Draft Quantitative Risk Assessment of vCJD Risk Potentially Associated with the Transfusion of Red Blood Cells in the U.S.

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Center for Biologics Evaluation and Research

US Food and Drug Administration

CONTRIBUTORS

Center for Biologics Evaluation and Research

Core Working Group

Hong Yang

Luisa Gregori

David M. Asher

Steven A. Anderson

Consultants

Xianglu Han

Yin Huang

Ginette Michaud

Pedro Piccardo

Richard Forshee

Mark Walderhaug

Jennifer Scharpf

Peter Marks

Jay Epstein

EXECUTIVE SUMMARY

The U.S. Food and Drug Administration (FDA) has conducted a risk assessment to estimate the probability of acquiring variant Creutzfeldt-Jakob disease (vCJD) infection and clinical disease in the U.S. through transfusion of red blood cells (RBCs or red cells). The RBC risk assessment model estimated the number of transfusion-transmitted vCJD (TTvCJD) infections that may have been present in the U.S. in the year 2011 and the number of those infections that might eventually progress to clinical cases of vCJD in the future. The risk assessment model further predicts the cumulative numbers of infections and clinical cases for the years 1980 to 2011. The FDA risk assessment model calculated the risk for four groups of U.S. donors: (1) donors who traveled to or lived in the U.K. during the years 1980-1996; (2) donors who traveled to or lived in France during the years 1980-2001; (3) donors who traveled to or lived in other countries in Europe since 1980; and (4) donors who were deployed to U.S. military bases in Europe during the years 1980-1996. FDA developed a computer-based simulation model that incorporated estimates of vCJD prevalence in at-risk countries in Europe, data on donor travel history to European countries, and the efficiency of donor deferral policy in reducing risk to estimate the vCJD risk for U.S. blood donors. The model estimated the number of infections among red cell recipients based on the annual numbers of blood donations and transfusions, amount of blood used per transfusion and the infectivity titer of infected blood. The model further estimated the number of infections that might eventually progress to clinical cases, taking into account the probable incubation period of the disease and post-transfusion survival of RBC transfusion recipients. The model uses two alternative assumptions for the possible prevalence of inapparent vCJD infections in the U.K.: **Low** and **High vCJD prevalence estimates**. Both those prevalence inputs are uncertain, resulting in great uncertainty in risk outcomes. However, one risk outcome predicted by the FDA model assuming the Low estimate of vCJD prevalence in the U.K. is consistent with current epidemiologic evidence (numbers of food-borne and transfusion-transmission overt clinical vCJD cases reported in the U.S. and transfusion-transmission overt clinical cases reported in the U.K. and France to date); when we assumed the High estimated U.K. prevalence, the model output greatly overestimated the numbers of clinical cases recognized to date.

vCJD is a fatal neurodegenerative disease with long asymptomatic incubation periods during which some blood donors, unknowingly infected with vCJD and healthy at the time of donation, might be found suitable to donate an infected RBC unit. Dietary exposure to the infectious agent of bovine spongiform encephalopathy (BSE) present in beef products derived from infected cattle is the most likely cause of primary transmission of vCJD to humans. As of November 2012, a total of 227 vCJD cases had been recognized worldwide; of those, 176 cases occurred in the U.K. The U.S. Department of Agriculture (USDA) has conducted BSE surveillance since 1990 and has concluded that the risk of BSE in the U.S. is very low (USDA, 2013b). In addition, protective measures to safeguard the human food supply (as well as measures to protect animals from contaminated feeds) have been in place in the U.S., minimizing the public's risk of potential exposure to the BSE agent. However, a vCJD risk remains for certain U.S. citizens including some blood donors who might have been exposed to the BSE agent during travel or residence in the U.K. or in other countries where BSE risk exceeded that in the U.S. Some of those donors might have unknowingly been infected with the BSE/vCJD agent. To reduce the risk of TTvCJD, FDA has, since 1999, recommended deferral of certain blood donors with history of travel or residence in many BSE-risk countries (FDA, 1999;FDA, 2002;FDA, 2010a).

Since 2003, a total of four vCJD infections have probably been transmitted by blood transfusions in the U.K. ((Hewitt et al., 2006;HPA, 2010;Llewelyn et al., 2004;Peden et al., 2005); a case of vCJD infection linked to treatment with a U.K.-sourced plasma-derived Factor VIII was also reported in the U.K. (Bennett and Ball, 2009;Peden et al., 2010). No cases of TTvCJD have been identified in the U.S. to date, and all three vCJD cases recognized in the U.S. to date have been attributed by the CDC to food-borne infections acquired in other countries; however, because of limitations of food-protective measures and donor deferral policies, some risk to RBC transfusion recipients in the U.S. may remain.

The FDA model used statistical distributions to represent the variability and uncertainty for most of its input data and assumptions. Monte Carlo simulation was applied to integrate all model inputs and generate outputs with statistical distributions representing the variability and uncertainty of the final risk estimates. We strongly emphasize that preliminary sensitivity analysis found vCJD prevalence estimates for the U.K. population to be the most critical FDA model input in determining the final risk of TTvCJD. The U.K. prevalence is used in the model to estimate the vCJD risk for U.S. donors who traveled to the U.K. (most important), France and other countries since 1980. However, those U.K. vCJD prevalence estimates remain highly uncertain; because of that uncertainty, the risk assessment model stratified its assumption of prevalence by incorporating **two** alternative U.K. prevalence estimates, each derived from a completely different source of information. The FDA model used a **Low U.K. Prevalence Estimate**—derived from an epidemiological model that relied on the number of clinical cases of vCJD recognized in the U.K. (Garske and Ghani, 2010) to estimate a relatively low prevalence of recent infections. The alternative assumption was derived from an immunohistochemical survey of thousands of blocks of surgically removed appendix tissue archived in the U.K., attempting to detect accumulations of the abnormal prion protein (PrP^{TSE}) thought to provide evidence of vCJD infection (HPA, 2012b); results of that survey suggested that there might be a very high prevalence of latent vCJD infections in the U.K.; that information is incorporated into the FDA model as a **High U.K. Prevalence Estimate**. Model findings based on these two quite different U.K. prevalence estimates yielded a very wide range of possible—and highly uncertain—results for prevalence of inapparent vCJD infections in U.S. blood donors who had been in the U.K. and other countries of Europe, with consequent uncertainty regarding the ultimate risk of TTvCJD to recipients of RBC transfusions in the U.S.

Estimated risk of TTvCJD to U.S. recipients of RBCs

The FDA RBC risk assessment estimates the potential annual number vCJD infections that might have been acquired through RBC transfusions in the U.S. in year 2011 and the number of infections that might eventually progress to clinical cases. The risk assessment also estimates the cumulative number of TTvCJD infections that might have been acquired between 1980 and 2011 and the clinical cases that should have been observed by 2011. The mean values, (2.5^{th} and 97.5^{th} percentiles) of output distributions are summarized in Table 1.

Table 2. Model Results Showing the Mean vCJD Infection Risk per RBC Transfusion, the Mean TTvCJD Risk for the Year 2011 and the Total Mean Cumulative Risk for the Years 1980 Through 2011 in the U.S. (2.5^{th}-97.5^{th} percentiles shown in parentheses).

		Annual risk (2011)		Cumulative risk 1980-2011	
	Risk per RBC transfusion	**Infections**	**Clinical cases**	**Infections**	**Clinical cases**
Low prevalence (1.7 infections per million)	1 in 134 million (0 to 1 in 8.7 million)	0 (0-0)*	0 (0-0)*	0.8 (0-0)*	0 (0-0)*
High prevalence (493 infections per million)	1 in 480,000 (1 in 4.3 million to 1 in 111,000)	6 (0-27)	1 (0-5)	210 (0-942)	9 (0-47)

*The (2.5^{th}-97.5^{th}) values of (0,0) indicate that the predicted risk is zero or nearly zero. Specifically, for at least 97.5% of the model runs there are zero infections or clinical cases predicted.

Using the Low U.K. Prevalence Estimate, the FDA model estimated the chance of a transfusion recipient receiving an infected unit to be a mean of one in 134 million transfusions. The result using the High U.K. Prevalence Estimate showed the mean chance to be one in 480,000 transfusions. The model also estimated an annual risk of zero TTvCJD infections for year 2011 with the Low U.K. Prevalence Estimate and 6 TTvCJD infections with the High U.K. Prevalence Estimate. Model results indicate that the mean numbers of clinical cases of vCJD in 2011 in the U.S. resulting from TTvCJD infections would be zero and one for the Low U.K. Prevalence and High U.K. Prevalence Estimate, respectively. The model also estimated a mean of approximately one cumulative infection and zero clinical cases when the Low U.K. Prevalence Estimate was used and a mean of 210 infections and nine overt clinical vCJD cases when the High U.K. Prevalence Estimate was used.

Predicting the number of primary cases of vCJD that may occur in the U.S.

As an exercise attempting to validate predictions made by the FDA model, the model was used to predict the vCJD risk for the general U.S. population by generating values for the possible number of primary (food-borne) clinical cases of vCJD that might have occurred in the U.S. since 1980. These results were compared to the number of vCJD cases actually reported to the U.S. CDC. As noted above, based on case histories for countries of residence, CDC concluded that all three vCJD cases reported in the U.S. were almost certainly acquired outside the U.S (Belay et al., 2005); .The FDA model predicted one case of food-borne vCJD in the U.S. since 1980 using the Low U.K.

Prevalence Estimate and a mean of 256 cases with the High U.K. Prevalence Estimate. The number of U.S. vCJD cases predicted to result from infections acquired in the U.K. when the Low U.K. Prevalence Estimate was used in the model was generally consistent with the two vCJD cases actually reported in the U.S. to date; using the High U.K. Prevalence Estimate, the model predicted many more overt clinical cases than have actually been observed.

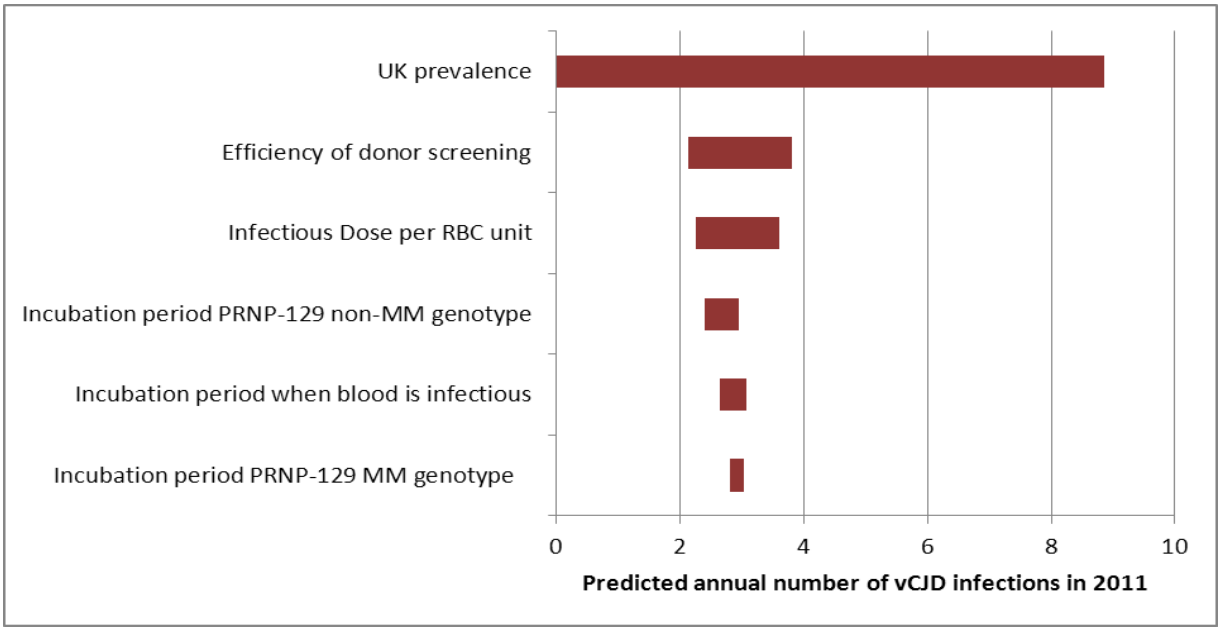
Use of the FDA model to predict the numbers of TTvCJD cases that may occur in the U.K. and France

We further validated the model by incorporating data for the U.K and France to generate cumulative numbers of TTvCJD cases predicted to occur in those countries between the years 1980 and 2011 and compared model predictions with the numbers of TTvCJD cases actually reported. Three clinical vCJD cases attributed to blood transfusion have been identified in the U.K. (CDC, 2010c), while no TTvCJD cases have been reported in France. The model predicted mean numbers of one and 289 cumulative TTvCJD cases in the U.K. using the Low Prevalence and High Prevalence Estimates, respectively, for the years 1980-2011. The model predicted means of 0.2 and 33 TTvCJD cases for France, using the Low U.K. Prevalence and High U.K. Prevalence estimates, respectively. In short, using the Low U.K. Prevalence estimate, the FDA model predicts numbers of cases of TTvCJD in the U.K. and France that are generally consistent with reported numbers of cases; the High U.K. Prevalence estimate causes the model to overestimate greatly the number of clinical cases of overt vCJD attributed to transfusion to date.

Sensitivity analysis to identify model inputs having greatest impact on final risk estimates

We conducted a type of sensitivity analysis known as an importance analysis to determine which inputs in the FDA RBC risk assessment model have the greatest impact on the final estimates of risk. The output selected for importance analysis was the number of RBC transfusion-transmitted infections acquired in U.S. in the year 2011. Six inputs shown on the left in Figure 1 were included in the analysis. For more information on the methods used in the importance analysis, please see section IV.C of the document. The results of the importance analysis indicated that the estimated prevalence of latent vCJD infections in the U.K. was the input exerting greatest impact on the final estimated number of new TTvCJD infections in the U.S. in the year 2011. The second greatest risk driver is Efficiency of Donor Deferral for risk of dietary exposure to the BSE agent in various countries.

Figure 1. Importance Analysis: Impact of Input Variables on the Model Outputs for the Annual Number of Infections in U.S. Donors in 2011



Uncertainties and Data Gaps

The largest uncertainty in the FDA RBC risk assessment results from the uncertain estimates of latent vCJD prevalence in the U.K. There is a very large discrepancy between the Low U.K Prevalence and High U.K. Prevalence Estimates used in the model, and both prevalence estimates have their limitations. An epidemiological model that used observed cases of overt clinical vCJD in the U.K. to project probable future vCJD cases (Garske and Ghani, 2010) estimated a Low Prevalence of latent vCJD infections in the U.K. population; the model relied on a number of simplifying assumptions that are a source of considerable uncertainty. A possible High U.K. Prevalence of latent vCJD infections was estimated based on results of a survey of abnormal accumulations of prion protein detected by immunohistochemistry in archived appendix tissue samples in the U.K. (HPA, 2012b); that survey also has limitations, one of which is that neither sensitivity nor specificity of the method is well established. In order to reduce model input uncertainties associated with both U.K. vCJD prevalence estimates, additional studies are needed to determine specificity and sensitivity of immunohistochemical tests of lymphoid tissues to detect persons latently infected with vCJD over time after infection was acquired, the time during infection when infectivity appears in blood, the susceptibility of populations to latent infection and later overt disease, the incubation periods for vCJD in persons of all prion protein (*PRNP*) genotypes, the possible roles of other genes and of age at exposure in susceptibility to infection, and possible variations in clinical manifestations of disease. This information would be helpful for more accurately estimating the true prevalence of latent vCJD infections in the U.K. and improving estimates for risk of TTvCJD to U.S. recipients.

Conclusions

The FDA model assumes that the major source of infection with the vCJD agent is from dietary exposure to beef products contaminated with the BSE agent that occurred during travel or residency in the U.K., France, or other countries after the U.K. BSE epidemic began, probably at the beginning of 1980. Donor deferrals recommended by the FDA, in place since 1999, are estimated to have removed more than 80% of the risk associated with blood donations from infected persons. However, it is likely that some potentially infected donors may not be deferred and so might potentially donate blood that contains the vCJD agent. Results from an FDA assessment model to estimate the risk of TTvCJD using an assumed Low Prevalence of latent vCJD infections in the U.K. population—an estimate that, when incorporated into the model, predicted reasonably well the numbers of overt clinical cases of vCJD cases reported in the U.S. to date—suggest that the risk of developing overt vCJD from transfusions of red cells to U.S. recipients is likely to be very small but may not be zero. When incorporating an alternative assumption, that true prevalence of latent vCJD in the U.K. population might be considerably higher, the model predicted many more overt U.S. vCJD cases from dietary sources than have actually been observed to date. Absent missing information about possible incubation periods—duration of latent infections before onset of overt illness—and the time after infection before abnormal prion protein appears in lymphoid tissues or infectivity appears in blood, neither (high or low) U.K. prevalence assumption can predict with certainty the number of U.S. recipients who might have been infected with the vCJD agent by RBC transfusion.

Results from the model also cannot estimate *precisely* the vCJD risk for either individual transfusion recipients or for the recipient population as a whole. The FDA risk assessment model indicates that the largest uncertainty is associated with the estimated U.K. latent vCJD prevalence. Given the state of the current TSE science, estimates of the probability of vCJD infection or illness arising from exposure to the vCJD agent via transfusion in the U.S. are still extremely uncertain. The FDA risk assessment model offers a range of conceivable risk estimates for TTvCJD in the U.S. and provides a basis to discuss research needed to improve risk estimates, to suggest possible risk control measures, and to enhance communication that appropriately conveys both the possible magnitude of risk and its attendant uncertainties.

RISK ASSESSMENT

Introduction

Variant Creutzfeldt-Jakob disease (vCJD) is a rare, fatal neurodegenerative disease of humans that can be transmitted through transfusions of blood and blood components. vCJD has long asymptomatic incubation periods during which a blood donor, unknowingly infected with vCJD and healthy at the time of donation, might donate potentially infectious blood. In December 2003, the U.K. announced the first case of vCJD presumably caused by a blood transfusion (Llewelyn et al., 2004). A total of three additional vCJD infections probably transmitted by blood transfusions (HPA, 2006;HPA, 2007;Peden et al., 2004) and a case of vCJD linked to U.K.-sourced plasma-derived Factor VIII have been reported in the U.K. (Peden et al., 2010). Dietary exposure to bovine spongiform encephalopathy (BSE)-contaminated beef products is the most likely cause of primary vCJD. The vast majority of BSE cases occurred in the U.K. and to lesser extent in France and in other Western European countries. However, some U.S. blood donors might have been exposed to the BSE agent during travel or residence in the U.K. or in other countries with BSE-risk and unknowingly been infected with vCJD. To reduce the risk of transfusion-transmitted vCJD (TTvCJD), the U.S. Food and Drug Administration (FDA) has recommended deferral of certain blood donors with history of travel or residence in BSE-risk countries (FDA, 2010a). These preventive measures have been in place since 1999, and no cases of transfusion-transmitted vCJD (TTvCJD) have been identified in the U.S.; however, some risk to recipients of Red Blood Cell (RBC) transfusions may still remain.

This document summarizes an FDA risk assessment that estimates the probability of vCJD infection and clinical disease acquired in the U.S. through transfusion of RBCs. This assessment assumes that the risk of acquiring vCJD in the U.S. from consuming domestically produced beef is negligible, an assumption is based on the very small number of BSE cases reported in U.S. cattle population (three native-born U.S. cows and one Canadian-imported cow since 2003) (CDC, 2012), and it is supported by lack of vCJD cases in U.S. residents despite longstanding surveillance. Three vCJD cases reported in the U.S. were almost certainly acquired while the patients lived abroad (CDC, 2010c). For the purpose of this analysis, FDA assumed that the only important potential source of vCJD risk to the domestic blood supply comes from U.S. donors who have traveled to or lived in the U.K., France or other countries in Europe since 1980. FDA developed a computer-based simulation model that incorporated estimates of vCJD prevalence in the UK, France and other countries in Europe, U.S. blood donor travel data, the annual number of blood donors in the U.S., and the efficiency of the U.S. donor deferral policy. These data inputs were used to generate estimates of vCJD risk for U.S. blood donors. The prevalence of vCJD in the U.K. population is the critical input in the FDA risk assessment and is used to derive the vCJD prevalence for other vCJD risk countries in Europe, and in turn, used to estimate the vCJD risk for U.S. travelers, blood donors, and blood transfusion recipients. However, U.K. prevalence is highly uncertain. Because of this uncertainty, the FDA model stratified the prevalence assumption, using two separate prevalence estimates in the model derived from two different sources of data. A Low vCJD U.K. Prevalence Estimate was derived from epidemiological modeling of predicted future vCJD cases and asymptomatic infections (Garske and Ghani, 2010). A High vCJD U.K. Prevalence estimate was derived from tissue surveillance studies (HPA, 2012a). The risk assessment model generated results for both prevalence assumptions for the risk of TTvCJD in the

U.S. including predictions of the annual number of infections in year 2011, the number of infections that may eventually lead to clinical cases, and the cumulative number of infections and clinical cases during the years 1980 to 2011.

Background

Epidemics of BSE and primary vCJD

The first BSE case was reported in U.K. cattle in 1986. The origin of the disease was traced to feeding of meat-and-bone meal (MBM) to cattle (Ducrot et al., 2008;Wilesmith et al., 1991) The U.K. BSE epidemic peaked in 1992; the number of BSE cases in U.K. cattle declined markedly after implementation of a stringent ban on feeding of MBM to farm animals (Ducrot et al., 2008). The first person later diagnosed with vCJD in the U.K. became ill in 1994 (Will et al., 1996); ten U.K. cases were described in 1996. Strong epidemiological evidence and experimental data suggest that dietary exposure to BSE agent is responsible for vCJD in humans (Bruce et al., 1997;Hill et al., 1997;Will et al., 1996). Since 1996, the U.K. has implemented a full range of measures to protect animal feed and human food from contamination with the infectious BSE agent. The U.K. has been the country most affected by vCJD (176 cases) followed by France (27 cases). The number of vCJD deaths in the U.K. peaked in 2000 (NCJDRSU, 2013), dropped sharply after 2003, and then fluctuated at around three per year until 2011; no new vCJD clinical cases were reported in 2012 in the U.K. (NCJDRSU, 2013), but two were recognized in France last year (Tomasulo, 2012). BSE and vCJD spread to other countries, most in Europe, generally attributed to exportation of feeds, live animals and beef/beef products for human consumption from the U.K. A total of 227 vCJD cases have been recognized worldwide as of February 2013.

vCJD transmission via blood, blood components and plasma-derived products

Early demonstrations of TSE infectivity in the blood of rodents and PrP^{TSE}, an abnormal form of the host-coded cellular prion protein, in lymphoid tissues of individuals clinically infected with vCJD alerted the blood transfusion community to the potential risk of TTvCJD. In 1997, a collaboration was established between the U.K. National Creutzfeldt-Jakob Disease Research and Surveillance Unit and the U.K. Blood Transfusion Services to survey blood transfusion records for evidence of vCJD transmission by transfusion. The resulting study, the Transfusion Medicine Epidemiological Review (TMER), attempted to identify all U.K. CJD cases, including sporadic CJD, familial CJD and vCJD, in patients who had either donated or received blood. The TMER study identified 18 individuals who had donated blood before clinical onset of vCJD and 67 individuals who received blood components donated by these infected individuals. As of September 2012, 50 recipients of blood from donors who later came down with vCJD have died and 17 are still alive (TMER, 2013). Four of the deceased recipients either died with or had evidence of infection with vCJD. All four cases received non-leukoreduced RBC. The first case of TTvCJD was reported in 2003 in a 69-year-old patient who received a transfusion in 1996 from a donor who became ill with vCJD three years after the blood donation. A second case, announced in July 2004, occurred in a patient who died of a ruptured aortic aneurysm without clinical evidence of vCJD, but postmortem testing detected abnormal PrP^{TSE} in spleen tissue and a cervical lymph node. In February 2006, a third case of probable TTvCJD was reported in a 31 year-old male who received a transfusion eight years earlier from a donor who died of vCJD 20 months after the donation. In January 2007, a fourth probable U.K. TTvCJD case was reported; that patient was diagnosed about nine years after receiving a blood transfusion from the same blood

donor implicated in a previously identified case. Additionally, in February 2009 a case of pre-clinical vCJD was recognized at autopsy in a man over 70 years old who had hemophilia; he had been treated 11 years earlier with U.K.-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 vCJD and other lots of the same product (Peden et al., 2010). This case confirmed that vCJD agent is present in human plasma. No cases of vCJD associated with either blood transfusion or treatment with plasma products have been reported outside the U.K.

BSE and vCJD risk in the U.S.

The U.S. Department of Agriculture (USDA) has conducted BSE surveillance in the U.S. since 1990. The current on-going surveillance program targets the cattle population where the disease is most likely to be found; in recent years approximately 40,000 animals have been tested annually (USDA, 2013a). (Beef carcasses selected for testing are not released into the food supply until after negative test results are returned.) As of December 2012, a total of four cases of BSE have been identified in U.S. cattle (CDC, 2013;USDA, 2013b;USDA, 2013d). The USDA announced the first recognized U.S. case of BSE in a non-ambulatory (downer) adult Holstein cow from Washington State on December 23, 2003, diagnosis later confirmed by the U.K. Veterinary Laboratories Agency BSE international reference laboratory in Weybridge, England. Trace-back confirmed that the BSE-infected cow had been imported into the U.S. from Canada in August 2001. In 2005, a second U.S. BSE-infected cow (in Texas) was also confirmed by Weybridge, however that cow was born and must have been infected with BSE in the U.S. A year later, the USDA found a third case of BSE in another downer cow of probable U.S. origin on a farm in Alabama. In 2012, a fourth case of probable indigenous BSE was reported by USDA in a downer cow from a farm in California. All three indigenous BSE cases were described as having "atypical" BSE ("L-type") based on the electrophoretic mobility of PrP^{TSE} extracted from brain and details of their histopathology (CDC, 2012). The origin of atypical BSE and its implication for public health are unknown; the World Organization for Animal Health (OIE) has not recognized atypical forms of BSE as constituting an infection distinct from classic BSE, though it has considered the possibility. Based on U.S. surveillance results, USDA (USDA, 2013c) has estimated that four to seven BSE-infected cattle may exist among the approximately 42 million U.S. adult cattle population, a risk considered very small.

In addition to BSE surveillance, animal feed controls and human food-protective measures are in place in the U.S. to minimize risk of potential human food-borne exposure to the BSE agent. As a result, autochthonous vCJD risk should also be very low in the U.S., and no indigenous vCJD cases have been reported in the U.S. despite continuous surveillance for all forms of CJD by the Centers for Disease Control and Prevention (CDC) in collaboration with the National Prion Diseases Pathology Research and Surveillance Center at Case Western Reserve University School of Medicine since 1997. Three cases of vCJD have been reported in the U.S.; based on their history of very long residence outside the U.S., all three cases are concluded to have acquired vCJD infection not in the U.S. In 2002, the first U.S. case of vCJD was reported in a 22-year-old woman who lived in the U.K. from her birth until 1992, when she immigrated to Florida; she died approximately 32 months after illness onset (Belay et al., 2005), and Western blot and immunohistochemical analysis confirmed the diagnosis. A second confirmed case of vCJD was diagnosed by the U.K. NCJDRSU in November 2005 in a 30-year old man who was born and lived in the U.K. for most of his life but who had moved to Texas four years earlier (Belay et al.,

2005;CDC, 2010c); he died in early 2006. A third patient was born and raised in the Kingdom of Saudi Arabia but came to the U.S. in late 2005, becoming ill and dying in 2006.

FDA's recommendation on blood donor deferral for vCJD risk

Even prior to identification of the first TTvCJD case in the U.K., FDA recognized a potential risk of TTvCJD. In 1999, consistent with advice from the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC), FDA recommended precautionary deferrals for blood and plasma donors who had traveled or lived for six months or longer in the U.K. from the presumed start of the BSE outbreak in 1980 until the end of 1996, when the U.K. had implemented a full range of measures to protect animal feed and human food from contamination with BSE infectious agent (FDA, 1999). 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 U.K. from six to three months (FDA, 2002). FDA also recommended deferring donors who had spent five or more years cumulatively in France or 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 U.K. after 1979. Since 2002, TSEAC has reviewed FDA vCJD and CJD blood donor deferral policies on several occasions, and advised FDA to recommend deferral of blood donors transfused in France since 1980. FDA has issued, in 2010, revised guidance document including that recommendation (FDA, 2010a).

FDA's previous risk assessments for vCJD risk associated with use of plasma-derived blood clotting factors

In 2003 FDA began to develop an assessment for the potential risk of vCJD transmitted via U.K.-manufactured plasma-derived factor XI administered under investigational use to approximately 50 patients in the U.S. (FDA, 2006b). FDA also began to develop a risk assessment for U.S.-licensed plasma-derived factor VIII (pdFVIII) to patients with a severe form of hemophilia A or von Willebrand disease (type-3 vWD). The computer-based risk assessment model incorporated information on donor travel exposure to the BSE agent while in the U.K., France and other countries in Europe since 1980, the effectiveness of current donor deferral policies, the frequency and type of plasma donation, plasma pooling and fractionation, purification and patient utilization of pdFVIII products. A draft version of the FDA pdFVIII Risk Assessment was presented at the December 15, 2006 TSEAC meeting (TSEAC, 2006). The risk assessment concluded that "the risk of vCJD transmitted via plasma-derived products is highly uncertain, but likely to be extremely small". The risk assessment document (dated November 27, 2006) was posted on the FDA website (FDA, 2006a).

In 2009 the FDA began updating the risk assessment in light of newly developed scientific evidence on the susceptibility of populations to the vCJD infection. The original 2006 FDA pdFVIII risk assessment assumed that only persons who were homozygous for methionine-methionine (MM) at codon 129 of the prion-protein-encoding (*PRNP)* gene were susceptible to vCJD infection, while, the updated model assumed all genotypes to be equally susceptible. The updates of the risk assessment were first presented at a TSEAC meeting in 2009 (TSEAC 2009), and a later revision was presented at the TSEAC meeting in 2010 (FDA, 2010b). Even though

some model inputs and assumptions had been changed, the conclusions from the updated risk assessment remained largely unchanged from the version issued in 2006 (FDA, 2006a).

Scope of the FDA RBC Risk Assessment

The scope of this FDA risk assessment is to estimate the annual potential exposure of U.S. RBC recipients to the vCJD agent and their subsequent risk of acquiring vCJD infection and developing clinically overt vCJD disease. The risk was estimated first for the year 2011 and then for the years 1980 through 2011 to generate a cumulative estimate of transfusion risk.

The FDA risk assessment modeled four groups of at-risk U.S. donors who traveled or lived in:

1. The U.K. during the years spanning 1980 to 1996;
2. France during the years spanning 1980 to 2001;
3. Other countries in Europe since 1980; or
4. Were deployed to a U.S. Military base in Europe during the years spanning 1980 to 1996.

In this analysis, the FDA risk assessment modeled all other countries in Europe outside the U.K. and France as a single group, and did not differentiate vCJD risk among them. This simplification was needed because of insufficient information on BSE and other risk factors for each European country and the overall conclusion that the risk of exposure in those countries relative to that in the U.K. and France was much smaller. This simplifying assumption may somewhat increase the uncertainty in our estimates of risk.

Risk Assessment Framework

This risk assessment follows the four-step paradigm described by the National Research Council (NRC, 1983), which includes the following elements: (I) hazard identification, (II) dose-response, (III) exposure assessment, and (IV) risk characterization. The hazard identification portion of the risk assessment provides an in-depth overview and analysis of available data and information to establish a causal relationship between the hazard and adverse effects on humans. The dose-response component relates the magnitude of exposure, which determines the infectious dose, to the probability of adverse consequence(s) such as infection, illness, mortality, etc., at the individual, subpopulation, or population level. The exposure assessment evaluates the possible routes of exposure to a hazard, the probability that exposure occurs and the amount (dose) of a hazardous agent to which a person or population may be exposed. Risk Characterization integrates the information from the hazard identification, dose-response and exposure assessment sections into the risk characterization which generates estimates of risk for individuals and populations.

I. HAZARD IDENTIFICATION

The hazard identification portion of the risk assessment provides an in-depth overview and analysis of information from laboratory studies, epidemiological studies, and other scientific literature, including government reports and other credible or peer-reviewed sources of data to establish a causal relationship between the hazard and adverse effects in humans. In this risk assessment, the vCJD agent is the hazard, and adverse effects are vCJD infection and symptomatic disease acquired through transfusion of an RBC unit collected from a vCJD-infected donor.

I.1 Primary vCJD and BSE

There is strong evidence and general agreement that human vCJD infection (like BSE in cattle) was likely acquired by dietary exposure, most by exposure to the BSE agent contaminating beef from infected cattle (Almond and Pattison, 1997;Bruce et al., 1997;Hill et al., 1997). Both vCJD and BSE belong to a class of fatal neurodegenerative diseases known as transmissible spongiform encephalopathies (TSEs). The mean incubation period of BSE in cattle is approximately five years (USDA has estimated between 2.5 years to 8 years (USDA, 2013c). For humans, we estimated the median incubation period of primary vCJD, acquired through dietary exposure, for persons of the *PRNP* codon-129 MM genotype to be 12 years, with a mean of 15 years. These estimates are described in details below in section B.2.a.vi. Individuals usually become symptomatic only in the last few months of the disease; however, the abnormal form of prion protein, PrP^{TSE}, has been detected in appendix tissue of asymptomatic individuals as early as two years prior to the disease onset (Hilton et al., 2004). There are currently no validated tests available to detect the disease before the onset of clinical signs of illness or to detect the presence of TSE agents in blood. Confirmation of vCJD requires postmortem examination of brain tissue. Individuals unknowingly infected with vCJD may transmit the disease through blood donation.

For reasons not fully understood, vCJD preferentially affects a population younger than the population affected by sporadic CJD. The median age at death for vCJD patients is 28 years (CDC, 2010c). All clinical vCJD cases genotyped to date, with only one exception, have been in individuals with the MM genotype (Ironside et al., 2006). This genotype occurs in approximately 40% of the white population in the U.K. One clinically typical foodborne vCJD case in a person with the *PRNP* methionine-valine (MV) genotype has been reported, although tissue was not available to confirm the diagnosis (Kaski et al., 2009). This case is particularly important because it suggests that individuals with MV genotype can develop clinical vCJD that is indistinguishable from the disease in persons of the MM genotype. Findings of abnormal prion protein in appendix tissue samples of individuals of the VV genotype (Ironside et al., 2006) also support the conclusion that all persons of all genotypes are, to some degree, susceptible to vCJD infection.

I.2 Evidence of TTvCJD

Transmission of different TSE agents by blood has been demonstrated with animal models of various TSEs for many years (Manuelidis et al., 1978). Several studies in large experimental animals confirmed transmissibility of TSEs by blood transfusion: sheep infected with BSE and scrapie (Andreoletti et al., 2012;Houston et al., 2000;Houston et al., 2008;Hunter et al., 2002) and deer infected with chronic wasting disease (Mathiason et al., 2006). In humans, vCJD infections were transmitted to four blood transfusion recipients in the U.K. who received red cells from apparently healthy donors unknowingly infected with vCJD. Statistical analysis convincingly concluded that these cases were almost certainly infected by transfusion and not through dietary exposure (Llewelyn et al., 2004).

In 2009, the first case of transmission by plasma-derived factor VIII was reported in an individual affected by hemophilia in the U.K. (Peden et al., 2010). A statistical analysis conducted to assess the most likely source of exposure for this case clearly pointed to the use of factor VIII rather than dietary exposure as the most probable source of infection (Bennett and Ball, 2009). In all cases, the donors were asymptomatic at the time of donation and the time between donation and donors' onset of vCJD varied from 17 to 42 months, indicating that blood can be infectious for at least 3.5

years before the onset of the disease. The incubation times of TTvCJD for the three transfusion recipients with clinical symptoms were 6.5, 7.8, and 8.3 years (TMER, 2013).

I.3 Potential TTvCJD risk in the U.S. and reduction of risk via donor deferral

U.S. travelers to the U.K., France and other countries in Europe during the period of the BSE epidemic may have been exposed to the BSE agent through dietary sources and may be at increased risk of vCJD infection. Public health and agricultural control measures, such as BSE surveillance, culling of sick animals, or banning of specified risk materials, and others have been instituted in many European countries, particularly in those with indigenous cases of confirmed BSE, in order to prevent products containing BSE agent from entering the human food supply. Since 1996, the U.K. has instituted stringent control measures, including a program that tests all animals older than 30 months of age and prevents high-risk tissues of slaughtered animals from entering the human food and animal feed supplies. As a result, in the U.K., the current risk of acquiring vCJD from eating beef and beef products is estimated to be extremely small, perhaps about 1 case per 10 billion servings (CDC, 2010b). In June 2000, the European Union Commission on Food Safety and Animal Welfare strengthened the European Union's BSE control measures by requiring all member states to remove specified risk materials from animal feed and human food chains. As of October 1, 2000 such bans had already been instituted in most member states of European Union. However, the risk of exposure in European countries (excluding the U.K.) cannot be determined precisely due to the uncertainty of available information on the effectiveness of many countries' surveillance programs for BSE and vCJD, their compliance with and success of the measures instituted in each country to prevent BSE contamination of human food, and patterns of trade and export of cattle products.

Based on the considerations above, the U.S. blood donor deferral criteria currently in effect defer donors that spent cumulatively three months or more in the U.K. from 1980 through 1996 and five years or more for France and other countries in Europe from 1980 through the present. This deferral policy should substantially reduce the risk of transmitting vCJD via blood collected from infected donors. FDA's previous vCJD risk assessment for pdFVIII concluded that the risk of vCJD transmission by plasma-derived products is highly uncertain but likely to be extremely small. The fractionations, filtrations, and other product purification processes used to manufacture plasma derivatives are likely to reduce risk significantly by removing the infectious agent present in the plasma, as demonstrated in studies at pilot scale using animal bioassays (Foster, 2004;Foster, 2008). Because similar manufacturing processes are not used to prepare RBC concentrates, the risk of TTvCJD from RBC is likely to be considerably higher than that of pdFVIII.

II. Dose-Response

The dose-response component of the risk assessment relates to the information in the exposure assessment, which determines the dose and the probability of adverse consequences such as infection, illness, and mortality estimated at the individual, subpopulation, or population levels.

Determining dose-response relationships can be difficult because human data on exposure and the corresponding probability of the adverse outcome are frequently limited. Many factors influence dose-response relationships such as characteristics of the hazard (e.g., infectious agent strain, chemical and physical make-up of material in which the agent is present, etc.), the route of exposure, and important host-specific factors such as the genetic makeup and predisposing conditions of exposed individuals. There are currently no validated tests available to detect the infectious agent of vCJD in the blood of infected individuals, which makes quantification of exposure dose in term of amount of infectious agent difficult. In the FDA RBC-vCJD risk assessment, exposure dose for an RBC recipient was represented by the number of infectious blood units received (estimated in Section III. Exposure Assessment). This section describes the relationship of probability of infection associated with the number of units of infectious blood received.

When human dose-response data are lacking, animal data are often used and extrapolated to approximate the expected dose-response relationship for humans. Experimental animal models infected with TSEs indicated that very low concentrations of infectious agent circulated in the blood of many kinds of experimentally infected animals (Brown et al., 1998;Brown et al., 1999;Cervenakova et al., 2003;Gregori et al., 2004;Hunter et al., 2002). Quantitative measurements of infectivity titers (concentrations of the infectious agent) in blood throughout the incubation period and during overt illness were conducted in rodent models (by animal bioassays). Rodent bioassays usually involved intracerebral (i.c.) inoculations of infectious rodent blood into the brains of a large number of susceptible animals of the same species (Brown et al., 1998;Brown et al., 1999;Cervenakova et al., 2003;Gregori et al., 2004). The FDA pdFVIII risk assessment derived the probable infectivity titer of whole human blood from such experimental animal data. FDA assumed a lognormal distribution of the infectivity in the blood of a person infected with vCJD with a minimum of 0.1 i.c. ID_{50} per ml, a median of 12 i.c. ID_{50} per ml, and a maximum of 1,000 i.c. ID_{50} per ml. The 5^{th} and 95^{th} percentiles of the distribution were: 2 i.c and 30 i.c. ID_{50} per ml. This assumed infectivity titer was then reduced somewhat in the FDA model, because transmissions of infectivity by the i.v. route are generally less efficient than those conducted by the i.c. route. The FDA pdFVIII assessment modeled the efficiency of transmission by the i.v. route relative to the experimental i.c. route as a uniform distribution between values of 0.1 (i.v. route 10-fold less efficient than i.c.) and 1 (no difference between the two routes—just as efficient). Applying this assumption and extrapolating ID_{50} in human blood from animal data, we arrived at the final estimates of thousands of ID_{50} in a unit of infected human Whole Blood (roughly ~ 500 ml per unit).

A more recent analysis of published data describing the four cases transfusion-transmitted vCJD in humans and of experimentally infected sheep suggested that not all individuals (humans or sheep) who received one unit of blood from infected donors acquired vCJD infectivity. If a unit of infected human blood contained thousands of ID_{50} we would expect the number of TTvCJD cases to be significantly higher than that actually observed until now. Extrapolation of the infectivity titer for humans from rodent data assumed that one infectious dose for a rodent is equivalent to one infectious dose for a human. This may have led to an overestimates of the number of infectious doses for human in a unit of human blood, because, typically, dose-response varies depending in large part on the biological species and body weights of the subjects involved. The new blood infectivity titers input used in this FDA RBC Risk Assessment are based on an analysis concluding that the probable mean vCJD infectivity content for human non-leukoreduced red blood cells was about 0.75 intravenous ID (ID_{iv}) per unit of blood (5^{th} and 95^{th} percentiles: 0.56 and 0.96),

meaning that three of four patients receiving a unit of blood from an infected donor would be predicted to develop clinical vCJD (Gregori et al., 2011). In this analysis, published data were reviewed and statistical models applied to estimate the probable doses of infectivity present in blood of humans latently infected with vCJD. Two statistical models were developed based on different assumptions. Model 1 was developed using the currently reported number of vCJD cases among recipients of vCJD-implicated blood; that model might have underestimated the infectious doses in human blood because postmortem tests to detect latent vCJD infection were not conducted on blood recipients who died, and the model assumed that blood recipients still alive with no symptoms of disease are not infected. Model 2 back calculated asymptomatic infections from three reported vCJD cases, taking into account the incubation period of the disease and the probability that a blood recipient survives the incubation period of vCJD. Model 2 estimated that a mean number of 21 out of 27 non-leukoreduced RBC recipients were infected with vCJD with 5^{th} and 95^{th} percentiles of 18 and 27 recipients. The second model estimated a mean of 0.75 ID_{iv}/unit for non-leukoreduced human blood. In this risk assessment, we applied the results of model 2, because the infectivity titer was calculated based on number of infections and thus, are more relevant to the transfusion-transmission risk analysis, while model 1 calculated the infectivity titer based only on number of clinical cases.

III. EXPOSURE ASSESSMENT

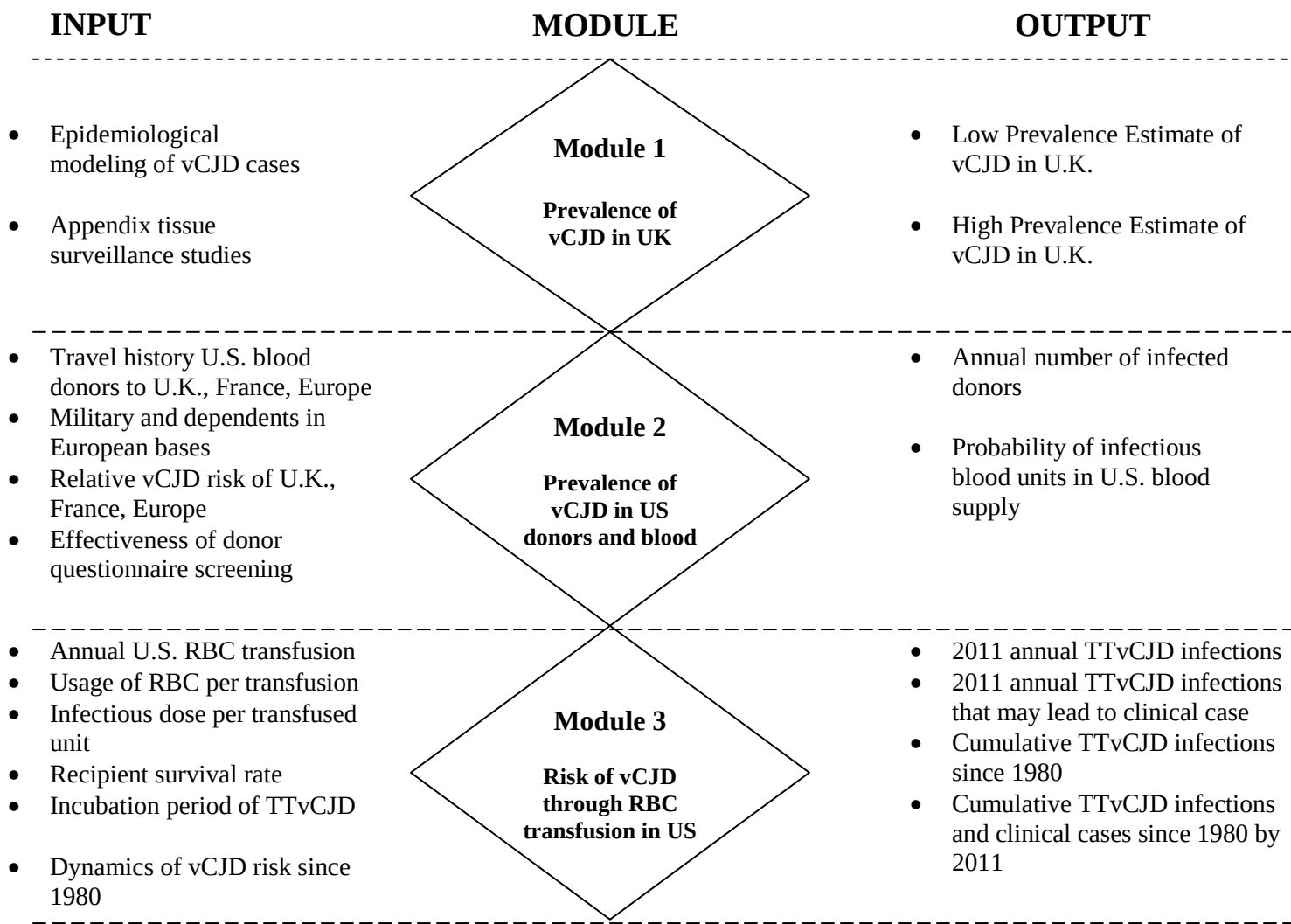
The exposure assessment component evaluates the possible sources of exposure to a hazard, the probability that exposure occurs and the amount (dose) of a hazardous agent to which a person or population may be exposed. This exposure assessment specifically addresses the probability of exposure to vCJD agent through the transfusion of an RBC unit in the U.S. and the quantity of vCJD agent that may be present. Potential vCJD risk for transfusion of a red cell unit in the U.S. may vary, to some degree, from year to year since 1980. In this risk assessment, the potential vCJD risk associated with RBC was first estimated for the year 2011; the cumulative risk sums the individual risks for each year during the period from 1980 through 2011, estimated by comparing the cumulative exposure risk to that of the individual year 2011. This section of the document provides a general description of the modeling approaches, rationale, input data, assumptions and results of the exposure assessment. The section titles and index numbers used in this document are consistent with those used in the accompanying model spreadsheets.

Overview of Model

The FDA risk assessment model for RBC and vCJD risk assumes that the major source of potential risk of vCJD in U.S. donors would likely be associated with a history of travel and residence in the U.K., France or other countries in Europe since 1980. Some donors may have been exposed to the BSE agent during their stays in those countries through consumption of beef products from infected cattle. A computer-based simulation model was developed that integrates information on several inputs including vCJD prevalence in the epidemic regions, travel history of U.S. donors, effectiveness of donor questionnaire screening, age-specific rates of blood donation, and transfusion in the U.S. The exposure assessment model consists of three modules (Figure III-1): Module 1. *Estimation of vCJD Prevalence in the U.K.*, Module 2. *vCJD Prevalence in U.S. Blood Donors and Blood Units*, and Module 3. *Potential number of vCJD Infections in the U.S. through Blood Transfusion*.

Most of the model inputs are statistical distributions representing the variability and uncertainty associated with the inputs (Table III-1). In general, we used sophisticated parametric distributions when there were enough data with which to fit a statistical distribution. A triangular distribution, consisting of a minimum, maximum and the most likely value was used when sufficient information was available to define these values. A uniform distribution, consisting of a minimum and maximum value, was used when there was only enough information to define a range of likely values. In cases where there was a set of correlated input variables, such as donation rates (in percentages) by individual age group, we used point estimates for each age group adding up to 100% across the range of age. We believe that point estimates give a reasonable representation of the input variables in this case; we acknowledge that this approach may have underestimated the uncertainty associated with the input variables. Most input distributions or values used in this risk assessment are the same as those used in the previous FDA pdFVIII Risk Assessment. However, some inputs have been updated based on new data and information. The updated inputs and the justification for the updates are summarized in Table III-2.

Figure III-1. Exposure assessment model diagram for potential vCJD exposure via RBC transfusion in the U.S.



Monte Carlo simulation was applied to integrate the variability and uncertainty of all model inputs by randomly selecting a single input value from each input in the model and generating the final risk estimate. This process was repeated thousands of times and the final risk estimates for each iteration integrated as a final aggregate distribution (which can be described using the mean, and 5^{th} and 95^{th} percentiles) which reflects the attendant variability and uncertainty of the final risk estimate. This approach is often used in situations when models are complex, non-linear, or involve uncertain parameters. Binomial functions were used in the risk assessment model on many occasions to reflect the random nature of binary events (either zero or one) such as travel/non-travel, infection/non-infection, success/non-success of donor questionnaire screening and survival/non-survival of recipients post-transfusion, etc. The model simulation was run until the mean, 2.5^{th} and 97.5^{th} percentiles of all model outputs converged to within 1% of variation.

Table III-1. Major input distributions used in exposure assessment model.

Variable name and description	Type of distribution or estimate used	Value and range	Reference
Prevalence estimates of vCJD in the UK 1. Low vCJD Case Prevalence (**$Pv_{vCJD\text{-}UK:}$**)	Triangular distribution	Mean= 1.7 cases/million, 95% CI=0.2-3.7 cases/million	(Garske and Ghani, 2010)
2 High vCJD Infection Prevalence (**$Pv_{vCJD\text{-}UK: (20\text{-}30yrs)}$**)	Triangular distribution	Mean= 493 cases/million, 95%CI=282-801 cases/million	(Hilton et al., 2004) (HPA, 2011b)
RR_{UK}: Relative vCJD exposure risk in the UK	Point estimate	1	(Williams, 2004)
RR_{FR}: Relative vCJD exposure risk in the France	Point estimate	0.10	(Williams, 2004)
RR_{EU}: Relative vCJD exposure risk in the other countries in Europe	Point estimate	0.015	(Williams, 2004)
RR_{DOD}: Relative vCJD exposure risk in the US military bases in Europe	Point estimate	0.35	(Williams, 2004)
$N_{DR\text{-}US}$: Annual number of blood donations in the US	Normal distribution	Mean=17 million SD = 189,000	(HHS, 2009)
$P_{DR\text{-}USa}$: Percentage of donors per US donor age group	Age-specific percentage		(Forshee and Walderhaug, 2009)
$N_{DN\text{-}DY\text{-}USa}$: Average number of donations per US blood donor per year	Age specific rate	Min=1, Mean=1.4, max=1.5	(HHS, 2009)
IP_{MM}: vCJD Incubation time for primary case with the MM genotype	Lognorm distribution	Median=12 years, 90%CI=9-35 years Mean=15 years	(Collinge et al., 2006;Garske and Ghani, 2010;Ghani et al., 2003)
$IP_{MV,}$ IP_{VV}: vCJD Incubation time for primary case with the MV and VV genotype	Lognorm distribution	Median=32 years 90%CI=23-55 years Mean=35 years	(Collinge et al., 2006)
IP_{infbl}: Percentage of late incubation period start having infectious agent present in blood	Triangular distribution	Min=50%, Most likely=75%, Max=90%	(Houston et al., 2008)
$Perc_{MM}$: Percentage of UK population who are MM genotype	Point estimate	40%	(Alperovitch et al., 1999)
$Perc_{MV}$: Percentage of UK population who are MV genotype	Point estimate	50%	(Alperovitch et al., 1999)
$Perc_{VV}$: Percentage of UK population who are VV genotype	Point estimate	10%	(Alperovitch et al., 1999)
R_{SC}: Efficiency of US donor screening	Uniform	Min=85%, Max=99%	(TSEAC, 2005;TSEAC, 2006)
$N_{TF\text{-}US}$: Annual number of blood transfusions in the US (million)	Normal distribution	Mean=3.8 million, 95%CI= 3.5-4.0	(HHS, 2009) (Anderson et al., 2007)
$N_{U\text{-}TF\text{-}US}$: Number of blood units per transfusion in the US	Empirical discrete distribution	95%CI=3.8-4.0	(Anderson et al., 2007)
ID: Infectious doses in RBC unit	Triangular distribution	Min=0.56, Mean=0.75, Max=0.96	(Gregori et al., 2011)

IS_{MM}: vCJD Incubation time for secondary transfusion-transmitted case with the MM genotype	Triangular distribution	Min=6 years, mean=10 years and Max=20 years	(Bennett and Daraktchiev, 2011)
IS_{MV}, IS_{VV}: vCJD Incubation time for secondary transfusion-transmitted case with the MV and VV genotype	Triangular distribution	Min=16 years, mean=20 years and Max=30 years	(Bennett and Daraktchiev, 2011)
S_{uv}: Post-transfusion survival rate	Function of number years after transfusion ($Year_{post\text{-}transfusion}$)	0.61 - 0.028 x $Year_{post\text{-}transfusion}$	Regression model derived from UK data (Bennett and Daraktchiev, 2011)

Table III-2. Summary Update of Input Assumptions for current FDA RBC-vCJD Risk Assessment (2013) from Previous FDA FVIII-vCJD Risk Assessment (2010)

Input Name	Current FDA RBC Risk Assessment (2013)	Previous FDA FVIII Risk Assessment (2010)	Justification
U.K. vCJD Low Prevalence Estimate	1.7 per million* (0.2-3.7 per million)	~4.5 per million	Current Low Prevalence Estimate used in the FDA RBC Risk Assessment (2013) used updated epidemiological model by Garske and Ghani (Garske and Ghani, 2010). Previous FDA FVIII Risk Assessment model (2010) Low Prevalence Estimate was generated using epidemiological model by Clarke and Ghani (Clarke and Ghani, 2005).
U.K. vCJD High Prevalence Estimate	493 per million* (282 - 801 per million)	267 per million * (55 - 779 per million)	Current High Prevalence Estimate used in the FDA RBC Risk Assessment (2013) was updated to include new results from surveys with a much larger number of appendices (HPA, 2012b). Previous High Prevalence Estimate for the FVIII Risk Assessment model (2010) was generated based on the first appendix study (Hilton et al., 2004).
Relative risk for France	10% (of UK)	5% (of UK)	Current relative risk for France in the FDA RBC Risk Assessment (2013) was updated to reflect the increased rate of cases in France relative to the UK. Accordingly, we increased the Relative Risk of France to 10% in this Red Cell Risk Assessment. Previous FDA FVIII risk assessment (FDA, 2010b) we assumed the Relative Risk for France is 5% of the UK risk.
Risk for France	1980 - 2001	1980 - current	Current risk for France in the FDA RBC Risk Assessment (2013) was updated to account for additional BSE and human food safety control measures implemented in France since 2001 (Afssa, 2007). Accordingly, we reduced the number of years in the risk window period for France to include the years 1980 through 2001. Previous FDA FVIII Risk Assessment (FDA, 2010b) assumed a risk period for France ranging from 1980 to present.
Incubation period for primary vCJD in MM	Lognorm distribution: Mean=15 years, Median=12 years 5^{th} =9 years, 95^{th} =35 years	Gamma distribution: Mean=15 years, Median=12 years 5^{th}=5 years, 95^{th}=35 years	Current incubation period for primary vCJD in MM persons in the FDA RBC Risk Assessment (2013) was updated and the 5^{th} percentile value was changed based on CDC's assumption that the minimum incubation period for vCJD in MM is 9 years. No Gamma distribution fit the required mean, medium, 5^{th} and 95^{th}, therefore, the Gamma distribution was replaced by Lognorm distribution.
Incubation period for primary vCJD in non-MM	Lognorm distribution: Mean=35 years, Median=32 years 5^{th} =23 years, 95^{th} =55 years	Gamma distribution: Mean=35 years, Median=32 years 5^{th}=25 years, 95^{th}=55 years	Current incubation period for primary vCJD in non-MM persons in the FDA RBC Risk Assessment (2013) was updated and the 5^{th} percentile value of 23 years was calculated by summing 9 years (5^{th} for MM) plus 14 years (the time delay on the appearance of the first MV case from that of the first MM case). No Gamma distribution fit the required mean, medium, 5^{th} and 95^{th}, therefore, the Gamma distribution was replaced by Lognorm distribution.

Infection dose in blood of infected donors	**ID per transfused unit (**1 transfused unit=500 ml**)** Triangular distribution (min, most likely, max) of 0.56, 0.75, 0.96	**ID_{50} per ml blood** Lognorm distribution Min=0.1 5^{th} perc =2 median=12 95^{th} perc =30 Max=1000	We recently reported a statistical analysis of published data from sheep transfusion experiments and U.K. Transfusion Medicine Epidemiology Review suggesting that the infection dose in infected blood is likely to be lower than previously assumed (Gregori et al., 2011). In our FVIII risk assessment we assumed a higher probable dose of infectious agent in blood of humans incubating vCJD based on published rodent studies.
Donor age	10-year age shifting to reflect aging of the donor populations	Age reported in a U.S. blood donor travel survey conducted in the year 2000	Donor travel data used in FDA model was collected approximately 10 years ago. In Red Cell Risk Assessment donor age was shifted by 10 years to reflect current donor age in 2011. In previous FVIII Risk assessment model we used donor age reported in the donor travel survey.

*mean value with 95% confidence interval in parentheses

MODULE 1

III. A. <u>Module 1</u>-Estimates of vCJD Prevalence in the U.K.

This module estimated the vCJD prevalence in the U.K. and, in turn, this estimate was used as the basis for estimating vCJD prevalence for France and other countries in Europe. Prevalence for France and other countries in Europe was estimated relative to the U.K vCJD prevalence using a relative-risk approach. Subsequently, the prevalence estimates for the U.K., France and other countries in Europe were used to estimate the vCJD prevalence estimates in U.S. blood donors who had traveled to those areas based on their dates of travel, the duration of their stay, and other factors. The estimates of U.K. vCJD prevalence are contained in the model worksheets labeled "III.A&B. TTvCJD risk-US". Two estimates of U.K. vCJD prevalence were applied using different data sources:

Low Prevalence Estimate: Generated based on epidemiological modeling of clinical cases (Garske and Ghani, 2010). The mean estimate is approximately 1.7 infections per million persons.

High Prevalence Estimate: Generated using data from appendix tissue survey studies (HPA, 2012b). The mean estimate is 493 infections per million persons.

III. A. 1. Low U.K. vCJD Prevalence Estimate

III. A. 1. a. U.K. asymptomatic vCJD infections in 2011

<u>Data:</u> Number of vCJD cases in the U.K. after 2010 predicted by epidemiological modeling (Garske and Ghani, 2010)

Epidemiological modeling by a U.K. research group (Garske and Ghani, 2010) predicted 100 (95% CI: 11-220) primary cases of vCJD would occur after 2010 and into the future. Because the U.K. had rigorously implemented a full range of measures to protect animal feed and human food from contamination with the infectious BSE agent by the end of 1996, we assumed that no primary infections were acquired in the U.K. after 1996 and all predicted cases after 2010 were incubating disease in 2011. Given a total U.K. population of 60 million, the estimated number of future vCJD cases was translated to a mean prevalence of approximately 1.7 asymptomatic vCJD infections per million U.K. population (95% CI: 0.2-3.7 infections per million) in the year 2011.

III. A. 1. b. Age distribution of asymptomatic vCJD for three genotypes

This section describes the information contained in the model worksheets "III.A&B. TTvCJD risk-US" and "age-asy-vCJD".

Assumption:

- Incubation period for primary vCJD in persons of the MM genotype — Lognormal distribution with a mean=15 years, median=12 years, 5th percentile = 9 years and 95th percentile = 35 years
- Incubation period for primary vCJD in non-MM genotype — Lognorm distribution with mean=35 years, median=32 years, 5th percentile =23 years and 95th percentile =55 years
- Persons of the MM, MV or VV genotypes are equally susceptible to vCJD
- The distribution of age at the time of initial infection for persons of the non-MM genotype is the same as that for persons of the MM genotype

Most primary vCJD cases in the U.K. were in young people (<34 yr of age). The median age at death is 28 years. Because the U.K. data indicated an age-dependent vCJD risk (Table III-3), in this risk assessment model we modeled vCJD risk in U.S. donor age groups based on U.K. data. For this purpose the estimated prevalence derived in section III. A. 1. a. was extrapolated for age-specific prevalence of potential preclinical and subclinical infections in U.K. population (described below in III. A. 1. c.) using the age distribution of vCJD infections calculated in this section.

Table III-3. Reported vCJD cases in the UK and percentage blood donation rate by age group in the U.S.

Age group	<10	10-14	15-17	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	27		32	30	22	13	5	3	5	0	5		
Percentage person in an age group donating [b]	n/a	n/a	n/a	12%	7%	6%	6%	6%	8%	7%	7%	6%	5%	3%	

[a] (Hilton et al., 2004)

[b] (Forshee and Walderhaug, 2009)

The age distribution of asymptomatic infections was used to extrapolate the age-specific vCJD infection prevalence from overall prevalence of the population estimated in III. A. 1. a. Asymptomatic infections should have been present for a period of time (incubation period) before progression to clinical cases. Therefore, the age profile for asymptomatic infections is expected to be younger than the reported age profile for clinical cases. To derive the age distribution of the U.K. population infected with vCJD but asymptomatic, we first calculated the distribution of age at initial infection for the *PRNP*-129 MM genotype subpopulation by shifting the distribution of age at diagnosis toward younger age by 15 years (estimated mean incubation period for persons of the MM genotype). The FDA model further assumed that the distribution of ages at the initial infection for persons of the non-MM genotypes is the same as those of the MM genotype. Thus, all genotypes have the same age distribution at the time of initial infection with the BSE agent. Second, the FDA model made a simplifying assumption that the incubation period for persons of non-MM genotypes is 20 years longer than that for persons with the MM genotype because there is

so little information available about the possible duration of incubation periods for persons of non-MM genotypes. The model generated the distribution of ages at the time of diagnosis for persons of non-MM genotypes by shifting the distribution of age at the diagnosis for MM genotype by 20 years toward increased age. Third, for any given age category, the probability that individuals are infected and asymptomatic was calculated by multiplying the cumulative probability that they are infected (cumulative form of distribution of age at the time of initial infection) by the cumulative probability that they have not been diagnosed (1- minus cumulative form of the distribution of age at diagnosis). These probabilities are then normalized to derive the age distribution for individuals who are infected and asymptomatic.

III. A. 1. c. Prevalence of asymptomatic vCJD in U.K. by age and genotype

Based on the age distribution of vCJD infections in the U.K. derived in the section above, the estimated vCJD prevalence for the U.K. population (section III. A. 1. a.) was extrapolated across the range of ages to generate age-specific prevalence estimates of potential preclinical and subclinical infections.

III. A. 2. High U.K. vCJD Prevalence Estimate derived using lymphoreticular tissue surveillance data

Data: The U.K. anonymous survey of appendix tissues for accumulation of abnormal prion protein (Hilton et al., 2004;HPA, 2012b).

Assumption: The vCJD infection prevalence is same across all age groups.

A retrospective survey study of stored tonsil and appendix tissues surgically removed from U.K. patients in 1995-1999 was published in 2004 (Hilton et al., 2004). The authors identified three appendices in which there were abnormal accumulations of abnormal prion protein out of a total of 12,674 samples tested using immunohistochemistry (IHC) (Hilton et al., 2004). All three positive tissues were from patients from the 1961 to 1985 birth cohort (Table III-4). In the same study, tonsil biopsies were also investigated, yielding no positive findings. The mean U.K. of abnormal prion protein (PrP^{TSE}) prevalence estimate calculated from this study was 237 per million (95% CI: 49-692 per million) or 1 in 4,225. This prevalence estimated has been used in previous FDA pdFVIII Risk Assessment as a High Prevalence Estimate for U.K. population.

To further investigate the prevalence of vCJD in the U.K. population, two larger scale tissue surveys were then initiated (Table III-4). In one study, 63,007 tonsil samples were examined for accumulation of PrP^{TSE} using a high throughput enzyme immunoassay (EIA); this study found no PrP^{TSE}-positive samples (Clewley et al., 2009). Subsequently, using IHC, one specimen with a single strongly positive follicle was found in a subset of 9,672 tonsil tissue samples that had tested negative using EIA (de Marco et al., 2010). The second large study tested archived appendix specimens using IHC to detect lymphoreticular accumulation of PrP^{TSE}. In Sept 2011, an interim report of this study described four PrP^{TSE} -positive tissues out of 13,878 samples tested (HPA,

2011b). Furthermore, positive appendices were detected in a wider birth cohort than previously reported in the Hilton study (Hilton et al., 2004). The final report of this last appendix study was released in July 2012, describing a total of 16 positive tissues out of 32,441 samples tested (ACDP, 2012;HPA, 2012b). The prevalence of PrP^{TSE} calculated based on this final result, presumed to represent the possible prevalence of latent vCJD infections, was endorsed by U.K. Advisory Committee on Dangerous Pathogens (ACDP) TSE Risk Assessment Subgroup in August 2012.

In this FDA RBC risk assessment, the High Prevalence Estimate for the U.K. population was assumed to be 493 per million persons (95% CI: 282-801 per million persons) as reported in the final report from HPA of 16/32,441 of PrP^{TSE}-positive appendix samples (Table III-5). This prevalence estimate was applied across all age groups, because the new tissue survey study found similar positive rates in all age groups tested. Thus, we applied no age adjustment to the High Prevalence Estimate analogous to that applied to the Low Prevalence Estimate. Data from the tonsil tissue studies were not included in the calculation of prevalence, because too few tonsil samples from the at-risk birth cohort (1961-1985 birth cohorts) were included in this study. We also excluded the EIA results, because EIA appeared to be less sensitive IHC in detecting of PrP^{TSE}.

Table III-4 Accumulation of abnormal prion protein (PrP^{TSE}) in the appendix and tonsil tissue samples from persons in the U.K.

(Positive/total, rate per million with 95% confidence intervals)

	1995-1999 National tissue survey (Hilton et al., 2004)		**2004-2012 National tissue surveys (HPA, 2012b)**		
	Appendices	**Tonsils**	**Appendices[1]**	**Tonsils**	
Birth cohort	**IHC[2]**	**IHC**	**IHC**	**EIA[3]**	**IHC**
Pre-1940	–	0/225	-	0/51	–
1941-1960	0/573	0/266	not provided 733 (269-1596)	0/648	–
1961-1985	3/10278 292 (60-853)	0/694	not provided 412 (198-758)	0/17786 0 (0-207)	1/9160 109 (3-608)
1986-1990	0/396	0/119	-	0/12799 0 (0-288)	0/135
1991-1995	–	0/106	-	0/15147 0 (0-244)	0/83
1996 and later	–	0/17	-	0/47518	0/294
Total	**3/11247[4] 267 (55-779)**	**0/1427 0 (0-2582)**	**16/32441[5] 493 (282-801)**	**0/93949 0 (0-39)**	**1/9672 103 (3-576)**

[1]The data in this column include the appendix data from 1995-1999 survey.
[2]IHC: immunohistochemistry technique
[3]EIA: enzyme immunoassay
[4]Data used in FDA pdFVIII-vCJD risk assessment for High Prevalence Estimate
[5]Data used in FDA RBC-vCJD risk assessment for High Prevalence Estimate

MODULE 2

III. B. Module 2. Estimation of vCJD Prevalence in U.S. Blood Donors and Number of Infectious Blood Units

Module 2 estimates the annual numbers of U.S. blood donors at risk of vCJD infection during travel to or residence in the U.K., France and other countries in Europe, who might carry the vCJD infectious agent in their blood at the time of donation. This part of Module 2 is found in the attached worksheet entitled "III.A&B. TTvCJD risk-US." This module integrates data and information on the risk associated with travel or residence in the U.K., France and other countries in Europe since 1980 based on estimates of vCJD prevalence for each country, blood collection in the U.S., efficiency of the U.S. donor deferral policy, and likelihood that the infectious vCJD agent is present in the donated unit. Similar calculations were conducted for travelers to the U.K. (B.2.a.), France (B.2.b.), other countries in Europe (B.2.c.) and for U.S. personnel deployed to military bases in Europe (B.2.d.). This part of the model provides estimates of vCJD prevalence in the U.S. blood donors and the probability that a blood unit might be contaminated with the infectious agent in 2011.

III. B. 1. Blood donors in the U.S. characterized by donor age

Data: annual units of U.S. blood supply and donation frequency per donor per year (HHS, 2009)

Data: age-specific donation rates (Forshee and Walderhaug, 2009)

This section computed the annual number of U.S. blood donors by age group based on mean annual units of blood donated in the U.S. and donation frequency per donor per year reported by the 2009 National Blood Collection and Utilization Survey (HHS, 2009). This part of the model is found in the model worksheet titled "III.A&B. TTvCJD risk-US". We then stratified the number of blood donors by age groups in five-year intervals based on 2002-2006 data on U.S. blood donations by age group, collected as part of the National Health Interview Survey (NHIS) (CDC, 2013a). The rates of blood donation for different age groups of U.S. donors are summarized in Table III-3.

III. B. 2. U.S. blood donors with history of travel to the U.K., France or other countries in Europe including military: Estimation of the annual number of donors potentially infected with vCJD and with infectivity in the blood

This section estimated the annual number of blood donors who might have been exposed to BSE agents, became infected with vCJD and had infectious vCJD agent in their blood in the year 2011. This part of model is found in the model worksheet titled "III.B.2.a. Travel-UK", "III.B.2.b.

Travel-FR", "III.B.2.c. Travel-EU" and "III.B.2.d. Military" and "III.A&B. TTvCJD risk-US". The exposure could have been from four sources: exposures that occurred when donors traveled to the U.K., France and other countries of Europe or resided on U.S. military bases in Europe during deployments. The numbers of infected donors were calculated separately in the worksheets, "III.B.2.a. Travel-UK", "III.B.2.b. Travel-FR", "III.B.2.c. Travel-EU" and "III.B.2.d. Military" for different exposure sources; then those figures were summarized to yield an annual total number of U.S. blood donors who might have been infected and had vCJD infectivity in blood in the year 2011 (III. B.2.e.) on worksheet "III.A&B. TTvCJD risk-US".

The model further incorporates the likely risk reduction resulting from current FDA donor deferral policies, implemented beginning in 1999 and last revised in 2010. This part of model is found in the model worksheet "III.A&B. TTvCJD risk-US." Current FDA donor deferral policy recommends deferring donors who:

- Traveled to or resided in the U.K. from 1980 – 1996 for ≥3 months
- Traveled to or resided in France since 1980 for ≥5 years
- Traveled to or resided in other countries in Europe since 1980 for ≥5 years (does not include source plasma donors)
- Were U.S. Military personnel or their dependents – deployed in U.K. or other countries in Europe from 1980 to 1996
- Received blood transfusion in the U.K. or in France since 1980

This geographic deferral policy should have deferred donors with a history of extended travel or residence in the U.K. and other countries in Europe since 1980. There is a small chance that infected donors might still donate for two reasons: first, some donors may have been infected while on a short stay in a BSE-risk country—a stay shorter than that recommended by the guidance deferral criteria—and, thus not deferred from donating blood; second, the screening process, based on donors' responses to a questionnaire, is not completely efficient and subject to bias and other limitations. Some donors with a history of an extended period of travel or residence in BSE countries may not be identified by questionnaire screening because of failure to recall their travel accurately, to understand the questions, or other reasons. Other sources of bias, such as missing data and false reporting, might introduce further inaccuracies in donor screening. Based on advice from TSEAC in meetings held in October 2005 and December 2006 (TSEAC, 2005;TSEAC, 2006), FDA has assumed that 85-99% of donors who meet deferral criteria are likely to have been identified and deferred by donor screening questionnaire.

III. B. 2. a. Estimation of the number of blood donors who are potentially infected with vCJD and who have vCJD agent in their blood at the time of donation and who have a history of travel to the *U.K.*

This section calculated the number of donors who were exposed to BSE agent and were infected with vCJD during travel in the U.K. specifically and who may consequently have vCJD infectivity

in the blood at time of donation. This part of model is found in the model worksheet titled "III.B.2.a. Travel-UK".

III. B. 2. a. i. Estimation of the percentage and number of U.S. donors who traveled to the U.K. and duration of travel

Data: Blood Donor Travel Survey (Watanabe, 2000)

Assumption: The total period of vCJD risk (risk of dietary exposure to the BSE agent) in the U.K. is thought to have extended from 1980 (presumed beginning of the BSE outbreak in cattle) through the end of 1996 (full implementation of rigorous efforts in the U.K. to prevent BSE-risk materials from entering animal feed and the human food supply). We considered the risk after 1996 to be negligible (TSEAC, 2006).

A Blood Donor Travel Survey was conducted by the American Red Cross (ARC) in 2000 (Watanabe, 2000) to collect information on historical travels of blood donors in the U.K, France and other countries in Europe during the period between the years 1980 and 1996. This section of the model determined the percentages of blood donors with a history of travel or residence in the U.K. during the years 1980 through 1996 by cumulative length of time for stay (1-30 days, 1-3 months, etc.).

III. B. 2. a. ii. Estimation of the percentage and number of donors by age group and year of travel

Data: Blood Donor Travel Survey (Watanabe, 2000)

Data: Annual number visits to Europe by North Americans during the years 1980 through 2005 (UK National Statistics, 2006)

vCJD risk may vary depending on the age of the donor and the specific year of travel. This section of the model further determined the number of donors who had a travel history to U.K. during the risk period when BSE occurred (III.B.2.a.i.) stratified by age group and the number of visits that occurred in each year during the years 1980 through 1996. The model determined the odds ratios of travel by donor age based on the ARC blood donor survey data. Because the donor travel data were collected in 2000, we shifted donor age by 10 years to reflect the present time and the aging of donors. Applying these odd ratios to the total number of donors who have a history of travel to or residency in the U.K., we derived the estimated number of donors who had a history of travel in each age group. We also developed a linear regression model to estimate the annual number of visits based on the available data on travel of North Americans to Europe (UK National Statistics, 2006). The regression model was applied to derive the number of visits by donors in each

individual year during the years spanning 1980 through1996 from the total number of visits in that time period. The output of sections III.B.2.a.i and ii is an estimate of the number of donors who traveled to U.K. by age, year of travel and duration of travel.

III. B. 2. a. iii. Adjustment of Relative Risk to account for variations in BSE risk by specific year and travel duration

Data: Annual number of BSE cases reported in the U.K. 1980-1996 (OIE, 2012)

Assumptions:

- The relative risk of vCJD in the U.K. is 1
- The risk of vCJD exposure is cumulative, proportional to the duration of stay or time spent in the BSE countries; for instance a person who lived in the U.K. for one year has one-sixteenth the risk of a full-time U.K. resident who lived there throughout the entire 16-year risk period (from mid 1980 through mid 1996**)** for foodborne vCJD.
- The risk of vCJD exposure for U.S. donor is correlated with the magnitude or intensity of the BSE epidemic at the time of travel or residence of the donor

This section calculated the relative risk of exposure to BSE in a specific year between 1980 and 1996 in the U.K. and for a specific duration of stay. Many of the reported cases of vCJD and BSE cases have occurred in the U.K. Accordingly, the risk of vCJD infection (as well as the prevalence of vCJD) in the U.K. is assumed to have been the highest in the world, so we assumed the relative risk for the U.K. to be 1 (or 100%). To calculate shorter-term exposures, this risk was prorated for each individual year in 16-year risk window period from 1980-1996. The magnitude of the risk (or exposure to the BSE agent) for each individual year is proportional to the number of reported BSE cases in the year of interest (divided by the total number of BSE cases from 1980-1996), so that the risk is higher in a year having more reported BSE cases. The relative risk of U.S. donors who traveled in a specific year between 1980 and 1996 in the U.K. for a specific length of duration was calculated by prorating the risk. We also assumed that donors with a cumulative stay of five years or longer at any time between 1980 and 1996 in the U.K. had the same risk as a U.K. resident.

III. B. 2. a. iv. Probability that a U.S. blood donor was infected with vCJD based on year, duration of travel and donor age

We multiplied the U.K. vCJD prevalence discussed in section A. Module 1. by the relative risk for U.S. donors who traveled in a specific year for a specific total length of stay (calculated in section B. 2. a. iii.) to derive the probability of exposure/infection stratified by donor age, year of travel and length of stay in the U.K.

III. B. 2. a. v. Estimation of the number of donors potentially infected with vCJD

This section of the model calculated the number of potentially vCJD-infected U.S. donors. For each donor group stratified by age, year and duration of travel (B.2.a.ii.), we generated a random of infected donors using the function of a binomial (*n*, *p*), where *n* is the number of donors of each group (calculated in B.2.a.ii.), and *p* is the corresponding probability of exposure/infection for each group (calculated in B.2.a.iv.).

III. B. 2. a. vi. Estimation of the number of donors potentially infected with vCJD who have infectivity in their blood at the time of donation

Assumptions:

- Approximately, 40%, 50% and 10% of U.S. donor population are of the MM, MV and VV genotype at codon 129 of the prion protein gene, respectively (Alperovitch et al., 1999).
- vCJD agent most likely first appears in the blood of infected persons early in the incubation period after the first 25% of the incubation period has elapsed. The model assumes that the vCJD agent may be present in the blood of an infected person during the last 75% of the incubation period (with a range of 50% to 90% of last portion of the incubation period).
- Accordingly, in the model we represent the time during the last portion of the incubation period when vCJD agent may be present in the blood of an infected person using a triangular distribution with a most likely value of 75%, a minimum of 50% and maximum of 90%.
- The incubation period for primary (foodborne) vCJD in persons having the MM genotype is represented in the model using a lognormal distribution with a mean of 15 years, a median of 12 years, and a 5^{th} percentile value of 9 years and 95^{th} percentile value of 35 years.
- The incubation period for primary vCJD in a person of a non-MM genotype is represented in the model using a lognormal distribution with a mean value of 35 years, a median value of 32 years, and a 5^{th} percentile of 23 years and 95^{th} percentile value of 55 years.

This section of the model calculated the number of infected donors who had vCJD agent present in their blood at the time of donation and so might transmit the infection. The model calculated the number of infected donors for the three genotypes—MM, MV and VV—by multiplying the total number of infected donors by the percentage of each genotype in the population (Alperovitch et al., 1999). Then, the model calculated the elapsed time from the year of travel (time of exposure) to the year 2011 and compared it with the required length of incubation for infectivity to be present in blood (second assumption above). For each iteration, the computer randomly selected input values from the distributions for length of incubation period and for incubation period when infectivity was predicted to be present in the blood. If the elapsed time since travel was equal to or longer than the time during which infectivity is likely to be present in blood; the model then assumed that infectivity was present in the blood of the donor (otherwise, even an infected donor would not be expected to transmit the disease because infectivity was not yet present in the blood at the time of donation).

Assumptions on length of the incubation periods for foodborne vCJD were made based on available epidemiological information. All reported vCJD cases genotyped to date, except one,

have had the MM genotype. We considered various mean estimates of 12 yr, 15 yr and 17 yr, for the incubation period of foodborne vCJD published by modeling groups in the U.K., U.S. and France (Belay et al., 2005;Boelle et al., 2003;Garske and Ghani, 2010) and selected an average number of 15 yr as a plausible consensus incubation period for individuals of the MM genotype. We assumed a median incubation period of 12 years based on the time delay of vCJD peak of onset in 1999 from the estimated time of highest exposure to BSE which must have been in the years before 1992 when the peak of BSE cases occurred in cattle. A reasonable adjusted interval between the probable peak in BSE-contaminated products, likely to have been in 1989 or earlier, and the peak in onset of new cases in 1999 is consistent with a mean incubation period exceeding 10 years. The shortest plausible incubation period for foodborne vCJD in persons of the MM genotype was estimated to be nine years, based on the observation that the ages at onset of the youngest vCJD cases were 11 years and 12 years and no case was less than 10 years old at onset; we assumed that babies consumed no significant amounts of beef during the first year of life (Verity et al., 2000). We further assumed a maximum incubation period of 35 years for persons of the MM genotype based on the known incubation periods of other human TSEs (in a few cases exceeding 35 year (Collinge et al., 2006;Croes et al., 2002). The information on infection and progression of vCJD in persons who are of non-MM genotypes is limited. The only case of foodborne vCJD was in a person having the non-MM genotype with onset of illness in 2008 (Kaski et al., 2009), which is 14 years later than the onset of the first three foodborne vCJD cases of MM genotype with onset in 1994 (Will et al., 1996). The model assumed the minimum incubation period for foodborne vCJD in non-MM persons to be 23 years (minimum incubation period for the MM genotype plus 14 years). The model further assumed the mean, minimum and maximum values for the incubation period for foodborne vCJD in persons having the non-MM genotype to be 20 years longer than those with the MM genotype.

The assumption that infectivity might first appear in blood after only 25% of the incubation period has elapsed was based on observations of sheep infected with scrapie (Houston et al., 2008) and human transfusions with RBC from vCJD-infected donors (TMER, 2013). The blood of some sheep collected after only 25% of the incubation period had elapsed was already infected. Available information from the TMER cohort indicated that vCJD infectivity was present in the blood of an infected donor 17 to 42 months before clinical onset, which would correspond with the last 12% and 29% of an assumed assuming median incubation period of 12 years for foodborne vCJD in persons of the donor's MM genotype. It is possible that infectivity might have been present in the blood even earlier than demonstrated by the small numbers of cases in the TMER series. Because human data are so limited, we made a conservative assumption that infectivity is most likely to be present in the blood during the last 75% of the incubation period (based on the sheep data) with a range that includes a minimum of 50% of the incubation period or a maximum of 90% of the incubation period.

III. B. 2. a. vii. Estimation of exposure of donors who traveled to the U.K. to the BSE agent: The number of U.S. donors who potentially carry infectivity in their blood and the estimated risk reduction via donor deferral

Assumptions: Efficiency of donor questionnaire to identify at-risk donors ranges from 85% to 99%.

This section of the model estimates the total number of donors who present to donate with infectivity in the blood (B.2.a.vi.), and incorporates the risk-reducing effect of FDA donor deferral policies that defer donors who traveled to or resided in the U.K. from 1980 through 1996 for three months or longer. This portion of the model is contained in the spreadsheet titled "III.A&B. TTvCJD risk-US". The number of infected donors who spent three months or more in the U.K. was summed to provide the total number of infected donors to be deferred under current FDA guidelines. However, some of these donors might still donate because of limitations of the donor questionnaire screening process. The random number of at-risk donors who are not identified and removed by donor questionnaire screening was calculated using a binomial (*n, p*) distribution, where *n* is the number at-risk donors who should have been deferred based on FDA guidance and *p* is probability of screening error calculated by subtracting the probable efficiency of donor questionnaire screening, represented by a range from 85% to 99%, from 100%. The numbers of infected donors who spent less than three months in the U.K. were also summed up; such infected donors would not be deferred and are considered suitable to donate blood under current FDA recommendation, adding to the remaining residual risk.

III. B. 2. b. Estimation of the number of blood donors who are potentially infected with vCJD and who have vCJD agent in their blood at the time of donation and who have a history of travel to France

Assumptions:

- The relative risk for France is 0.1 that of the U.K.
- The risk period for becoming infected with foodborne vCJD in France was from 1980-2001

This section calculated the number of donors who were exposed to the BSE agent and became infected with vCJD during travel to France since 1980; some may carry vCJD infectivity in their blood at time of donation. This portion of the model is contained in the spreadsheet titled "III.B.2.b. Travel-FR." In earlier FDA analyses (Williams, 2004), the potential vCJD risk for donors who traveled to France was estimated relative to the risk in the U.K. (relative risk) based on the amount of beef that France was thought to have imported from the U.K., the number of cases of domestically acquired BSE in French cattle, the number of vCJD cases in humans living in France, and other factors. In the previous FDA pdFVIII Risk Assessment, the relative risk of vCJD in France was assumed to be 0.05 times (5%) that of the U.K. In this risk assessment, we updated and increased the relative risk for France to 0.1 (or 10%) because of the increased number of vCJD cases reported in France in recent years. Based on later information, we have concluded that France, since 2001, has implemented effective control measures similar to those implemented in the U.K. (Afssa, 2007). Considering the uncertainty regarding the efficiency, compliance and implementation of these control measures, the FDA RBC model assumes that the risk period for France extends from 1980 to the end of 2001. This is a change from previous FDA risk assessments in which a risk period for dietary exposure to the BSE agent in France was assumed to extend from 1980 through the present time (FDA, 2006a;FDA, 2010b). Based on these changes the probable vCJD prevalence for France was calculated to be 0.1 x U.K. prevalence (or 10% that of the U.K. prevalence). All other calculations in this section are similar to those described in the previous sections for travel exposure in the U.K. The same ARC blood donor survey data (Watanabe, 2000) was used to estimate the number of U.S. donors who traveled/resided in France

during the risk period, who were potentially infected, and consequently might have infectivity in their blood.

III. B. 2. c. Estimation of the number of blood donors who are potentially infected with vCJD and who have vCJD agent in their blood at the time of donation and who have a history of travel to other countries in Europe

Assumptions:

- The risk for the other countries in Europe is 0.015 relative to that in the U.K.
- The risk period for foodborne vCJD in other countries of Europe was from 1980 to the present time

This section calculated the number of donors who were exposed to BSE agent and infected with vCJD when traveled to **other countries in Europe** outside the U.K. and France, and who therefore might carry vCJD infectivity in their blood at time of donation. This portion of the model is contained in the spreadsheet titled "III.B.2.c. Travel-EU". The BSE/vCJD risk varies among the other countries in Europe. However, there is insufficient information allowing us to distinguish quantitatively or qualitatively the level of risk for each individual country for countries other than the U.K and France. In this model we modeled most other countries in Europe outside the U.K. and France as a group. As for France, in previous analyses we estimated the potential vCJD risk for donors who traveled to other countries in Western Europe relative to the risk in the U.K. The relative risk of vCJD for other countries in Europe was assumed to be 0.015 times that for the U.K. (1.5% of U.K.) based on available BSE surveillance data from Switzerland (Williams, 2004). There is less information on implementation of control measures for many other countries in Europe outside the U.K. and France, thus, this model assumed the risk period for these countries to be from 1980 to present (likely to be overstated for some countries that have presumably implemented precautionary measures similar to those in the U.K. and France). Based on these estimates, we calculated vCJD prevalence for those European countries to be 0.015 x U.K. prevalence. All other calculations in this section are similar to those described in the previous sections for travel exposure to the U.K. We used the same ARC blood donor survey data to estimate the number of U.S. donors who traveled to or resided in other countries of Europe during the risk period and were exposed to the BSE, potentially infected and who might have vCJD agent present in their blood at the time of donation.

III. B. 2. d. Blood donors potentially infected with vCJD during deployment or residence at US *military* facilities in Europe during the years 1980 to 1996

Data: Annual number of persons deployed to U.S. military bases in Europe (DOD, 2012)

Assumptions:

- The relative vCJD risk for U.S. military bases in Europe is 0.35 relative to that in the U.K.
- The risk period for vCJD risk for persons residing on U.S. military bases in the Europe was during the years 1980 to 1996.
- The average period of deployment to the military base was two years.

This section calculated the number of donors who were exposed to BSE agent and infected with vCJD during residence or deployment on a **U.S. military base in Europe**, and who may have vCJD agent present in their blood at time of donation. This portion of the model is contained in the spreadsheet titled "III.B.2.d. Military". The U.S. military bases in Southern Europe participated in the U.K. beef program between 1980 and 1996 and the military bases in Northern Europe from 1980 to 1990. However, in this risk assessment for simplicity we used a conservative single period from 1980 to 1996. It was estimated that 35% of the beef consumed on those bases during that period of time was imported from U.K. Therefore, in the same analysis described above for France and other counties in Europe the relative risk for U.S. military bases in Europe was assumed to be 0.35 (or 35%) that of U.K. and the risk period is assumed to be the years spanning 1980 through 1996. Also for this section, the other calculations were similar to those in the U.K. section above. The estimate of the total number of U.S. donors who were deployed to the military bases in Europe 1980-1996 was derived from the ARC blood donor survey. Data on the annual number of persons deployed (DOD, 2012) was applied to donor data on rate and age of donation and used to estimate the number of donors deployed in each year during 1980 through1996. (We must note that no cases of vCJD have been recognized in this group of persons to date.)

III. B. 2. e. Estimation of the total number of vCJD donors and number of donations made in 2011

Data: Frequency of donations per donor per year (HHS, 2009)

This section summed the number of all infected donors who might have vCJD agent present in their blood at the time of donation in 2011 from previously computed numbers of infections in four BSE-agent-exposed groups (the U.K., France, other countries in Europe, and military bases in Europe described in sections B.2.a. through d.). This portion of the model is contained in the spreadsheet titled "TTvCJD risk-US." The total number of infectious donations was calculated by multiplying the number of infected blood donors with the average frequency of blood donations per donor per year (HHS, 2009). The prevalence of vCJD infectious blood units in the U.S. blood supply (or probability of an infectious blood unit) was calculated by dividing the number of infectious blood donations by the total number of blood donations.

Model results for module 2: Estimation of the number of vCJD-infected donors and the number of donations possibly containing vCJD agent

The model results from section B.2.e. above estimates the number of donors potentially infected with vCJD who presented to donate in 2011 and the number of donors who were not removed by

the deferral policies and donated blood. Table III-5 displays model results for the year 2011 according to the destination of travel/residence and stratified by the two U.K. vCJD prevalence estimates. The results with the Low Prevalence Estimate indicate that no infected donors are predicted to present to donate. However, with the High Prevalence Estimate, a mean total of 41 vCJD-infected individuals are predicted by the model to have presented to donate in the year 2011, and eight persons are predicted to have donated These data indicate that the current donor deferral policies reduced risk by approximately 80%. This actual percentage of risk reduction is lower than the efficiency of donor questionnaire screening assumed above, because some donors who had a short-term stay in vCJD risk regions also contributed to a small portion of risk. The residual risk after implementing donor deferral includes both non-deferrable risk (from infected suitable blood donors) and remaining deferrable risk associated with unsuitable donors allowed to donate because of errors in donor questionnaire screening. More than 80% of the residual risk is associated with donors who had a history of travel to the U.K. The model also estimated that the probability of an infectious blood unit containing vCJD agent entering the U.S. blood supply was 2.2×10^{-9} (1 in 455 million) with the Low Prevalence Assumption and 6.1×10^{-7} (1 in 1.6 million) when the High Prevalence Assumption is used.

Table III- 5

Model results for number of predicted vCJD-infected U.S. donors by region of travel who might present to donate and the number of vCJD-infected donors likely not removed by screening in 2011 and donated.

		Destination of travel/residence				
		UK	**France**	**EU**	**Military**	**Total**
Low Prevalence (1.7 infections per million)	**vCJD donors presented**	0.152 (0-1)	0.006 (0-0)	0.007 (0-0)	0.008 (0-0)	0.2 (0-1)
	vCJD donors who donated	0.030 (0-1)	0.002 (0-0)	0.004 (0-0)	0.001 (0-0)	0.04 (0-1)
High Prevalence (493 infections per million)	**vCJD donors presented**	35.28 (15-59)	1.45 (0-4)	1.54 (0-5)	2.39 (0-7)	41 (18-67)
	vCJD donors who donated	6.47 (1-14)	0.50 (0-2)	0.76 (0-3)	0.19 (0-1)	8 (2-17)

MODULE 3

III. C. Module 3-Estimated number of potential transfusion-transmitted vCJD infections in the U.S.

The number of vCJD-infected donors and donations possibly containing vCJD agent determined in Module 2 was used in Module 3 to calculate the annual number of vCJD infections that were transmitted in the year 2011 and the number of these infections that may lead to clinical cases. The module also calculated the cumulative number of TTvCJD infections acquired since 1980 and the cumulative number of TTvCJD clinical cases that should have been observed.

III. C. 1. Estimation of the annual number of TTvCJD infections in year 2011 in the U.S. and the number of infections that may progress to clinical cases

III. C. 1. a. Annual number of TTvCJD infections in year 2011

Data: Annual number transfused blood units in the U.S. (HHS, 2009)

Data: Number of blood units administered per patient hospital stay (Anderson et al., 2007)

Assumption: Infectious dose per unit red blood cells is triangular distribution (0.56, 0.75, 0.96 ID_{iv}) (Gregori et al., 2011)

This portion of the model is contained in the spreadsheet titled "III.A&B. TTvCJD risk-US;" we first calculated the probability a U.S. RBC recipient would receive infected red blood cells through a transfusion using function of 1-Binomdist *(n, N, p,)*; where *n* (the number of infected units received) is equal to 0, *N* is the number of blood units administered per transfusion and *p* is the prevalence of vCJD-infected blood units in the blood supply (calculated in III. B. 2. e.). The number of blood units administered per transfusion was not available. For approximation, we developed an empirical statistical distribution representing the number of blood units administered per patient hospital stay using data from Center for Medicare & Medicaid Services (Anderson et al., 2007).

The annual number of transfusion-transmitted vCJD infections in the year 2011 was further computed as a random variable binomial *(n, p)*. The *n* parameter represents the annual number of blood transfusions in the U.S, which was calculated by dividing the annual number of transfused blood units (HHS, 2009) by the mean number of blood units transfused per patient hospital stay derived from distribution above. The *p* parameter is the product of the probability of a patient receiving a unit of blood containing the vCJD agent as calculated above and the quantity of infectious agent or doses in a unit of blood. In the FDA pdFVIII risk assessment we assumed that the infectivity in blood of a person infected with vCJD was represented by a statistical distribution having a minimum value of 0.1 i.c. ID_{50} per ml, a 5^{th} percentile of 2 i.c. ID_{50} per ml, a median of 12 i.c. ID_{50} per ml, a 95^{th} percentile of 30 i.c. ID_{50} per ml and a maximum value of 1,000 ic ID_{50} per ml (FDA, 2010a). As discussed previously, these estimates suggested that a unit of blood could

contain thousands of ic ID_{50} of infectivity. This is likely an overestimate of vCJD infectivity in human blood. In the present FDA RBC risk assessment we used a more recent analysis suggesting that the mean infectivity in non-leukoreduced RBCs from donors incubating vCJD is likely to be less than 1 IDiv per unit. The infectious dose (ID) per unit blood is represented using a statistical distribution known as a triangular distribution having a minimum value of 0.56 ID, a most likely value of 0.75, and maximum of 0.96 IDiv per unit based on an analysis of TTvCJD transfusion data (Gregori et al., 2011). For the details of the analysis on infectivity titer in human blood please refer to Section II, Hazard Characterization.

III. C. 1. b. The annual number of TTvCJD infections in year 2011 predicted to progress to clinical cases

Data: Post-transfusion survival data (HPA, 2011a)

Assumption:

- Among all vCJD infections, 40% are associated with persons of the MM genotype and 60% are associated with persons having non-MM genotypes.
- Incubation periods for TTvCJD in persons of the MM genotype are represented by a triangular distribution having a most likely value of 10 years, a minimum value of 6 years, and maximum value of 20 years.
- The incubation periods for TTvCJD occurring in persons of non-MM genotypes are represented by a triangular distribution having a most likely value of 20 years, a minimum value of 16 years, and a maximum value of 30 years.
- Infections will progress to clinical cases only when individuals survive longer than the incubation period of the disease.

In this section, the model calculates the annual number of transfusion-transmitted infections in 2011 that may progress to clinical cases by using a random variable binomial (n, p). The n parameter represents the annual number of infections expected to occur by RBC transfusion in the year 2011. The p is the probability of infected RBC recipients surviving incubation period of the disease and developing symptomatic vCJD. The model assumes that all infected individuals will eventually become clinically ill cases provided they survive longer than the incubation period. The incubation times of TTvCJD for the three symptomatic cases reported in the U.K. were 6.5, 7.8, and 8.3 years. All three cases were of the MM genotype. The U.K. HPA assumed the mean incubation period for TTvCJD in persons of the MM genotype to be 10 years (Bennett and Daraktchiev, 2011). This assumed incubation period is slightly longer than the average for the observed incubation periods of the three reported cases under the assumption that cases appearing earlier are likely to be those with shorter incubation periods. The FDA risk assessment model used a triangular distribution with a most likely value of 10 years, a minimum value of six years (as the shortest observed incubation time for a case of TTvCJD) and a maximum value of 20 years to represent the uncertainty in the estimate of incubation period of TTvCJD for persons of the MM

genotype. There is no information on infection and progression of vCJD infection in persons of the non-MM genotypes. Previously, we assumed the incubation period for primary foodborne vCJD occurring in the non-MM population as being 20 years longer than that of the MM population. The FDA risk assessment model assumed an incubation period of 10 years longer for TTvCJD in persons having the non-MM genotype than for those of the MM genotype based on the assumption that the difference in incubation times due to genotype for human-to-human transmission (TTvCJD) is probably shorter than that estimated for cattle-to-human foodborne transmissions (primary vCJD) and the iv route of exposure more invasive. The resulting most likely value of 20 years incubation period (10 years incubation period for MM genotype plus 10-year difference between MM and non-MM genotype) of TTvCJD for non-MM genotypes is consistent with the HPA's assumption used in its report on examination of scenarios for transfusion-transmission of vCJD (Bennett and Daraktchiev, 2011). To reflect the uncertainties of these assumptions, the model used a triangular distribution having a most likely value of 20 years, a minimum value of 16 years and maximum value of 30 years for incubation periods. The model randomly selected length of incubation period for persons of the MM and non-MM genotypes from statistical distributions. A statistical regression model was also developed to estimate the probability of surviving through the incubation period, $0.61 - 0.028 \times Year_{post\text{-}transfusion}$ (Shown in Table III-1 and Table III-2), was developed as a function of the year post-transfusion ($Year_{post\text{-}transfusion}$) that incorporated the post-transfusion survival rate from U.K. data (Bennett and Daraktchiev, 2011). Applying the annual number of TTvCJD infections acquired in year 2011 (calculated in section III. C. 1. a.**)** and the probability of the recipient surviving through the entire incubation period, the model used the binomial function to calculate the number of transfusion-transmitted infections in 2011 predicted to progress to clinical vCJD.

III. C. 2. Estimation of the total, cumulative number of TTvCJD infections predicted to have occurred since 1980 (model worksheet "III.A&B. TTvCJD risk-US")

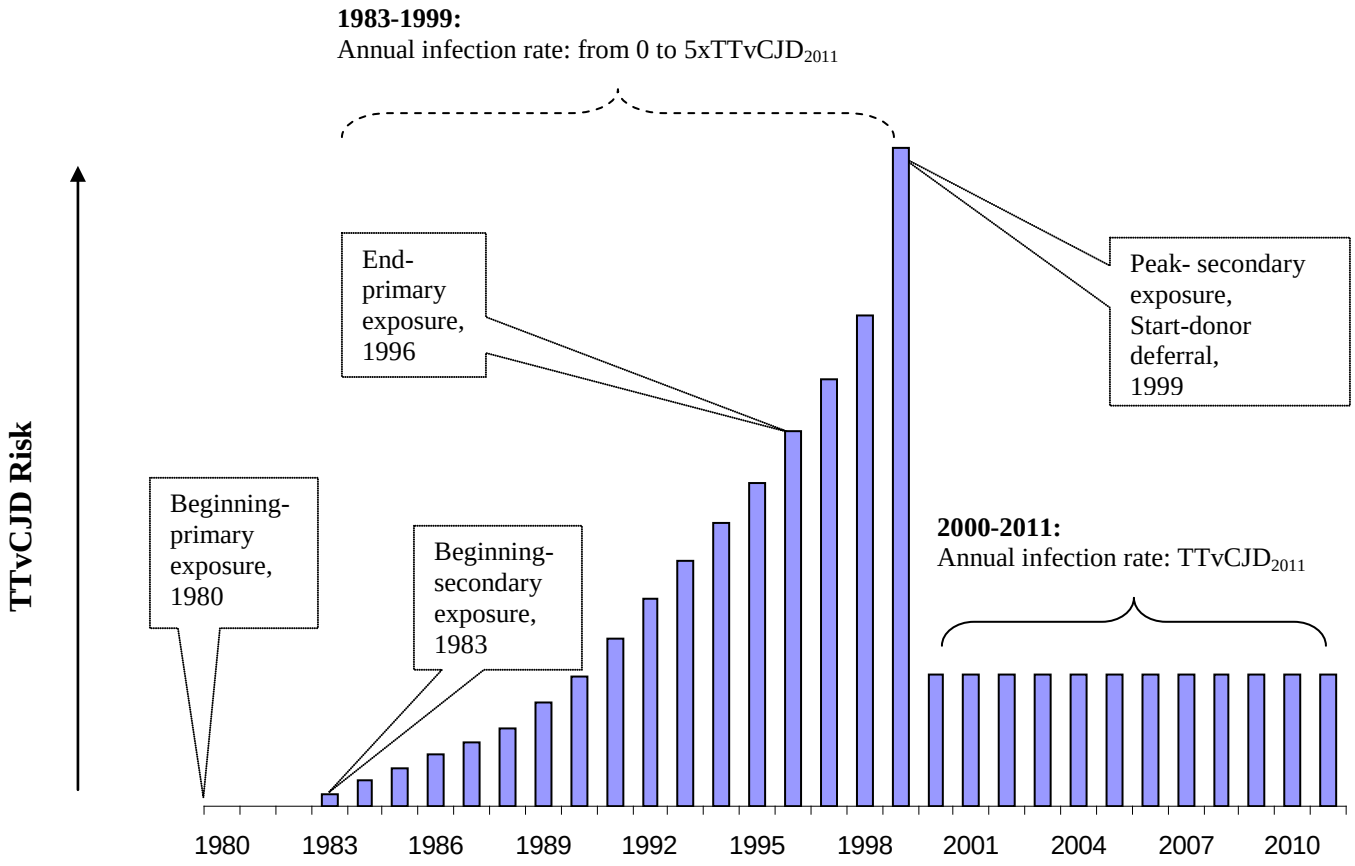
III. C. 2. a. Estimation of the cumulative number of TTvCJD infections since 1980

Assumptions:

- There is three-year delay in the presence of infectivity in the blood from time of infection.
- TTvCJD risk emerged in year 1983 (three-year delay from beginning of BSE epidemics in 1980).
- TTvCJD risk peaked in 1999 (three-year delay from 1996, the end of risk period for food-borne vCJD in the U.K.).
- The risk-time curve for TTvCJD (1983 to 1999) is in parallel with the BSE-time curve (1980-1999) with three-year delay.
- TTvCJD risk has been greatly reduced since donor deferrals in the U.S. were implemented in the year 1999.
- TTvCJD risk has largely remained unchanged after 2000.

This section of the model estimates the total number of TTvCJD infections predicted for the U.S. since 1980. In previous sections we assumed the median incubation period of foodborne vCJD in persons having the MM genotype to be 12 years, and, based on animal studies, we also assumed that the vCJD agent is present and blood is most likely infectious for the last 75% of the incubation period. These two assumptions lead to an estimate of three-year delay between the time of initial infection and the time that vCJD agent may appear in the blood of infected persons, potentially transmitting vCJD. Accordingly, although the BSE epidemic has been assumed to start in 1980, our model assumes that the risk of TTvCJD risk was delayed and did not start until three years later, in 1983. Therefore, the model estimates the total number of TTvCJD infections acquired during two time periods: (1) 1983 through1999 and (2) during the period from 2000 through 2011; we summed TTvCJD infections estimated for the two periods to derive a cumulative total number of infections for the years spanning 1980 through 2011. Calculation of the cumulative number of TTvCJD infections are illustrated in Figure III-2 and described in more detail below:

Figure III-2. Graphical representation of calculations of cumulative risk for TTvCJD in the U.S. from 1980 to 2011



Calculation of TTvCJD risk during the years 1980 through1982 (three years): We assumed that there was no TTvCJD risk present, because exposure of donors to the BSE agent was assumed to

have started only in 1980 (when the BSE epidemic began in U.K. cattle) the agent would not be expected to appear in their blood until three years later, after 25% of the mean vCJD incubation period had elapsed.

Calculation of TTvCJD risk during the years 1983 through1999 (17 years): The annual TTvCJD infection rate would be expected to have increased since 1983 (in parallel with the increasing BSE epidemic that peaked in 1999), reaching a maximum in 1999. The infection rate in 1999 can be estimated based on the model-estimated infection rate for 2011 (represented by $TTvCJD_{2011}$ in Figure III-2) and the estimated risk reduction from FDA donor deferral policies. The model results above (Table III-6) indicated that vCJD risk has been reduced by approximately 80% from the initial risk because of donor deferrals. This means the annual TTvCJD risk in 2011 was 20% that in 1999 (maximum risk before implementation of FDA donor deferral policy); otherwise stated, the risk of TTvCJD in 1999 was five-times $TTvCJD_{2011}$. TTvCJD infection rates from 1983 to 1999 were calculated yearly using the number of reported BSE cases in the U.K. for each year from 1980 to1996 (three-year delay). Therefore, the vCJD risk paralleled the increase of BSE cases during the U.K. epidemic.

Calculation of TTvCJD risk during the years 2000 through 2011 (12 years): The annual infection rate for each individual year of this period was assumed to be the same as that for year 2011 ($TTvCJD_{2011}$).

III. C. 2. b. Estimation of the cumulative number of TTvCJD clinical cases in the U.S. since 1980

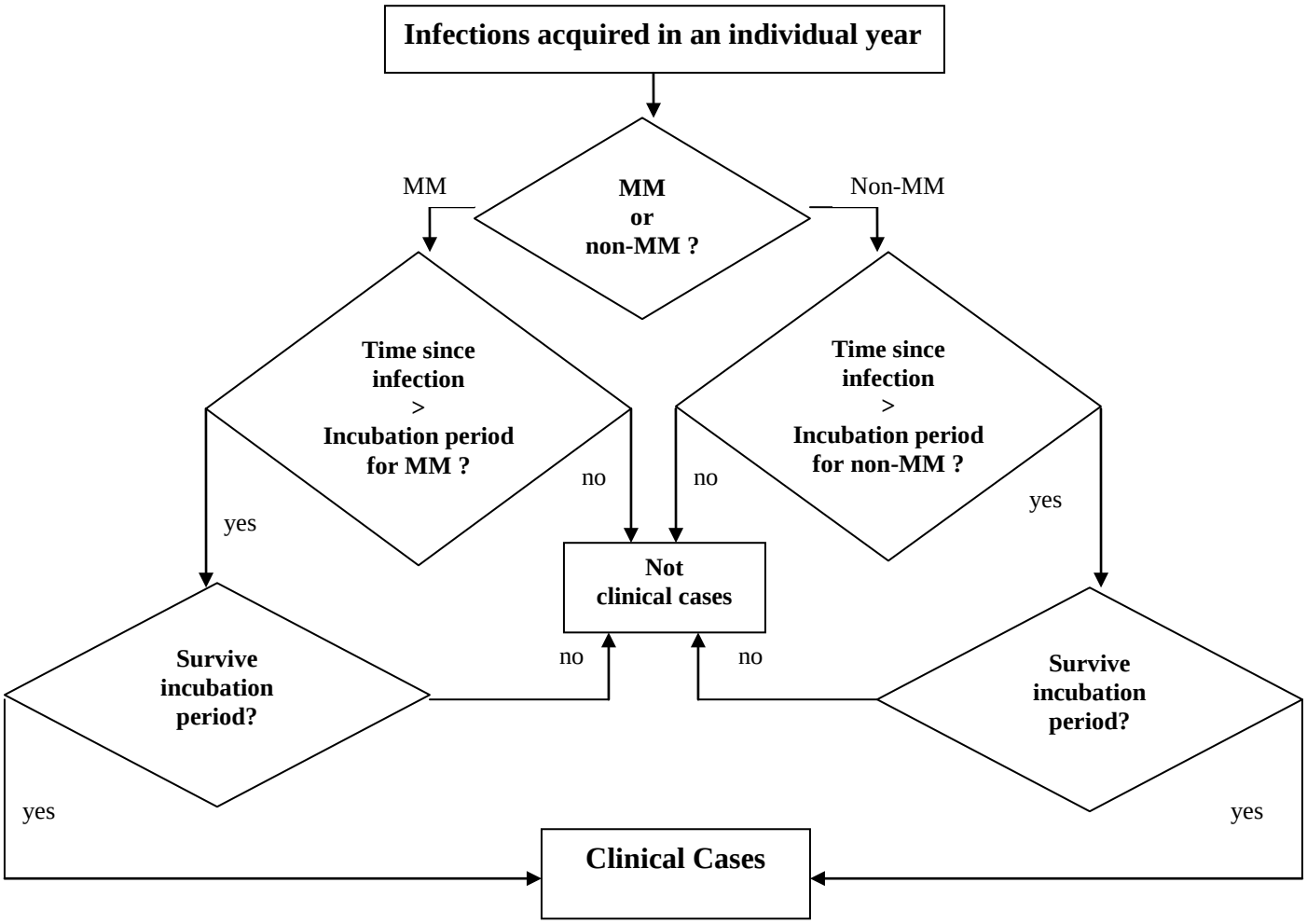
Data: Post-transfusion survival data (Bennett and Daraktchiev, 2011)

Assumption:

- 40% of vCJD infections are associated with MM genotypes and 60% are associated with a non-MM genotype.
- The uncertainty of the incubation period for TTvCJD in persons of the MM genotype is represented using a triangular statistical distribution with a most likely value of 10 years, a minimum value of 6 years, and a maximum value of 20 years.
- The uncertainty of the incubation period for TTvCJD in persons of the non-MM genotype is represented using a triangular statistical distribution with a most likely value of 20 years, a minimum value of 16 years, and a maximum value of 30 years.
- A vCJD-infected person will develop clinical disease only after surviving longer than the incubation period of the disease.

This section of the model calculated the cumulative number of clinical cases observed by 2011 in the U.S. The model used the decision tree described in Figure III-3 to estimate cases that survived longer than the incubation period of the disease and should have been observed by 2011. The computer-based model randomly assigned each infected person generated in previous section (section III. C. 2. a.) for each year between 1983 and 2011 into two groups of genotypes: 40% for MM and 60% for non-MM. The model then randomly selected the length of the incubation period for TTvCJD from statistical distributions that we previously described for persons of MM and non-MM genotypes, calculated the elapsed time from initial time of infection (or time of travel) to 2011, and compared the elapsed time with the incubation period of the disease to determine whether the infection had been incubating long enough to exceed the incubation period of the disease. Finally, a regression model, developed using U.K. post-transfusion survival data (Bennett and Daraktchiev, 2011), was applied to predict the number of infections expected to exceed the incubation period of the disease and so likely progress to overt clinical cases.

Figure III-3. Decision tree for determination of observed clinical cases



IV. RISK CHARACTERIZATION

The risk characterization section of the risk assessment integrates information from the hazard identification, dose-response and the exposure assessment components to provide estimates of the magnitude of the risks posed by a hazard.

IV. A. Model Results:

The final results of the FDA RBC-vCJD risk assessment predict the number of vCJD infections that might have been be transmitted through RBC transfusions in the U.S. in the year 2011 as well as the number of infections that might eventually progress to clinical cases. The risk assessment further estimates a total number of cumulative vCJD infections and clinical cases predicted to have occurred during the years 1980 through 2011. The outputs generated by the model were aggregate distributions generated from thousands of iterations of Monte Carlo simulation, which reflect the underlying uncertainty and variability of the risk outcomes resulting from model inputs and assumptions. The aggregate distributions are summarized using mean values (which are measures of central tendency), and the 2.5^{th} and 97.5^{th} percentile values and are shown in Table IV-1. The output distributions are also shown in the appendix (Figures A1 ―A4).

Using the Low vCJD Prevalence Estimate, the model estimated that the chance of receiving an infected unit in a transfusion is a mean of one in 134 million (Table IV-1). The estimate using the High vCJD Prevalence estimated a mean chance of one in 480,000. The model also estimated an annual risk of zero infections for year 2011 with the Low Prevalence Estimate and six infections when the High Prevalence Estimate was used. To estimate the infections that may develop into clinical cases we adjusted the number of infections to account for incubation period of the disease and post-transfusion survival by recipients. The model estimated the number of infections acquired in 2011 as zero and one clinical cases for the Low and the High Prevalence Estimates, respectively, which represent the current annual risk in the U.S. Furthermore, the model estimated the total number of cumulative infections and clinical cases in the U.S. for the years spanning 1980 through 2011. The model results predicted one infection and zero clinical cases when the Low Prevalence Estimate was used to estimate the cumulative risk, and 210 infections and nine clinical cases when the High Prevalence Estimate was used. If the model results are accurate, the predicted cumulative number of clinical cases between 1980 and 2011 should closely approximate the number of cases that have been reported in the U.S. As of now, no TTvCJD clinical case has been reported in the U.S. The model estimates using the Low Prevalence Estimate appear to reflect reality more accurately, because CDC reports that no cases of TTvCJD have been recognized in the U.S. On the other hand, the result using the High Prevalence Estimate appears to overestimate the risk and to be inconsistent with current epidemiological surveillance that has detected no TTvCJD cases in the U.S.

Table IV-1. Model Results Showing the Mean vCJD Infection Risk per RBC Transfusion, the Mean TTvCJD Risk for the Year 2011 and the Total Mean Cumulative Risk for the Years 1980 Through 2011 in the U.S. (2.5^{th}-97.5^{th} percentiles shown in parentheses).

	Risk per RBC transfusion	Annual risk (2011)		Cumulative risk 1980-2011	
		Infections	Clinical cases	Infections	Clinical cases
Low prevalence (1.7 infections per million)	1 in 134 million (0 to 1 in 8.7 million)	0 (0-0)*	0 (0-0)*	0.8 (0-0)*	0 (0-0)*
High prevalence (493 infections per million)	1 in 480,000 (1 in 4.3 million to 1 in 111,000)	6 (0-27)	1 (0-5)	210 (0-942)	9 (0-47)

*The (2.5^{th}-97.5^{th}) values of (0,0) indicate that the predicted risk is zero or nearly zero. Specifically, for at least 97.5% of the model runs there are zero infections or clinical cases predicted.

IV. B. Model Validation: Model Prediction of primary vCJD cases in the U.S. and comparison to the reported number of cases

As part of the model validation process, we changed or added several data inputs, generating estimates of the number of vCJD cases to compare with epidemiological data; the intent of this exercise was to assess the ability of the model to estimate risk in two situations where the numbers of vCJD cases are already known.

IV. B. 1. Estimation of the number of primary (foodborne) vCJD cases in the U.S.

Assumptions:

- The vCJD prevalence for the U.S. general population is the same as that of the U.S. donor population.
- Five percent of the U.S. population donates blood.
- U.S. risk of primary vCJD increased from zero before 1980 to a maximum risk in 1996. Risk dropped to essentially zero after U.K implementation in 1996 of control measures to prevent materials from infected cattle that may have contained the BSE agent from entering both animal feeds and human food.
- Among vCJD infections, 40% are likely to be in persons having the MM genotype and 60% in persons having a non-MM genotype.
- The incubation period for primary vCJD in an individual of the MM genotype can be represented using a lognormal distribution with a mean value of 15 years, a median value of 12 years, a 5^{th} percentile value of 9 years and a 95^{th} percentile value of 35 years
- The incubation period for primary vCJD in a person having the non-MM genotype was represented in the model using a lognormal distribution with a mean value of 35 years, a

median value of 32 years, a 5th percentile value of 23 years and a 95th percentile value of 55 years

To validate the model, we used it to predict a cumulative number of primary vCJD cases in the U.S. since 1980 and compared the model prediction with cases actually reported. First, we estimated potential number of vCJD infections acquired in each year 1980-2011. We started with model output of number of vCJD-infected donors who presented to donate in 2011 (Table III-5, mean of 0.2 for low prevalence and 41 for high prevalence), and multiplied it by 20 times to arrive potential total infected population in the U.S. in 2011, because approximately 5% (one twentieth) of the general population donates blood each year. We assumed that no infections were acquired after implementation of control measures in the U.K. in 1996 and all infected individuals would have acquired infections during the years1980 through 1996. We allocated the total number of infections to each individual year during that period based on the magnitude of the BSE epidemic in each year as indicated by the proportion of BSE cases reported in each year. The computer then randomly assigned each infection case into two groups of genotypes (40% for MM and 60% for non-MM). The model compared the elapsed time from the year infection was acquired (year of travel) to 2011; the model randomly selected an incubation period and assigned a clinical case of vCJD infection when the elapsed time exceeded the incubation period for that genotype. The final result estimated the number of vCJD cases that should have been reported in the U.S. for travelers infected during travel or residence in the U.K., France and other countries in Europe during the years 1980 through 1996.

Three vCJD cases have been reported in the U.S. Based on history of residency, CDC concluded that all three cases were likely to have acquired the disease while outside the U.S. (CDC, 2010a). The FDA model results predicted a mean of cumulative estimate of one case of vCJD occurring in the U.S. since 1980 when the Low Prevalence Estimate was used and 256 cases when the High Prevalence Estimate (Table IV-2) was used. The model prediction using the Low Prevalence Estimate appears to be consistent with epidemiological reports of cases in the U.S., while the model prediction using the High Prevalence Estimate overestimated the number of cases.

Table IV-2. Observed and model-Predicted Mean Numbers of vCJD Cases in the U.S. (2.5th-97.5th percentiles shown in parentheses)

Observed cases*	**Model Prediction (cases)**	
	Low Prevalence Estimate (1.7 infections per million)	**High Prevalence Estimate** (493 infections per million)
3	1 (0-8)	256 (0-528)

*****Note that CDC attributed all three cases to infection acquired outside of the U.S.

IV. B. 2. & IV. B. 3. Estimation of the number of TTvCJD cases in the U.K. and France and comparison to reported numbers of cases

To evaluate the FDA modeling approach and to assess if it would provide reasonable estimates of TTvCJD cases in the U.S., we replaced the major U.S. data inputs in the model with data inputs for U.K. blood collection and transfusion. We then repeated the same approach using data for France. Finally, we compared the model predictions with epidemiological data on the reported number of vCJD cases in U.K. and France.

Data: Post-transfusion survival data (Bennett and Daraktchiev, 2011)

Assumptions:

- The TTvCJD risk increased from zero before the year 1983 (three-year delay from beginning of BSE), increased in subsequent years and then peaked in 1999 (three-year delay from end of risk period). Since 1999 the risk has remained unchanged in the U.K. and France.
- The annual risk for TTvCJD in the U.K. during the years 1983 to 1999 parallels the BSE epidemic as reflected in reports of the annual numbers of BSE cases (during the years 1980-1996) in the U.K. and accounts for a three-year delay for the start of TTvCJD risk. We assumed the same increasing slope for the annual risk during the years 1983 to 1999 in France.
- Among persons infected, 40% are of the MM genotype and 60% have non-MM genotypes.
- The incubation period for TTvCJD in persons of the MM genotype is represented using a triangular statistical distribution with a most likely value of 10 years, a minimum value of 6 years, and a maximum value of 20 years.
- The incubation period for TTvCJD in persons of the non-MM genotype is represented using a triangular statistical distribution with a most likely value of 20 years, a minimum value of 16 years, and a maximum value of 30 years.
- A TTvCJD infection case can progress into a clinically overt case only when the blood recipient survives longer than the minimal incubation period of the disease.

We modified the FDA RBC-vCJD risk assessment model to predict cumulative TTvCJD cases in the U.K. and France during the years 1980 through 2011 and then compared the model predictions with actual number of TTvCJD cases reported from these two countries. Module 1 of the model remained unchanged, and a 10% relative risk (compared with U.K. risk) was applied to derive the prevalence for France. The model component for estimation of risk of travel exposure specific to U.S. donors in module 2 was removed. In Module 3, we used blood donation and transfusion data from the U.K. and France (Table IV-3) retrieved from websites (see references in Table IV-3). As described in Figure III-2, we assumed that the annual infection rate of TTvCJD in the U.K. and France increased from zero in 1983 to a maximum level in 1999, and then remained at the same level after 1999. The annual infection rates for individual years between 1999 and 2011 were the same as the rate in 2011. The annual rate for individual years between 1983 and 1999 was

proportional to the number of reported BSE cases in each year divided by the total number of infected animals in 1983 through 1999.

Three clinical vCJD cases attributed to blood transfusion have been recognized in the U.K., while no TTvCJD cases have been reported in France to date. The model predicted one and 289 cumulative TTvCJD cases in the U.K. since 1980 and zero and 33 cases in France respectively, using the Low Prevalence Estimate and High Prevalence Estimate assumptions (Table IV-4). Similar to the previous model validation exercise described in the section above, the model predictions derived using the Low Prevalence Estimate were consistent with the number of reported cases while risk estimates based on the High Prevalence Estimate overestimated the numbers of cases reported to date.

Table IV-3. U.K. and France specific data and major model input distributions used in the model validation of TTvCJD predictions. Normal statistical distributions are used where a mean and a standard deviation are provided.

Variable name and description	Input value/distribution	
	U.K.	**France**
N_{DR}: Annual number blood donors	Mean: (b)(4); SD=(b)(4) ((b)(4), 2012) [1]	Mean: 1,582,546; SD: 112,235 (afssaps, 2010) [2]
N_{DN}: Annual number blood donations	Mean: (b)(4); SD=(b)(4) ((b)(4), 2012) [1]	Mean: 2,720,017; SD: 198,825 (afssaps, 2010) [2]
P_{DRa}: Percentage blood donors per age group	Age-group specific percentages (Clarke et al., 2007;ONS, 2013)	Age-group specific percentages (afssaps, 2010)
$N_{DN\text{-}DYa}$: Average number of donations per blood donor per year	Mean=(b)(4); SD=(b)(4) ((b)(4), 2012) [1]	Mean: 1.72; SD: 0.046 (afssaps, 2010) [2]
N_{TF}: Annual number blood transfusions	Point estimate: 430,000 (Clarke et al., 2007;ONS, 2013)	Mean: 490,960; SD=66319.6 (afssaps, 2010)
$N_{U\text{-}TF}$: Number of blood units per transfusion	Mean: 5.7; SD: 0.04 (MHRA, 2012)	Mean: 5.6; SD: 0.04 (afssaps, 2009) [3]

Notes: [1] ----------(b)(4)----------

[2] For N_{DR}, N_{DN}, and $N_{DN\text{-}DYa}$, data of 2003-2009 were used since 2000-2002 data are incomplete.

[3] For $N_{U\text{-}TF}$, data of 2005-2009 were used since 2000-2004 data are not stable.

Table IV-4. Observed and model-Predicted Mean Numbers of TTvCJD Cases in the U.K. and France (2.5^{th}-97.5^{th} percentiles shown in parentheses)

	Observed cases	**Model Predictions (cases)**	
		Low Prevalence Estimate (1.7 infections per million)	**High Prevalence Estimate** (493 infections per million)
U.K.	3	1 (0-7)	289 (3-925)
France	0	0.2 (0-0)*	33 (0-0)*

*The (2.5^{th}-97.5^{th}) values of (0,0) indicate that the predicted risk is zero or nearly zero. Specifically, for at least 97.5% of the model runs there are zero infections or clinical cases predicted

In conclusion, model validation exercises (IV. B. 1 and 2) showed that the FDA RBC risk assessment model using the U.K. Low Prevalence Estimate provided reasonably accurate predictions for primary clinical cases vCJD actually observed in the U.S. to date and of TTvCJD clinical cases in the U.K. and France. Model predictions using the High Prevalence Estimate appeared to over-predict the mean number of clinical cases by approximately 165 fold to 290 fold. These discrepancies derive from the very large difference between the Low and High vCJD Prevalence Estimates.

We offer several biologically plausible explanations for the difference between the Low and High vCJD Prevalence Estimates. First, some individuals may be susceptible to vCJD infection and accumulate abnormal PrP^{TSE} in lymphoid tissues but do not develop clinical disease because of their genetic make up or other unknown reasons. Second, the incubation periods may be very long in some individuals, and some of those individuals may eventually either develop vCJD in the future or may die of other causes before onset of clinical disease. Experimental TSEs in mice and hamsters showed that cross-species infections of lymphoid tissues may not progress readily to brain (Beringue et al., 2012;Collinge, 2012); the same phenomenon might occur in some humans infected with the BSE agent. Third, the tissue survey itself might have overestimated the prevalence of latent vCJD infection in the U.K. population because specificity of the IHC test remains undetermined due to absence negative controls, so that false-positive test results cannot be completely excluded.

IV. C. Importance and Sensitivity Analyses

IV.C. 1 Importance analysis to determine the major risk drivers

An importance analysis was conducted to determine which inputs in the model would have the largest impact on estimates of annual infection risk in 2011. Six input variables used in the RBC-vCJD risk assessment model including: the UK vCJD Prevalence Estimate, Efficiency of Donor Deferral, Incubation Period Primary vCJD for MM genotype, Incubation Period of Primary vCJD for non-MM genotype, and Infectious Dose per Unit of Blood, were included in the analysis. The statistical distributions of these model inputs were generated with assumptions based on limited information for human vCJD, other TSEs or animal models and, therefore, they are less certain than the other model inputs. The importance analysis was conducted using Monte Carlo simulation, sequentially varying one of those inputs by using a low value and then a high value while randomly selecting values of other inputs from statistical distributions. The low and high values of the inputs (shown in Table IV-2) were the 2.5^{th} and 97.5^{th} percentiles of the input distributions used in the FDA RBC-vCJD risk assessment (see Table III-1). The outputs of the Monte Carlo simulation for low and high values of all input variables were aggregated and plotted as a tornado chart (Figure IV-1). Each bar in the chart represents the variation of the model outputs that estimate the annual number of vCJD infections in 2011 when one input is varied from the low to the high value. The tornado chart ranks input variables based on their impacts on risk outcome.

The input variable having greatest impact is represented by the longest bar at the top of the chart, while the input variables with smaller impacts are represented by the shorter bars below.

Table IV-5. Input Variables Included in Importance Analysis

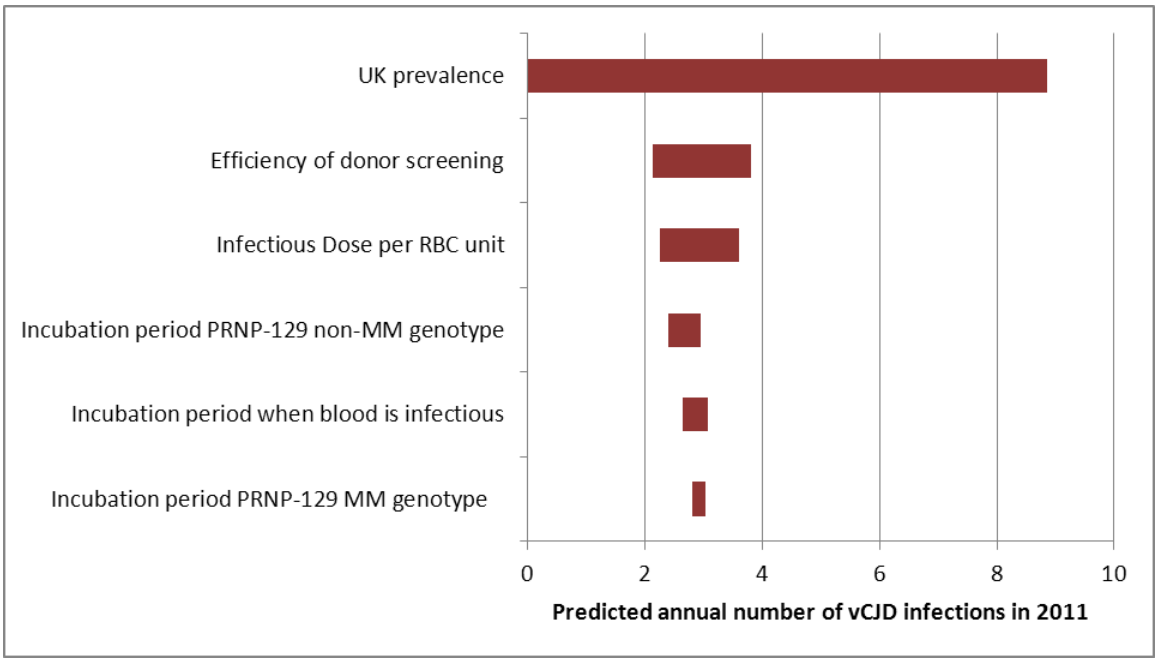
Description of variable	Value for analysis	
	Low value [1]	High value [2]
Prevalence estimates of vCJD in the UK	0.4 cases/million	768 cases/million
vCJD Incubation time for primary case with the MM genotype	8 years	47 years
vCJD Incubation time for primary case with the MV and VV genotype	21 years	62 years
Percentage of late incubation period start having infectious agent present in blood	55%	86%
Efficiency of US donor screening	85%	99%
Infectious doses in RBC unit	0.60	0.91

[1] 2.5th value of input distribution shown in Table III-1

[2] 97.5th value of input distribution shown in Table III-1

The tornado chart from the importance analysis indicated the model input for UK vCJD Prevalence Estimate had the greatest impact on the model estimation of annual number of TTvCJD infections in the U.S. in year 2011. The 2nd and 3rd greatest risk drivers are Efficiency of Donor Deferral and the quantity of the Infectious Dose present in the RBC Unit at the time of transfusion.

Figure IV-1. Importance Analysis: Impact of Input Variables on the Model Outputs for the Annual Number of Infections in U.S. Donors in 2011



IV. D. Uncertainty and Data Gaps

Uncertainty of the final risk estimates (outputs) from probabilistic models generally arises either from incorrect or imprecise model structure or model inputs. When information was absent or limited, we made assumptions based on our best knowledge. In the FDA RBC-vCJD risk assessment model, we used statistical distributions, where possible, to represent the uncertainty of the information used in the model. We express the uncertainty of the final risk estimates generated from the model as an aggregate statistical distribution representing the results of thousands of iterations of the model. The aggregate distribution is described using the mean and 2.5th and 97.5th percentiles of the distribution.

IV. D. 1. Largest source of uncertainty in the model: Estimation of U.K. vCJD Prevalence

The largest source of uncertainty in this RBC-vCJD risk assessment is associated with the estimates of U.K. vCJD prevalence. There is a large discrepancy between the Low and High Prevalence Estimates used in the model, and both prevalence estimates have their limitations. The Low Prevalence Estimate was calculated based on future vCJD cases in the U.K. predicted by an epidemiological model which has limitations. Many of the published models including Garske and Ghani (Garske and Ghani, 2010), Clarke and Ghani (Clarke and Ghani, 2005), and Cooper and Bird (Cooper and Bird, 2003) used simplifying assumptions to generate their predictions. Generally, the types of assumptions used to estimate vCJD cases in the U.K. fall into four areas: (1) estimation of the number of sick and latently BSE-infected cattle slaughtered in the U.K., which was used to estimate the intensity of human exposure to the BSE agent through the human food supply; (2) effectiveness of the 1989 Specified Ban on Offals in human food, which was assumed to reduce the quantity of infectious BSE agent in the food supply, thereby reducing human exposure in the U.K; (3) a mathematical representation (statistical distribution) of the vCJD

incubation period and susceptibility of humans to the disease; and (4) age-specific dependencies that influence exposure, susceptibility to the disease, and incubation period. Although these simplifying assumptions required to estimate vCJD cases, they contribute considerable uncertainty, both individually and in aggregate, to the final case estimates.

The High Prevalence Estimate was calculated using data from an appendix tissue surveillance study. This method also has limitations. First, the prevalence of infection may have been underestimated because the stage of vCJD infection during which abnormal prion protein is detectable in the appendix is not known, and accumulations of PrP^{TSE} are not uniformly distributed throughout the tissue; together those may have led to result some false negative results and underestimates of latent infections. Second, the study design did not permit an estimate of specificity of the method by examining similarly obtained appendices from a population with a negligible-vCJD risk; interestingly, none of the PrP^{TSE}-positive tissue samples has yet been traced back to a patient later confirmed with vCJD (HPA, 2012b). Thus, the possibility of false positives cannot be excluded, which may lead to an overestimation of prevalence. Third, the relationship between accumulation of abnormal prion protein in lymphoreticular tissue and presence of infectivity in the blood and its transmissibility is not clearly established, although, to protect public health, we conservatively assume that the presence of abnormal prion protein in the appendix might indicate a preclinical or subclinical vCJD infection with infectivity in the blood (ACDP, 2012).

To reduce model uncertainties associated with the vCJD prevalence estimates, more studies are needed to address the deficiencies in the data. Many research questions that remain concern the susceptibility of population to infection, incubation period, and disease susceptibility and dependency of incubation period on age and genotype. This information is critical to reconcile discrepant prevalence estimates from the epidemiological model and tissue studies and to determine which of the two prevalence estimates more accurately reflects the real of TTvCJD. Based on results of the FDA model, it seems that the High Prevalence Estimate of vCJD in the U.K. overestimates the actual number of observed cases and the risk to date. On the other hand, the U.K. tissue surveys have provided reasonably consistent results with thousands of samples and cannot be completely discounted. At this time, the FDA believes that the Low Prevalence Estimate for vCJD and its resulting model predictions, while highly uncertain, are consistent with epidemiological data on the reported number of vCJD cases and represent a more reasonable estimate of vCJD risk for U.S. donors and transfusion recipients at the present time.

IV. D. 2. Efficiency of Donor Questionnaire Screening

In the FDA RBC-vCJD risk assessment model, we assumed that the efficiency of donor questionnaire screening ranges from 85% to 99% based on input provided by the TSEAC (TSEAC, 2005;TSEAC, 2006). Because no donor deferral data for vCJD were available, FDA initially made that assumption based on data of on-site deferrals for other transfusion-transmitted diseases, such as HIV, HBV and HCV. FDA consulted the TSEAC (TSEAC, 2005;TSEAC, 2006) and received advice on this assumption, suggesting that a reasonable range for the assumed efficiency of donor questionnaire screening to reduce vCJD risk should be 85% to 99%. This assumption may incorporate a bias potentially leading to an overestimate of the risk, since geographical deferrals do not have the social stigma associated with some of those to reduce HIV, HBV and HCV risk, so potential donors may be more likely to answer travel questions more

truthfully than questions about sexual practices or use of injected drugs. Because of these uncertainties, further studies on the efficiency of donor questionnaire screening based on history of travel and residence are needed.

IV. D. 3. vCJD Dose-Response

Typically, a dose-response relationship is established using data from studies that include graded exposures to multiple doses over a relevant range with a well-defined clinical endpoint for the adverse event of concern. Dose-response data for vCJD in humans are not available. Some animal data are available, but extrapolation of dose-response from animals to humans or from one route of exposure to another is challenging. The input for the quantity of infectious agent in a unit of human RBC used in FDA RBC-vCJD Risk Assessment was based on a statistical analysis of U.K. TMER data (Gregori et al., 2011). Some assumptions were made in this analysis when we back-calculated the number of infections among recipients of infected RBCs. For example, we assumed persons of MM and non-MM genotypes to be equally susceptible to vCJD infection, 40% of RBC recipients to be of the MM genotype, and the incubation periods of TTvCJD in persons of the MM genotype to range from 6 to 9 years. These assumptions were made based on our best knowledge at the time of analysis, but they might not be accurate; uncertainty regarding dose-response also contributes to the uncertainty of the final estimate for the risk of TTvCJD in the U.S.

IV. E. Conclusions

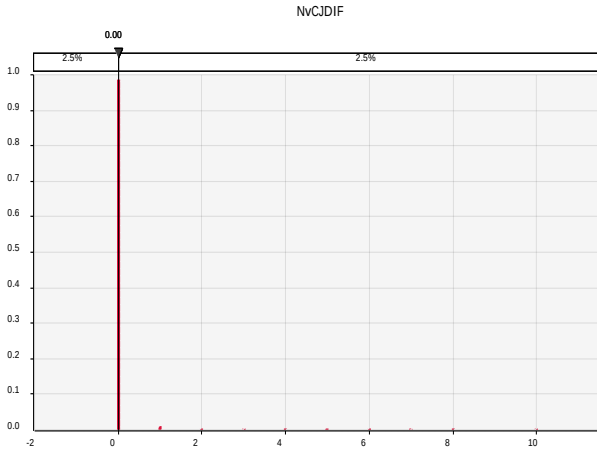
Results from the FDA RBC-vCJD risk assessment model for the Low Prevalence Estimate, while highly uncertain, are consistent with epidemiological data on the reported number of vCJD cases and suggest that the risk of vCJD infection from red cell transfusion is likely to be very small but may not be zero. For U.S. blood donors, the major source of vCJD risk is assumed to result from dietary exposure to the BSE agent during travel to or residence in the U.K., France, or other countries in Europe since 1980. Although donor deferral criteria in place in the U.S. since 1999 have reduced the risk of donation by exposed persons, some potentially at-risk donors may not be deferred and may donate blood and RBCs that contain the vCJD agent. However, the model suggests that the likelihood of collecting an RBC unit from a vCJD-infected donor is small.

It is not possible for the model to provide a *precise* estimate of the vCJD risk for the general population or for individual patients. Although the actual risk is highly uncertain, the risk assessment model indicates that the most important factor affecting risk is the vCJD prevalence in the U.K. population.

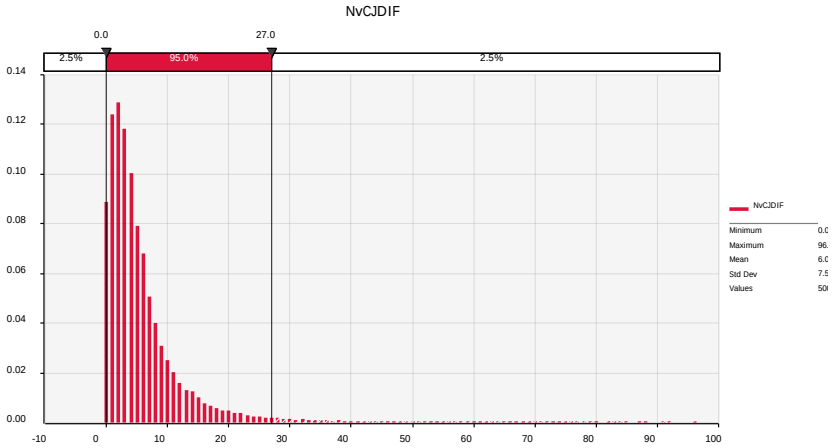
APPENDIX

Figures A-1. Model output distribution for annual number of vCJD infections in the U.S. in 2011 with (a) Low Prevalence Estimate and (b) High Prevalence Estimate

(a)



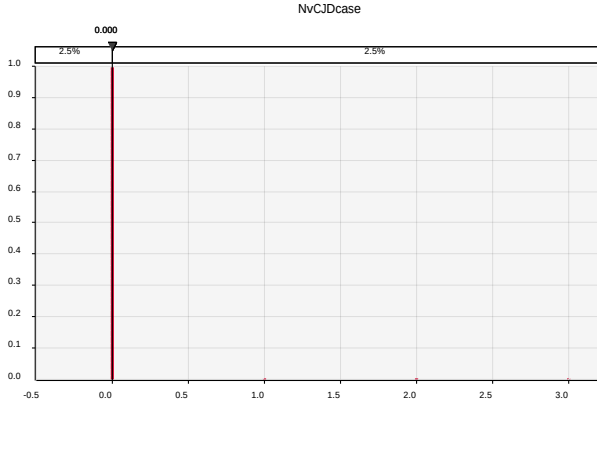
(b)



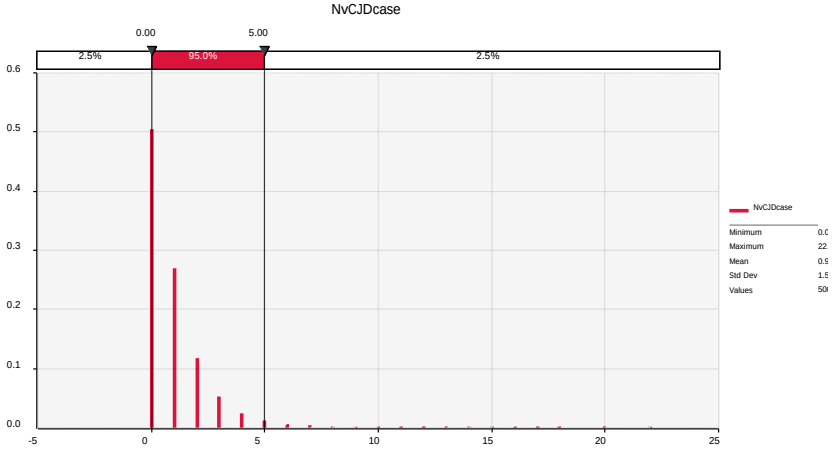
*NvCJDIF = annual number of vCJD infections

Figures A-2. Model output distribution for vCJD infections in 2011 that may lead to clinical cases with (a) Low Prevalence Estimate and (b) High Prevalence Estimate

(a)

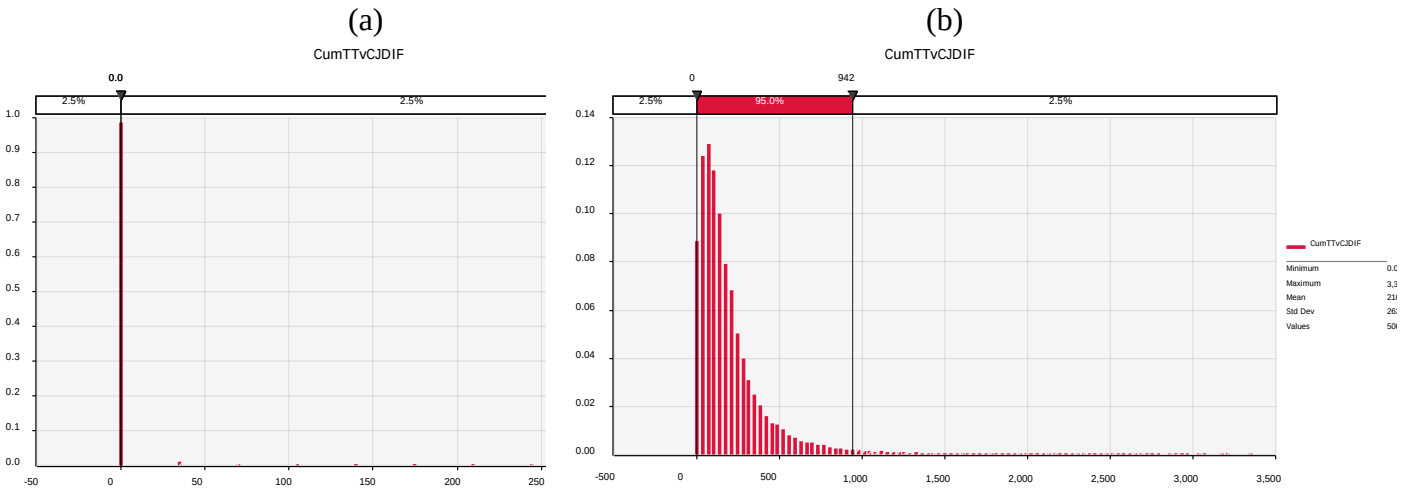


(b)



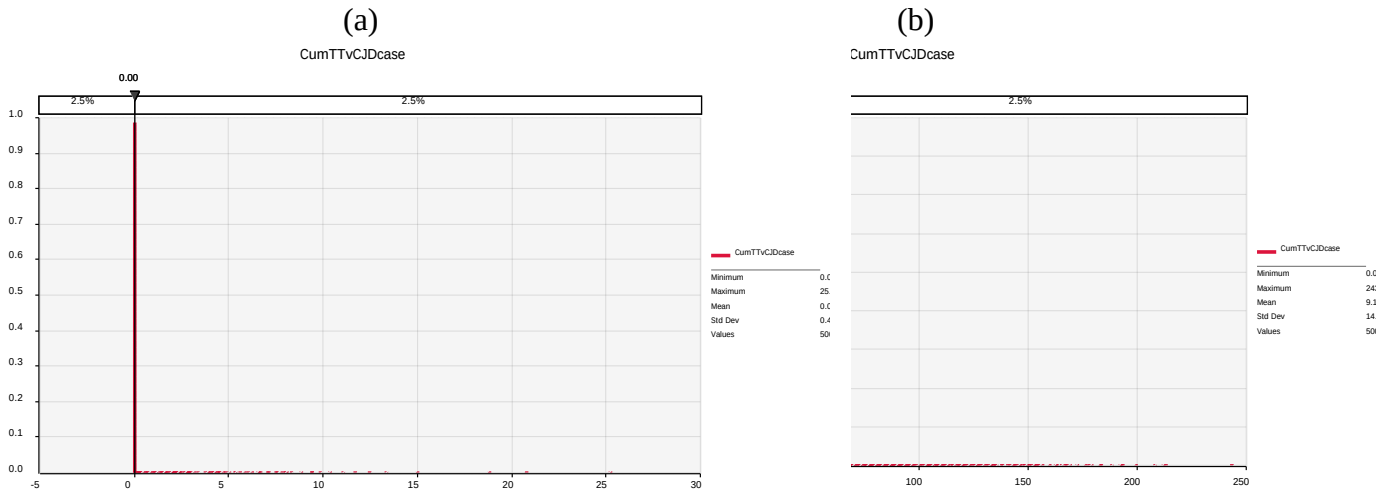
*NvCJDcase = annual number of vCJD infections that may lead to cases

Figures A-3. Model output distribution for cumulative number of vCJD infections in the U.S. since 1980 with (a) Low Prevalence Estimate and (b) High Prevalence Estimate



*CumTTvCJDIF = cumulative TTvCJD infections 1980-2011

Figures A-4. Model output distribution for cumulative number of vCJD clinical cases in the U.S. since 1980 with (a) Low Prevalence Estimate and (b) High Prevalence Estimate



*CumTTvCJDcase = cumulative TTvCJD cases 1980-2011

Literature Cited

ACDP. 2012. Advisory Committee on Dangerous Pathogens (ACDP) TSE Risk Assessment Subgroup Position Statement on occurrence of vCJD and prevalence of infection in the UK population. In.

Afssa. 2007. Opinion of the French Food Safety Agency (Afssa) assessing the effectiveness of the measures taken in November 2000 to control the BSE epidemic. http://www.afssa.fr/Documents/ESST2006sa0329EN.pdf (Accessed on February 12, 2013). In.

afssaps. 2009. Annual Haemovigilance Report 2008. http://ansm.sante.fr/content/download/23651/299890/version/3/file/Haemovigilance-annual-report-2008.pdf (Accessed on January 4, 2013). In.

afssaps. 2010. France Annual Haemovigilance report 2009 Summary. http://www.ansm.sante.fr/var/ansm_site/storage/original/application/f7f46f68337331dab039c08c3c4ff909.pdf (Accessed on January 4, 2013). In.

Almond J, and Pattison J. 1997. Human BSE. Nature 389:437-438.

Alperovitch A, Zerr I, Pocchiari M, Mitrova E, de Pedro CJ, Hegyi I, Collins S, Kretzschmar H, van DC, and Will RG. 1999. Codon 129 prion protein genotype and sporadic Creutzfeldt-Jakob disease. Lancet 353:1673-1674.

Anderson SA, Menis M, O'Connell K, and Burwen DR. 2007. Blood use by inpatient elderly population in the United States. Transfusion 47:582-592.

Andreoletti O, Litaise C, Simmons H, Corbiere F, Lugan S, Costes P, Schelcher F, Vilette D, Grassi J, and Lacroux C. 2012. Highly efficient prion transmission by blood transfusion. PLoS Pathog 8:e1002782.

Belay ED, Sejvar JJ, Shieh WJ, Wiersma ST, Zou WQ, Gambetti P, Hunter S, Maddox RA, Crockett L, Zaki SR, and Schonberger LB. 2005. Variant Creutzfeldt-Jakob disease death, United States. Emerg Infect Dis 11:1351-1354.

Bennett P, and Daraktchiev M. 2011. Blood-borne transmission of vCJD re-examination of scenarios. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_129925 (Accessed on January 4, 2013). In.

Bennett P, and Ball J. 2009. vCJD risk assessment calculations for a patient with multiple routes of exposure. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_100357 (Accessed on March 5, 2013). In.

Beringue V, Herzog L, Jaumain E, Reine F, Sibille P, Le DA, Vilotte JL, and Laude H. 2012. Facilitated cross-species transmission of prions in extraneural tissue. Science 335:472-475.

Boelle PY, Thomas G, Valleron AJ, Cesbron JY, and Will R. 2003. Modelling the epidemic of variant Creutzfeldt-Jakob disease in the UK based on age characteristics: updated, detailed analysis. Stat Methods Med Res 12:221-233.

Brown P, Cervenakova L, McShane LM, Barber P, Rubenstein R, and 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 Creutzfeldt-Jakob disease in humans. Transfusion 39:1169-1178.

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

Bruce ME, Will RG, Ironside JW, McConnell I, Drummond D, Suttie A, McCardle L, Chree A, Hope J, Birkett C, Cousens S, Fraser H, and Bostock CJ. 1997. Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. Nature 389:498-501.

CDC. 2010a. Confirmed Case of Variant Creutzfeldt Jakob Disease (vCJD) in the United States in a Patient from the Middle East. http://www.cdc.gov/ncidod/dvrd/vcjd/other/vcjd_112906.htm (Accessed on January 18, 2013). In.

CDC. 2010b. vCJD (Variant Creutzfeldt-Jakob Disease) Risk for Travelers. http://www.cdc.gov/ncidod/dvrd/vcjd/risk_travelers.htm (Accessed on February 7, 2013). In.

CDC. 2010c. vCJD Cases Reported in the US. http://www.cdc.gov/ncidod/dvrd/vcjd/factsheet_nvcjd.htm#reported (Accessed on February 7, 2013). In.

CDC. 2012. BSE (Bovine Spongiform Encephalopathy, or Mad Cow Disease). http://www.cdc.gov/ncidod/dvrd/bse/ (Accessed on January 3, 2013). In.

CDC. 2013. Bovine Spongiform Encephalopathy and Variant Creutzfeldt-Jakob Disease. http://www2.ncid.cdc.gov/travel/yb/utils/ybGet.asp?section =dis&obj=madcow.htm&cssNav=browsecyb (Accessed on January 3, 2013). In.

CDC. 2013a. National Health Interview Survey. Questionnaires, Datasets, and Related Dcomumentation 1997 to the Present. http://www.cdc.gov/nchs/nhis/quest_data_related_1997_forward.htm (Accessed on March 5, 2013). In.

Cervenakova L, Yakovleva O, McKenzie C, Kolchinsky S, McShane L, Drohan WN, and Brown P. 2003. Similar levels of infectivity in the blood of mice infected with human-derived vCJD and GSS strains of transmissible spongiform encephalopathy. Transfusion 43:1687-1694.

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

Clarke P, Will RG, and Ghani AC. 2007. Is there the potential for an epidemic of variant Creutzfeldt-Jakob disease via blood transfusion in the UK? J R Soc Interface 4:675-684.

Clewley JP, Kelly CM, Andrews N, Vogliqi K, Mallinson G, Kaisar M, Hilton DA, Ironside JW, Edwards P, McCardle LM, Ritchie DL, Dabaghian R, Ambrose HE, and Gill ON. 2009. Prevalence of disease related prion protein in anonymous tonsil specimens in Britain: cross sectional opportunistic survey. BMJ 338:b1442.

Collinge J. 2012. Cell biology. The risk of prion zoonoses. Science 335:411-413.

Collinge J, Whitfield J, McKintosh E, Beck J, Mead S, Thomas DJ, and Alpers MP. 2006. Kuru in the 21st century--an acquired human prion disease with very long incubation periods. Lancet 367:2068-2074.

Cooper JD, and Bird SM. 2003. Predicting incidence of variant Creutzfeldt-Jakob disease from UK dietary exposure to bovine spongiform encephalopathy for the 1940 to 1969 and post-1969 birth cohorts. Int J Epidemiol 32:784-791.

Croes EA, Roks G, Jansen GH, Nijssen PC, and van Duijn CM. 2002. Creutzfeldt-Jakob disease 38 years after diagnostic use of human growth hormone. J Neurol Neurosurg Psychiatry 72:792-793.

de Marco MF, Linehan J, Gill ON, Clewley JP, and Brandner S. 2010. Large-scale immunohistochemical examination for lymphoreticular prion protein in tonsil specimens collected in Britain. J Pathol 222:380-387.

DOD. 2012. Department of Defense (DOD) Personnel $ Procurement Statistics. Military Personnel Historical Reports. Active Duty Military Personnel by Regional Area and by Country. http://siadapp.dmdc.osd.mil/personnel/MILITARY/history/309hist.htm (Accessed on December 19, 2012). In.

Ducrot C, Arnold M, de KA, Heim D, and Calavas D. 2008. Review on the epidemiology and dynamics of BSE epidemics. Vet Res 39:15.

FDA. 1999. Food and Drug Administration. Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products. November 1999. In.

FDA. 2002. 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. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074089.htm (Accessed on December 17, 2012). In.

FDA. 2006a. 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. http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/UCM095104.pdf (Accessed on January 4, 2013). In.

FDA. 2006b. DRAFT Risk Assessment: Potential Exposure to the variant Creutzfeldt-Jakob Disease Agent in United States Recipients of Factor XI Coagulation Product Manufactured in the United Kingdom. http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/UCM095120.pdf (Accessed on January 4, 2013). In.

FDA. 2010a. 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. http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/ucm213415.pdf (Accessed on December 17, 2012). In.

FDA. 2010b. US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research. A 2010 Update of the 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. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/TransmissibleSpongiformEncephalopathiesAdvisoryCommittee/UCM231018.pdf (Accessed on January 7, 2013). In.

Forshee R, and Walderhaug M. 2009. 2009 Joint Statistical Meetings. Washington, DC. Data from Data File Documentation, National Health Interview Survey, 2002-2006 (machine readable data file and documentation). National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland. http://www.amstat.org/meetings/jsm/2009/onlineprogram/index.cfm?fuseaction=abstract_details&abstractid=304401 (Accessed on February 12, 2013). In.

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

Foster PR. 2008. Selection of spiking materials for studies on the clearance of agents of transmissible spongiform encephalopathy during plasma fractionation. Biologicals 36:142-143.

Garske T, and Ghani AC. 2010. Uncertainty in the tail of the variant Creutzfeldt-Jakob disease epidemic in the UK. PLoS One 5:e15626.

Ghani AC, Donnelly CA, Ferguson NM, and Anderson RM. 2003. Updated projections of future vCJD deaths in the UK. BMC Infect Dis 3:4.

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

Gregori L, Yang H, and Anderson S. 2011. Estimation of variant Creutzfeldt-Jakob disease infectivity titers in human blood. Transfusion 51:2596-2602.

Hewitt PE, Llewelyn CA, Mackenzie J, and Will RG. 2006. Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study. Vox Sang 91:221-230.

HHS. 2009. The 2009 National Blood Collection and Utilization Survey Report. http://www.aabb.org/programs/biovigilance/nbcus/Documents/09-nbcus-report-508.pdf (Accessed on February 7, 2013). In.

Hill AF, Desbruslais M, Joiner S, Sidle KC, Gowland I, Collinge J, Doey LJ, and Lantos P. 1997. The same prion strain causes vCJD and BSE. Nature 389:448-50, 526.

Hilton DA, Ghani AC, Conyers L, Edwards P, McCardle L, Ritchie D, Penney M, Hegazy D, and Ironside JW. 2004. Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. J Pathol 203:733-739.

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

Houston F, McCutcheon S, Goldmann W, Chong A, Foster J, Siso S, Gonzalez L, Jeffrey M, and Hunter N. 2008. Prion diseases are efficiently transmitted by blood transfusion in sheep. Blood 112:4739-4745.

HPA. 2006. UK Health Protection Agency. New case of transfusion-associated variant-CJD. CDR weekly 16.

HPA. 2007. UK Health Protection Agency.Fourth case of transfusion-associated variant-CJD infection. Health Protection Report 1.

HPA. 2010. Incidence of variant Creutzfeldt-Jakob disease diagnoses and deaths in the UK. January 1994 - December 2009. http://s3.amazonaws.com/zanran_storage/www.cjd.ed.ac.uk/ContentPages/181148252.pdf (Accessed on December 3, 2012). In.

HPA. 2011a. Incidence of variant Creutzfeldt-Jakob disease diagnoses and deaths in the UK. January 1994 - December 2010. In.

HPA. 2011b. Interim data from the current national survey of abnormal prion prevalence in archived appendix specimens.

http://www.hpa.org.uk/hpr/archives/2011/news3611.htm#cjd (Accessed on December 3, 2012). In.

HPA. 2012a. Incidence of variant Creutzfeldt-Jakob disease diagnoses and deaths in the UK. January 1994 - December 2011. http://www.cjd.ed.ac.uk/documents/cjdq72.pdf (Accessed on December 3, 2012). In.

HPA. 2012b. Summary results of the second national survey of abnormal prion prevalence in archived appendix specimens. http://www.hpa.org.uk/hpr/archives/2012/news3212.htm#bnrmlprn (Accessed on January 20, 2013). In.

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

Ironside JW, Bishop MT, Connolly K, Hegazy D, Lowrie S, Le GM, Ritchie DL, McCardle LM, and Hilton DA. 2006. Variant Creutzfeldt-Jakob disease: prion protein genotype analysis of positive appendix tissue samples from a retrospective prevalence study. BMJ 332:1186-1188.

Kaski D, Mead S, Hyare H, Cooper S, Jampana R, Overell J, Knight R, Collinge J, and Rudge P. 2009. Variant CJD in an individual heterozygous for PRNP codon 129. Lancet 374:2128.

Llewelyn CA, Hewitt PE, Knight RS, Amar K, Cousens S, Mackenzie J, and Will RG. 2004. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Lancet 363:417-421.

Manuelidis EE, Gorgacs EJ, and Manuelidis L. 1978. Viremia in experimental Creutzfeldt-Jakob disease. Science 200:1069-1071.

Mathiason CK, Powers JG, Dahmes SJ, Osborn DA, Miller KV, Warren RJ, Mason GL, Hays SA, Hayes-Klug J, Seelig DM, Wild MA, Wolfe LL, Spraker TR, Miller MW, Sigurdson CJ, Telling GC, and Hoover EA. 2006. Infectious prions in the saliva and blood of deer with chronic wasting disease. Science 314:133-136.

MHRA. 2012. Report on the UK Regulation of Blood Safety and Quality 2005 - 2010. http://www.mhra.gov.uk/home/groups/dts-bs/documents/websiteresources/con146675.pdf (Accessed on January 4, 2013). In.

NCJDRSU. 2013. Twentieth Annual Report 2011. Creutzfeldt-Jakob Disease Surveillance in the UK. http://www.cjd.ed.ac.uk/documents/report20.pdf (Accessed on December 3, 2012). In.

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

OIE. 2012. Number of cases of bovine spongiform encephalopathy (BSE) reported in the United Kingdom. http://www.oie.int/animal-health-in-the-world/bse-specific-data/number-of-cases-in-the-united-kingdom/ (Accessed on December 17, 2012). In.

ONS. 2013. Office for National Statistics. Census 2011 statistics on nomis. http://www.nomisweb.co.uk/census/2011/key_statistics (Accessed on February 19, 2013). In.

Peden A, McCardle L, Head MW, Love S, Ward HJ, Cousens SN, Keeling DM, Millar CM, Hill FG, and Ironside JW. 2010. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. Haemophilia 16:296-304.

Peden AH, Head MW, Ritchie DL, Bell JE, and Ironside JW. 2004. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. Lancet 364:527-529.

Peden AH, Ritchie DL, and Ironside JW. 2005. Risks of transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Folia Neuropathol 43:271-278.

TMER. 2013. Transfusion Medicine Epidemiology Review (TMER). http://www.cjd.ed.ac.uk/TMER/TMER.htm (Accessed on February 12, 2013). In.

Tomasulo A. 2012. French Press Reports New Case of variant Creutzfeldt-Jakob. http://www.healthmap.org/news/french-press-reports-new-case-variant-creutzfeldt-jakob-71112 (Accessed on February 12, 2013). In.

TSEAC. 2005. Food and Drug Administration (FDA) Transmissible Spongiform Encephalopathies Advisory Committee. October 31, 2005 meeting transcript.http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4189t1.htm (Accessed on January 24, 2013). In.

TSEAC. 2006. 2006 December Food and Drug Administration Transmissible Spongiform Encephalopathies Advisory Committee. http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4271t1.pdf (Accessed on December 17, 2012). In.

UK National Statistics. 2006. Travel Trends A report on the 2005 International Passenger Survey. http://www.ons.gov.uk/ons/rel/ott/travel-trends/2005/travel-trends---2005.pdf (Accessed on December 5, 2012). In.

USDA. 2013a. BSE Ongoing Surveillance Program. Bovine Spongiform Encephalopathy (BSE). http://usda.gov/wps/portal/usda/usdahome?contentid=BSE_Ongoing_Surveillance_Information_Center.html (Accessed on February 7, 2013). In.

USDA. 2013b. History of BSE in the United States. http://www.aphis.usda.gov/animal_health/animal_diseases/bse/history.shtml (Accessed on February 7, 2013). In.

USDA. 2013c. Q&A on Bovine Spongiform Encephalopathy (BSE). http://www.usda.gov/wps/portal/usda/usdahome?contentid=BSE_FAQs.xml (Accessed on February 7, 2013). In.

USDA. 2013d. Update from APHIS Regarding Release of the Final Report on the BSE Epidemiological Investigation. http://www.aphis.usda.gov/newsroom/2012/08/bse_update.shtml (Accessed on February 7, 2013). In.

Verity CM, Nicoll A, Will RG, Devereux G, and Stellitano L. 2000. Variant Creutzfeldt-Jakob disease in UK children: a national surveillance study. Lancet 356:1224-1227.

Watanabe K. 2000. Estimates of US Blood Donors Who Traveled/Lived in Countries Exposed to BSE During 1980-1996. TSEAC June 2000. http://www.fda.gov/ohrms/dockets/ac/00/slides/3617s1_09_watanabe.pdf (Accessed on February 7, 2013). In.

Wilesmith JW, Ryan JB, and Atkinson MJ. 1991. Bovine spongiform encephalopathy: epidemiological studies on the origin. Vet Rec 128:199-203.

Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, Poser S, Pocchiari M, Hofman A, and Smith PG. 1996. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet 347:921-925.

Williams A. 2004. Development of FDA Recommendation for Deferral of Donors Based on Risk of BSE Exposure. Presentation in TSE Advisory Committee Meeting, Oct. 2004. http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4075S1_12.ppt (Accessed on December 18, 2012). In.