HA patients use pdFVIII products, while most others use recombinant FVIII. (Data from a CDC-sponsored epidemiological study of HA patients were used to generate the statistical distribution of pdFVIII usage by patients [http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4271t1.pdf; http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4240t1.pdf; http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4240t2.pd]). Using these estimates, the risk assessment evaluated different treatment regimens. The five groups of patients requiring the largest amounts of product are, in increasing order of usage, (1) those treated with pdFVIII prophylaxis, (2) those treated with prophylaxis plus treatment for FVIII inhibitor, and (3) those treated with prophylaxis and having an inhibitor plus requiring induction of FVIII-immune tolerance. Patients generally requiring treatments with the smallest amounts of product are (4) those needing only episodic treatment, and (5) those needing episodic treatment plus having a FVIII inhibitor. We have also evaluated the potential risk to patients with severe von Willebrand disease (vWD), who are treated with pdFVIII containing von Willebrand Factor (vWF), because no recombinant vWF is available yet.

Results of the Updated Risk Assessment

Results from the updated FDA 2009 Risk Assessment Model for potential annual individual exposure and vCJD risk are shown in the Appendix in Table I. Results for potential annual individual exposure range from a low of approximately 1.7×10^{-7} iv ID_{50} per person per year (risk of 1 in 12 million) for patients who receive episodic treatment and have no inhibitor, to a higher potential exposure of approximately 1.6×10^{-4} iv ID_{50} per person per year (risk of 1 in 12,000) for patients on a prophylactic treatment regimen having both a FVIII inhibitor and induction of immune tolerance. A side-by-side comparison of the potential annual exposure estimates from FDA 2006 and 2009 Risk Assessments for all HA patients using a hypothetical pdFVIII product manufactured by a process that reduces the amount of infectious vCJD agent 4-6 $\log_{10}$-fold is shown in Appendix Table II. The comparison suggests that, even allowing for additional susceptibility of donors to vCJD, there is very little overall difference between the vCJD risk predicted by the FDA 2006 Risk Assessment Model and that generated by the updated FDA 2009 Risk Assessment Model. The biggest difference in the estimates (for 2009 versus 2006) was an approximately 4.5-fold difference (7.3×10^{-6} vs 1.57×10^{-6}) in annual exposure risk for patients who received a prophylactic treatment regimen and had both a FVIII inhibitor and needed treatment for immune

tolerance. However, even this difference is likely to have resulted from the large uncertainty and variability in the model inputs and probably does not represent a large increase in overall estimated vCJD risk.

A side-by-side comparison of model results from the FDA 2006 and 2009 Risk Assessments for the mean per patient risk at two levels of manufacturing process clearance of vCJD agent of 7-9 $\log_{10}$–fold and 4-6 $\log_{10}$-fold shows very little difference (Appendix Table III). As in Appendix Table II, the biggest difference in the estimates generated in 2009 versus 2006 was a less than 5-fold difference (1 in 270,000 vs 1 in 1.3 million) in annual exposure for patients who received a prophylactic treatment and additional treatment for both FVIII inhibitor and for induction of immune tolerance. Comparison of results from the FDA 2009 and 2006 Risk Assessments for vWD patients with severe disease (Appendix Table IV-A and IV-B) indicates little difference between estimates generated by each model. In some cases results in certain cells of Tables II, III, IV-A and IV-B indicate the risks for 2009 may appear lower or higher than the corresponding results for 2006. Because the results of each cell in each table are calculated independently of one another, and because of the significant uncertainty and variability in the model, one would expect this type of variation in the observed estimates of risk. Overall, even adding to a part of the FDA 2009 Risk Assessment the assumption that the entire UK population is susceptible to vCJD infection (the rest of the original FDA Risk Assessment in 2006 already assumed universal susceptibility), the results for 2009 and 2006 remain similar, supporting the same basic conclusions. Given the uncertainties of the models, it is still not possible to provide a precise estimate of the vCJD risk or to attempt to predict the actual risk to individual patients. As in 2006, the current results of the model continue to suggest that some users of pdFVIII might be exposed to the vCJD agent, so that there is a potential risk of infection, but that risk is likely to be extremely small, even for those patients using the largest amounts of product.

Interpretation

Results from the updated FDA 2009 vCJD pdFVIII Risk Assessment Model suggest that the risk of vCJD infection from US-licensed pdFVIII is likely to be extremely small but may not be zero. For US plasma donors, the major source of vCJD risk is dietary exposure during travel and/or residence in the UK, France, or other countries in Europe since 1980. Blood and plasma donor deferral criteria in place since 1999 have reduced the risk posed by donations from BSE-exposed and vCJD-exposed persons.

Manufacturing processes for human pdFVIII products are likely to reduce the quantity of vCJD agent, if present, but the level of reduction achieved by manufacturing steps is not precisely known. Clearance of TSE agents in manufacturing appears to vary among products, but clearance has not been measured in standardized studies that might allow more meaningful direct comparisons. Based on currently available experimental studies, it is estimated that pdFVIII products potentially undergo 4 $\log_{10}$ (10,000-fold) or greater reduction of the vCJD agent during the manufacturing process. Assuming a 4-6 $\log_{10}$ reduction in infectivity by the manufacturing process, modeling predicts that the potential risk per person per year for patients with severe HA using pdFVIII ranges from 1 in 12,000 for the higher vCJD infection prevalence estimate and high product usage, to as little as 1 in 12 million for the lower vCJD case prevalence estimate and low product usage. While higher levels of

clearance of vCJD infectivity by manufacturing are likely to reduce risk, it is not possible at this time to determine with certainty if a specific product may be more or less safe than another; that is due to the wide range of methods used for clearance studies, the results of clearance studies, and gaps in information. Although results of the model suggest that exposure to vCJD agent is possible, with a potential risk of infection that is likely to be extremely small, the model itself cannot provide a precise estimate either of the vCJD risk in general or of the actual risk to individual patients. Nonetheless, despite the uncertainties in the model, we believe this is information that patients and physicians might consider when making treatment decisions.

B. Risk Management Strategy

FDA's current risk management strategy for vCJD has evolved in response to emerging epidemiologic findings and basic scientific developments pertinent to the epidemic. The overall risk management strategy for vCJD includes the following:

- Deferral of donors at increased risk of vCJD based on epidemiological data, and withdrawal of certain products at increased vCJD risk:
    - Donor deferrals: Guidance since August 1999 (most recently updated in January 2002) to defer donors with "geographic risk," e.g., donors who visited or resided in countries where BSE prevalence is higher; deferral of donors who used UK-sourced bovine insulin; deferral of donors transfused in the UK since 1980 (note also that a draft guidance published in August 2006 proposed deferral of donors transfused in France since 1980); and
    - Withdrawal of vCJD-implicated blood components and plasma derivatives is recommended if a donor is diagnosed with vCJD (which has not occurred).

- Facilitating development, validation, and information sharing (including product labeling) regarding the performance of manufacturing processes in clearance of TSE agents from blood products:
    - FDA reviews requests for TSE clearance labeling claims which may be approved if detailed, validated TSE clearance study data are provided.
    - On September 18, 2006, FDA discussed with TSEAC the feasibility and scientific value of standardized assessments of TSE clearance in the manufacturing processes for pdFVIII. The topic will be addressed again at this meeting.

- Facilitating development of candidate donor screening and diagnostic tests for vCJD and other TSEs:
    - FDA has held meetings with candidate test kit manufacturers to discuss developmental pathways.
    - A public discussion of validation for donor screening tests for vCJD and other TSEs was held with the TSEAC on September 19, 2006.

- Risk assessment and communication to inform patients and physicians about the current scientific understanding regarding vCJD risk from blood products and to help inform treatment decisions:

- FDA has engaged in periodic reassessment of TSE epidemiology and pathogenesis to determine whether guidance/policies need to be revisited in light of new information.
- FDA performed risk assessments for potential exposure to vCJD in investigational pdFXI made from plasma donated in the UK, and for US-licensed pdFVIII made from plasma donated in the US.
- FDA developed and posted risk communication materials on the FDA website.
- FDA communicates with patients organizations when new events occur regarding vCJD.
- FDA encourages physicians and patients to consider this risk in making treatment decisions.

Questions for the Committee:

Based on an updated risk analysis, FDA continues to believe that the risk of variant Creutzfeldt-Jakob disease (vCJD) to patients who receive US-licensed plasma-derived coagulation factor VIII (pdFVIII) products is likely to be extremely small, although we do not know the risk with certainty.

1. Should the recent report from the UK Health Protection Agency, attributing a case of vCJD infection to treatment 11 years earlier with a "vCJD-implicated" pdFVIII, alter FDA's interpretation of the risk for US-licensed preparations of pdFVIII?

2. If so, should FDA consider:
   a. Recommending additional risk-reducing steps for manufacture of plasma derivatives (e.g., modifications to current donor deferral policies)?
   b. Recommending revised warning labels for plasma derivatives?
   c. Recommending modifications to FDA's public communications (e.g., to Web postings) regarding the risk of vCJD associated with the use of FDA-licensed plasma derivatives?

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Appendix with Tables I through IVB

Table I. Updated FDA 2009 Model results for all hemophilia A patients with severe disease using hypothetical pdFVIII produced by process with 4-6 Log_{10} Reduction Factor (LRF) of vCJD infectivity: Potential mean per person exposure to vCJD iv ID_{50} and mean per person vCJD risk per year

				4 - 6 Log_{10} Reduction Factor (LRF)			
				Model Output for LOWER vCJD Case Prevalence of ~4.5 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}* per person per year (5^{th} - 95^{th} perc)**	**Mean** potential vCJD risk per person per year (5^{th} - 95^{th} perc)**	**Mean exposure to vCJD iv ID_{50}* per person per year (5^{th} - 95^{th} perc)**	**Mean** potential vCJD risk per person per year (5^{th} - 95^{th} perc)**
Prophylaxis	No Inhibitor	**578**	**157,949 IU** (21242 , 382316)	**4.9×10^{-7}** (0-0)	1 in 4.0 million (0-0)	**4.5×10^{-5}** (0 - 2.1×10^{-4})	1 in 44,000 (0 - 1 in 4,700)
	With Inhibitor – No Immune Tolerance	**63**	**190,523 IU** (26956 , 447639)	**7.5×10^{-7}** (0-0)	1 in 2.7 million (0-0)	**5.4×10^{-5}** (0 - 2.6×10^{-4})	1 in 37,000 (0 - 1 in 3,900)
	With Inhibitor – With Immune Tolerance	**62**	**558,700 IU** (33235, 1592943)	**7.3×10^{-6}** (0-0)	1 in 270,000 (0-0)	**1.6×10^{-4}** (0 - 7.4×10^{-4})	1 in 12,000 (0 - 1 in 2,700)
Episodic	No Inhibitor	**946**	**85,270 IU** (4633, 244656)	**1.7×10^{-7}** (0-0)	1 in 12 million (0-0)	**2.5×10^{-5}** (0 - 1.1×10^{-4})	1 in 81,000 (0 - 1 in 18,000)
	With Inhibitor	**151**	**160,458 IU** (5314 , 488906)	**8.6×10^{-7}** (0-0)	1 in 2.3 million (0-0)	**4.6×10^{-5}** (0 - 2.0×10^{-4})	1 in 43,000 (0 - 1 in 9,800)

*iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.

**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})

Table II. Comparison of FDA 2006 and 2009 Risk Assessment results estimating mean potential annual exposures to vCJD iv ID_{50} for all hemophilia A patients using hypothetical pdFVIII produced by process with 4-6 LRF of vCJD infectivity

					4 - 6 Log_{10} Reduction Factor (LRF)	
					Model Output for LOWER vCJD Case Prevalences based on Clark and Ghani (2005)	*Model Output for HIGHER vCJD Infection Prevalences based on Hilton et al (2004)*
Treatment Regimen	**Inhibitor Status**	**Total Number patients in US**	**Mean quantity FVIII used per person per year (from FDA 2006)**	**Year FDA Risk Assessment Conducted**	**Mean exposure to vCJD iv ID_{50}* per person per year**	**Mean exposure to vCJD iv ID_{50}* per person per year**
Prophylaxis	No Inhibitor	**578**	**157,949 IU**	**2009**	**4.9×10^{-7}**	**4.5×10^{-5}**
				2006	4.99×10^{-7}	3.67×10^{-5}
	With Inhibitor – No Immune Tolerance	**63**	**190,523 IU**	**2009**	**7.5×10^{-7}**	**5.4×10^{-5}**
				2006	4.21×10^{-7}	4.86×10^{-5}
	With Inhibitor – With Immune Tolerance	**62**	**558,700 IU**	**2009**	**7.3×10^{-6}**	**1.6×10^{-4}**
				2006	1.57×10^{-6}	1.30×10^{-4}
Episodic	No Inhibitor	**946**	**85,270 IU**	**2009**	**1.7×10^{-7}**	**2.5×10^{-5}**
				2006	2.12×10^{-7}	1.91×10^{-5}
	With Inhibitor	**151**	**160,458 IU**	**2009**	**8.6×10^{-7}**	**4.6×10^{-5}**
				2006	2.49×10^{-7}	4.19×10^{-5}

*iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.
**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}.

TABLE III. Comparison of results from FDA 2006 and 2009 Risk Assessments for mean potential per-patient vCJD risk for all hemophilia A patients using hypothetical pdFVIII at two levels of manufacturing process reduction in vCJD agent infectivity (7-9 LRF and 4-6 LRF) and assuming both LOWER and HIGHER prevalence estimates

					7 - 9 Log_{10} Reduction Factor (LRF)		**4 - 6 Log_{10} Reduction Factor (LFR)**	
					Model Output for LOWER vCJD Case Prevalences based on Clark and Ghani (2005)	*Model Output for HIGHER vCJD Infection Prevalences based on Hilton et al (2004)*	*Model Output for LOWER vCJD Case Prevalences based on Clark and Ghani (2005*	*Model Output for HIGHER vCJD Infection Prevalences based on Hilton et al (2004)*
Treatment Regimen	**Inhibitor Status**	**Total Number patients in US**	**Mean quantity FVIII used per person per year (from FDA 2006)**	**Year FDA Risk Assessment Conducted**	**Mean potential vCJD risk per person per year**	**Mean potential vCJD risk per person per year**	**Mean potential vCJD risk per person per year**	**Mean potential vCJD risk per person per year**
Prophylaxis	**No Inhibitor**	**578**	**157,949 IU**	**2009** / 2006	**1 in 5.4 billion** / 1 in 4.1 billion	**1 in 44 million** / 1 in 50 million	**1 in 4.0 million** / 1 in 4.0 million	**1 in 44,000** / 1 in 54,000
	With Inhibitor – No Immune Tolerance	**63**	**190,523 IU**	**2009** / 2006	**1 in 2.8 billion** / 1 in 3.5 billion	**1 in 37 million** / 1 in 40 million	**1 in 2.7 million** / 1 in 4.8 million	**1 in 37,000** / 1 in 41,000
	With Inhibitor – With Immune Tolerance	**62**	**558,700 IU**	**2009** / 2006	**1 in 200 million** / 1 in 551 million	**1 in 12 million** / 1 in 15 million	**1 in 270,000** / 1 in 1.3 million	**1 in 12,000** / 1 in 15,000
Episodic	**No Inhibitor**	**946**	**85,270 IU**	**2009** / 2006	**1 in 12 billion** / 1 in 3.2 billion	**1 in 81 million** / 1 in 100 million	**1 in 12 million** / 1 in 9.4million	**1 in 81,000** / 1 in 105,000
	With Inhibitor	**151**	**160,458 IU**	**2009** / 2006	**1 in 1.8 billion** / 1 in 4 billion	**1 in 44 million** / 1 in 50 million	**1 in 2.3 million** / 1 in 8million	**1 in 43,000** / 1 in 23,000

Table IV-A. Comparison of results from FDA 2006 and 2009 Risk Assessments for vonWillebrand disease (vWD) patients with severe disease: Predicted potential annual exposures to vCJD agent in iv ID_{50} and vCJD risk assuming 4-6 LRF by manufacturing process

YOUNG vWD (≤ 15 yrs of age)

				4 - 6 Log_{10} Reduction Factor (LRF)			
				Model Output for LOWER vCJD Case Prevalences based on Clark and Ghani (2005)		*Model Output for HIGHER vCJD Infection Prevalences based on Hilton et al (2004)*	
	Est. Total Number patients in US	**Mean quantity product used per person per year (from FDA 2006)**	**Year FDA Risk Assessment Conducted**	**Mean exposure to vCJD iv ID_{50}* per person per year (5^{th} - 95^{th} perc)**	**Mean** potential vCJD** risk **per person per year (5^{th} - 95^{th} perc)**	**Mean exposure to vCJD iv ID_{50}* per person per year (5^{th} - 95^{th} perc)**	**Mean** potential vCJD** risk **per person per year (5^{th} - 95^{th} perc)**
Prophylaxis	**39**	165,713 IU	**2009** 2006	**3.6×10^{-7}** 4.3×10^{-7}	**1 in 5.6 million** 1 in 4.7 million	**3.4×10^{-5}** 3.81×10^{-5}	**1 in 59,000** **1 in 52,000**
Episodic	**60**	11,045 IU	**2009** 2006	**2.7×10^{-8}** 4.14×10^{-8}	**1 in 75 million** **1 in 48 million**	**3.2×10^{-6}** **2.06×10^{-6}**	**1 in 630,000** **1 in 971,000**

Table IV-B. Comparison of results from FDA 2006 and 2009 Risk Assessments for vonWillebrand disease (vWD) patients with severe disease: Predicted potential annual exposures to vCJD agent in iv ID50 and vCJD risk assuming 4-6 LRF by manufacturing process

ADULT vWD (> 15 yrs of age)

				4 - 6 Log_{10} Reduction Factor (LRF)			
				Model Output for LOWER vCJD Case Prevalences based on Clark and Ghani (2005)		*Model Output for HIGHER vCJD Infection Prevalences based on Hilton et al (2004)*	
Prophylaxis	**73**	186,880 IU	**2009** / 2006	**5.2×10^{-7}** / **4.89×10^{-7}**	**1 in 3.9 million** / **1 in 4.1 million**	**4.1×10^{-5}** / **4.32×10^{-5}**	**1 in 49,000** / **1 in 46,300**
Episodic	**78**	86,923 IU	**2009** / 2006	**2.2×10^{-7}** / **1.99×10^{-7}**	**1 in 9.3 million** / **1 in 10million**	**2.22×10^{-5}** / **1.90×10^{-5}**	**1 in 75,000** / **1 in 53,000[#]**

[#]The original risk estimate for this cell in the FDA Risk Assessment of 2006 (FDA 2006) was incorrect – the corrected estimate is provided in this table