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

## 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)

**Assumption used in the model:** 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:** $I_{vr}$- Annual exposure of individual vWD patients to vCJD through use of pdFVIII (i.v. $ID_{50}$/yr, person)

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

86 A -

# 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

[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.

the human situation might be greater. This is because the form of TSE infectivity in the blood of an infected animal is more likely to resemble that found in human blood, as compared to brain or spleen derived spiking material. Because of the very small amounts of agent likely to be present in endogenously TSE-infected blood, any failure of complete TSE clearance would be highly significant.

On September 18, 2006, the Committee was asked to comment whether a minimum TSE reduction factor, demonstrated using an exogenous model in scaled-down manufacturing experiments, might serve as an appropriate standard for demonstrating vCJD safety of pdFVIII products. The TSEAC was also asked to comment on what actions FDA might consider if such a minimum TSE reduction factor were not achieved. The discussion was deferred to the current meeting so that the Committee could respond in the context of recently completed FDA risk assessments.

**Discussion**

To determine a likely appropriate threshold level of TSE clearance for pdFVIII, two separate lines of evidence should be considered: the amount of clearance needed to assure that infectivity is removed (based on amount of starting infectivity in plasma), and the impact of clearance results on the pdFVIII risk assessment.

In the somewhat similar case of viral clearance validation studies, typical results accepted by FDA in support of label claims usually demonstrated at least 4 $\log_{10}$ of clearance by each of two mechanistically dissimilar (orthogonal) steps.[2] In the case of TSEs, the amount of infectivity in blood or plasma of experimentally infected animals has been estimated as 2-30 intracerebral infectious units (i.e. IU)/mL (2-4). An IU is the quantity of infectivity associated with a 100% probability of infection in recipients. An $ID_{50}$ is the amount of infectivity associated with a 50% probability of infection in recipients. Therefore 1 IU = 2 $ID_{50}$ . The amount of infectivity in the blood of BSE-infected and scrapie-infected ruminants and in the blood of vCJD-infected persons is unknown. If vCJD infectivity levels in human blood are similar to those found in rodent blood or plasma, then effective clearance might necessitate a reduction of infectivity by at least 4 $\log_{10}$, plus an additional margin of safety. Calculations of pathogen reduction are based upon removal of the absolute amount of infectivity, rather than upon infectivity concentration. For example, a plasma unit of 800 ml that contained infectivity of 2-30 IU/ml would contain 1,600 - 24,000 IU (3.2 - 4.4 $\log_{10}$).[3] A precise margin of safety for TSE clearance studies is difficult to specify, given current limitations in test methodology and uncertainties about the maximum infectivity titers in blood of asymptomatic vCJD-infected donors. In viral studies, an additional margin of safety that assures clearance of at least 2-3 $\log_{10}$ more than the highest anticipated titers of the viral pathogen has often been considered prudent.

The pdFVIII risk assessment provides additional information about TSE clearance and risk of vCJD exposure. The risk assessment was performed using $\log_{10}$ clearances of 2-3, 4-6, and 7-9. The level of risk is highly impacted by the amount of clearance achieved in product manufacturing. For example, assuming a higher prevalence of vCJD based on the UK tissue survey, a patient with severe hemophilia A who has no inhibitors and is on episodic treatment with pdFVIII is estimated to have a potential mean annual risk of vCJD of 1 in 159 if exposed to

[2] Estimated maximum levels of viremia range from $10^4$ to $10^7$ for enveloped viruses e.g. HIV-1, HCV, and HBV (5), and from $10^5$ to $10^{10}$for non-enveloped viruses, HAV(6) and B19 (7) virus.

[3] Plasma collection volumes recommended by FDA are 625-800 mL, depending upon the donor's weight (http://www.fda.gov/ber/bldmem/110492.pdf).

a product with 2-3 $\log_{10}$ vCJD reduction, 1 in 105,000 if exposed to a product with 4-6 $\log_{10}$ vCJD reduction, and 1 in 100 million if exposed to a product with 7-9 $\log_{10}$ vCJD reduction (Attachment 1). Assuming a lower prevalence of vCJD based on the number of cases that have occurred and are projected to occur in the UK, a patient with severe hemophilia A who has no inhibitors and is on episodic treatment with pdFVIII is estimated to have a potential mean annual risk of vCJD of 1 in 21,500 if exposed to a product with 2-3 $\log_{10}$ vCJD reduction, 1 in 9.4 million if exposed to a product with 4-6 $\log_{10}$ vCJD reduction, and 1 in 3.2 billion if exposed to a product with 7-9 $\log_{10}$ vCJD reduction (Attachment 1)

In spite of the limitations of clearance studies and the uncertainties of risk assessment, a scientifically-based opinion about meaningful clearance of infectivity would provide a useful interim target to assess pdFVIII safety. FDA is considering what level of clearance, demonstrated in a well-designed scaled-down study using an exogenous spiking model, might provide a sufficient assurance of safety with respect to TSEs.

## Questions for the Committee:

1. Based on available scientific knowledge, please discuss whether a minimum TSE agent reduction factor, demonstrated using an exogenous (spiking) model in scaled-down manufacturing experiments, would enhance vCJD safety of the products.

2. If the Committee identifies a minimum TSE reduction factor that would enhance vCJD safety what actions should FDA consider in cases when a licensed pdFVIII has a lower reduction factor:
   a. Labeling that would differentiate the lower TSE clearance products from the higher TSE clearance products;
   b. Recommending addition of TSE clearance steps to the manufacturing method;
   c. Performance of TSE clearance experiments using endogenous infectivity models;
   d. Any other actions?

References

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2. Taylor DM, et al. Infectivity in the blood of mice with a BSE-derived agent. J Hosp Infect 2000;46(1):78-79.

3. Cervenakova L, et al. Similar levels of infectivity in the blood of mice infected with human-derived vCJD and GSS strains of transmissible spongiform encephalopathy. Transfusion 2003;43(12):1687-1694.

4. Brown, P, et al. Further studies of blood infectivity in an experimental model of transmissible spongiform encephalopathy, with an explanation of why blood components do not transmit Creutzfeldt-Jakob disease in humans. Transfusion 39: 1169-78, 1999.

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6. Bower, WA, et al. Duration of viremia in Hepatitis A virus infection. Journal of Infectious Diseases 182: 12-17, 2000.

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**Attachment 1 - Range of *Predicted Annual Mean Potential vCJD risk for pdFVIII per HA Patient* –** at *three levels of clearance: 7-9 $log_{10}$, 4-6 $log_{10}$, and 2-3 $log_{10}$ and at Higher Prevalence and Lower Prevalence estimates and at different treatment doses. (excerpted from table 5.3.A in the FDA's Draft Quantitative Risk Assessment of vCJD Risk Potentially Associated with the Use of Human Plasma-Derived Factor VIII Manufactured Under United States (US) License From Plasma Collected in the US*

| | | | | 7 - 9 $Log_{10}$ Reduction | | 4 - 6 $Log_{10}$ Reduction | | 2 - 3 $Log_{10}$ Reduction | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005) | Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225 by Hilton *et al* (2004) | Model Output for LOWER vCJD Case Prevalence estimate ~1.8 in 1,000,000 based on Clark and Ghani (2005) | Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225 by Hilton *et al* (2004) | Model Output for LOWER vCJD Case Prevalence estimate ~1.8 in 1,000,000 based on Clark and Ghani (2005) | Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225 by Hilton *et al* (2004) |
| Treatment Regimen | Inhibitor Status | Est. Total Number patients in US | Mean quantity of product used per person per year ($5^{th}$ - $95^{th}$)[b] | Mean potential vCJD risk per person per year[a] ($5^{th}$ - $95^{th}$ perc)[b] | Mean potential vCJD risk per person per year[a] ($5^{th}$ - $95^{th}$ perc)[b] | Mean potential vCJD risk per person per year[a] ($5^{th}$ - $95^{th}$ perc)[b] | Mean potential vCJD risk per person per year[a] ($5^{th}$ - $95^{th}$ perc)[b] | Mean potential vCJD risk per person per year[a] ($5^{th}$ - $95^{th}$ perc)[b] | Mean potential vCJD risk per person per year[a] ($5^{th}$ - $95^{th}$ perc)[b] |
| *Prophylaxis* | No Inhibitor | 578 | 157949 IU (21242, 382318) | 1 in 4.1 billion (0-0)[c] | 1 in 50 million (0 - 1 in 11 million) | 1 in 4 million (0-0)[c] | 1 in 54,000 (0- 1 in 12,000) | 1 in 15,000 (0-0)[c] | 1 in 82 (0 - 1 in 17) |
| | With Inhibitor – No Immune Tolerance | 63 | 190523 IU (26956, 447639) | 1 in 3.5 billion (0-0)[c] | 1 in 40 million (0 - 1 in 8.8 million) | 1 in 4.8 million (0-0)[c] | 1 in 41,000 (0- 1 in9,000) | 1 in 12,000 (0-0)[c] | 1 in 65 (0 - 1 in 13) |
| | With Inhibitor – With Immune Tolerance | 62 | 558700 IU (33235, 1592943) | 1 in 551 million (0-0)[c] | 1 in 15 million (0 - 1 in 3.4 million) | 1 in 1.3 million (0-0)[c] | 1 in 15,000 (0- 1 in3,700) | 1 in 2,700 (0-0)[c] | 1 in 24 (0 - 1 in 3) |
| *Episodic* | No Inhibitor | 946 | 85270 IU (4633, 244656) | 1 in 3.2 billion (0-0)[c] | 1 in 100 million (0 - 1 in 24 million) | 1 in 9.4 million (0-0)[c] | 1 in 105,000 (0- 1 in 24,000) | 1 in 21,500 (0-0)[c] | 1 in 159 (0 - 1 in 34) |
| | With Inhibitor | 151 | 160458 IU (5314, 488906) | 1 in 4 billion (0-0)[c] | 1 in 50 million (0 - 1 in 11 million) | 1 in 8 million (0-0)[c] | 1 in 23,000 (0- 1 in 12,000) | 1 in 23,000 (0-0)[c] | 1 in 73 (0 - 1 in 16) |

[a] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.

[b] The $5^{th}$- $95^{th}$ perc (percentiles) are the minimum and maximum numbers that define the range constituting the 90% confidence interval. Accordingly, the mean risk estimates from the model should fall within this defined interval at least 90% of the time.

[c] For a $5^{th}$ and $95^{th}$ percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of pdFVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a pdFVIII plasma pool would be rare and more than 90% of pdFVIII product lots (of vials) would not be predicted to contain vCJD agent.

Attachment 2 – TSE Clearance Study Results for pdFVIII, presented by the Plasma Protein Therapeutics Association at the TSEAC meeting of 9/18/06 at http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4240S1_7_files/frame.htm.

PPTA Plasma Protein Therapeutics Association

## Company A

| Step | MAB column | Q-Sepharose chromatography |
|---|---|---|
| Spike | Scrapie strain 263K | Scrapie strain 263K |
| Preparation | 10% brain homogenate | 10% brain homogenate |
| Prion detection / quantification method | - Hamster bioassay<br>- Western blot confirmation | - Hamster bioassay<br>- Western blot confirmation |
| No. of independent runs per spike preparation | one | one |
| Log reduction(s), $ID_{50}$ | 4.6 | 3.5 |

**TOTAL REDUCTION: 8.1 $\log_{10} ID_{50}$**

→ Product is licensed in the USA

PPTA Plasma Protein Therapeutics Association

## Company B

| Step | 3.5 % PEG Precipitation | Heparin Affinity Chromatography* | Saline Precipitation and Final Filtrations | TOTAL |
|---|---|---|---|---|
| Spike | $PrP^{Sc}$ 263K Scrapie | $PrP^{Sc}$ 263K Scrapie | $PrP^{Sc}$ 263K Scrapie | |
| Preparations | 1) Microsomal fraction<br>2) Detergent treated preparation | 1) Brain homogenate<br>2) Detergent treated preparation | 1) Microsomal fraction<br>2) Detergent treated preparation | |
| Prion detection / quantification method | WB | WB | WB | |
| No. of independent runs per spike preparation | 2 | 2 | 2 | |
| Log reduction(s) | 3.21 – 3.43 | ≥3.44 – ≥3.45 | 2.08 – 2.47 | |
| Mean | 3.32 | ≥3.45 | 2.28 | ≥9.05 |

* Preliminary results

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PPTA
Plasma Protein Therapeutics Association

## Company D

| Steps | Subsequent Precipitation Steps | Precipitation Step Followed by Polishing Step and Sterile Filtration |
|---|---|---|
| Spike | 263K Scrapie | 263K Scrapie |
| Preparation | Microsomes // purified $PrP^{Sc}$ | Microsomes // purified $PrP^{Sc}$ |
| Prion detection/quantification method | CDI (conformation-dependent immunoassay) | CDI (conformation-dependent immunoassay) |
| No. of independent runs/spike preparation | 2 per spike preparation | 2 per spike preparation |
| **Log reduction(s), Mean** | **3.5 // 3.9** | **2.9 // 4.0** |

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Plasma Protein Therapeutics Association

## Company E

| Steps | Adsorption, Precipitation, and Chromatography |
|---|---|
| Spike | 263K Scrapie |
| Preparation | Clarified Scrapie Brain Homogenate (cSBH) and Microsomal Fraction |
| Prion detection/quantification method | PK treatment, 0.5 log titration, and one-step Western blot |
| No. of independent runs/spike preparation | 1 per spike preparation |
| Log reduction(s) | 3.8 for cSBH spike, 3.7 for microsomal spike |
| **Mean** | **3.7 to 3.8** |
| Comments: Consistent results were also obtained from partially combined experiments. An additional step is under evaluation. | |

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Attachment 3 – Summary of Topic I, TSE meeting 9/18/06 (at http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4240M-updated.pdf

**Abbreviated Summary**
**For the**
**TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES**
**ADVISORY COMMITTEE MEETING**
**September 18 & 19, 2006**
**Gaithersburg, MD**
At: http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4240M-updated.pdf

**Topic I: Experimental Clearance of Transmissible Spongiform Encephalopathy Infectivity in Plasma-derived Factor VIII Products**
FDA asked the Committee to discuss whether standardized methods and assessment criteria are feasible and appropriate for determining clearance of TSE agents by the manufacturing processes for plasma-derived FVIII (pdFVIII) products.
Dr. Dorothy Scott introduced the topic summarizing TSE safety concerns, the importance of TSE clearance, upstream pdFVIII manufacturing processes, and methodological and logistical challenges of TSE clearance studies using exogenous spiking materials or endogenously infected blood. She also discussed the question of whether a minimum TSE agent reduction factor might serve as an appropriate standard for demonstrating vCJD safety, similar to analogous precedents from viral validation studies. Then Dr. Thomas Kreil, PPTA, discussed specific TSE clearance study challenges with regard to scale-down and conditioning. Dr. Kreil also presented data from industry-sponsored TSE clearance studies for pdFVIII.
**Questions for the Committee**

**1. a. Please comment on the feasibility and scientific value of adopting standardized exogenous (spiking) study methods to assess TSE clearance in manufacturing of pdFVIII including the following:**

**Optimal spiking material and its preparation from the standpoint of relevance to blood infectivity**

The committee discussed several possibilities, including TSE-infected brain-derived spiking materials, such as hamster 263K brain homogenate which is frequently used, is partially characterized with regard to partitioning during fractionation, and provides sufficiently high titers of infectivity and $PrP^{TSE}$ to allow demonstration of a broad range of clearance in studies. Spleen-derived spikes have lower titers, and there is no guarantee that they represent the physical form of TSE agent in blood better than do brain spikes. It was suggested that, since VLDL fractions of blood may preferentially contain TSE infectivity (based on data from Dr. Safar), such fractions might usefully represent endogenous infectivity. Committee members felt that current experiments might begin with brain homogenate preparations, and that more definitively blood-relevant spikes or endogenous infectivity needed further study. It was widely acknowledged that the physical form of TSE agents in endogenously infected blood must be better understood before the most relevant spiking materials can be selected.

**II) Selection of a TSE strain and animal model**

Several models were discussed (e.g., PrP-bovinized transgenic mice, sheep, and chimeric transgenic mice). Bovinized mice are very susceptible to infection with vCJD agent, and conventional RIII mice can be used to model vCJD as well. It was suggested that, in theory, TSE-infected sheep blood could be assayed with RIII mice, enabling titration of large amounts of plasma or product intermediates. Mice lacking the PrP GPI anchor were also suggested as a possible model, since their blood titers of infectivity have been very high (although it is not known whether the form of infectious TSE agent and its associations in such deficient mice would faithfully model more typical infections). Some members of the committee felt that the most relevant strains of TSE agent to be studied would be derived from humans with vCJD or cows with BSE.

**III) TSE immunoassays for $PrP^{TSE}$ and bioassays for infectivity**

Members commented that conformation-dependent immunoassay (CDI) or protein misfolding cyclic amplification (PMCA) technique showed preliminary promising results. However, the committee discussed the need to compare and carefully validate CDI, PMCA, and other binding assays with bioassays, and some members felt that infectivity still should be demonstrated by bioassay.

**IV) Identification of manufacturing processes that might alter TSE agent properties**

The Committee members commented that the manufacturing process itself is not standardized and varies from product to product and manufacturer to manufacturer so that developing a standard method for validation will require further consideration.
Overall, efforts at standardization were felt by some to be premature, since characteristics of endogenous infectivity are still not well understood, and therefore difficult to model; standardization might even impede research to address remaining challenges in TSE clearance studies. A second viewpoint was expressed, that some standardization now might be useful, because as better methods are discovered they are inevitably adopted.

**1. b. Please comment on the feasibility and scientific value of adopting standardized endogenous study methods to assess TSE clearance in manufacturing of pdFVIII.**

The Committee discussed the merits of various models including the use of transgenic mice (e.g., PrP-cervidized mice for CWD, PrP-bovinized mice for BSE, and PrP GPI-deficient mice) and sheep models of infectivity. Dr. Kreil warned that a potential limitation of endogenous infectivity studies is that animal plasma is known to have characteristics somewhat different from those of human plasma when fractionated, so that manufacturing processes might not be comparable and results with animal models not predictive of those with human plasma. While data were not presented to support or refute this contention, the committee agreed that it might pose an additional limitation of studies using endogenous TSE infectivity in animal plasma.

**2. Based on available scientific knowledge, please discuss whether a minimum TSE agent reduction factor, demonstrated using an exogenous (spiking) model in scaled-**

**down manufacturing experiments, might serve as an appropriate standard for demonstrating vCJD safety of the products.**
A detailed discussion of this question was postponed until the next meeting when risk assessment results will be discussed. One member reminded the Committee of the need for a clear definition for "log reduction" of infectivity, recognizing that the 50-percent infectious dose (ID50) is a continuous rather than a discrete variable and that estimated reductions to less than a single ID50 do not guarantee safety.

**3. Considering the outcome of the discussion on Item 2, in cases where a lower reduction factor is demonstrated for a pdFVIII, should FDA consider the following:**

**a. Labeling that would differentiate the lower clearance products from other products with sufficient TSE clearance;**

**b. Recommending addition of TSE clearance steps to the manufacturing method;**

**c. Performance of TSE clearance experiments using endogenous infectivity models;**

**d. Any other actions?**

This answer depends on the answer to the previous questions, thus definitive discussions were deferred until more information is available. In limited discussion, some members felt that labeling of a product as having less clearance might unfavorably dispose consumers or physicians against certain products even though no vCJD infection has ever been attributed to any plasma derivative. A member felt that the patient community might favor adding effective clearance steps to a manufacturing process but that labeling of products with low clearance values is not indicated now and would not be helpful.

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| 識別番号・報告回数 | | | 報告日 | 第一報入手日<br>2006年11月7日 | 新医薬品等の区分<br>該当なし | 厚生労働省処理欄 |
|---|---|---|---|---|---|---|
| 一般的名称 | 人ハプトグロビン | | 研究報告の公表状況 | Plos Pathogens 2006;<br>2(10):956-963 | 公表国<br>フランス | |
| 販売名<br>(企業名) | ハプトグロビン注ーヨシトミ(ベネシス) | | | | | |

**研究報告の概要**

現在まで、BSE と vCJD は単一のプリオン株と関係していた。この株は、感染した動物およびヒトの脳から分離された異常なプロテアーゼ抵抗性プリオン蛋白（$PrP^{res}$）の唯一の且つ極めて安定な生化学的側面によって特徴付けられている。しかし、従来とは異なるウシの $PrP^{res}$ が、最近、大規模なスクリーニングによって発見された。これらもまた別のプリオン株を代表するか否かを調査するため、我々は、より大きな分子量の $PrP^{res}$（H型と呼ばれる）の特徴を有するフランスのウシの株を、ウシまたは羊の PrP を発現するトランスジェニックマウスに接種した。全てのマウスは神経学的症状を呈し、この株に感染したが、このことは、これらの株が感染性プリオンの新規の株であることを示している。重要なことにこの病原体は、同じマウスー継代感染が維持されたーに接種された BSE 病原体の特徴とは明らかに異なる株の特有の特徴を示した。加えて、この病原体は、これまで羊の PrP 発現マウスにおいて継代感染させた羊スクレイピー株とも異なっていた。我々の知見は、様々なプリオン株がウシに存在するか、または BSE 病原体がある種の動物において分岐し進化した可能性を示している。

**使用上の注意記載状況・その他参考事項等**

2. 重要な基本的注意
(1)略
1)略
2)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

| 報告企業の意見 | 今後の対応 |
|---|---|
| ウシから従来の BSE 病原プリオンとは異なるプリオン株の分離した報告である。<br>これまで血漿分画製剤によってvCJDを含むプリオン病が伝播したとの報告はない。しかしながら、万一vCJD感染者の血漿が本剤の原料に混入した場合には、製造工程においてプリオンを低減し得るとの報告があるものの、製剤から伝播する可能性を完全には否定し得ない。そのため、弊社の血漿分画製剤の製造工程におけるTSE感染性低減に関する検証実験を加速し、自社データを早期に取得し、工程評価を行い、必要に応じて工程改善を実施する予定である。 | vCJD に関連する情報については、今後も注視することとする。 |