The probability of either a vCJD donation being present in a Source Plasma pool is represented by the variable $Pr(vCJD\text{-}pool_S$ and the probability of a vCJD donation being present in a recovered plasma pool is represented by the variable, $Pr(vCJD\text{-}pool_R$, which was calculated in the section above. A discrete distribution (X1, X2; p1, p2) represents two discrete values for the probabilities that a pool may contain a vCJD donation, X1(or $Pr(vCJD\text{-}pool_S)$ and X2 (or $Pr(vCJD\text{-}pool_R)$ and the associated probabilities of each value occurring with the probabilities, p1 and p2, respectively. Based on the assumptions above that Source Plasma pools are used more frequently in the manufacture of pdFVIII and, on average contain fewer donations, the probability of a Source Plasma pool containing vCJD agent is different from the probability a recovered plasma pool containing vCJD agent. Overall probability of a single plasma pool (including source and recovered plasma pool) containing vCJD agent is a probability weight based on the percentages of the two types of plasma pools [redacted] for Source and [redacted] for recovered plasma pools) used to make pdFVIII. $Pr(vCJD\text{-}pool)$ is sampled from $Pr(vCJD\text{-}pool_S$ and $Pr(vCJD\text{-}pool_R$ using the discrete distribution:

$$\Pr(vCJD-pools) = Discrete(\,Pr(vCJD\text{-}pool\text{-}s),\ Pr(vCJD\text{-}pool\text{-}R);\ Perc_S,\ Perc_R)\,) \qquad \text{(IV.C.5-3)}$$

or

$$\Pr(vCJD-pools) = Discrete(\,Pr(vCJD\text{-}pool\text{-}s),\ Pr(vCJD\text{-}pool\text{-}R);\ \text{[redacted]}\ \text{[redacted]}\,)$$

A-IV. D. Annual total number of all plasma pools and number of plasma pools potentially containing a vCJD donation that are used to make pdFVIII in the US

A-IV. D.1. Annual amount of pdFVIII distributed in the US

Variable: IU_{FVIII} -Annual number of all units of human pdFVIII manufactured and distributed in the US .

Data used in the model: Based on data provided to FDA from manufacturers, a total of [redacted] million units of pdFVIII was made and distributed in the US.

Variable: $Perc_s$ – Represents the percentage of pdFVIII assumed in the model to be made from <u>Source Plasma</u> (same as variable used in A-IV. C. 5. b.)

Variable: $Perc_R$ – Represents the percentage of pdFVIII assumed in the model to be made from recovered plasma (same as variable used in A-IV. C. 5. b.)

Variable: $IU_{FVIII\text{-}S}$ –The total annual number of units of pdFVIII made from <u>Source Plasma</u> and is represented by the equation:

$$IU_{FVIII-S} = IU_{FVIII} \times Perc_s \qquad \text{(IV.D.1-1)}$$

Variable: $IU_{FVIII\text{-}R}$ -The total annual number of units of pdFVIII made from recovered plasma and is represented by the equation:

$$IU_{FVIII-R} = IU_{FVIII} \times Perc_R \qquad \text{(IV.D.1-2)}$$

A-IV. D. 2. Annual total number of all plasma pools used to make pdFVIII and plasma pools with vCJD agent

The total number of plasma pools used to make pdFVIII in the US each year can be back-calculated from the total number of units of human plasma-derived pdFVIII distributed in the US each year. Based on information described in earlier sections, it was assumed that approximately [redacted] of the total pdFVIII supply distributed annually in the US is manufactured from Source Plasma and [redacted] from recovered plasma pools. Information on pool size (number of donors), average number of donations per donor, size of individual recovered plasma donations (200 mls) and Source Plasma donations (700 mls) were used to first determine the amount of plasma present in a pool. Then, data on the average yield of pdFVIII per liter of plasma (187 IU), was used to calculate the total number of Source and recovered plasma pools and the results were summed to determine the total number of plasma pools used to manufacture pdFVIII in the US each year. The total number (or percentage) of plasma pools potentially containing vCJD agent was determined in the model based on pool size and the probability that a pool contained a vCJD agent.

A-IV. D. 2. a. Amount plasma per pool

Variable: DN_{V-s} – Volume of single unit Source Plasma (ml).

Variable: DR_{pool-s} – Number donors per Source Plasma pool (same variable as used in A-IV.C. 5).

Variable: $Freq_{DN-S}$ –Average frequency of donations from a single Source Plasma donor that contribute Source Plasma for pdFVIII manufacture (same variable as used in A-IV.C. 3).

Variable: V_{pool-S} – Volume of a Source Plasma pool (ml).

$$V_{pool-S} = DR_{pool-S} \times Freq_{DN-S} \times DN_{V-S} \quad \text{(IV. D. 2-1)}$$

Variable: DN_{v-R} – Volume of single unit recovered plasma (ml).

Variable: DR_{pool-R} – Number donors per recovered plasma pool (same variable as used in A-IV.C. 5. a.)

Variable: $Freq_{DN-S}$ –Average frequency of donations from a single recovered plasma donor that contribute recovered plasma for pdFVIII manufacture (same variable as used in A-IV.C. 3)

Variable: V_{pool-S} – Volume of a recovered plasma pool (ml)

$$V_{pool-R} = DR_{pool-R} \times Freq_{DN-R} \times DN_{V-R} \quad \text{(IV. D. 2-2)}$$

A-IV. D. 2. b. Annual number of plasma pools used to manufacture pdFVIII in the United States

Variable: $IU_{FVIII-S}$ -Annual units of pdFVIII made from Source Plasma (calculated in A-IV. D. 1)

Variable: Y_{avg} –Average yield of pdFVIII (IU/L plasma)

Assumption used in the model: Based on the data provided by WFH (1998) and FDA-CBER (2003) we assumed average yield of pdFVIII (including high purity and intermediated purity pdFVIII) being 187 IU per liter plasma.

The total number of Source Plasma pools and recovered plasma pools used each year in manufacturing US pdFVIII are calculated separately in the model. Estimates from each type of pool are then summed to get a total value for all pools.

Variable: $Pool_s$–Annual number Source Plasma pool used to make pdFVIII

$$Pool_s = Round((IU_s / Y_{avg}) / (V_{pool-s} / 1000)) \qquad \text{(IV. D. 2-3)}$$

Variable: $IU_{FVIII-R}$ -Annual units of pdFVIII made from recovered plasma (calculated in A-IV. D. 1.).

Variable: $Pool_R$–Annual number of recovered plasma pools used to make pdFVIII

$$Pool_R = Round((IU_R / Y_{avg}) / (V_{pool-R} / 1000)) \qquad \text{(IV. D. 2-4)}$$

Finally, the number of possible Source and recovered plasma pools are summed to generate the total number of plasma pools used in the manufacture of pdFVIII in the US.

Variable: Pool–Annual total number of plasma pool used to make pdFVIII

$$Pool = Pool_S + Pool_R \qquad \text{(IV. D. 2-5)}$$

A-IV. D. 2. c. Annual number vCJD plasma pools used to manufacture pdFVIII in the United States

Annual number of vCJD pools is expected to be low because the US vCJD prevalence, even among donors that traveled to the UK, France or other countries in Europe since 1980, is likely very low and presumably varies from year to year. A binomial distribution (n, p) is used to reflect the variation in the number of vCJD pools present in a single year. A binomial distribution is usually used when the number of positive observations (p) or in this case the number of vCJD containing pools is very low compared to the total number of pools (n).

Variable: $Pr(vCJD\text{-}pool_s)$- Probability of a Source Plasma pool containing vCJD agent

Variable: $Pool_{vCJD-S}$ – Annual number Source Plasma pools that contain vCJD agent used to make pdFVIII

$Pool_{vCJD-S} = Binomial(Pool_{S,} \Pr(vCJD - pool_S)$ (IV. D. 2-6)

Variable: ***Pr(vCJD-pool$_R$)-*** Probability of a recovered plasma pool containing vCJD agent

Variable: Pool$_{vCJD-R}$ – Annual number of recovered plasma pools that contain vCJD agent used to make pdFVIII

$Pool_{vCJD-R} = Binomial(Pool_{R,} \Pr(vCJD - pool_R)$ (IV. D. 2-7)

Variable: Pool$_{vCJD}$ – Annual total plasma pools that contains vCJD agent used to make pdFVIII

$Pool_{vCJD} = Pool_{vCJD-S} + Pool_{vCJD-R}$ (IV. D. 2-8)

A-IV. D. 3. Percentage of pools potentially containing vCJD agent

Variable: Perc $_{vCJD-S-pool}$ -Percentage Source Plasma pools used to make pdFVIII that contains vCJD donations

$Perc_{vCJD-S-pool} = (Pool_{vCJD-S} / Pool_S) \times 100\%$ (IV. D. 3-1)

Variable: Perc $_{vCJD-R-pool}$ -Percentage recovered plasma pools used to make pdFVIII that contains vCJD donations

$Perc_{vCJD-R-pool} = (Pool_{vCJD-R} / Pool_R) \times 100\%$ (IV. D. 3-2)

Variable: Perc $_{vCJD-pool}$ –Overall percentage plasma pools used to make pdFVIII that contains vCJD donations

A-IV. E. Module 2: Estimation of Quantity of vCJD agent in a plasma pool that contains a donation from a donor potentially infected with vCJD

A-IV.E.1. Quantity of vCJD agent present in a donation of a specific donor potentially infected with vCJD

Variable: I_{bl} – Represents the i.c. ID_{50} present in the blood of individual infected donor (ID_{50}/ml) in the last half of the incubation period of vCJD.

Assumption used in the model: Whole blood collected from a vCJD-infected individual can vary from person to person in the quantity of infectivity it contains. The model used a log normal statistical distribution to represent the variability and uncertainty of the quantity of infectivity in blood. It was assumed that whole blood from an infected person potentially carries a minimum of 0.1 i.c. ID_{50} per ml, a 5th percentile of 2 i.c. ID_{50} per ml, a median of 12 i.c. ID_{50} per ml, a 95th percentile of 30 i.c. ID_{50} per ml and a maximum of 1,000 i.c. ID_{50} per ml. Attempts to identify vCJD infectivity titers in human blood have not been successful, but the assay sensitivity for vCJD *in vitro* and in animal models is limited (Bruce *et al* 2001 and Wadsworth *et al* 2001). Wadsworth *et al* estimated a limit of sensitivity of about 1,000 ID_{50}/ml by their assay meaning that infected blood containing less than 1,000 ID_{50} would not have elicited infection or disease in their animal model, hence infectivity would not have been detected (Wadsworth, 2001).

Variable: $I_{pl\text{-}perc}$ – Percent (%) i.v. ID_{50}s associated with plasma

Studies in animal models have shown that greater than 50% of transmissible spongiform encephalopathy agent present in whole blood is associated with plasma. Experiments by Gregori *et al.* (2004) using a hamster – sheep scrapie model showed that approximately 58% of infectivity in whole blood is associated with plasma.

Assumption used in the model: The model assumes that 58% of infectivity is associated with plasma.

Assumption used in the model: Exposure to infectivity by the i.v. route is between 1 and 10 times less efficient at causing infection than introduction via the intracerebral route. Using a value of 1 for the ratio of the lower bound of the efficiency is a conservative estimate and assumes that theoretically there would be no difference between the efficiency in initiating infection between the i.c. and i.v. routes.

Variable: DN_V-Volume of one unit of plasma, depending on plasma type (same as $DN_{V\text{-}S}$ used in A-IV. D. 2 for Source Plasma, same as $DN_{V\text{-}R}$ used in A-IV. D. 2. for recovered plasma)

Variable: I_{DN}-Quantity of vCJD agent in one donation of infected plasma (i.v. ID_{50}/ml)

$$I_{DN} = I_{bl} \times DN_V \times I_{Pl-perc} \times A_{iv-ic} \qquad \text{(IV.E.1-1)}$$

A-IV.E. 2. Quantity of vCJD agent in a plasma pool containing a donation from donor potentially infected with vCJD

Variable: DN_{DR} - Number of donations from an infected plasma donor, which varies based on type of plasma donated.

Assumption used in the model: We assumed individual infected Source Plasma donor most likely give [redacted] donations to a pool, with minimum of 1, maximum of 12 donations. Individual infected recovered plasma donors most likely give only one donation to a pool.

Variable: I_{Pool}- Initial infectivity in an infected plasma pool is represented by the equation:

$$I_{Pool} = I_{DN} \times DN_{DR} \qquad \text{(IV.E.2-1)}$$

A-IV. F. Estimation of the potential quantity of vCJD agent in pdFVIII products manufactured from pool(s) potentially containing a vCJD donation

The FDA model employed three stratifications of clearance:

- 2 – 3 $\log_{10}$
- 4 – 6 $\log_{10}$
- 7 – 9 $\log_{10}$

Each of these levels of clearance was modeled separately. Most of the results are presented for the 4-6 $\log_{10}$ reduction during manufacture processing in the risk characterization section (Section V.) of this risk assessment.

Assumptions used in the model: The model assumed there are potentially three levels of reduction that may be achieved: a lower level of reduction (a range of 2 - 3 $\log_{10}$)-represented by uniform distribution (2, 3), medium level of reduction (a range of 4-6 logs, most likely, 5 $\log_{10}$)-represented by triangular distribution (4, 5, 6) and higher level of reduction (a range of 7-9 $\log_{10}$, most likely, $\log_{10}$)-represented by triangular distribution (7, 8, 9).

Variable: I_{Pool}- Initial infectivity in a specific infected plasma pool (calculated in A-IV. E.2)

Variable: R_{Log}- Potential log reduction in infectivity during processing

Variable: $I_{Pool-Ap}$- Remaining infectivity in a specific infected plasma pool after processing

$$I_{Pool-Ap} = I_{Pool} / 10^{R_{Log}} \qquad \text{(IV.F-1)}$$

Variable: DR_{Pool}- Size of plasma pool (number of donors/pool).

Assumption used in the model: The size of the plasma pools used in manufacturing was assumed to vary from pool to pool. In this risk assessment model, two different general distributions were used to represent frequency distribution of sizes of Source and recovered plasma pool based on the data provided by pdFVIII manufacturers.

Data used in the model: Information for Source Plasma pool size was collected by the FDA from pdFVIII manufacturers. The size of Source Plasma pools ranged from 6,000 donors per pool to 60,000 donors per pool with mean of [redacted] donations per pool. The distribution was generated based on the pool size data provided by pdFVIII manufacturers and the market share of the products based on information supplied annually to the FDA by manufacturers. Manufacturers supplied FDA with information on the average number of donations from individuals in the pool.

Data used in the model: Information for recovered plasma pool sizes was collected by the FDA from pdFVIII manufacturers. The size of recovered plasma pool ranged from 150,000 to 360,000 donations per pool. The distribution was generated based on the pool size data provided by pdFVIII manufacturers and the market share of the products. Manufacturers supplied FDA with information on the average number of donations from individuals in the pool.

Variable: DN_{DR-Avg}-Average number of donations from individual donors in the pool

Assumption used in the model: Data on the average number of donations per donor per pool were provided by manufacturers. We assumed the average number donations from individual donors varied from pool to pool. For Source Plasma, it was assumed to range from [redacted] donations per donor, with a most likely of [redacted] donations per donor. For recovered plasma, it was assumed that the most likely number of donations per donor was only 1.

Variable: DN_V-Volume of one unit of plasma, depending on plasma type (for Source Plasma, same as DN_{V-S} used in A-IV. D. 2, recovered plasma, same as DN_{V-R} used in A-IV. D. 2.)

Variable: Y_{FVIII}-Yield of pdFVIII (IU/L plasma)

Assumption used in the model: Based on the data provided by the World Federation of Hemophilia (2004) we assumed pdFVIII yield varies from pool to pool with minimum of 120, most likely of 187 and maximum of 250 IU per liter plasma.

Variable: I_{iu}- Quantity of infectivity in the pdFVIII product made from a specific infected pool (i.v. ID_{50} per IU)

$$I_{IU} = (I_{Pool-Ap} / (DR_{Pool} \times DN_{DR-Avg} \times DN_V)) \times 1000 / Y_{FVIII} \qquad \text{(IV. F-2)}$$

A-IV. G. FVIII utilization by HA and vWD patients and potential exposure to the vCJD agent through use of human pdFVIII

A-IV. G. 1. FVIII utilization and potential exposure to the vCJD agent through use of human plasma-derived FVIII by severe HA patients

This risk assessment provides outputs that estimate the annual exposure for several patient subpopulations with **Severe HA** disease for patients in the following clinical treatment groups:

- Prophylaxis – No inhibitor

- Prophylaxis - With inhibitor
- Prophylaxis - With inhibitor and immune tolerance
- Episodic – No inhibitor
- Episodic - With inhibitor

The study collected a total of 17,848 records, each record representing a single year of medical data for a single HA patient. The comprehensive study collected standardized information on patient demographics, clinical treatment and outcome data. Patient medical records were obtained from treatment sites including: hemophilia treatment centers (HTCs), hospitals, clinics, physician's offices, home-care agencies, nursing homes, prison infirmaries, and dispensers of factor concentrates. The data, abstracted from medical records, tabulated all recorded factor concentrate utilization prescribed by quantity, type, purpose (e.g., prophylaxis, treatment of acute bleeds, or immune tolerance therapy) and total quantity used per calendar year. Among all the records collected in the study from 1993-1998, 1,993 were from HA patients with severe disease that had been treated with human pdFVIII and the records were further grouped into five clinical treatment subcategories based on treatment regimen, including: prophylaxis, no inhibitor; prophylaxis,with inhibitor; prophylaxis, with inhibitor and immune tolerance; episodic, no inhibitor; and episodic, with inhibitor. Data from each of the five subpopulations were analyzed individually using the statistical package "JMP" (SAS Institute, Cary, NC) to generate initial descriptive statistics and distributions of pdFVIII usage by the HA patients. The data containing annual pdFVIII utilization information for patients in each of the five treatment groups were further analyzed using Best Fit software (Palisade Corp, New York) to generate a statistical distribution(s) for each patient treatment group that best reflected the variation in pdFVIII utilization. Overall, the Generalized Beta distribution provided the most reasonable and consistent fit for the pdFVIII utilization data among all of the patient treatment groups. The Generalized Beta distributions were then used in the model to approximate the distribution of utilization of pdFVIII in each of the five HA patient subpopulations. FDA used the original patient data to not only generate statistical distributions for each patient treatment subpopulation. FDA also used the original data to identify the minimum and maximum dosages used by patients in each specific treatment subcategory and truncated each distribution using these values. Graphical representations of the original data and the fitted Generalized Beta distributions are shown in Appendix C. We also provide a summary of the pdFVIII usage data from the CDC sponsored six state study, and also summarize the input Generalized Beta distributions generated with each subset of data in Table A-4.5.

Table A-4.5. Annual usage of pdFVIII by individual HA patients with severe disease-data and input distribution

		Original Data			Input distribution (Generalized Beta distribution)				
Treatment Regimen	Inhibitor Status	n	Mean	95% CI	α	β	(min, max)	Mean	95% CI
Prophylaxis	No Inhibitor	678	164394 IU	(13574, 518781)	1.5159	10.02	(300, 1200000)	157949	(21242, 282316)

	With Inhibitor – No Immune Tolerance	63	198781	(7859, 937480	1.4640	6.2861	(2000, 800000)	190523	(28956, 447639)
	With Inhibitor – With Immune Tolerance	62	569707	(14315, 3222471)	0.8782	5.5081	(100000, 2000000)	558700	(33235, 1592943)
Episodic	No Inhibitor	946	90489	(3001, 345416)	0.9882	10.60	(0, 1000000)	85270	(4633, 244656)
	With Inhibitor	151	169710	(4099, 835729)	0.6950	3.6822	(2200, 1000000)	160458	(5314, 488906)

Variable: IU_{Yr} - Annual usage of pdFVIII by individual HA patient of a specific clinical group (IU/yr, person)

Variable: IU_{vial} - Vial size (IU/vial)

Assumption used in the model: We assumed there were equal numbers of vials for each of the four different package sizes (250, 500, 1000 and 1500 IU/vial) that are distributed in the US.

Variable: $Vial_{Tot}$ - Annual number of pdFVIII vials used by individual patient (vials/yr, person)

Assumption used in the model: We assumed individual patient uses pdFVIII products of the same package size throughout the whole year period of 2002 for which the model was run.

$$Vial_{Tot} = IU_{Yr} / IU_{Vial} \qquad \text{(IV.G. 1-1)}$$

Variable: ***Pool*** - Annual number of plasma pool used to make pdFVIII (calculated in A-IV.D.2.b.)

Variable: $Pool_{vCJD}$ - Annual number of vCJD plasma pool used to make pdFVIII (calculated in A-IV.D.2.c.)

Variable: $Perc_{vCJD\text{-}vail}$ – Percentage pdFVIII vials containing vCJD agent

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Variable: $Vial_{vCJD}$ - Annual number of pdFVIII vials used by individual patient (vials/yr, person)

$$Vial_{vCJD} = Vial_{Tot} \times Perc_{vCJD-vial} \qquad \text{(IV.G. 1-2)}$$

Variable: I_{iu} - Quantity of infectivity in the pdFVIII product made from a specific infected pool (i.v. ID_{50} per IU) (calculated in IV. F)

Variable: I_{yr} - Annual exposure to vCJD through use of pdFVIII (i.v. ID_{50}/yr, person)

$$I_{yr} = \sum_{i=1}^{Vial_{vCJD}} I_{IU} \times IU_{Vial} \qquad \text{(IV.G. 1-3)}$$

A-IV. G. 2. pdFVIII utilization and annual exposure of severe von Willebrand disease patients

The CDC and six state Hemophilia Surveillance System project conducted from 1993-1998 did not include patients with vWD. We assumed that vWD patients with severe disease would largely use Humate P product only for factor replacement treatment. A search of records in the Hemophilia Surveillance System project data revealed a total of 58 records that indicated Humate P had been used, among which, 8 records indicates patients had developed inhibitor, which are considered uncommon among vWD patients and were excluded from analysis. Among the 58 records, 35 were from Adults (≥15 yrs of age) and 23 records were from young persons (<15 yrs of age). Records for each age group were further grouped by clinical treatment using either a prophylaxis or episodic treatment regimen. Data were initially analyzed individually using the statistical package "JMP" (SAS Institute, Cary, NC) to generate descriptive statistics and statistical distribution(s) for each patient treatment group that best reflected the variation in pdFVIII utilization. The Generalized Beta distribution was identified as the best fit to the pdFVIII utilization data (as determined by using the software Best Fit (Palisade Corp, NY) and was used as the input distribution for pdFVIII usage by individual vWD patients in the model. Graphical representations of the original data and the fitted Generalized Beta distributions are shown in Appendix C. Table A-4.6. summarizes pdFVIII usage data from CDC sponsored study and the input distribution generated based on the data. FDA used data in the CDC and six state Hemophilia Surveillance System project conducted from 1993-1998 to estimate FVIII utilization by all vWD patients. The data represent only a sample of all possible vWD patients with severe disease in the US. FDA estimated that there were approximately 250 patients in the US with Type 3 vWD. To calculate the total number of patients in each age group and treatment regimen group we adjusted the 58 patient population to equal a total of 250 patients by multiplying the patient population in each group by a factor of 4.3 (250/58 = ~4.3). The utilization data for patients in each treatment regimen in the sample population were used in the risk assessment model to generate outputs for the annual exposure to vCJD for all vWD for Adult (>15 yrs of age) and Young (≤15 yrs of age) persons in the US among clinical treatment groups of prophylaxis and episodic.

Table A-4.6. Annual usage of pdFVIII by individual severe vWD patient -data and input distribution We need to update the information in this table – based on new calculations for a total of 58 cases (previously it was 50 cases)

	Original Input Data				Input Distribution (Generalized Beta distribution)				
Treatment Regimen	n	Percent of total population	Mean	95% CI	α	β	(min, max)	Mean	95% CI
Young (≤15 yrs of age)									

Prophylaxis	9	16%	164193	(9200, 504625)	0.4523	0.9794	(9200, 504625)	165713	(9346, 479457)
Episodic	14	24%	11122	(1010, 41850)	0.3900	1.1973	(1010, 41850)	11045	(1013, 37543)
Adult (>15 yrs of age)									
Prophylaxis	17	29%	187538	(15000, 772800)	0.5741	1.9569	(15000, 7728000)	186880	(15570, 606699)
Episodic	18	31%	845556	(1000, 293800)	0.5855	1.4097	(1000, 293800)	86923	(1361, 260660)

Variable: ***IUyr*** - Annual usage of pdFVIII by individual vWD patient of a specific clinical group (iu/yr, person)

Variable: IU_{vial} - Vial size (IU/vial)

<u>Assumption used in the model</u>: We assumed that equal numbers of vials in each of three different package sizes (250, 500, 1000 IU/vial) are distributed on the market.

Variable: $Vial_{Tot}$ - Annual number of pdFVIII vials used by individual patient (vials/yr, person)

Assumption used in the model: We assumed individual patients used pdFVIII products of the same package size through out whole year period of 2002 for which the model was run.

$$Vial_{Tot} = IU_{Yr} / IU_{Vial} \qquad \text{(IV.G. 2-1)}$$

Variable: ***Pool*** - Annual number of plasma pool used to make pdFVIII (calculated in A-IV. D .2.b.).

Variable: $Pool_{vCJD}$ - Annual number of vCJD plasma pool used to make pdFVIII (calculated in A-IV.D.2.c.)

Variable: $Perc_{vCJD\text{-}vail}$ – Percentage pdFVIII vials containing vCJD agent

Variable: $Vial_{vCJD}$ - Annual number of pdFVIII vials used by individual patient (vials/yr, person)

$$Vial_{vCJD} = Vial_{Tot} \times Perc_{vCJD-vial} \qquad \text{(IV.G. 2-2)}$$

Variable: I_{iu}- Quantity of infectivity in the pdFVIII product made from a specific infected pool (iv. ID_{50} per IU) (calculated in IV.F.)

Variable: I_{yr}- Annual exposure of individual vWD patients to vCJD through use of pdFVIII (i.v. ID_{50}/yr, person)

$$I_{yr} = \sum_{i=1}^{Vial_{vCJD}} I_{IU} \times IU_{Vial} \qquad \text{(IV.G. 2-3)}$$

DRAFT ISSUE SUMMARY
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE (TSEAC) MEETING
December 15, 2006
Silver Spring, Maryland

Topic II: Experimental Clearance of Transmissible Spongiform Encephalopathy (TSE) Infectivity in Plasma-derived Factor VIII (pdFVIII) Products

Issue: FDA seeks the Committee's advice on whether a minimum TSE agent reduction factor, demonstrated in laboratory-based experimental models, would enhance vCJD safety of the products.

Background and Rationale

Although variant Creutzfeldt-Jakob (vCJD) transmission by plasma derivatives has not been reported, plasma from experimental animals has been shown to contain TSE infectivity, and human blood transfusions have probably transmitted vCJD in the UK. Results from the FDA risk assessment model for potential exposure to the vCJD agent through the use of U.S. licensed pdFVIII products indicate that a major factor in reducing the potential risk of such exposure is the amount of TSE agent clearance that occurs during manufacturing (Attachment 1). TSE clearance in plasma products has been studied by many manufacturers on a voluntary basis. On February 20, 2003, the TSEAC voted that FDA should consider labeling claims for TSE clearance when manufacturers have submitted clearance studies using viral validation-style methods and model TSE spiking agents. To date, FDA has approved labeling claims for TSE clearance for two IGIV products and an Antithrombin III product. These approvals were based upon viral validation-style studies using brain-derived spikes for input infectivity, and bioassays as a read-out. Various other studies of pdFVIII products that have been performed by manufacturers were reported to the TSEAC on September 18, 2006 (Attachment 2)(1).
At the September 18, 2006 meeting, the Committee discussed TSE clearance study methods (1) (Summary, Attachment 3). Most members thought that it would be premature to standardize TSE clearance studies. Exogenous ("spiking") models for TSE clearance were deemed more feasible than experiments using plasma of infected animals because of logistical constraints on the endogenous model.[1] The Committee agreed that exogenous clearance studies have limitations, particularly due to lack of certainty about the form of the TSE agent in blood. However, should an exogenous model demonstrate that a process step or series of steps achieves a relatively low $\log_{10}$ reduction of spiked TSE infectivity, a study using a large volume of endogenously infected plasma might still be useful to determine whether or not the low demonstrated level of exogenous model clearance still offered some potential benefit. In these scaled-down endogenous model clearance experiments, it would be especially important to test most if not all of the final product using animals and routes of inoculation known to be highly sensitive for detecting infectivity. Although the logs of infectivity removed will not be large compared with an exogenous spiking experiment, the relevance of the endogenous experiment to

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[1] Constraints include low dynamic range of clearance that can be demonstrated, scale of the experiment, number of assay animals required, and lengthy incubation times.