$$\Pr_{vCJD\ -EU\ (age\ )} = \Pr_{vCJD\ -UK\ (age\ )} \times R_{EU} \qquad \text{(IV.C.1.e-7)}$$

Variable: $DR_{vCJD\text{-}EUBL(age)}$-Annual number of infected European donors who contributed Euroblood that was transfused into US plasma donors during a one-year period by age group.

Number of infected Euroblood donors among each age group was estimated using a binomial distribution function with the estimated total number of donors in the subgroup ($DR_{EUBL(age)}$ estimated in section A-IV.C. 1.e. ii) and the probability of infection for the individual of this age group of Euroblood donors ($Pr_{vCJD\text{-}DR\text{-}EUBL(age)}$ estimated in this section A-IV. C. 1. e. ii) as parameters of the distribution.

$$DR_{vCJD-EUBL(age)} = Bionomial(DR_{EULL(age)}, \Pr_{vCJD-EU(age)}) \qquad \text{(IV.C.1.e-8)}$$

Variable: $EUBL_{vCJD}$ - Total units of infected Euroblood received by US plasma donors of one year period

Potential infected European donor may give multiple donations in a single year, however the chance of more than one donation being from a single infected European donor being shipped to the US, and used by US plasma donors is expected to be small.

Assumption about variable: One infected European donor produces one unit of infected Euroblood.

$$EUBL_{vCJD} = \sum_{age=18-19}^{>65} DR_{vCJD-EUBL(age)} \qquad \text{(IV.C.1.e-9)}$$

A-IV. C. 1. e. iii. Annual number of plasma donors potentially infected with vCJD via transfusion with Euroblood

A-IV. C. 1. e. iii. a. Annual potential number of vCJD infected plasma donors

Variable: $Pr_{vCJD\text{-}EUBL}$ - Probability a single unit of Euroblood contains vCJD agent

$$\Pr_{vCJD-EUBL} = EUBL_{VCJD} / EUBL_{Tot} \qquad \text{(IV.C.1.e-10)}$$

Variable: $Pr_{vCJD\text{-}EUBL\text{-}Recip}$ - Probability a Euroblood recipient is infected with vCJD

Assumption used in the model: We assumed that a Euroblood recipient is likely infected if he/she receives one unit or more of blood blood from a vCJD-infected donor.

$$\Pr_{vCJD-EUBL-recip} = 1 - Binomdist(0, EUBL_{avg}, \Pr_{vCJD-EUBL}, false) \qquad \text{(IV.C.1.e-11)}$$

The Excel function Binomdist (n, N, p, false) calculates the probability of n "success" outcomes in a test, if the outcome of each trial of the test is either "success" or "failure", the probability of getting the outcome of "success" in an individual trial throughout the test is a constant p, and the number of trials in the test is N. In the problem we addressed here the outcomes are the probability of a donation being from a Euroblood recipient that receives a donation that is either infected or not infected. In equation IV.C.1.e-11, $Binomdist(0, EUBL_{avg}, Pr_{vCJD\text{-}EUBL}, false)$ calculated the probability of a recipient receiving no infected unit (n=0), under the condition that average number of units received by a recipient is $EUBL_{avg}$ (N=$EUBL_{avg}$) and probability a single unit of Euroblood being infected is $Pr_{vCJD\text{-}EUBL}$ (p=$Pr_{vCJD\text{-}EUBL}$).

The number of Source and recovered plasma donors infected through transfusion with Euroblood was estimated using a binomial distribution function with the estimated total number of source and recovered plasma donors who have received Euroblood ($DR_{S\text{-}EUBL}$ and $DR_{R\text{-}EUBL}$ estimated in section A-IV.C. 1.e. ii.) and the probability of infection for the individual Euroblood recipient ($Pr_{vCJD\text{-}EUBL\text{-}receip}$ estimated in section A-IV. C. 1. e. iii) as parameters of the distribution. The total estimated number of potential plasma donors infected due to transfusion using Euroblood is the sum of potential infected source and recovered plasma donors.

Variable: $DR_{vCJD\text{-}S\text{-}EUBL}$ - Annual Number of Source Plasma donors being infected due to transfusion with a Euroblood unit:

$$DR_{vCJD-S-EUBL} = Binomial(DR_{S-EUBL}, \Pr_{vCJD-EUBL-recip}) \quad \text{(IV.C.1.e-12)}$$

Variable: $DR_{vCJD\text{-}R\text{-}EUBL}$ - Annual number of recovered plasma donors possibly infected via transfusion with a unit of Euroblood

$$DR_{vCJD-R-EUBL} = Binomial(DR_{R-EUBL}, \Pr_{vCJD-EUBL-recip}) \quad \text{(IV.C.1.e-13)}$$

Variable: $DR_{vCJD\text{-}EUBL}$ - Annual number of all plasma donors possibly infected through transfusion with a unit of Euroblood

$$DR_{vCJD-EUBL} = DR_{vCJD-S-EUBL} + DR_{vCJD-R-EUBL} \quad \text{(IV.C.1.e-14)}$$

Variable: $DR_{vCJD\text{-}EUBL\text{-}Def}$- Annual number of plasma donors possibly infected through transfusion with a unit of Euroblood and meet deferral criteria and presumably deferred from donation.

Variable: $DR_{vCJD\text{-}EUBL\text{-}Res}$- Annual number of plasma donors potentially infected via transfusion with a unit of Euroblood and does not meet deferral criteria and likely not deferred from donation.

Under current blood donation policies recipients of Euroblood are not deferred and represented by the expressions:

$$DR_{vCJD-EUBL-Def} = 0 \quad \text{(IV.C.1.e-15)}$$

$$DR_{vCJD-EUBL-Res} = DR_{vCJD-EUBL} \quad \text{(IV.C.1.e-16)}$$

A-IV. C. 1. e. iii. b. Annual number of plasma donors that received Euroblood and are potentially infected and vCJD agent is present in the blood

Assumption used in the model: All infected Euroblood recipients have vCJD agent present in their blood (prionemic)

Variable: $DR_{vCJD\text{-}EUBL\text{-}Pn}$ - Annual number of plasma donors infected via transfusion using Euroblood and are prionemic in 2002

$$DR_{vCJD-EUBL-Pn} = DR_{vCJD-EUBL} \quad \text{(IV.C.1.e-17)}$$

Variable: $DR_{vCJD\text{-}EUBL\text{-}Def\text{-}Pn}$- Annual number of plasma donors infected via transfusion using Euroblood, and may have vCJD agent present in their blood and plasma (prionemic) in 2002 and meet deferral criteria

$$DR_{vCJD-EUBL-Def-Pn} = DR_{vCJD-EUBL-Def} \quad \text{(IV.C.1.e-18)}$$

Variable: $DR_{vCJD\text{-}EUBL\text{-}Res\text{-}Pn}$- Annual number of plasma donors who are possibly infected with vCJD via transfusion with Euroblood, that had vCJD agent present in their blood and plasma (prionemic) in 2002 and did not meet deferral criteria (likely not deferred)

$$DR_{vCJD-EUBL-Res-Pn} = DR_{vCJD-EUBL-Res} \quad \text{(IV.C.1.e-19)}$$

A-IV. C. 1. f. Total number all plasma donors who may potentially be infected with vCJD through all sources of exposure and vCJD agent is present in the blood

Variable: $DR_{vCJD\text{-}S\text{-}Pn}$ - Estimated total annual number of Source Plasma donors infected with vCJD who potentially had the agent present in blood and plasma (prionemic) in 2002:

$$DR_{vCJD-S-Pn} = DR_{vCJD-S-UK-LH} + DR_{vCJD-S-FR-HL} + DR_{vCJD-S-DOD-LH} + DR_{vCJD-S-EUBL-Pn} \quad \text{(IV.C.1.f-1)}$$

Variable: $DR_{vCJD\text{-}R\text{-}Pn}$ - Estimated total annual number of recovered plasma donors potentially infected with vCJD with the agent present in blood and plasma (prionemic) in 2002

$$DR_{vCJD-R-Pn} = DR_{vCJD-R-UK-LH} + DR_{vCJD-R-FR-HL} + DR_{vCJD-R-EU-LH} + DR_{vCJD-R-DOD-LH} + DR_{vCJD-R-EUBL-Pn}$$

(IV.C.1.f-2)

Variable: $DR_{vCJD\text{-}Pn}$ - Total annual number of all US plasma donors potentially infected with vCJD with the agent present in blood and plasma (prionemic) in 2002

$$DR_{vCJD-Pn} = DR_{vCJD-S-Pn} + DR_{vCJD-R-Pn} \quad \text{(IV.C.1.f-3)}$$

A-IV. C. 2. Annual number of all US plasma donors potentially infected with vCJD agent present in the blood and who may not be deferred by questionnaire screening

A-IV. C. 2. a Annual number of US Source Plasma donors potentially infected and vCJD agent is present in the blood that may not be deferred by questionnaire screening

Variable: Eff_{Def} - Effectiveness of US donor deferral policy

Assumption about variable: Based on advice from the TSEAC at the October 31, 2005 meeting, the FDA model assumed 85-99% of potential vCJD infected donors would have been deferred just prior to donation.

Variable: $DR_{vCJD\text{-}S\text{-}Def\text{-}Pn}$ - Estimated annual number of Source Plasma donors potentially infected with and having vCJD agent present in blood and plasma (prionemic) that are deferred by current policy

$$DR_{vCJD\text{-}S\text{-}Def\text{-}Pn} = DR_{vCJD\text{-}S\text{-}UK\text{-}Def\text{-}Pn} + DR_{vCJD\text{-}S\text{-}FR\text{-}Def\text{-}Pn} + DR_{vCJD\text{-}S\text{-}DOD\text{-}Pn} \quad \text{(IV.C.2-1)}$$

Assumption about variable: This population includes the potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) that have long-term travel history to the UK (≥3 mo), and France (≥ 5 yrs); and a history of military deployment (or military dependent, etc.) in Europe from 1980 – 1996.

Variable: $DR_{vCJD\text{-}S\text{-}Res}$ - Estimated annual number of Source Plasma donors potentially infected with vCJD with agent present in blood and plasma (prionemic) that have short term travel history (UK (<3 mo), and France and/or Europe (< 5 yrs); and not deferred by deferral policy.

$$DR_{vCJD\text{-}S\text{-}Res\text{-}Pn} = DR_{vCJD\text{-}S\text{-}UK\text{-}Res\text{-}Pn} + DR_{vCJD\text{-}S\text{-}FR\text{-}Def\text{-}Pn} + DR_{vCJD\text{-}S\text{-}DOD\text{-}Pn} \quad \text{(IV.C.2-2)}$$

Assumption about variable: This population includes the potential Source Plasma donors with vCJD with agent present in blood and plasma (prionemic) that have short-term travel history to the UK (< 3 mo), France (< 5 yrs), and a history of receiving Euroblood.

Variable: $DR_{vCJD\text{-}S\text{-}Pn\text{-}NR}$ - Annual total number of potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) and were not removed by deferral screening

Assumption used in model: This includes potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) who meet deferral criteria but for a variety of reasons are not deferred.

$$DR_{vCJD\text{-}S\text{-}Pn\text{-}NR} = DR_{vCJD\text{-}S\text{-}Res\text{-}Pn} + DR_{vCJD\text{-}S\text{-}Def\text{-}Pn} \times (1 - Eff_{Def}) \quad \text{(IV.C.2-3)}$$

A-IV. C. 2. b Annual number of US recovered plasma donors potentially infected and vCJD agent is present in the plasma that may not be deferred by questionnaire screening

Variable: Eff_{Def} - Effectiveness of donor deferral policy

Assumption about variable: Based on advice from the TSEAC at the October 31, 2005 meeting, the FDA model assumed 85-99% of potential vCJD infected donors would have been deferred just prior to donation.

Variable: $DR_{vCJD\text{-}R\text{-}Def\text{-}Pn}$ - Estimated annual number of potential recovered plasma donors with vCJD agent present in blood and plasma (prionemic) who are deferred by current policy

$$DR_{vCJD\text{-}R\text{-}Def\text{-}Pn} = DR_{vCJD\text{-}R\text{-}UK\text{-}Def\text{-}Pn} + DR_{vCJD\text{-}R\text{-}FR\text{-}Def\text{-}Pn} + DR_{vCJD\text{-}R\text{-}EU\text{-}Def\text{-}Pn} + DR_{vCJD\text{-}R\text{-}DOD\text{-}Pn} \quad \text{(IV.C.2-4)}$$

Assumption about variable: Model includes potential recovered plasma donors with vCJD agent present in blood and plasma (prionemic) that have long term travel history to the UK (≥3 mo), France (≥ 5 yrs), and Europe (≥5 yrs); and history of military deployment, military dependent or related travel or residence in Europe.

There is a possibility that some individuals that traveled to the UK, France, and other countries in Europe since 1980 stayed for periods of time that were shorter than the deferral period, were exposed to BSE agent, and were infected with vCJD. These individuals represent a source of residual risk – or the remaining risk after interventions (in this case donor deferral policies) are applied. The section below addresses the calculation of residual risk for non-deferred at risk donors that traveled for periods of time that were shorter than recommended guidelines.

Variable: $DR_{vCJD\text{-}R\text{-}Res}$ - Annual number of potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) that have short term travel history and are not covered by and deferred by deferral policy.

$$DR_{vCJD\text{-}S\text{-}Res\text{-}Pn} = DR_{vCJD\text{-}S\text{-}UK\text{-}Res\text{-}Pn} + DR_{vCJD\text{-}S\text{-}FR\text{-}Def\text{-}Pn} + DR_{vCJD\text{-}S\text{-}DOD\text{-}Pn} \quad \text{(IV.C.2-2)}$$

Assumption about variable: Estimation of the possible vCJD residual risk includes potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) that have short-term travel history to the UK (< 3 mo), France (< 5 yrs), history of travel to Europe and history of receiving Euroblood.

Variable: $DR_{vCJD\text{-}S\text{-}Pn\text{-}NR}$ - Annual total of potential Source Plasma donors with vCJD agent present in blood and plasma (prionemic) and were not removed by deferral screening

Assumption used in model: This includes all potential donors with vCJD agent present in blood and plasma (prionemic) that do not meet deferral criteria and who meet deferral criteria but wrongly not deferred.

$$DR_{vCJD-S-Pn-NR} = DR_{vCJD-S-Res-Pn} + DR_{vCJD-S-Def-Pn} \times (1 - Eff_{Def}) \quad \text{(IV.C.2-3)}$$

Variable: $DR_{vCJD-R-Pn-NR}$ - Annual total of potential recovered plasma donors with vCJD agent present in blood and plasma (prionemic) not removed by deferral screening

$$DR_{vCJD-R-Pn-NR} = DR_{vCJD-R-Res-Pn} + DR_{vCJD-R-Def-Pn} \times (1 - Eff_{Def}) \quad \text{(IV.C.2-4)}$$

A-IV. C. 2. c Total number of all US plasma donors potentially infected and vCJD agent is present in the plasma but may not be deferred by questionnaire screening

The total number of all US plasma donors potentially infected with vCJD with agent present in blood and plasma (prionemic) that may not be deferred by questionnaire screening was determined by summing the estimates generated for both Source and recovered plasma donors that may not be deferred by current screening procedures, and is described by the equation:

$$DR_{vCJD-Pn-NR} = DR_{vCJD-S-Pn-NR} + DR_{vCJD-R-Pn-NR} \quad \text{(IV.C.2-5)}$$

A-IV. C. 3. Total number of all US plasma donations potentially containing vCJD agent

Variable: $Freq_{DN-S}$–Average frequency of donations from a single Source Plasma donor who contributes Source Plasma for FVIII manufacture (times/year)

Variable: DN_{vCJD-S} - Annual number of potential vCJD donations of Source Plasma

$$DN_{vCJD-S} = DR_{vCJD-S-Pn-NR} \times Freq_{DN-S} \quad \text{(IV.C.2-6)}$$

Assumption used in the model: The average frequency of donations from a single Source Plasma donor who contributes Source Plasma for a FVIII plasma pool used in manufacturing ranges from ----- and most likely to be --- based on data from pdFVIII manufacturers. [FOI REVIEW]

Variable: $Freq_{DN-R}$–The average frequency of donations from a single recovered plasma donor who contribute plasma for pdFVIII manufacture (times/year) is 1.

Variable: DN_{vCJD-R} - Annual number of potential vCJD donations of recovered plasma

$$DN_{vCJD-R} = DR_{vCJD-R-Pn-NR} \times Freq_{DN-R} \quad \text{(IV.C.2-7)}$$

Assumption used in the model: The average frequency of donations from a single blood donor that contributes recovered plasma for pdFVIII manufacture is 1.

A-IV. C. 4. Probability that a US plasma donation potentially contained vCJD agent among all donations

Variable: $Pr(DN_{vCJD-S})$ - Probability a donation of Source Plasma contained vCJD agent

Variable: DN_s-Annual units of Source Plasma used to make pdFVIII (calculated in A-IV. B. 1)

$$Pr(DN_{vCJD-S}) = DN_{vCJD-S} / DN_S \qquad \text{(IV.C.4-1)}$$

Variable: $Pr(DN_{vCJD-R})$ - Probability a donation of recovered plasma contained vCJD agent.

Variable: DN_R-Annual number of units of recovered plasma used to make pdFVIII from plasma collected in the US (calculated in A-IV. B. 2).

$$Pr(DN_{vCJD-R}) = DN_{vCJD-R} / DN_R \qquad \text{(IV.C.4-2)}$$

A-IV. C. 5. Probability of a Source or recovered plasma pool potentially containing a vCJD donation(s)

A-IV. C. 5. a. *Probability that a plasma pool may contain a specific number of* vCJD donations

Assumption used in the model: Consistent with manufacturing practices in which commingling of Source and recovered plasma is uncommon, the risk assessment considered plasma pools to consist entirely of only Source Plasma donations or only recovered plasma donations.

Variable: $n_{vCJD-DN-pool}$ - Designated number of vCJD donors in a single plasma pool.

Assumption used in the model: The number of vCJD donations in a single vCJD pool could be 0, 1, 2, 3 or 4, but because of the low prevalence of vCJD most of the time there would be 0 vCJD donations in a pool

Variable: DR_{pool-S} -Size of Source Plasma pool (donors/pool)

Data used in the model: Based on information provided to the FDA by pdFVIII manufacturers, an individual Source Plasma pool may contain 6,000 to 60,000 donors [FOI REVIEW]. A statistical distribution representing the variation in the size (number of donations per pool) of plasma pools used in the manufacture of pdFVIII was generated by combining information on pool size with information on the percentage of market share for several individual pdFVIII products.

Variable: $Pr(n_{vCJD-DR-pool-S})$- Probability a Source Plasma pool containing $n_{vCJD-DN-pool}$ infected donations ($n_{vCJD-DR-pool}$=0, 1, 2, 4)-are determined by density frequency of DR_{pool-S} at $X=n_{vCJD-DR-pool}$

Variable: $DN_{pool\text{-}R}$ -Size of recovered plasma pool (donors/pool)

Data used in the model: Based on information from manufacturers, individual Source Plasma pool may contain 6,000 to 60,000 donors. [FOI REVIEW].

Variable: $Pr(n_{vCJD\text{-}DR\text{-}pool\text{-}S})$- Probability a Source Plasma pool containing $n_{vCJD\text{-}DN\text{-}pool}$ infected donations ($n_{vCJD\text{-}DR\text{-}pool}$ =0, 1, 2, 4)-are determined by density frequency of $DR_{pool\text{-}S}$ at $X=n_{vCJD\text{-}DR\text{-}pool}$

Variable: $DN_{pool\text{-}R}$ -Size of recovered plasma pool (donors/pool)

Data used in the model: Based on information provided to the FDA by pdFVIII manufacturers, an individual recovered plasma pool may contain 150,000 to 360,000 donors [FOI REVIEW]. As with Source Plasma pools described above, a statistical distribution representing the variation in the size (number of donations per pool) of plasma pools used in the manufacture of pdFVIII was generated.

Assumptions used in the model: The size of recovered plasma pools was represented in the model by using a uniform distribution ranging from 150,000 to 360,000 donations per pool (Figure 4-3) [FOI REVIEW]. – representing the range of pool sizes used by manufacturers of pdFVIII. The uniform distribution provided the best fit for the range of possible recovered plasma pool sizes that may be used in the US to manufacture pdFVIII.

Variable: $Pr(n_{vCJD\text{-}DN\text{-}pool\text{-}R})$-Probability a recovered plasma pool containing $n_{vCJD\text{-}DN\text{-}pool}$ infected donations ($n_{vCJD\text{-}DN\text{-}pool}$ =0, 1, 2, 4)-are determined by density frequency of $DR_{pool\text{-}R}$ at $X=n_{vCJD\text{-}DR\text{-}pool}$

A-IV. C. 5. b. Probability a plasma pool may potentially contain a vCJD donation(s)

Variable: $Pr(vCJD\text{-}pool_S)$-Probability of a Source Plasma pool containing one or more vCJD donations

$$\Pr(vCJD\_pool_S) = 1 - \Pr(n_{vCJD-DN-poolS} = 0) \quad \text{(IV.C.5-1)}$$

Variable: $Pr(vCJD\text{-}pool_R)$-Probability of a recovered plasma pool containing one or more vCJD donations

$$\Pr(vCJD\_pool_R) = 1 - \Pr(n_{vCJD-DN-pool\,R} = 0) \quad \text{(IV.C.5-2)}$$

Variable: $Pr(vCJD\text{-}pool)$-The Probability that a plasma pool (including Source and recovered plasma pools) contained one or more vCJD donations- The distribution for pool size (or number of donations per pool) incorporated information on pool size.

Variable: $Perc_S$ – Percentage of Source Plasma pools used to manufacture pdFVIII in the US

Variable: $Perc_R$ – Percentage of recovered plasma pools used to manufacture pdFVIII in the US

Assumption used in the model: Estimates suggest that approximately --- of pdFVIII products were made from Source Plasma, and --- were made from recovered plasma.

The probability of either a vCJD donation being present in a Source Plasma pool is represented by the variable ***Pr(vCJD-pool$_S$*** and the probability of a vCJD donation being present in a recovered plasma pool is represented by the variable, ***Pr(vCJD-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-pool$_S$***) and X2 (or ***Pr(vCJD-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 (--- for Source and --- for recovered plasma pools) used to make pdFVIII. *Pr(vCJD-pool)* is sampled from ***Pr(vCJD-pool$_S$*** and ***Pr(vCJD-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

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

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 --- million units of pdFVIII was made and distributed in the US. [FOI REVIEW].

Variable: $Perc_S$ – Represents the percentage of pdFVIII assumed in the model to be made from Source Plasma (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 Source Plasma 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 — of the total pdFVIII supply distributed annually in the US is manufactured from Source Plasma and — 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: $\mathbf{DN_{V\text{-}s}}$ – Volume of single unit Source Plasma (ml).

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

Variable: $\mathbf{Freq_{DN\text{-}S}}$ –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: $\mathbf{V_{pool\text{-}S}}$ — 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: $\mathbf{DN_{V\text{-}R}}$ – Volume of single unit recovered plasma (ml).

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

Variable: $\mathbf{Freq_{DN\text{-}S}}$ –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: $\mathbf{V_{pool\text{-}S}}$ — Volume of a recovered plasma pool (ml)

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

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-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

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

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

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

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

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

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

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

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

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

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 - 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 ------ donations per pool. [FOI REVIEW] 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. [FOI REVIEW] 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: $DN_{DR\text{-}Avg}$-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 ------- donations per donor, with a most likely of ---- donations per donor. [FOI REVIEW] 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 $DN_{V\text{-}S}$ used in A-IV. D. 2, recovered plasma, same as $DN_{V\text{-}R}$ 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)

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

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