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.c. 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?

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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 , 382316)	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 - Western blot confirmation	- Hamster bioassay - 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 2) Detergent treated preparation	1) Brain homogenate 2) Detergent treated preparation	1) Microsomal fraction 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

→ Product is licensed in the USA

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**

→ Product is licensed in the USA

PPTA
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.	

→ Product is licensed in the USA

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 1: 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.

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2007. 1. 26	該当なし	

一般的名称	(製造承認書に記載なし)	研究報告の公表状況		公表国
販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社) 合成血-LR「日赤」(日本赤十字社) 照射合成血-LR「日赤」(日本赤十字社)		HPA Press Statement. 2007 Jan 18.	英国

研究報告の概要

○輸血関連変異型クロイツフェルト・ヤコブ病の4例目

変異型クロイツフェルトーヤコブ病(vCJD)の可能性のある新規発症例が、後にvCJDを発症した供血者に由来する輸血を受けた患者で診断された。これは英国におけるvCJD患者で輸血後感染の可能性があるものの4症例目となる。

最初の輸血関連vCJD症例の発症は2003年12月に確認された。輸血の6年半後に発症し、供血の3年半後にvCJDを発症した供血者由来の血液を輸血されていた。2例目は、供血の18ヶ月後にvCJDを発症した供血者からの赤血球を輸血された受血者に発生した。この患者はvCJDとは無関係な原因で輸血5年後に死亡した。3例目の患者は輸血後6年で発症し8年8ヶ月で死亡したが、供血者は供血後約20ヶ月でvCJDを発症していた。

新規の、4例目となる感染症例は輸血を受けた8年半後にvCJDの症状を来した。患者はプリオンタンパク遺伝子のコドン129にメチオニンホモ接合体が見られた。この患者はまだ生存している。供血者は供血の17ヶ月後にvCJDを発症していた。また、3例目の症例にもvCJDに汚染された血液を供血していた。

4症例全てが1996年から1999年の間に白血球除去をされていない赤血球製剤を輸血されていた。1999年10月から英国では全ての輸血用血液から白血球が除去されたが、vCJD伝播リスクの削減効果については不確定である。

4番目の症例は、輸血によるvCJD伝播のリスクへの関心を高めるが、多くは不明のままである。血液と血液製剤によるvCJD伝播リスク軽減のための現在の予防措置の重要性が強調される。血漿分画製剤と関連したvCJD症例は報告されていない。

英国でvCJDに汚染された血液を輸血された少数の生存者は、輸血による潜在的なvCJD曝露を通知されている。彼らは医療行為によるvCJD伝播リスクを軽減させる適切な予防策を求められ、専門家による神経学的な評価とアドバイスを受けている。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」
合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
英国で輸血による感染が疑われる変異型クロイツフェルト・ヤコブ病の4例目が報告され、当該患者に赤血球を提供した供血者は3例目の患者にも血液を提供していたとの報告である。	日本赤十字社は、輸血感染症防止のため輸血歴のあるドナーを無期限に献血延期としている。vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より英国滞在歴1日以上の方からの献血を制限している。さらに、血液製剤の保存前白血球除去を導入し、平成19年1月16日には全ての輸血用血液への保存前白血球除去の導入が完了した。今後もCJD等プリオン病に関する新たな知見及び情報の収集に努める。

News

Last updated: **19 January 2007**; Volume 1; No 3

- ***Fourth case of transfusion-associated variant-CJD infection***

Fourth case of transfusion-associated variant-CJD infection

A new case of probable variant Creutzfeldt-Jakob disease (vCJD) has recently been diagnosed in a patient who received a blood transfusion from a donor who later developed vCJD [1]. This is the fourth case of probable transfusion transmission of vCJD infection in the United Kingdom (UK). Three of the four recipients developed symptoms of vCJD.

The first symptomatic case of vCJD disease associated with blood transfusion was identified in December 2003. This individual developed vCJD six and a half years after transfusion of red cells donated by an individual who developed symptoms of vCJD three and a half years after donation.

A second case of vCJD 'infection' was identified a few months later in a recipient of red cells from a donor who developed symptoms of vCJD 18 months after donation. This case died from causes unrelated to vCJD five years after transfusion. Post-mortem investigations found abnormal prion protein in the spleen and a cervical lymph node, but not in the brain, and no pathological features of vCJD were found.

A third case developed symptoms of vCJD 6 years and died eight years and eight months after receiving a transfusion of red blood cells from a donor who developed vCJD about 20 months after this blood was donated. These three cases have been published as case reports [2-4] and in findings of the ongoing collaborative study between the National Blood Services, the National CJD Surveillance Unit, and the Office for National Statistics to collect evidence about transmission of CJD or vCJD via the blood supply [5].

The new, and fourth, case of infection developed symptoms of vCJD eight and a half years after receiving a transfusion of red blood cells from a donor who developed vCJD about 17 months after this blood was donated [1]. The donor to this case also donated the vCJD-implicated blood transfused to the third case. As for all other reported clinical vCJD cases that have been tested for genotype, this patient is a methionine homozygote at codon 129 of the prion protein gene. The patient is still alive.

All four cases had received transfusions of non-leucodepleted red blood cells between 1996 and 1999. Since October 1999, leucocytes have been removed from all blood used for transfusion in the UK. The effect of leucodepletion on the reduction of the risk of transmission of vCJD from an infective donation is uncertain.

This fourth case of vCJD infection associated with blood transfusion further increases the level of concern about the risk of vCJD transmission between humans by blood transfusion, although much remains unknown. This reinforces the importance of the existing precautions that have been introduced to reduce the risk of transmission of vCJD infection by blood and blood products [6]. No cases of vCJD have been associated with fractionated plasma products. The small group of living recipients of vCJD-implicated blood transfusion in the UK have been informed of their potential exposure to vCJD by blood transfusion, asked to take certain precautions to reduce the risk of onward person-to-person transmission of vCJD during healthcare, and offered specialist neurological evaluation and advice.

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医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2007年2月19日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	①乾燥抗HBs人免疫グロブリン ②ポリエチレングリコール処理抗HBs人免疫グロブリン		研究報告の公表状況	Journal of The Royal Society Interface DOI: 10.1098/RSIF.2007.0216	公表国 イギリス	
販売名 （企業名）	①ヘブスブリン（ベネシス） ②静注用ヘブスブリンーIH（ベネシス）					

研究報告の概要

輸血を介したvCJDに感染したと疑われる3症例の発見によって、英国でヒトからヒトへの二次感染の流行が起きる可能性の懸念が高まった。英国保健省は、直ちにこの脅威に対応し、1980年以降に輸血を受けた人からのドネーションを禁止した。我々は、この文書で血液由来のvCJDの流行の大きさを探るために感度分析（sensitivity analysis：vCJD感染者1名を流行開始時点で感受性者集団に入れた時の感染者数の期待値）を行い、公衆衛生的介入の有効性について調査した。数学的モデルを、基本再生産感染者数（basic reproduction number）の表現と併せて開発した。感染した血液を介したvCJDの伝播を決める未知のパラメーターに対するモデルの予測の感度を、悲観的なモデルを使った仮定のもとで評価した。自己持続的流行（RO>1）が起こりうるなら流行（2080年まで）の大きさは900例以内であることを我々は見出した。しかし、そのような流行が起こるシナリオは、生物学的にありそうもないことが判った。楽観的な仮定では、公衆衛生への介入は上限を250例に減らし、生物学的に妥当なシナリオのみを考慮したときには更に小さくなった。我々の結果は、大規模な又は自己持続性流行に至るシナリオの可能性はあるが実現性は低く、公衆衛生的介入が有効であるという考えを支持している。

使用上の注意記載状況・その他参考事項等

代表として静注用ヘブスブリンーIHの記載を示す。
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
輸血を介したvCJDのヒトからヒトへの二次感染の流行が起こる可能性について、大規模な又は自己持続性流行に至るシナリオの可能性はあるが実現性は低く、輸血を受けたヒトからのドネーション禁止措置等の公衆衛生的介入が有効であることを統計的に説明した報告である。 これまで血漿分画製剤によってvCJD、スクレイピー及びCWD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。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。