Results from the Model

While the risk assessment suggests that the possibility of exposure to vCJD in FXI could be potentially significant the actual risk is highly uncertain. One important, highly uncertain parameter in driving the risk assessment results is what estimate is used for vCJD prevalence in the UK. The prevalence of vCJD in the UK population was estimated in the model using two different approaches. The first approach to estimating vCJD prevalence in the UK was from a study based on epidemiological modeling that was derived using actual reported vCJD cases in the UK and an estimate, based on the epidemic, of future vCJD cases (Clarke and Ghani, 2005). Several factors used in epidemiologic modeling approaches are difficult to quantify and add uncertainty to the final estimated number of future vCJD cases. These factors include: the intensity of human exposure to the BSE agent, incubation period, time of infection, and whether illness will develop in individuals who are not homozygous for methionine at codon 129 of PrP. All cases of vCJD to date have occurred in individuals who are homozygous for methionine at this location. Our calculations, based on results from Clarke and Ghani (2005), yielded an estimate of approximately 4 vCJD cases per million. Running the model with this vCJD case prevalence estimate of 4 per million produces an estimate suggesting that, on average, there is a 1.6% likelihood that a plasma pool of 20,000 donations will contain at least one donation from a vCJD-infected individual. Therefore, on average, 98.4% of the time the model predicts the product as administered will contain no vCJD agent and this is reflected in the (0 – 0) values for the 5th and 95th percentiles shown for the lower prevalence estimate results in Table I (below).

However, it is possible that the prevalence of vCJD in the UK is higher than the estimate based on the epidemiological model-based approach noted above. This could happen if there are people infected who never develop the disease (but can still spread the infection) or if some individuals take extremely long to become ill. Therefore, a second approach to estimating vCJD infection prevalence was used based on a relatively small tissue surveillance study by Hilton, *et al* (2004), which tested stored tonsil and appendix tissues from the UK for accumulation of prion protein. It yielded a much higher estimate of 1 in 4,225 (237 infections per million). This study was not controlled using tissues from a non-BSE exposed population, and false positive findings or interpretations from the tissue samples are possible. It is also not known whether the staining of appendicial tissues used in this study is a reliable marker for vCJD pre-clinical infection or for an individual's capability to transmit the infection through blood donation. However, while unconfirmed, the findings from this study provide a higher prevalence estimate and therefore should also be considered. Use of these data as the basis for a vCJD infection prevalence estimate which is then used in the model produces a significantly higher estimate suggesting that, on average, if it were correct, there could be a 50% likelihood that a plasma pool containing 20,000 donations will contain at least one donation from an individual whose blood contains the vCJD agent. (see Sections III. A.1.a.iii and III. A. 1. b. below for a more complete discussion of some of the uncertainties in these prevalence estimates).

Table I – Mean Potential vCJD Risk per Person per FXI Treatment Scenario

		MODEL OUTPUT USING LOWER PREVALENCE ESTIMATE *vCJD Case Prevalence from epidemiological modeling ~4 per million (Clark and Ghani, 2005)*	*MODEL OUTPUT USING HIGHER PREVALENCE ESTIMATE* *vCJD Infection estimate from tissue surveillance study 1 in 4,225 (Hilton et al 2004)*
Scenario	**Quantity* FXI Utilized**	**Mean potential vCJD risk per person **** (5^{th}, 95^{th} perc)	**Mean potential vCJD risk** per person** (5^{th}, 95^{th} perc)
Scenario 1: Treatment 3,000u	3,000 u	1 in 643 (0 - 0)	1 in 17 (0 – 1 in 3.5)
Scenario 2: Treatment 9,000 u	9,000 u	1 in 214 (0 - 0)	1 in 5.6 (0 – 1 in 1.2)
Scenario 3: Treatment 15,000 u	15,000 u	1 in 129 (0 - 0)	1 in 3.4 (0 – 1 in 1)

*u - represents units of FXI

**Mean potential vCJD risk per treatment scenario – the risk of potential vCJD infection based on animal model dose-response information.

Results from the model are presented in **Table I**. The mean potential vCJD risk per person per treatment scenario is based on data derived from rodent animal models. Although we assume that results from the animal model are similar for humans, it is uncertain whether this is the case.

Three scenarios were modeled to depict various plausible levels of utilization of FXI. FXI doses in the literature typically range from 20 – 50 u/kg, and total doses as high as 15,000 u/patient have been administered as the sum of several doses during the postoperative setting, over a period of days. Therefore, Scenario 1 involves the treatment of a 60 kg individual with 20 – 50 u/kg, or a total of 3,000 units given to restore FXI levels to normal. Scenario 2 and Scenario 3 assume a treatment regimen consisting of 9,000 units, and 15,000 units of FXI, respectively.

The model estimates risk ranges from a high in Scenario 3, using the high prevalence estimate, with a mean estimated per person (per treatment course) risk of vCJD infection of 1 in 3.4. The lower end of the range of risk is illustrated in Scenario 1, at the lower prevalence estimate which is based on the current epidemic of disease, with a mean estimated per person (per treatment course) risk of vCJD infection of 1 in 643. It can be seen that in this model that the prevalence estimate may determine whether anyone receiving this product may or may not have been likely to be

exposed to a vCJD risk. It is simply not known at present which prevalence estimate may more accurately reflect the true prevalence of vCJD in the UK.

Readers may notice that the 5th and 95th percentile intervals for all of the model outputs using the lower prevalence estimate are from 0 to 0 meaning that the chance of an infected donor donating to a plasma pool would be an infrequent event. This means that at least ninety five percent of the time the model estimates the risk to be zero because vCJD agent was not present in FXI product vials used during treatment. However, the model predicts that 1.6% of the time the exposure to vCJD may be greater than zero. Although the model suggests that exposure of FXI recipients may have occurred, it is not possible at this time to determine if exposure did in fact occur because of the large variability and uncertainties in the data used in the model.

Conclusions

No UK-manufactured FXI product used in the US under IND from 1989 to 2000 was manufactured from "implicated" plasma pools that were known to have contained plasma from a donor later diagnosed with vCJD. With use of the lower, case-based, prevalence estimate for vCJD of ~ 4 vCJD cases per million, the model predicts that only about 1.6% of plasma pools, on average, might contain the vCJD agent. However, if the higher prevalence estimate, based on a single tissue study, for vCJD in the UK of 1/4,225 is used as a possible higher estimate of the actual vCJD prevalence, the model predicts that most (50%) plasma pools used to manufacture FXI until 1998 could have contained a plasma donation from a person infected with vCJD. Although results of the model suggest there may have been exposure to the vCJD agent, and there could be a potential risk of infection, it is not possible to provide a truly meaningful or accurate estimate of the vCJD risk to individual patients who used FXI manufactured from UK plasma through 2000. Assuming that the UK vCJD prevalence estimate generated from epidemiological modeling is correct, the possibility of exposure and the risk of infection would be considerably lower. Again, although the risk may be low, it is difficult to actually estimate the risk with confidence given the multiple unknowns and uncertainties of the available data used in the model (see sections III.A.1. and IV.D. for discussion). In considering which prevalence estimate is more likely to be correct and in considering in general the risk estimates from the model, it is important to note that to date we are not aware of any cases of vCJD having been reported worldwide in patients receiving plasma-derived products. This includes patients receiving this product as well as patients receiving large amounts of other products manufactured from UK plasma donations over a long period of time. Although the actual risk is highly uncertain, the risk assessment model indicates that the most important factors affecting risk are the clearance of the vCJD agent though manufacturing steps, how much product individuals used, efficiency of the i.v. versus the i.c. route of exposure, and the vCJD prevalence in the UK donor population.

RISK ASSESSMENT

BACKGROUND

FXI

FXI is a clotting factor present in blood plasma that plays a role in the very early stages of the blood coagulation pathway. FXI is normally present in human plasma at concentrations of 50-70 u/dl.

FXI deficiency is a rare bleeding disorder first described in the 1950s. Unlike hemophilia A or B, it is an autosomal bleeding disorder that affects both genders equally. Generally, bleeding in patients with FXI deficiency is less severe than with hemophilia A or B and does not usually involve joints or muscles, or spontaneous bleeding in those areas (http://www.hemophilia.org/bdi/bdi_types9.htm). FXI deficiency is usually categorized as severe or partial. Those with severe deficiency have FXI levels below 15 u/dl and are at high risk of excessive bleeding if injured, or after surgery or dental extractions. Medical intervention that brings FXI levels to the 50 u/dl to 70 u/dl range is recommended (BPL, 2001) prior to surgical procedures on severely deficient patients.

FXI, manufactured from UK donor plasma collected through 1997, was used by a small group of patients in several IND studies in the US between 1989 and 2000, and this risk assessment estimates the potential exposure to vCJD agent via that product. Currently, in the United States where there is no commercially licensed FXI product; clinicians typically utilize Fresh Frozen Plasma from US donors, and/or antifibrinolytic agents for therapy.

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, the scientific literature, government reports and other credible or peer-reviewed sources of data that establish a causal relationship between the hazard and adverse effects on humans. To date, no epidemiological evidence suggests that vCJD has been transmitted by plasma derivative products.

A new human variant of Creutzfeldt-Jakob disease (vCJD) was first described in the UK in 1996. As of August 2006, 195 cases worldwide have been reported including 162 in the UK (United Kingdom National CJD Surveillance Unit, August 2006).

Both vCJD and BSE belong to a class of diseases known as transmissible spongiform encephalopathies (TSEs). The leading theory concerning the agent responsible for infection is that of a proteinaceous infectious agent, or "prion," that originates in the misfolding of a ubiquitous prion protein (PrP) normally expressed in many cells. The altered PrP, which is now suggested to be designated as PrP^{TSE}, (World Health Organization Guidelines, 2006, also known as PrP^{res}, or PrP^{Sc}) is highly stable and resistant to degradation by high heat and many chemical treatments commonly used to denature proteins. The incubation from the time of exposure to TSEs to the

development of symptoms of disease is long. For example, the mean incubation period for BSE in cattle (interval between first exposure to contaminated feed and onset of illness) has been estimated at about 5 years, and that for food-borne vCJD is estimated to exceed 10 years. Individuals become symptomatic with vCJD only in the last few months of life, making early detection very difficult. Confirmatory diagnosis of vCJD requires postmortem examination of brain tissue. However abnormal prion protein has been detected in some antemortem tonsil biopsies early in clinical illness, and in an archived appendix sample from an asymptomatic individuals several months prior to the onset of symptoms (Hilton *et al* 1998). There are currently no validated tests available to detect the vCJD infectious agent in early stages of infection or to detect the presence of TSE agents in blood.

I.A. Transmission of TSEs through transfusion of blood products in animal models

Transmission of different TSE agents through the transfusion of blood or blood products has been demonstrated in animal models on multiple occasions. At least four studies reported transmission via blood transfusion in the same animal species: sheep experimentally infected with BSE (Houston *et al* 2000) and naturally infected with scrapie (Hunter *et al* 2002), and experimentally infected rodents (hamsters with scrapie and mice with a human TSE) (Rohwer 2004, Brown *et al* 1999).

Brown, Rohwer, Taylor (Taylor *et al* 2000) and others have attempted to estimate the amounts of intracerebral (i.c.) infectivity present in blood, which generally fell between 2 and 20 i.c. ID_{50}/ml. A recent study of scrapie-infected hamsters concluded that approximately 58% of the infectivity present in whole blood was associated with plasma (Gregori *et al* 2004). The model uses this more conservative estimate in the published literature and assumes that 58% of infectivity is associated with plasma.

I. B. Transfusion transmission of vCJD in the UK

In December 2003 the UK government announced that vCJD had likely been transmitted to a 69 year-old patient via blood transfusion. The patient had received non-leukoreduced red blood cells in 1996 from a donor who died three years later of vCJD. This first report was followed by the announcement in July 2004 of another probable case of transfusion-transmitted vCJD. The patient died of a ruptured aortic aneurysm without clinical evidence of vCJD, but postmortem testing detected PrP^{TSE} in spleen tissue and cervical lymph node. In February 2006 a third case of probable transfusion transmitted vCJD was reported in the UK in a 31 year-old male; the patient had received a transfusion eight years earlier from a donor who died of vCJD 20 months after donation. None of the donors were known to have had vCJD at the time of donation.

It is possible that dietary exposure may have been responsible for some or all of the three cases that were reported after red blood cell transfusions. However, the probabilities for occurrence of either a single, or, particularly, two or three such events are small. As Llewelyn *et al* (2004) pointed out in their publication discussing the first presumed transfusion-transmitted case "the age of the patient was well beyond that of most vCJD cases, and the chance of observing a case of vCJD in a recipient in the absence of transfusion transmitted infection is about 1 in 15,000 to 1 in 30,000." The combined probability that the first two transfusion cases both acquired infection

from food, identified in two elderly patients in a small cohort of transfusion recipients in an age group underrepresented among vCJD cases, is remote.

The presumptive transmission of vCJD via red blood cell transfusion in the UK raises the possibility that plasma derivatives may pose a risk, based on the finding in animal models that plasma contains the infectious agent when blood is infectious. The UK authorities have notified physicians in the UK and their patients who received plasma derivatives made from plasma from UK donors about the potential for risk of vCJD from these products. These plasma derivative products included coagulation factors, as well as antithrombin III, and intravenous immune globulins. The derivatives of concern were manufactured from plasma of UK donors between 1980 and late in 1999, when--consistent with a decision announced in 1998—UK manufacturers stopped using UK plasma. The last expiry date for any of the UK products was in 2001. To date, no cases of vCJD have been reported in any recipients of plasma derivatives, either in the UK, where the risk is considered greatest, or elsewhere, including in patients who have received human plasma-derived coagulation products from implicated lots (i.e. lots that were later found to contain donations from people who later developed vCJD) made in the UK.

This risk assessment examines the possible exposure to vCJD agent and the risk of vCJD infection for FXI manufactured from UK plasma between 1989 and 1997 and used by a small group of patients in several IND studies in the US between 1989 and 2000.

II. HAZARD CHARACTERIZATION

The hazard characterization component (also known as dose-response) relates the information in the exposure assessment, which determines the dose, to the adverse consequence(s) such as infection, illness, etc., at the individual, subpopulation, or population level. Determining dose-response relationships can be difficult to accomplish because data are limited, especially exposure and outcome data for humans. Other factors such as characteristics of the hazard (e.g. strain, chemical make-up, etc.), route of introduction, and genetics of exposed individuals, influence the dose-response relationship but are often difficult to characterize. Often in lieu of human data, animal data are used and appropriately extrapolated as best as is possible to estimate the dose-response relationship for humans.

The rodent animal models drawn on for this risk assessment on vCJD risks use other TSE agents such as the scrapie agent – hamster model used by Rohwer (2004) and the CJD agent-mouse model used by Brown (1998, 1999). Brown (1998, 1999) and Rohwer (2004) use the metric of infectious unit (IU), which is the minimal amount of any inoculum required to initiate an infection in 100% of the rodent population using the intracerebral (i.c.) route of introduction. The FDA model assumes that this infectious unit is equivalent to two ID_{50}s which assumes the two metrics are linearly related, further adding to the uncertainty of the model.

Another challenge is estimating the probability of infection when the exposure to TSEs is small and/or occurs repeatedly over a period of time. It is unknown whether, for TSE diseases there is a minimal amount of the agent (presumably the prion protein PrP^{TSE}), or threshold that is needed to initiate infection in an individual, such as is seen with many other pathogens such as viruses or bacteria, for which infection requires exposure to at least one, and often more, units of the infectious agent. Furthermore, it is not known whether the effects of small multiple exposures

over a period of time are cumulative and may result in the possibility of infection and disease equivalent to a single, larger exposure (e.g., via intracerebral injection in laboratory animals). Some risk assessments have made assumptions concerning the exposure and dose for TSE agent that lead to infection. For instance, the Det Norske Veritas (Feb 2003) blood products risk assessment assumes that exposure to infectivity, quantified in ID_{50} units, is cumulative over the period of one year. Based on advice from the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) (2005), and consistent with suggestive data from studies of TSE agents in animal models (Diringer *et al* 1998, Jacquemot *et al* 2005), FDA also assumes that exposure to vCJD ID_{50} is cumulative over a one year period. The ID_{50} is the common metric used to quantify the infectivity of TSEs. One ID_{50} is defined as the amount of infectious material or tissue that is necessary to initiate infection in 50% of the treated population. The route of exposure to TSE infectious material influences the efficiency of transmission of the disease. Based on advice provided to FDA by the TSEAC (October 31, 2005) the model assumes that transmission via the intravenous (i.v.) route is between 1 and 10 times less efficient than the transmission via intracranial (i.c.) route.

In estimating the dose-response relationship for TSEs one could use a strict interpretation of the ID_{50} and assume a linear relationship between exposure and infection. In the FXI model FDA assumed there was a linear relationship between the exposure dose of vCJD agent and the probability of infection. The ID_{50} relationship used in the model was based on infectious TSE units estimated from rodent model studies (Brown 1998, 1999; Rowher 2004). We further assumed there was no threshold or minimum dose necessary to initiate infection, that is, exposure to even low quantities of vCJD agent have a probability of initiating infection in an individual, albeit the probability of infection would likely be low at low levels of exposure. The model further assumes that in such a case exposure to 1 ID_{50} would suggest a 50% probability of infection, exposure to 0.1 ID_{50} would suggest a 5% probability of infection, and so on. However, given the lack of information and high degree of uncertainty on the dose-response relationship because of the limited data available for TSE agents it is plausible that low level exposures, even on a chronic basis, may not attain a threshold or minimum quantity of agent necessary to initiate infection in humans. Again, FDA makes a conservative assumption that low-level exposure(s) over the period of one year to any quantity of vCJD agent could potentially lead to infection and that there is not a minimum dose necessary to initiate infection.

There are considerable uncertainties in determining the correct form for the vCJD-human dose-response model. For instance, the nature of the dose-response line, its slope, or whether it is more accurately described using a dose-response curve is uncertain because animal data are so limited and human data are not available. The FDA risk assessment estimates the potential individual risk of infection and assumes that a linear interpretation of the rodent model accurately reflects the pathology and progression of vCJD infection and disease in humans, but it may not. Furthermore, exposure to the vCJD agent may not necessarily lead to infection, and vCJD infection may not necessarily produce symptomatic vCJD disease or illness in an individual or population.

III. EXPOSURE ASSESSMENT

Exposure assessment evaluates the routes of exposure to a hazard, the probability that exposure occurs and the amount of a hazardous agent to which a person or population may be exposed. This exposure assessment specifically addresses exposure to the vCJD agent that may have been present

in FXI manufactured in the UK and administered to US patients during clinical studies under several IND applications. The administration of FXI, and thus the route of exposure, is intravenous and used in the clinical prophylactic treatment of individuals prior to surgery and after surgery to control bleeding.

Pools consisting of 20,000 or more plasma donations collected from UK plasma donors were used as the starting material from which FXI was purified. Because of the number of donations per plasma pool and the prevalence of vCJD in the UK population, it is possible that some plasma pools may have contained one or more plasma donations from asymptomatic donors unknowingly infected with vCJD.

Overview of Model

Figure 1 depicts the major elements and some of the types of input data and information used in the FDA FXI – vCJD risk assessment. Module A (vCJD ID_{50} per plasma pool) uses two different estimates of UK vCJD prevalence. The first is a vCJD case prevalence based on epidemiological modeling of actual reported cases in the UK and an estimate of future vCJD cases (Clarke and Ghani, 2005), which yielded an estimate of approximately 4 vCJD cases per million. Limitations associated with estimates of future vCJD cases and vCJD incidence in the UK generated by epidemiological modeling based on the current reported vCJD cases are described in section A.1.a. The second is a vCJD infection prevalence based on a tissue surveillance study by Hilton *et al* (2004), which yielded an estimate of 1 in 4,225 (237 infections per million) which represents a possible higher prevalence scenario. However, there are limitations to using the Hilton et al tissue surveillance study in estimating vCJD prevalence and those are described in section A.1.b.

After accounting for the age distribution and/or incubation period of possible vCJD cases, these prevalence estimates are used to predict the number of vCJD donations that could be present in a plasma pool of 20,000 donations. After adjusting for the relative efficiency of intravenous and intracerebral administration, the output of this module is an estimate of the vCJD i.v. ID_{50} per plasma pool. Module B approximates the reduction of vCJD agent during manufacturing. The model estimates a reduction of between 0 and 4 $\log_{10}$ (10,000 fold) in the amount of agent with a most likely level of reduction of 2 $\log_{10}$ (100 fold). The output of this module is an estimate of the ID_{50} per vial of FXI. Module C (Dose for Pre- / Post- surgical treatment) estimates utilization of FXI by patients. Estimates for potential exposure and potential vCJD infection risk were generated by the model for three possible clinical treatment scenarios.

Revisions of the February 8, 2005 FDA DRAFT Factor XI – vCJD risk assessment and model

FDA presented the first version of the risk assessment: "Draft Risk Assessment: Potential Exposure to the vCJD agent in United States recipients of Factor XI coagulation product manufactured in the United Kingdom" at the February 8, 2005 meeting of the TSEAC for review and comment. The risk assessment model predicted that recipients of UK manufactured FXI may have potentially been exposed to the vCJD agent. On October 31, 2005 FDA sought advice from the TSEAC and discussion on several risk assessment model inputs for plasma derivatives and potential vCJD risks. This newly updated, second iteration of the FDA Draft FXI vCJD risk assessment incorporates many of the comments and much of the advice provided by the TSEAC at the February 8, 2005 and October 31, 2005 meetings, and more recently by FDA staff and peer reviewers (revisions summarized in Table 1).

Figure 1. Model of Exposure Assessment

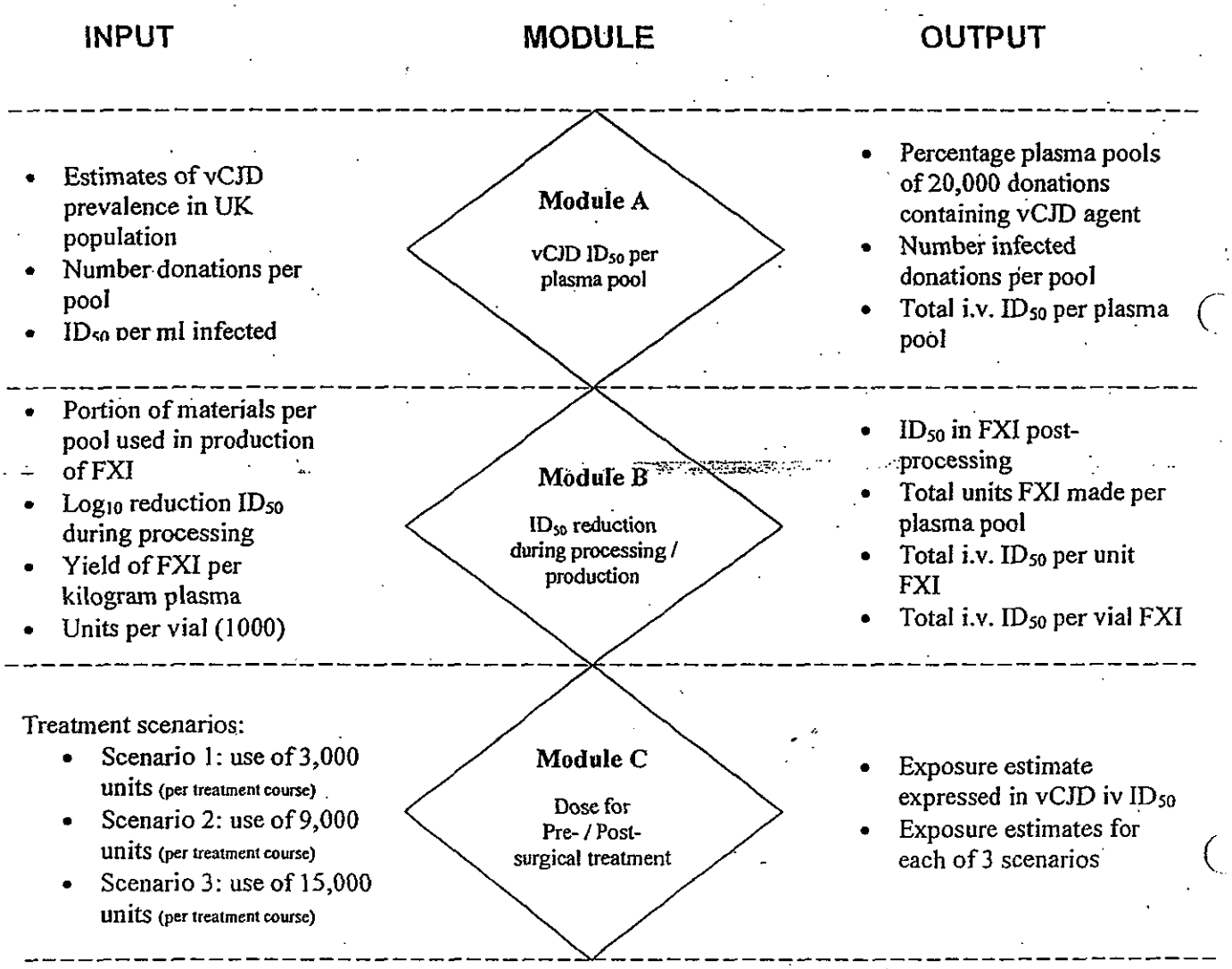

Table 1. FXI Model Input Changes from February 2005 to September 2006

	Model: Presented before TSEAC February 8, 2005 **Document:** Draft Risk Assessment: Potential Exposure to the vCJD Agent in United States Recipients of FXI Coagulation Product Manufactured in the United Kingdom	**Model: Revised September 2006** **Document:** FDA Draft Risk Assessment: Potential Exposure to the variant Creutzfeldt-Jakob Disease Agent in United States Recipients of FXI Coagulation Product Manufactured in the United Kingdom
Input Parameter Name and description	**Data and Parameters**	**Data and Parameters** TSEAC provided advice on vCJD and plasma derivatives at the October 31, 2005 meeting
UK vCJD Prevalence	Prevalence: **1 in 4,225** The UK vCJD Infection prevalence based on Surveillance study of tonsils /appendices samples from patients mostly 20 – 30 yrs of age *(Hilton et al 2004)*	Use two separate prevalence estimates: 1) HIGHER prevalence estimate – of UK vCJD Infection prevalence was based on Surveillance study tonsils/appendices of **1 in 4,225** *(Hilton et al 2004)* 2) LOWER prevalence estimate – vCJD Case prevalence estimate based on predictive modeling estimates - implies prevalence of **~4 vCJD infections per million** *(based on Clark and Ghani, 2005)*
Tissue surveillance or vCJD Infection prevalence: adjustment for donor age	No age adjustment was made. Prevalence based on surveillance study of tonsils /appendices samples from patients mostly 20 – 30 yrs of age was used.	Prevalence adjusted based on: 1) Age of donor population 2) Age information of reported vCJD cases
Time during incubation period when infectivity is present in blood	Infectivity assumed to be present **throughout the entire incubation period**	Infectivity assumed to be present only during **last half of incubation period**
Quantity of infectivity present in blood	Distribution: Triangular Minimum: **0.1** Most likely: **10** Maximum: **1,000** i.c ID50/ml	Distribution: LogNormal Minimum: **0.1** 5th percentile: **2** Median (50th perc): **12** 95th percentile: **30** Maximum: **1,000** i.c ID_{50}/ml
Adjustment for efficiency of transmission via intravenous (i.v.) versus intracerebral (i.c.) exposure	**0.5 -1**	**0.1 - 1**

III. A. Probability of donation containing vCJD infectivity and the total quantity of intravenous vCJD infectivity (i.v. ID_{50}) per plasma pool

Potential exposure to vCJD infectivity via UK manufactured FXI is a function of the probability that a plasma pool contains a donation with vCJD agent and the quantity of agent present in the donation and the larger assembled plasma pool. Prevalence of vCJD in the UK population directly influences the probability that a donation with vCJD agent will be present in a plasma pool.

III. A.1. Estimation of UK vCJD prevalence via two methods

The potential prevalence of vCJD in the UK was and continues to be dynamic and changes over time as people are exposed to the BSE agent, potentially infected with vCJD, develop the disease and eventually die. Variant CJD exposure and infections in the UK population likely occurred in proportion to the UK BSE epidemic which peaked in 1992. The first human vCJD cases were referred to UK public health authorities in 1994. To date, the number of cases in the UK reached a maximum of 28 in the year 2000, and since then has been declining annually with a total of 5 deaths in 2005. During the manufacture of FXI in the UK from plasma collected as late as 1997, the prevalence of human vCJD was likely higher than it is today in 2006 since exposure to BSE agent has ebbed and deaths of infected individuals lower the total number of infected persons. As of August, 2006 the UK recorded a total of 162 cases of definite or probable vCJD (CJD Surveillance Unit, 2006). However, the disease is likely to still be present in at least some members of the population as pre-clinical and asymptomatic infections. Most known infections and deaths have occurred in individuals who are homozygous methionine, or MM, at codon 129 of the PrP gene product. Prion positive tissue has been observed in individuals who are heterozygous methionine and valine (or MV) or homozygous valine (VV) at codon 129 (also called non-MM individuals) but to date none have developed symptoms and died of vCJD. Whether non-MM individuals will become symptomatic with vCJD or are capable of transmitting the disease is unknown.

In the scientific literature estimates of the rate of incubating vCJD cases in the UK have been derived from two potential sources: (1) epidemiological modeling studies based on the actual number of reported vCJD cases, and (2) a single study of surveillance testing for possible vCJD related protein accumulation, in tissues such as tonsil and appendix, which may or may not indicate a vCJD infectivity risk. This risk assessment used prevalence estimates derived both from the results of the appendix surveillance study, which yielded a vCJD prevalence estimate that may be representative of a possible higher prevalence scenario for potential vCJD infection, and from the epidemiological model, which yielded a lower vCJD prevalence estimate of potential vCJD cases based on a number of assumptions.

These estimates were used independently to generate two distinct estimates for UK vCJD prevalence for use in the model. Prevalence estimates derived from each data source are dramatically different. The mean vCJD case prevalence estimated using an epidemiological approach based on actual cases and projected case numbers, 4 infections per million people, is approximately 60 times lower than the mean infection prevalence estimated based on the study of tissue surveillance, 1 in 4,225. The data used to generate each prevalence estimate have limitations and uncertainties that contribute to the pronounced difference and uncertainty between the prevalence estimates, as noted above and cited below.