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

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

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

		Original Data			Input distribution (Generalized Beta distribution)				
Treatment Regimen	Inhibitor Status	n	Mean	95% CI	α	β	(min, max)	Mean	95% CI
Prophylaxis	No Inhibitor	578	164394 IU	(13574, 518781)	1.5159	10.02	(300, 1200000)	157949	(21242, 282316)

	With Inhibitor – No Immune Tolerance	63	198781	(7859, 937480	1.4640	6.2861	(2000, 800000)	190523	(26956, 447639)
	With Inhibitor – With Immune Tolerance	62	569707	(14315, 3222471)	0.8782	5.5081	(100000, 2000000)	558700	(33235, 1592943)
Episodic	No Inhibitor	946	90489	(3001, 345416)	0.9882	10.60	(0, 1000000)	85270	(4633, 244656)
	With Inhibitor	151	169710	(4099, 835729)	0.6950	3.6822	(2200, 1000000)	160458	(5314, 488906)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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)

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

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

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

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

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	総合機構処理欄
一般的名称	－		研究報告の公表状況	http://www.fda.gov/cber/blood/vcjdrisk.htm	公表国：米国	
販売名（企業名）	－					

研究報告の概要

FDA が米国内で承認されている血液凝固第 8 因子、第 9 因子およびその他の免疫グロブリンやアルブミンを含む血漿分画製剤のリスク評価を実施した。
その結果、米国で承認されている血液凝固第 8 因子製剤を投与されている患者の vCJD 発症リスクは極めて小さいとしており、第 9 因子などの他の血漿分画製剤についてはこれと同等か、さらに小さいとしている。
vCJD 病原体が存在する場合、他の血漿分画製剤、例えば第 9 因子、アルブミン、および免疫グロブリンなどが得られる血漿画分よりも、第 8 因子が得られる血漿画分には vCJD 病原体が多く含まれている可能性が高いため、FDA は第 8 因子のリスク評価を実施した。
第 8 因子を含む画分は、vCJD を減らしたり除去するための様々な方法を用いて製剤化される。また、vCJD を減らしたり除去したりできると考えられる方法は、他の血漿由来製剤の製造でも用いられている。
vCJD 発症リスクが最も高い英国で献血された血漿から製造された血液凝固因子製剤を大量に長期間にわたって投与されていた患者もいるが、FDA、CDC および NIH が把握する世界中の血友病患者、フォンウィルブランド病患者または他の血液凝固障害患者において、vCJD の発症が報告された症例はない。

報告企業の意見	今後の対応
米国 FDA による血漿分画製剤の vCJD に対するリスク評価の情報で、現時点まで血漿分画製剤からの vCJD 伝播の報告はないと述べている。また、異常プリオン蛋白については、血漿分画製剤の製造工程で除去できるとの考え方がある。	今後とも vCJD に関する安全性情報等に留意していく。

使用上の注意記載状況・その他参考事項等

重要な基本的注意
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。

Potential Risk of Variant Creutzfeldt-Jakob Disease (vCJD)

From Plasma-Derived Products

In recent years, questions have been raised concerning the potential risk of variant Creutzfeldt-Jakob disease (vCJD - a rare but fatal brain infection) for recipients of plasma- derived clotting factors, including United States (US) licensed Factor Eight (pdFVIII), Factor Nine (pdFIX), and other plasma-derived products such as immune globulins and albumin. In response to these questions, FDA conducted a risk assessment. Based on the risk assessment, the US Public Health Service believes that the risk of vCJD to patients who receive US licensed pdFVIII products is most likely to be extremely small, although we do not know the risk with certainty. vCJD risk from other plasma derived products, including Factor IX, is likely to be as small or smaller.

This web page provides FDA's risk assessment for US licensed pdFVIII and risk communication materials for this product and other plasma derivatives. Included are Key Points, and Questions and Answers. Additional links are provided to FDA's current guidance documents on deferral of blood and plasma donors who may be at increased risk of vCJD, and to other sources of information regarding vCJD.

Documents Regarding US Licensed pdFVIII, and Other US Licensed Plasma Derivatives Including pdFIX

- Potential vCJD Risk From US Licensed Plasma-Derived Factor VIII (pdFVIII, Antihemophilic Factor) Products: Summary Information, Key Points
- Risk Assessment (PDF, 582 KB)
- Risk Assessment Appendix (PDF, 623 KB)
- Questions and Answers on vCJD and pdFVIII
- Questions and Answers on vCJD and Plasma Derivatives Other than pdFVIII

Guidance on Donor Deferral Related to CJD and vCJD

- Draft Guidance for Industry: Amendment (Donor Deferral for Transfusion in France Since 1980) to "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products" - 8/2006
- Questions and Answers on FDA Guidance: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob (CJD) Disease and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products - 1/22/2004
- Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products - 1/2002

Other Sources of Information

- Transmissible Spongiform Encephalopathies Advisory Committee
- Blood Products Advisory Committee Meeting – Summary of Recent TSEAC Meeting and Statement about FXI from the UK, on October 21, 2004
- Information on vCJD: Centers for Disease Control and Prevention
- Information on Bovine Spongiform Encephalopathy ("Mad Cow Disease"): US Department of Agriculture

Patient Organizations:

- Committee of Ten Thousand
- Hemophilia Federation of America
- National Hemophilia Foundation and/or HANDI
- World Federation of Hemophilia

Updated: March 15, 2007

Potential Variant Creutzfeldt-Jakob Disease (vCJD) Risk

From US Licensed Plasma-Derived Factor VIII (PdFVIII, Antihemophilic Factor) Products

Summary Information

Key Points:

- In recent years, questions have been raised concerning the risk of variant Creutzfeldt-Jakob disease (vCJD) (a rare but fatal brain infection) to hemophilia A and von Willebrand disease patients who receive US licensed plasma-derived Factor Eight (pdFVIII, Antihemophilic Factor) products.
- Based on a risk assessment, the US Public Health Service (PHS), including FDA, CDC, and NIH, believes that the risk of vCJD to hemophilia A and von Willebrand disease patients who receive US licensed pdFVIII products is most likely to be extremely small, although we do not know the risk with certainty. vCJD risk from other plasma derived products, including Factor IX, is likely to be as small or smaller.
- Contacting a specialist in hemophilia or von Willebrand disease at a Hemophilia Treatment Center is a good way to learn about new information as it becomes available.

Additional Information:

- Between December 2003 and January 2007, there have been four reports of people, all in the UK, who probably acquired the vCJD agent through red blood cell transfusions. This has increased concern about the potential transmission of vCJD by blood products.
- Principal concerns are whether persons infected with vCJD could donate plasma in the U.S., and whether clotting factor products made from their plasma donations might transmit the disease.
- To address these concerns FDA recommends the deferral of donors who may have lived in or traveled extensively to countries with a higher prevalence of vCJD and bovine spongiform encephalopathy (BSE) than in the U.S.
- In the United States, pdFVIII products have not been made from the plasma of anyone known to have developed vCJD, and no one who received any of these products is known to have developed vCJD.
- FDA conducted a risk assessment for pdFVIII because the plasma fraction from which it is made is likely to contain more of the vCJD infectious agent, if present, than plasma fractions from which other plasma-derived products are made, such as Factor IX, (used to treat hemophilia B), albumin, and immune globulins. The FVIII-containing fraction is further processed using a variety of methods that are likely to reduce or potentially eliminate vCJD from the final pdFVIII product. Methods likely to reduce or potentially eliminate vCJD are also used in the manufacture of other plasma-derived products.
- FDA, CDC, and NIH are not aware of any cases of vCJD having been reported worldwide in patients with hemophilia, von Willebrand disease, or other blood clotting disorders. This includes those who have received, over a long period of time, large amounts of blood clotting factor products manufactured from plasma donations from the UK where the risk of vCJD is highest because of a previous higher risk of potential exposure to BSE- infected beef in the UK diet.
- The FDA has taken a number of steps to further reduce the potential vCJD risk from blood components. These steps include donor deferral recommendations, and quarantine and withdrawal of products at increased vCJD risk. Donor deferral guidance, first issued in August 1999 and subsequently updated, includes, among other things, deferral of donors who visited or resided in Europe where BSE prevalence is higher than in the US. Also, blood components and plasma derivatives are to be withdrawn if a donor is later diagnosed with vCJD. The potential spread of vCJD through red blood cell or plasma transfusion is limited by these deferral and quarantine measures that are in place.
- Additional steps FDA is taking to reduce potential vCJD risk from plasma derivatives include gathering, evaluating, and disseminating information about manufacturing processes that potentially could reduce the vCJD infectious agent in blood products. FDA is helping to develop donor screening and diagnostic tests for vCJD, and to inform patients and physicians about the current scientific understanding of vCJD risk from blood products.
- Using a computer model, FDA assessed the potential risk of vCJD infection from the current use of

pdFVIII products. However, because so much is unknown about vCJD and its prevalence, the risk assessment performed by FDA has a lot of uncertainty, making it impossible to precisely estimate the risk of vCJD in general, or of the actual risk to individual hemophilia A or von Willebrand disease patients. Meaningful distinctions also could not be made among specific products. There is no test yet available to detect vCJD infection in healthy donors or recipients.

- Although the risk of vCJD exposure from US pdFVIII products is most likely to be extremely small, it may not be zero, and FDA is encouraging physicians and patients to consider this risk, in the context of all remaining real or potential risks and the known benefits of product use, when making treatment decisions.
- At this time, the PHS does not believe there is a need for hemophilia A and von Willebrand disease patients who receive pdFVIII to inform their surgeons or dentists about their potential exposure to vCJD. Also, there is no recommendation for surgeons and dentists to take any special precautions based on such potential exposures. This belief is based on the results of the FDA risk assessment, as well as on the lack of known cases of vCJD transmitted by plasma-derived clotting factor products in the UK or anywhere else in the world. PHS agencies will continue to monitor and reevaluate the situation as new information becomes available.
- vCJD originally came from a disease in cattle called "mad cow disease" or BSE (bovine spongiform encephalopathy) . Transmission of the BSE agent to humans, leading to vCJD, is believed to occur primarily from eating beef and beef products contaminated with the BSE agent. Both BSE and vCJD are invariably fatal brain diseases with incubation periods typically measured in years.
- From 1995 through January 22, 2007, 201 individuals with vCJD were reported worldwide, with 165 in the United Kingdom (UK), and three in the United States. Two of the individuals in the United States had lived in the UK from 1980-1996 during a key exposure period to the BSE agent. The third individual most likely acquired the disease in Saudi Arabia. The reported incidence of vCJD in the UK based on disease onset peaked in 1999 and has been declining thereafter. In the UK, where most cases of vCJD have occurred, the current risk of acquiring vCJD from eating beef and beef products appears to be negligible.
- More information about vCJD is available on these government websites:
  - FDA: Potential Risk of Variant Creutzfeldt-Jakob Disease (vCJD) From Plasma-Derived Products
  - Centers for Disease Control and Prevention: vCJD (Variant Creutzfeldt-Jakob Disease)
  - US Department of Agriculture
- Information also may be obtained from these non-government sources:
  - Committee of Ten Thousand
  - Hemophilia Federation of America
  - National Hemophilia Foundation and/or HANDI
  - World Federation of Hemophilia

Updated: March 15, 2007

Questions and Answers

Variant Creutzfeldt-Jakob Disease (vCJD) and Plasma Derivatives Other than Factor VIII (pdFVIII)

Q. What is the risk of vCJD for a patient who receives a US licensed plasma-derived product other than plasma-derived Factor VIII (pdFVIII)?

A. The US Public Health Service, including FDA, CDC, and NIH, believes that vCJD risk from US licensed pdFVIII products is most likely to be extremely small, although we do not know the risk with certainty. We believe that the risk of other plasma derived products including plasma derived Factor IX, is likely to be as small as or smaller than for pdFVIII.

FDA conducted a risk assessment for pdFVIII because the plasma fraction from which it is made is likely to contain more of the vCJD infectious agent, if present, than plasma fractions from which other plasma-derived products are made, such as Factor IX, (used to treat hemophilia B), albumin, and immune globulins. The FVIII-containing fraction is further processed using a variety of methods that are likely to reduce or potentially eliminate vCJD from the final pdFVIII product. Methods likely to reduce or potentially eliminate vCJD are also used in the manufacture of other plasma-derived products, including Factor IX, albumin, and immune globulins.

Updated: March 15, 2007

別紙様式第 2-1
番号 5

医薬品
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 2006 年 11 月 29 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	FDA/Transmissible Spongiform Encephalopathies Advisory Committee December 15, 2006	公表国 アメリカ	
販売名 （企業名）	①ヘプスブリン（ベネシス） ②静注用ヘプスブリン－IH（ベネシス）					

研究報告の概要

トピックⅠ：米国で認可されたヒト血漿由来第 VIII 凝固因子製剤（pdFVIII）の使用が関与する可能性がある vCJD についての FDA のリスク評価、及び公衆衛生局の考えられる対応

FDA は、血友病 A およびフォンウィルブランド病患者(vWD)によって使用される米国で認可された pdFVIII に係る vCJD リスク評価文書（Draft Quantitative Risk Assessment of vCJD Risk Potentially Associated with the Use of Human Plasma-Derived Factor VIII Manufactured Under United States License From Plasma Collected in the US）を作成した。

リスク評価を行った背景には、2003 年以来、英国で輸血により vCJD に感染したと見られる 3 例が発見されたことがある。米国では BSE は 3 例発見されたのみで、米国で vCJD に感染したケースはまったくないため、血漿供与者が米国で生産された牛肉を食べて vCJD に感染するリスクは極度に低いと考えられる。しかし、米国の少数の供血者が英国、フランス、その他のヨーロッパ諸国への旅行や滞在で BSE に曝露された可能性はあり、従って一定のリスクを否定できない。これら供血者の一部は知らずに食事を通して vCJD に感染した可能性があり、米国で製造される pdFVIII に使われる血漿のプールにこれら感染者の血漿が入った恐れはある。供血停止政策で大部分の vCJD リスクは排除されている可能性が高いが、供血停止基準に合致しない供血者や、基準に合致していてもスクリーニングで排除されなかった供血者からのリスクは残存する。FDA はコンピュータシミュレーション・モデルを用い、pdFVIII 製品を利用した重症血友病 A 患者及び重症 vWD 患者について vCJD 病原体曝露の確度とそのレベルおよび vCJD 感染リスクを推定した。

FDA は、TSEAC にこのリスク評価文書を提示し、リスク評価の結果と解釈及びこの情報を医師、患者並びに一般大衆に知らせることに関する伝達の要点についての助言を求めようとしている。

トピックⅡ：pdFVIII での伝達性海綿状脳症（TSE）感染性実験のクリアランス

pdFVIII のリスクを、2-3、4-6 及び 7-9 の log クリアランス値を使って評価した。血友病 A の重症患者のリスクは、英国組織サーベイに基づく vCJD の高感染率を仮定した場合は年間平均 1/159～1/100,000,000、低感染率を仮定した場合は 1/21,500～1/3,200,000,000 と予想される。

FDA は委員会に対して以下の質問を行った。①製造工程をスケールダウンしスパイキングモデルを使った実験で示された TSE 病原体のミニマムのリダクション値によって、製品の vCJD 安全性が強化されるか？②もし委員会が vCJD 安全性を強化するミニマムの TSE リダクションを定めた場合、承認を受けた pdFVIII のリダクション値がそれより低い場合に FDA は如何なる対応をしなければならないか？

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プスブリン－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
2006 年 12 月 15 日開催の米国海綿状脳症委員会の議題であり、資料の中に血液凝固第Ⅷ因子製剤の vCJD についての FDA のリスク評価案及び公衆衛生局が医師や患者に事実を如何に伝えるかについての案が示されている。(BENE2006-031 が審議結果の報告) 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。

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE MEETING
December 15, 2006

ISSUE SUMMARY

Topic I: **FDA's Risk Assessment for Variant Creutzfeldt- Jakob Disease (vCJD) Potentially Associated with the Use of US Licensed Human Plasma-Derived Factor VIII (pdFVIII, Antihemophilic Factor) Products, and Potential Public Health Service Responses**

Issue: **FDA has prepared a risk assessment of the potential, but unproven, risk related to pdFVIII products, which are used by some patients with the blood clotting disorders hemophilia A and von Willebrand disease. The risk of the potential of pdFVIII products to transmit vCJD, the agent which causes the human form of "Mad Cow Disease," is highly uncertain, but appears likely to be very low. FDA is presenting the risk assessment to the TSEAC to seek advice on key message points concerning both the risk assessment and appropriate ways to communicate this information to physicians, patients, and the general public. Prior to the TSEAC meeting, FDA has obtained input on the risk communication from individual special government employees (SGE's) who represent various hemophilia advocacy organizations.**

BACKGROUND:

vCJD is a fatal neurodegenerative disease acquired through infection with the agent that causes bovine spongiform encephalopathy (BSE) by consumption of beef products from infected cattle. The first human cases of vCJD were reported in the United Kingdom (UK) in 1996, and as of August 2006, 195 cases have been reported worldwide, 162 of them in the UK.

In 1999, based on the potential, but unknown risk of vCJD from blood products, and consistent with advice from TSEAC, FDA recommended deferral of blood and plasma donors who had traveled or lived for 6 months or longer in the UK from the presumed start of the BSE outbreak in the UK in 1980 until the end of 1996 when the UK had fully implemented a full range of measures to protect animal feed and human food from contamination with the infectious agent causing BSE. In January 2002, FDA recommended enhancing the vCJD geographical donor deferral policy by reducing the time that an otherwise suitable blood donor might have spent in the UK from six to three months. FDA also recommended deferring donors who had spent five or more years in France or cumulatively in any European country listed by the USDA as either having had BSE or having a significant risk of BSE, and adding certain other measures to reduce potential risk, such as deferring any donor with a history of blood transfusion in the UK after 1979. Taken together, these steps were estimated to have excluded donors representing slightly more than 90% of the potential BSE/vCJD risk while deferring about 7% of otherwise suitable donors. Since 2002, TSEAC has several times reviewed FDA vCJD/CJD blood donor deferral policies, most recently advising FDA to recommend deferral of blood donors transfused in France. FDA has issued draft guidance containing such recommendations..